School for Cardiovascular Diseases

CARIM SELF EVALUATION 2007 2012

Faculty of Health, Medicine and Life Sciences,
Maastricht University

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CARIM – School for Cardiovascular Diseases

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CARIM
School for Cardiovascular Diseases
Self-Evaluation 2007-2012

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INTRODUCTION

Tempora mutantur et nos mutamur in illis

Until recently, cardiovascular research was defined as research into well-defined cardiovascular diseases such as hypertension, atherothrombosis, coronary heart disease, congestive heart failure, arrhythmias and stroke, and was based on concepts of distinct organ pathology derived, in principle, from the nineteenth century. While these diseases are still clinically prevalent, concepts concerning their aetiology, pathomechanisms, and interdependency have drastically changed over recent years and given rise to new avenues of integrative scientific thinking and approaches. In this context the integral approach is twofold: first, to identify pathological "undercurrents" such as inflammation, proliferation or fibrosis that link together diseases that were previously thought to be more or less separate entities. Examples include certain forms of lung and kidney disease on the basis of fibrotic processes, atrial fibrillation as a consequence of microvascular disease, diabetes mellitus and coronary heart disease on the basis of endothelial dysfunction, and hypertension and dementia on the basis of cerebral small vessel disease. The second approach is to increasingly integrate cardiovascular research into a societal context. Demographic, societal and economic factors such as old age or gender, and also the age-related clustering of chronic cardio-metabolic diseases, their relationship to proliferative and degenerative disorders, the imperative demand society makes of the medical profession to guarantee a long 'healthy' life and, last but not least, economic sustainability all play prominent roles in today's biomedical research. These developments are reflected in the recently-released new European Union funding program Horizon 2020. Coping with these new concepts and demands means rethinking and restructuring research away from classical organ pathology and therapy to interdisciplinary, translational approaches that recognise the undercurrents and respect societal demands.

CARIM (Cardiovascular Research Institute Maastricht), School for Cardiovascular Diseases, is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded in the Maastricht University Medical Centre+ (MUMC+). With more than 250 researchers in the cardiovascular field (including about 120 PhD students) and an annual budget of approximately € 25,000,000, CARIM is one of the largest cardiovascular research institutes in Europe, producing more than 500 scientific articles and 30 PhD dissertations per year.

CARIM was officially established in 1988 and in 1992 together with the Institute for Cardiovascular Research of the Free University of Amsterdam (ICaR-VU) established a PhD program and successfully applied to become a research school approved by the Royal Netherlands Academy of Arts and Sciences (KNAW). CARIM was re-approved by the KNAW in 1997, 2002, 2007, and this year, CARIM will apply for the fourth re-accreditation.

An essential part of the KNAW re-accreditation process is the report of an international External Review Committee (ERC), which consists of members with leading scientific expertise in one or more areas of CARIM's research. These members are independent and impartial, and have insight into and a vision on international developments in cardiovascular research. This self-evaluation report, covering the years 2007-2012, is written for the ERC that will review the quality of CARIM on June 4 – June 6, 2014, and gives a concise picture of the research school's work, ambitions, output and resources.

The self-evaluation report of CARIM follows the Standard Evaluation Protocol 2009-2015 (SEP), which has been developed by the KNAW, VSNU (Association for Co-operating Dutch Universities) and NWO (Netherlands Foundation for Scientific Research) as a protocol for the evaluation of research in the Netherlands. The aim of the SEP is to provide common guidelines for the evaluation and improvement of research and research policy, based on expert assessments.

At its last meeting (2007), the ERC was impressed by the overall high quality of CARIM. The organisational changes that CARIM was in the middle of at that time were considered to be a sign of vitality and of the potential of CARIM. Based on the recommendations of the ERC, a number of measures have been taken.

To strengthen CARIM's scientific program, the Research Council (paragraph 1.2) was installed in 2009, and the Strategic Board (paragraph 1.2) in 2012. To improve academic education and opportunities for students, a Training Program for MDs, Master's- and PhD students (see Chapter 10 on Next Generation) has been introduced and an initiative for a Marie Curie ITN (Innovative Training Network) within the EU program Horizon 2020 between Maastricht,

Aachen, Stockholm and London, aimed at joint doctorates between the institutions has been started (paragraph 1.3). The newly established tenure track program of CARIM (paragraph 10.3), as well as the "*Toptalenten*" (Top Talents) program of the university (9.1), allow advanced young scientists to permanently enter the academic rank and file. To further improve scientific quality, collaborations between Maastricht and other national and international academic institutions have been intensified or established. Examples are RWTH Aachen (joint doctorate within the EuCAR program) and the universities of Mainz and Münster.

Particular progress has thus been made in the field of cardiogenetics and genomics and thrombosis/haemostasis by establishing joint professorships for mutual programs. A particular asset is the Maastricht Study (1.2, 8.1), mainly organised and run by CARIM researchers since 2009, a longitudinal observation study aimed at comparing 5000 diabetic with 5000 non-diabetic participants from the region in an extensive investigative protocol. Both clinicians and basic researchers can exploit a host of relevant data in a unique interdisciplinary, translational approach. The implementation of the Maastricht Cardiovascular Centre (CVC), in which outstanding patient care and hospital organisation are given the scientific background provided by CARIM, will provide MUMC with a unique chance to excel in translational academic medicine. Last but not least, continuing education and scientific exchange are guaranteed by the weekly 'Cardiovascular Grand Rounds' with lecturers from both inside and outside the institution, by the yearly 'CARIM Symposium' and 'CARIM Strategic Retreat' and by the monthly 'CARIM Joint Theme Seminars' that are currently being established.

Internal and external circumstances require CARIM to continue its high quality research activities. The amount of money from the externally financed projects is under severe pressure, because in the upcoming years (2013-2015) the first round of the prestigious TTI projects (Technological Top Institute) will be terminated and no new public-private initiatives such as the former TTIs are foreseen by the government. Furthermore, the allocation of budgets within the FHML has been adjusted by the introduction of output financing in 2011. This has also had negative consequences for CARIM. Rather severe cutbacks were introduced by the Board of the Faculty at both institutional and departmental levels. However, these challenging internal and external circumstances also carry great possibilities. CARIM has to bring its research up to an even higher level by sharpening its scientific profile and by increasing its visibility and influence in the cardiovascular field.

After the last ERC visitation, a mid-term self-evaluation was performed over the period 2007-2011. Following the SEP evaluation cycle, this mid-term review should have been roughly three years after the last evaluation in 2007. Due to changes in leadership the organisational and structural changes to CARIM's research were not fully implemented and the mid-term review was therefore postponed. As the mid-term review and this self-evaluation report were developed only one year apart, the mid-term review was used as a basis for this report.

CARIM

School for Cardiovascular Diseases

Self-Evaluation 2007-2012

A_ DOCUMENTATION AT THE LEVEL OF THE SCHOOL

A.1 OBJECTIVES AND RESEARCH AREA

A.1.1 Mission statement

The research institute's main tasks include high-quality scientific research and the training of PhD students within the broad area of cardiovascular disease. The research effort not only aims to contribute to our understanding of the processes underlying cardiovascular disease, but also helps students to become independent researchers. A second aim of CARIM's research is that it should translate into clinical practice. The specific PhD and Master's training programs provide a broad approach within our knowledge domain and aim to introduce the students to aspects of basic and applied science. This aim is reflected in the research institute's course program, which includes courses introducing students to new developments in molecular biology and sophisticated physical measuring methods, for example, as well as courses focusing on clinical problems. Most courses are based on the principles of active participation and problem solving. Seminars and Master classes organised by the institute, as well as one-day scientific meetings organised by the various research groups or departments within the school, also address basic and applied aspects of research.

To translate research into clinical practice, CARIM, in close collaboration with the Heart and Vascular Centre (HVC) of the Academic Hospital Maastricht, under the name of the Cardiovascular Centre Maastricht (CVC) is aiming to develop into a unique internationally recognised centre of excellence in cardiovascular medicine in research (including translational research and medical care).

To summarise, CARIM's mission is to:

1. Improve current knowledge of the processes underlying cardiovascular diseases by carrying out pioneering and excellent scientific research extending from 'molecule to patient to population', i.e. the epidemiology of cardiovascular and metabolic diseases;

2. Stimulate and facilitate the collaboration between basic and clinical scientists, as an essential factor in ultimately improving health care;

3. Develop into an internationally recognised centre of excellence in cardiovascular medicine;

4. Train Master's students, PhD students and MD students to become independent researchers and post-docs to become leading scientists who are capable of functioning in multidisciplinary research programs at universities or companies;

5. Evaluate new findings, products and techniques for applicability in health care, often in collaboration with private companies;

6. Publish scientific results in highly ranked journals.

A.1.2 Research area and programs

Research area
At CARIM, basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular diseases are studied, allowing faster translation of new research concepts to clinical practice. New findings, products and techniques which can be applied in healthcare are evaluated, often in collaboration with private companies, and the results of scientific research are published in high-ranking international journals. Master's students, PhD students and MD students are trained to become independent researchers, and post-docs are trained to become leading scientists in the field of cardiovascular disease.

Themes and programs
CARIM is built around three broader research themes, each led by a program leader, on which the second part of the self-evaluation will be based (see Table 1): I) **Thrombosis and Haemostasis**, II) **Cardiac Function and Failure** and III) **Vascular Biology**.

The focus of Theme I 'Thrombosis and Haemostasis' (Theme leader: Prof. Tilman Hackeng) is directed at deciphering impairments of proteins, platelets, and the vessel wall in relation to the development of venous and arterial thrombosis. Reflecting on the blueprint of Virchow's triad that defines thrombosis as an imbalance between blood composition, vessel wall and components of flow, Theme I explores the multifactorial cause of thrombosis that has a high societal impact on the population, i.e. venous thrombosis (oral contraceptive use; pregnancy), and worldwide is the major cause of mortality, i.e. arterial thrombosis.

Research within Theme II 'Cardiac Function and Failure' (Theme leader: Prof. Harry Crijns) ranges from mechanistic studies to clinical trials and surveys of specific cardiac diseases. It focuses on heart failure, ventricular arrhythmias and atrial fibrillation. The main aims of the programs in this theme are to gain insights into the basic biology of heart failure and arrhythmias and, on the other hand, to develop early diagnostic and therapeutic strategies based on concepts developed in the laboratory and vice versa. In future care for patients with cardiac failure and arrhythmias will be significantly individualised by applying in-depth clinical, molecular and genetic phenotyping including versatile everyday biomarkers and advanced imaging supported by computer science.

Research in Theme III 'Vascular Biology' (Theme leader: Prof. Coen Stehouwer) is now centred around the following eight key processes underlying cardiovascular disease:
1) microvascular dysfunction; 2) atherothrombosis; 3) arterial stiffening; 4) vascular smooth muscle cell plasticity; 5) endothelial dysfunction; 6) calcification; 7) advanced glycation; and 8) inflammation. These processes are studied in the context of specific cardiovascular diseases that are major burdens to an ageing society, namely 1) diabetes and the metabolic syndrome; 2) hypertension and chronic kidney disease; 3) stroke and cognitive impairment; 4) acute coronary syndrome and heart failure; 5) aortic aneurysm; and 6) venous disease.

These three themes comprise 27 programs, each led by a Principal Investigator (PI). The PIs are responsible for the scientific progress of their program, for linking activities and seeking collaborations between PIs and themes, for mentoring of PhD students and post-docs and, finally, for the financial basis of the program. All three themes involve basic and clinical programs. Detailed information regarding the CARIM themes is given in part B of this self-evaluation report

In 2009, it was decided to change the organisational structure from three themes to eight research clusters to stimulate cooperation between the research programs. However, this reorganisation never came to full maturity since it did not seem to be as efficient as was anticipated. Therefore, it was decided to keep the three main themes and encourage bottom-up collaborations between researchers from different themes. Several inter-theme collaborations are ongoing, e.g. Dr Rory Koenen and Dr Leon Schurgers (Theme I) participate in the Theme III vascular network group, Prof. Chris Reutelingsperger (Theme I) collaborates with Prof. Erik Biessen in the ZonMW project 'MKMD', and a firm collaboration exists between Prof. Uli Schotten (Theme II) and Prof. Hugo ten Cate (Theme I) on the role of thrombin activation in electrical and structural remodelling in patients with lone AF, or AF associated with minimal heart disease (early AF). In the future, regular scientific in-house meetings covering the three CARIM themes will be organised by the Strategic Board to further stimulate inter-theme collaboration.

The PIs, together with the chairpersons of the departments connected to CARIM, constitute the **School Council**. The

Table 1: Themes, programs and PIs within CARIM

	Program	PI
Theme I, leader Tilman Hackeng	Blood proteins & engineering	Tilman Hackeng
	Vascular aspects thrombosis and haemostasis	Chris Reutelingsperger
	Cell biochemistry of thrombosis and haemostasis	Johan Heemskerk
	Clinical thrombosis and haemostasis	Hugo the Cate
Theme II, leader Harry Crijns	Clinical atrial fibrillation	Harry Crijns
	Cardiomyopathy	Stephane Heymans
	ECM + Wnt signalling	Matthijs Blankesteijn
	Arrhythmogenesis and cardiogenetics	Paul Volders
	Clinical heart failure	Hans Peter Brunner-La Rocca
	Intermediate cardiac metabolism	Jan Glatz
	Gene regulation	Leon de Windt
	Electro mechanics	Frits Prinzen
	Cardiovascular system dynamics	Tammo Delhaas
	Mitochondrial disease	Bert Smeets
	Experimental atrial fibrillation	Uli Schotten
	Surgical intervention	Jos Maessen
Theme III, leader Coen Stehouwer	Vascular complications of diabetes and the metabolic syndrome	Coen Stehouwer
	Hypertension and target organ damage	Peter de Leeuw (retired 2013, Bram Kroon interim PI)
	Cerebral small vessel disease	Robert van Oostenbrugge
	Microvascular dysfunction and glycocalyx	Hans Vink
	Vascular remodelling in cardiovascular disease	Harry Struijker Boudier
	The vulnerable plaque: makers and markers	Erik Biessen
	Structure-function analysis of the chemokine interactome for therapeutic targeting and imaging in atherosclerosis	Christian Weber
	Regenerative and reconstructive medicine for vascular disease	Mark Post
	Cardiovascular biomaterials	Leo Koole
	Utilising network pharmacology and common mechanisms for cardiovascular target validation and drug discovery	Harald Schmidt
	Imaging	Joachim Wildberger

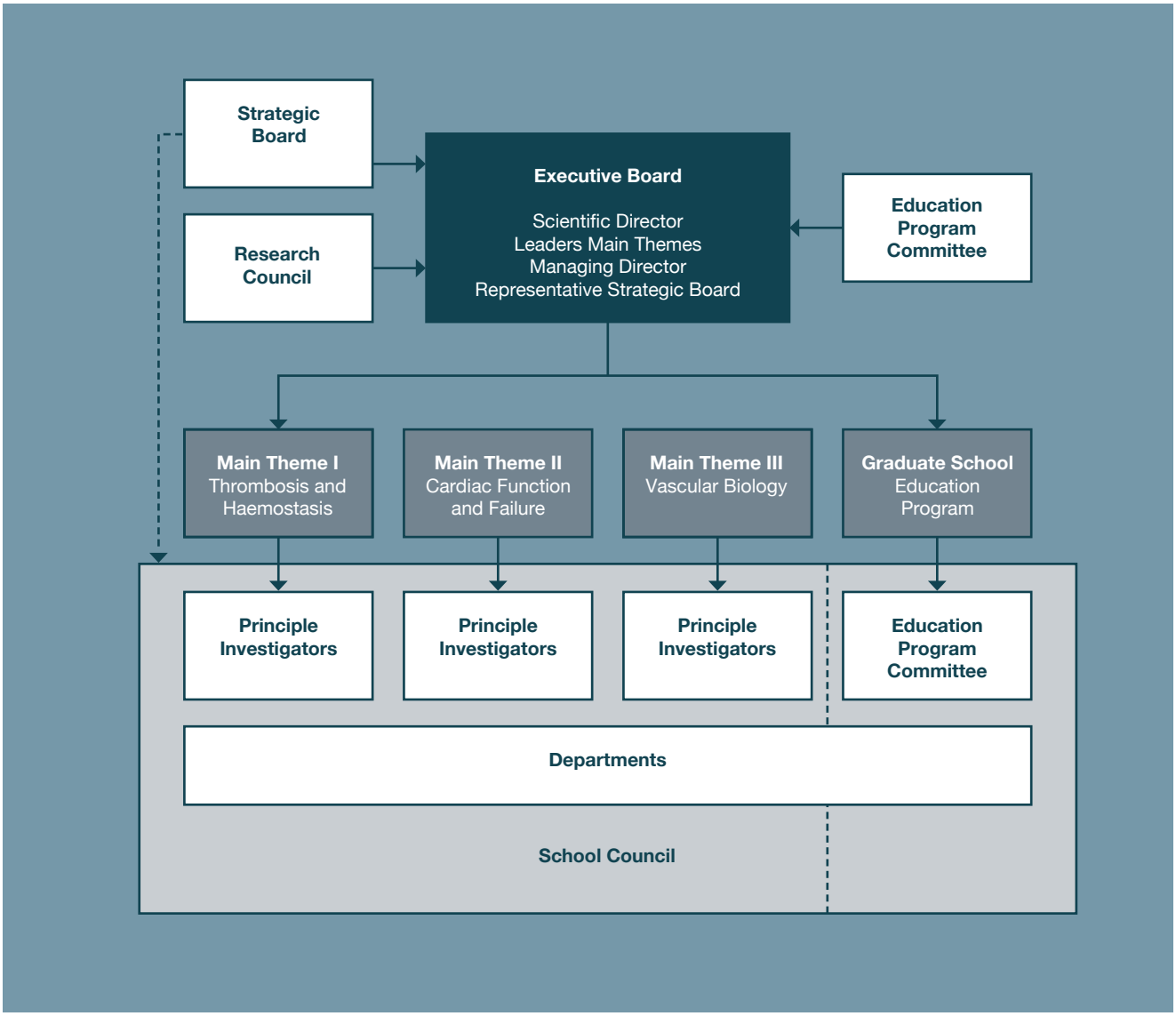
School Council meets four times a year and is headed by the Scientific Director.

Management

CARIM's **Scientific Director**, Professor Thomas Unger, has the final responsibility for the research institute, including the organisation and management of the research program, the scientific output, the training of Master's and graduate students and post-doctoral fellows, and the financial management and the public relations of the institute. At the end of 2012, the so-called **Strategic Board** (SB) was formed to advise and support the Scientific Director in managing long term policy. The board is also a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive European scientific environment. The SB meets regularly to discuss issues such as grant applications, national and international collaboration networks, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

The Scientific Director is assisted by the **Managing Director**, Rob van der Zander, who takes care of the financial and human resource management. Together with the three leaders of the main themes and a representative from the SB, the Scientific and Managing directors make up the *Executive Board* (EB) of the institute (see Figure 1). The EB meets monthly to discuss and decide upon issues at strategic and operational level. Compared with other national and international academic institutions this is a unique organisational structure in which CARIM is the budget holder, not the individual departments. Funding of research and training programs is organised through the institute and not through the departments. Once a year all PIs, including the department leaders, report to the Scientific and Managing Director of CARIM on their finances, scientific output and educational matters ('planning and control' meeting).

Figure 1: Organogram CARIM



The EB is advised by three councils/committees: the SB, the Education Program Committee and the CARIM Research Council. The **Educational Committee** coordinates both the PhD- and Master's training programs and consists of the PhD Program Coordinator, the Master Program coordinator, four CARIM staff members (of which two clinical) and three PhD students. The committee advises the EB on all issues regarding the PhD and Master's programs. At the end of 2009 the EB established the **Research Council** (RC). The RC advises the EB and PIs on the quality of all research proposals and meets regularly to discuss grant applications. Whereas the Strategic Board is thus a more general discussion forum for strategy formation, the RC only discusses individual grant applications. The structure of the RC is being optimised by the SB to improve the guidance and reviewing of applications.

Finally, the **School Council** consists of the Principle Investigators and department heads (see Table 2 for participating departments in CARIM) and meets four times a year.

Table 2: Participating departments in CARIM

Basic Research Departments	Clinical Departments
Biochemistry	Cardiology
Biomedical Engineering	Cardio-thoracic Surgery
Genetics and Cell Biology	Clinical Chemistry
Pharmacology	Internal Medicine
Physiology	Neurology
	Pathology
	Radiology
	Surgery

A.1.3 Objectives

CARIM has the ambition to be one of the leading research institutes in translational cardiovascular research in Europe, to be a top 10 player in the period leading up to 2020. In order to reach and maintain this long-term goal it has several objectives.

Training program PhD students

Master's students, PhD students and MD students are trained to become independent researchers and post-docs are trained to become leading scientists in the field of cardiovascular disease. The training program will be extensively described in Chapter 10.1. In the context of the Horizon 2020 program of the European Union, there is an initiative to create a Marie Curie ITN between CARIM, RWTH Aachen, the Karolinska Institute, Stockholm and King's College, London. Based on the solid background of the existing joint PhD program between Aachen and Maastricht (EuCAR), a joint/double doctorate network (European Joint Doctorate, EJD) between the four participating institutions is foreseen. PhD students, recruited for individual research projects within the theme complex "vulnerable patient", will be assigned to a coordinated course program involving all academic sites as beneficiaries, as well as to those of industrial contributors as associated partners (Philips, Medtronic, AstraZeneca, Bayer Pharma, Vicore Pharma).

The aim is to train a new generation of creative, entrepreneurial and innovative early-stage researchers, able to face the current and future challenges of translational science.

Attracting scientific excellence

In a highly competitive field and under increasingly restrictive financial conditions, recruiting scientific excellence from outside/abroad has become a critical challenge. An internal tenure track system, introduced to CARIM 6 years ago, together with the *"Toptalenten"* program of Maastricht University supports young, promising talents in their advanced post-doc phase to become tenured or even advance to professorship. In January 2012, Dr Blanche Schroen was the first 'tenure tracker' to successfully meet the high-standard criteria of CARIM's tenure track system and has been given a permanent position. At present (count of 31-12-2012), nine young researchers are following the track and steadily flowing into the system. Recently, the proportion of female scientists in the tenure track system increased to over fifty percent.

The field of cardiogenetics has been restructured. CARIM was able to recruit Prof. Monika Stoll, an internationally-recognised expert in complex cardiovascular genetics from Münster University, who has a part-time professorship with the team, led clinically in the Department of Cardiology by Dr Paul Volders. Within a few months, this step has proven to be extremely successful and has moved cardiogenetics/informatics to being a highly effective operation.

Collaboration and translation

There are many scientific collaborations within CARIM. In general, these are not forced by top-down rules but rather encouraged as bottom-up collaborations. Indeed, with almost thirty independent PI groups running their own projects with a huge diversity of approaches and methods, CARIM oversees the critical mass of researchers and facilities to provide ample cooperative possibilities.

In 2007 in a collaborative strategic plan, the ERC advised the translation of the alignment of activities and the translation of science into clinical innovation in the HVC of the MUMC+. This plan (Annex 2), which has been under development for several years, has recently, been put into operation by the foundation of CVC, the Cardiovascular Centre of the MUMC+ which combines the clinical forces of the HVC with the theoretical forces of CARIM. Although the rules of this intensive collaboration between clinic and basic research still have to be refined, the CVC is undoubtedly an extremely important step towards translational cardiovascular research combined with high–standard patient care. It may become a unique selling point of Maastricht University and its Academic Hospital.

One of the largest translational projects of recent years is the **Maastricht Study**, a unique research project into the causes and treatment of type 2 diabetes and its accompanying cardiovascular complications. Research is increasingly focusing on diseases such as diabetes which are closely related to cardiovascular diseases, and the Maastricht Study is a great treasure house for researchers in the cardiovascular-metabolic field. The Maastricht Study will have an important impact on the health of people of South Limburg and on the battle against diabetes and cardiovascular disease in general. Research on thrombosis, the treatment of atherosclerosis, heart failure, arrhythmias and vascular diseases are also central research issues with a large societal impact.

A.2 COMPOSITION

A.2.1 Total number of employees

Over the last two years, scientific collaborations between CARIM and academic institutions outside Maastricht have been intensified. Besides the RWTH Aachen, a natural partner in the close vicinity with whom collaborative programs (EuCAR) and initiatives (ITN Marie Curie) have already been established, an academic research collaboration between CARIM/HVC (Prof. Hugo ten Cate, Prof. Johan Heemskerk) and the CTH (Centre for Thrombosis and Haemostasis; Prof. Ulrich Walther, Prof. Thomas Münzel) at the University of Mainz has been started and is now being formalised between the two institutions. In addition, numerous project-based co-operations exist with other academic institutions both in the Netherlands and internationally, as evidenced in Annex 3.

Organised by the Department of Cardiology, a weekly lecture series, called 'Cardiovascular Grand Rounds' has been established which is open to all scientific themes of CARIM. In addition, every year in autumn the CARIM Symposium is organised with lectures and posters from within CARIM as well as internationally recognised scientific authorities. The program includes the 'Robert Reneman' lecture presented by an internationally recognised authority who is active in the field of CARIM's research activities. Previous eminent speakers include Prof. D. Kass (Baltimore, USA), Prof. W. Ouwehand (Cambridge, UK), Prof. D. Wagner (Boston, USA), Prof. J. Yudkin (London, UK), Prof. A. Zeiher (Frankfurt, Germany) and Prof. P. Vanhoutte (Courbevoie, France).

In 2012 the total number of CARIM staff was 262.8 FTE (full-time equivalent), of which a scientific staff of 190.4 FTE (40.4 FTE tenured and 51.6 FTE non-tenured staff) and 98.4 FTE PhD students. The overview of the research input within CARIM from 2007-2012 shows a gradual increase in research staff over the last six years. This is mainly due to an increase in the number of PhD students (2007: 74.9 FTE, 2012: 98.4 FTE). This increase is explained by the Maastricht Study (from 2009), and grants obtained from TI Pharma and CTMM (Centre for Translational Molecular Medicine), which attracted many PhD students. To keep this number will be a challenge in the years to come, because of the financial restrictions mentioned above and the discontinuation of grants from TI Pharma and CTMM.

The number of tenured staff increased in the first years of the evaluation period, but for CARIM as a whole decreased from 2011 and in two of the three research themes. However, the number of non-tenured staff on the other hand first decreased, but has increased again over the last few years. The number of FTE technical staff within CARIM has remained nearly the same over these years.

Table 3a: Research staff at institutional level

	2007	2008	2009	2010	2011	2012
Tenured staff (1)	41.0	43.6	48.0	51.3	45.3	40.4
Non-tenured staff (2)	41.9	38.9	38.5	33.9	44.6	51.6
PhD students (3)	74.9	81.0	80.4	84.8	100.9	98.4
Total research staff	**157.8**	**163.5**	**166.9**	**170.0**	**190.8**	**190.4**
Support staff	68.8	64.0	57.9	64.2	65.2	72.4
Total staff	**226.6**	**227.5**	**224.8**	**234.2**	**256.0**	**262.8**

Table 3b: Research staff at Theme level

	2007	2008	2009	2010	2011	2012
THEME I THROMBOSIS AND HAEMOSTASIS						
Tenured staff	7.3	8.0	8.8	8.5	9.0	8.6
Non-tenured staff	7.6	8.4	8.1	9.3	12.9	13.6
PhD students	17.4	16.2	14.4	20.0	24.4	25.6
Total research staff	**32.3**	**32.6**	**31.3**	**37.8**	**46.3**	**47.8**
Support staff	14.9	10.9	10.8	10.7	13.3	12.4
TOTAL STAFF	**47.2**	**43.5**	**42.1**	**48.5**	**59.6**	**60.2**
THEME II CARDIAC FUNCTION AND FAILURE						
Tenured staff	14.8	17.7	19.4	22.2	16.6	14.9
Non-tenured staff	14.6	11.6	11.6	7.8	14.9	16.8
PhD students	27.9	28.5	25.1	25.5	33.5	33.9
Total research staff	**57.3**	**57.8**	**56.1**	**55.5**	**65.0**	**65.6**
Support staff	23.7	23.8	17.4	22.0	22.5	23.1
TOTAL STAFF	**81.0**	**81.6**	**73.5**	**77.5**	**87.5**	**88.7**
THEME III VASCULAR BIOLOGY						
Tenured staff	18.9	17.9	19.8	20.6	19.7	16.9
Non-tenured staff	19.7	18.9	18.8	16.8	16.8	21.2
PhD students	29.7	36.2	40.9	39.2	43.0	38.9
Total research staff	**68.3**	**73.0**	**79.5**	**76.6**	**79.5**	**77.0**
Support staff	30.2	29.4	29.7	31.6	29.3	36.8
TOTAL STAFF	**98.5**	**102.4**	**109.2**	**108.2**	**108.8**	**1138**

1) Comparable with WOPI categories Professor, Associate Professor, Assistant Professor
2) Comparable with WOPI category Researcher, including post docs
3) PhD students with an employee status

One of the comments made by the ERC in 2008 was that it would be desirable to have more female role models within CARIM. While the gender issue* is still a problem, CARIM made modest progress during the previous years by attracting more female researchers. Table 4 gives an overview of the male/female ratio in the scientific staff, post docs, PhD students and technical staff. Within every group there is a slight increase in the percentage of females. Especially in the tenure track program was paid special attention to this gender issue by creating a balanced pool of tenure trackers and by focusing on expertise and gender (Chapter 10).

Table 4: Male/female ratio within CARIM

	2007		2012	
	Female (%)	Male (%)	Female (%)	Male (%)
Scientific staff	13	87	15	85
Post docs	40	60	52	48
PhD students	42	58	51	49
Support staff	59	41	63	37

* Please notice that this situation is not specific for CARIM, but that our data reflect the situation in the Netherlands.

A.2.2 Internal and external sources of financing

Table 5a offers an overview of CARIM's annual funding and expenditures (in K€) over the past six years, distinguishing between direct funding through the University, research funds and contract research. The presented numbers correspond with the CARIM annual statements of account.

Table 5a: Funding and expenditure at institutional level

	2007 K€	2008 K€	2009 K€	2010 K€	2011 K€	2012 K€
Funding						
Direct Funding structural	8,055	8,239	8,653	8,411	8,242	7,391
Direct Funding specific programs	3,346	3,044	3,606	3,603	2,830	2,717
Total Direct Funding (1)	**11,401**	**11,283**	**12,259**	**12,014**	**11,072**	**10,108**
Research grants (2)	1,751	1,411	1,201	2,140	1,284	1,566
Contract research (3)	10,400	8,812	9,385	9,900	13,202	13,464
	12,151	**10,223**	**10,586**	**12,040**	**14,486**	**15,030**
Total funding	**23,552**	**21,506**	**22,845**	**24,054**	**25,558**	**25,138**
Expenditure						
Personnel costs	13,401	13,534	14,656	15,024	15,984	16,492
Other costs	9,650	7,144	6,469	7.474	7,855	8,475
Total Expenditure	**23,051**	**20,678**	**21,125**	**22,498**	**23,839**	**24,967**
Result	**502**	**828**	**1,720**	**1,556**	**1,719**	**171**

(1) Direct funding originating from the University as provided by the Dutch government

(2) Research funds received in competition from national science foundations and governmental organisations e.g. NWO, ZonMW, STW, KNAW

(3) Third party funding received in competition from European Union, Netherlands Heart Foundation, Dutch Kidney Foundation, Industry

Direct funding from MUMC+ increased over the period 2007-2011. In 2012 CARIM encountered freezes and cuts in direct funding. As a consequence we had to keep several vacant positions in the tenured staff open and were forced to reduce other expenditures in order to prevent deficits. Over the total period, CARIM managed to keep income and expenditures in balance.

In the period covered by the report, more than 50% of CARIM's funding was derived from third parties. In 2011-2012 the contribution of third-party funds has increased to about 60%, due to the fact that CARIM was able to attract major grants in the framework of the TTIs TI Pharma, CTMM and BMM.

The distribution of funding over the main research themes is shown in Table 5b. An extensive overview of externally funded CARIM research projects in the period of 2007-2012 is provided in Addendum 1.

Table 5b: Funding at theme level

Funding	2007		2008		2009		2010		2011		2012	
	K€		K€		K€		K€		K€		K€	
THEME I THROMBOSIS AND HAEMOSTASIS												
Direct Funding (1)	2,052		2,031		2,247		1,971		2,214		2,152	
Grants & Contract Funds	1,445		1,941		1,911		2,416		3,209		3,434	
Subtotal Theme I	**3,497**	**15%**	**3,972**	**18%**	**4,158**	**18%**	**4,387**	**18%**	**5,423**	**21%**	**5,586**	**22%**
THEME II CARDIAC FUNCTION AND FAILURE												
Direct Funding	4,104		4,626		4,955		5,149		4,097		3,728	
Grants & Contract Funds	3,678		3,143		3,035		4,486		4,985		4,669	
Subtotal Theme II	**7,782**	**33%**	**7,769**	**36%**	**7,990**	**35%**	**9,635**	**40%**	**9,082**	**36%**	**8,397**	**33%**
THEME III VASCULAR BIOLOGY												
Direct Funding	5,245		4,626		5,057		4,894		4,761		4,228	
Grants & Contract Funds	7,028		5,139		5,640		5,139		6,291		6,927	
Subtotal Theme III	**12,273**	**52%**	**9,765**	**45%**	**10,697**	**47%**	**10,033**	**42%**	**11,052**	**43%**	**11,155**	**44%**
Total funding	**23,552**	**100%**	**21,506**	**100%**	**22,845**	**100%**	**24,054**	**100%**	**25,558**	**100%**	**25,138**	**100%**

Note: the sum of the funding over the themes is higher than the total funding of the Institute, because some grants cannot be allocated to one of the themes only.

Although the external funding per theme varied over the evaluation period, on average all the themes managed to expand their direct income from the University by at least 100%, taking the ratio grants/contract funds and direct funding into account.

The figures listed in Tables 5a and 5b do not show that CARIM researchers are involved in clinical trials and applied research. In our organisation, this part of the external contract funding is administrated by the Academic Hospital and/or the Clinical Trial Centre Maastricht (CTCM).

The turnover in the report period was as follows:

	2007	2008	2009	2010	2011	2012
	K€	K€	K€	K€	K€	K€
Funding administrated by:						
CTCM (Sum Theme I, II, III)	n/a	2,635	1,751	2,099	1,604	1,604
AZM (Sum Theme I, II, III)	n/a	227	233	1,143	1,527	61

A.3 RESEARCH ENVIRONMENT AND EMBEDDING

CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University, embedded within the MUMC+.

The six research schools are:

- School for Cardiovascular Diseases: CARIM
- School for Health Professions Education: SHE
- School for Mental Health and Neurosciences: MH&NS
- School for Nutrition, Toxicology and Metabolism: NUTRIM
- School for Oncology and Developmental Biology: GROW
- School for Public Health and Primary Care: CAPHRI

There has always been extensive collaboration between CARIM and the other research schools. A few examples may suffice here. Within the Maastricht Study (Theme III) there are structural collaborations with CAPHRI groups (Dr Martin Van Boxtel) and MH&NS (Prof. Frans Verheij). Prof. Tilman Hackeng and Dr Ingrid Dijkgraaf (Theme I) collaborate with GROW (Prof. Geerard Beets and Prof. Regina Beets-Tan) on the design and synthesis of contrast agents for the detection of tumour angiogenesis in colorectal cancer, while Prof. Hugo ten Cate (Theme I) collaborates with groups in CAPHRI (Prof. Martin Prins and Dr Manuela Joore) on epidemiology and medical technical assessment (MTA). Prof. Robert van Oostenbrugge, who recently became PI in CARIM, is bridging CARIM's microvascular biology activities (Theme III) and clinical neurology in MH&NS with his research topic "Brain microvascular disease and dementia". Prof. Stephane Heymans (Theme II) collaborates with Dr Ronit Sverdlov on the implication of proteoglycans in the heart-liver connection in diabetes and with Dr Patrick Schrauwen on cachexia and heart failure: involvement of inflammation and mitochondrial changes (both NUTRIM). More examples can be found in the theme parts of this evaluation report and Annex 3.

A.3.1 National and international positioning

When looking at CARIM's position in the national and international (European) context using non-scientific parameters, it can be stated that CARIM is one of the largest centres in the field both nationally and internationally. Key parameters in such an analysis are: 1) programs, 2) strategic embedment within the institution's policy, 3) structure, 4) personnel, 5) and functional integration. A final parameter which could be used is the close proximity of clinical facilities. The first five parameters are also used in the current policy framework of the European Union regarding Centres of Excellence.

National positioning

After a first qualitative analysis, based on the above-mentioned parameters and the existence of eight University Medical Centres (UMCs), it can be stated that Academic Medical Centre Amsterdam (AMC), Erasmus University Medical Centre Rotterdam (Erasmus MC), Leiden University Medical Centre (LUMC) and the VU University Medical Centre Amsterdam (VUMC) are CARIM's direct competitors. This statement is based on the fact that these UMCs have institutionalised their cardiovascular research in a program-based way and that this is also strategically embedded within the general policy of the institution (with the exception of the LUMC). When looking at this program-based structure in relation to the range of themes, CARIM scores better than the other centres.

In addition three of the four UMCs have combined their cardiovascular research in organisational units with a certain independent structure. For instance, the AMC has organised a large part of its cardiovascular research (basal, translational and clinically applied) in the Heart Failure Research Centre (HFRC) which has a certain degree of independence. However, since the MUMC+/Maastricht University have organised their research into schools, which are focused on a number of larger subject areas, CARIM has the greatest independence of the five medical centres.

Furthermore, the way in which the various cardiovascular disciplines are integrated into the institute (in this case the School) – both organisationally and content-wise – is different for each institute. With its fully integrated structure, CARIM has the largest degree of integration in comparison with its national competitors.

Finally, when looking at the number of staff members (critical mass is important for the positioning of an institute), CARIM, the AMC and Erasmus MC are the major players.

Based on these arguments, it can be concluded that CARIM is among the largest integrated cardiovascular research institutes in the Netherlands.

International positioning

With its unique geographic position in the south of the Dutch province of Limburg, Maastricht University, and with it CARIM, enjoys the great advantage of being positioned in the heart of the Euregion between Belgium and Germany and close to France, but it also suffers from the potential disadvantage of being too far away from the academic and business centres of the central and northern Netherlands.

When applying the parameters above in placing CARIM in an international (European) context, four centres show similar characteristics:

- Imperial College Healthcare NHS Trust (the Cardiovascular Centre of Imperial College London, UK)
- LIRYC (l'Institut de Rhythmologie et Modélisation Cardiaque; a collaboration between the l'Hôpital Cardiologique du Haut Lévêque of the Academic hospital Bordeaux, the University of Bordeaux, INSERM, CNRS and Inria)
- The cardiovascular program of the Karolinska Institute, Stockholm, Sweden
- Centre for Cardiovascular Research (CCR) Charité Berlin, Germany

In comparison with these renowned top centres, CARIM has the broadest spectrum of thematic topics in its programs. LYRIC and – to a lesser extent – Charité do not profile themselves on the basis of a broad spectrum of topics. LYRIC even focuses in-depth on one subject only, even though it is the same size as CARIM in terms of the number of staff members. Using this criterion CARIM and LYRIC are the largest centres.

With regard to the degree of integration, CARIM also scores better than the other centres. Of all the centres Imperial College Healthcare NHS Trust and the Karolinska Institute are the most comparable with CARIM. Where the strategic embedment of the research within the institute is concerned, LYRIC scores the best, followed by CARIM and the Imperial College Healthcare NHS Trust.

It is safe to conclude that CARIM is among the top integrated cardiovascular research institutes within Europe, even if not one of the largest.

Close proximity of clinical facilities

It is self-evident that the close proximity of clinical facilities has a positive impact on translational research. A comparison within the Netherlands shows that there is little difference between the UMCs. However, in comparison with the European cardiovascular centres mentioned above, close proximity does play a role. In its classical cardiovascular domains, CARIM undoubtedly ranks among the top ten percent of top institutions in Europe with as its particular strength the ability to combine basic research into blood, heart and vasculature as three, closely interrelated themes with multiple crossovers and immediate interaction with the clinic. It is indeed this rigid translational approach under one roof, manifested not only in the Maastricht Study and the CVC initiative, but also in many other joint research projects between basic and clinical scientists. Together this results in the unique flair of the MUMC. Furthermore, between 2007 and 2012 CARIM participated in several international networks such as the Leducq Translatlantic network, EU Framework Programs, the CardioRisk Consortium, the European Network on Diagnostic Molecular Imaging (DiMI), InGenious HyperCare Network and the European Network for Translational Research in Atrial Fibrillation. These joint international projects and professorships are detailed in other chapters of this report.

A.3.2 Guest researchers

CARIM's most important guest researchership is the Hein Wellens Visiting Professorship, installed and funded by the St. Annadal Foundation to stimulate clinical research in the field of cardiovascular disease. The purpose of this chair is to give renowned scientists the opportunity to teach and apply their knowledge at CARIM. The chair is named after Prof. Hein Wellens, a Dutch cardiologist who is considered to be one of the founding fathers of the cardiology subspecialty of clinical cardiac electrophysiology. From 1978 until 2002 Prof. Wellens held a chair at Maastricht University as Professor and Head of the Department of Cardiology. In 2004, Prof. Jagat Narula, Professor of Medicine and Chief of Cardiology at UCI Medical Center (Irvine), was the first holder of the Hein Wellens Chair. In the last few years, several internationally distinguished scientists have occupied the Hein Wellens Chair. Table 6 gives an overview of the candidates that have held this chair.

Another chair attached to CARIM from 1998-2008 was the Edmond Hustinx Chair, funded by the Edmond Hustinx Foundation. This chair focused on research in the area of molecular and chemical aspects of cardiovascular diseases. CARIM was able to appoint internationally recognised top scientists to this chair. The last professor to hold this chair in 2007-2008 was Prof. Stefanie Dimmeler, Professor of Experimental Medicine and Head of Molecular Cardiology at the University of Frankfurt, Germany.

Table 6: Hein Wellens Chair Holders 2006-2012

2006-2007	Prof. Mitchell Krucoff, Duke VA Medical Center, Durham, USA, Medicine - Cardiology
2007-2008	Prof. Yoram Rudy, Washington University, St. Louis, USA, Cell Biology & Physiology, Medicine, Pediatrics, and Radiology
2010-2011	Prof. Raymond Kim, Duke Cardiovascular Magnetic Resonance Center, Durham, USA, co-director CV Imaging Center: MRI
2012-2013	Prof. Kevin Mayo, University of Minnesota, USA, Biochemistry

A.4 QUALITY AND SCIENTIFIC RELEVANCE

Scientists at CARIM annually publish a large number of scientific publications in journals both within and outside their own field (see paragraph 5.1). Not only is the number of publications high, but so is their scientific impact. In recent years the average impact factor (IF) of the journals in which these articles are published has shown a clear increase to an average IF of 5.5 in 2011. Up to 44% of the articles produced by CARIM in the period 2007-2012 have been published in international journals that are in the top 10% in their field.

Commissioned by the Dutch Federation of University Medical Centres (NFU), the Centre for Science and Technology Studies (CWTS) performs an annual analysis of the bibliometric data from the eight Dutch UMCs. Since this analysis started, CARIM has scored consistently at a level that is well above the world average. However, it is striking that CARIM has shown a very sharp increase in more recent years. There has been an **increase from 1.37 in 2007 to 1.79 in 2010,** meaning that in the crown indicator MNCS (Mean Normalised Citation Score), CARIM scores well above the world average. The MNCS indicates the impact of a research unit's articles compared to the world citation average (being 1.0) in the subfields in which the research unit is active. That means that the publications of CARIM are cited 1.79 times more frequently than the world average.

Table 7 gives a year-weighted overview of CARIM's bibliometric statistics indicating; **P**: Number of articles (normal articles, letters, notes and reviews) published in journals processed for the Web of Science (WoS) version of Thomson Scientific's Citation Indexes (CI), **CPP**: Average number of citations per publication, or citations per publication ratio. Self-citations are excluded, **MNCS**: The impact of a research unit's articles, compared to the world citation average in the subfields in which the research unit is active and **MNJS:** The impact of the journals in which a research unit has published (the research unit's journal selection), compared to the world citation average in the subfield covered by these journals.

Table 7: Bibliometric analysis CARIM 2007-2010

School level	P	CPP	MNCS	MNJS
2004-2007	1,442.30	9.56	1.37	1.24
2005-2008	1,531.80	10.70	1.45	1.26
2006-2009	1,552.50	12.33	1.64	1.33
2007-2010	1,681.30	12.92	**1.79**	1.39

In terms of the MNCS score, CARIM scores the highest of all schools within the FHML (see Figure 2). In the most recent analysis in the fields of Cardiology and the Cardiovascular System, Maastricht UMC+ scores the highest of all Dutch UMCs (1.90). Articles from the CARIM Department of Cardiology are quoted 2.67 times more often than the world average, while various sections of the Department of Internal Medicine (Diabetes Cardiovascular, Haematology, Clinical Immunology and Nephrology) are cited more than twice as frequently as the world average.

When assessing the quality of scientific output, it is also important to look at the number of publications in the top 10% and top 10%-25% of ranking journals. In the period from 2007-2012 approximately one-third of CARIM publications ranked in the top 10% journals (Table 8a), i.e. those journals that have been ranked as the top 10% in various subject categories by the Journal Citation Reports of the ISI. In 2012 this percentage was as high as 44%. An additional one-third of our papers are published in the top 10%-25% ranking journals (Table 8b). The total number of publications over the period 2007-2012 is discussed in paragraph 5.1.

Publication highlights

Finally, the quality of our output is illustrated by the fact that a considerable fraction of papers are published in the absolute top ranking journals (impact factor above 10), such as New England Journal of Medicine, JAMA, Nature Medicine, Journal of Experimental Medicine, Circulation, Lancet Neurology, and Journal of American College of Cardiology. Examples of these major publications are given below divided over the three themes (Tables 9a, 9b and 9c), while a full overview of all CARIM publications for 2007-2012 is presented in Addendum 2.

CARIM researchers also sit on numerous committees and scientific and editorial boards (see Chapter 7 and Annex 4). Also the number of CARIM staff invited to give lectures at national and international meetings between 2007 and 2012, as well as the overview of awards and prizes that CARIM staff members received over this period (Annex 5) indicate that our work is highly valued by our international peers.

Figure 2: MNCS FHML Schools

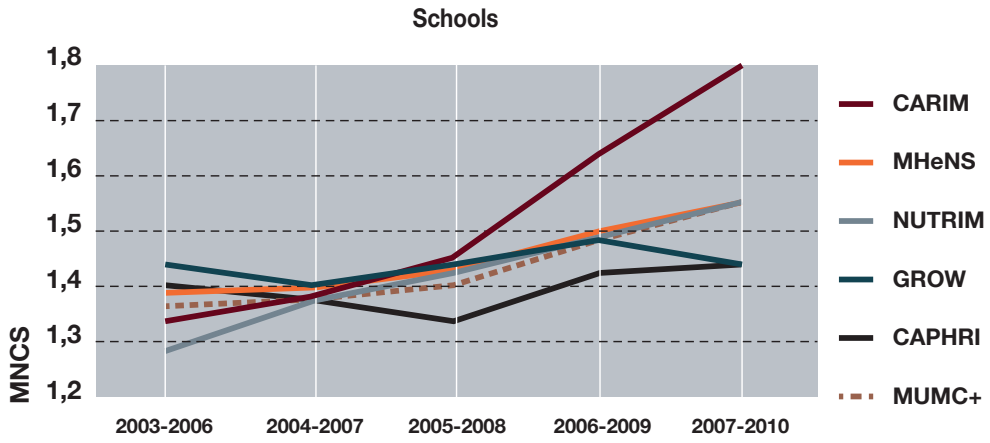


Table 8a: Overview of the number and percentage of publications in the top 10% ranking scientific journals 2007-2012

	Publications in top 10% ranking journals	
2007	128	29%
2008	140	36%
2009	134	34%
2010	171	36%
2011	219	44%
2012	187	34%

Table 8b: Overview of the number and percentage of publications in the top 10%-25% ranking scientific journals 2007-2012

	Publications in top 10% ranking journals	
2007	125	29%
2008	114	29%
2009	130	33%
2010	159	34%
2011	156	32%
2012	176	32%

Table 9a: Recent top publications Theme I

Borissoff JI, Heeneman S, Kilinc E, Kassak P, van Oerle R, Winckers K, Hackeng TM, Spronk HMH, Govers-Riemslag JWP, Hamulyak K, Daemen M, Ten Cate H -
Early Atherosclerosis Exhibits an Enhanced Procoagulant State. Circulation 2010; 122(8): 821-30
IF 14.816

Oostendorp M, Douma K, Wagenaar A, Slenter J, Hackeng TM, van Zandvoort M, Post MJ, Backes WH -
Molecular Magnetic Resonance Imaging of Myocardial Angiogenesis After Acute Myocardial Infarction. Circulation 2010; 121(6): 775-83
IF 14.816

Borissoff JI, Spronk HMH, ten Cate H -
The Hemostatic System as a Modulator of Atherosclerosis. New England Journal of Medicine 2011; 364(18): 1746-60
IF 53.486

Laeremans H, Hackeng TM, van Zandvoort M, Thijssen V, Janssen BJA, Ottenheijm HCJ, Smits JFM, Blankesteijn WM -
Blocking of Frizzled Signaling With a Homologous Peptide Fragment of Wnt3a/Wnt5a Reduces Infarct Expansion and Prevents the Development of Heart Failure After Myocardial Infarction. Circulation 2011; 124(15): 1626-35
IF 14.432

Doring Y, Manthey HD, Drechsler M, Lievens D, Megens RTA, Soehnlein O, Busch M, Manca M, Lutgens E, Koenen RR, Pelisek J, Daemen MJ, Zenke M, Binder CJ, Weber C, Zernecke A -
Auto-Antigenic Protein-DNA Complexes Stimulate Plasmacytoid Dendritic Cells to Promote Atherosclerosis. Circulation 2012; 125(13): 1673-83
IF 14.739

Table 9b: Recent top publications Theme II

Glatz JF, Luiken J, Bonen A -
Membrane Fatty Acid Transporters as Regulators of Lipid Metabolism: Implications for Metabolic Disease. Physiological Reviews 2010; 90(1): 367-417
IF 37.726

Da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, Bierhuizen MF, de Weger R, Hansen A, Coenen-de Roo CJ, van der Nagel R, van Kuik J, Condorelli G, Arbones ML, de Bruin A -
MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signaling. Nature Cell Biology 2010; 12(12): 1220-27
IF 19.527

Van Gelder IC, Groenveld HF, Crijns HJ, et al.; the RACE II Investigators –
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. N Engl J Med 2010; 362: 1363-73
IF 51.296

Schotten U, Verheule S, Kirchhof P, Goette A -
Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal. Physiological Reviews 2011; 91(1): 265-325
IF 28.417

Houthuizen P, van Garsse L, Poels TT, de Jaegere P, van der Boon RMA, Swinkels BM, ten Berg JM, van der Kley F, Brueren GRG, Schalij MJ, Baan J, Cocchieri R, van Straten AHM, den Heijer P, Stella PR, Bentala M, van Ommen V, Kluin J, Prins MH, Maessen JG, Prinzen FW -
Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. Circulation 2012; 126(6): 720-28
IF 14.739

Kappert K, Böhm M, Schmieder R, Schumacher H, Teo K, Yusuf S, Sleight P, Unger T -
Impact of Sex on Cardiovascular Outcome in Patients at High Cardiovascular Risk Analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation 2012; 126(8): 934-41
IF 14.739

Table 9c: Recent top publications Theme III

Koenen RR, Weber C -
Therapeutic targeting of chemokine interactions in atherosclerosis. Nature Reviews Drug Discovery 2010; 9(2): 141-53
IF 29.059

Jager J de, Kooy A, Lehert P, Wulffelé MG, Kolk J van der, Bets D, Verburg J, Donker AJM, Stehouwer CDA -
Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised, placebo controlled trial. Brit Med J 2010; 340: c2181
IF 13.66

Gaens KHJ, Niessen PMG, Rensen SS, Buurman WA, Greve JWM, Driessen A, Wolfs MGM, Hofker MH, Bloemen JG, Dejong CH, Stehouwer CDA, Schalkwijk CG -
Endogenous formation of N ε-(carboxymethyl)lysine is increased in fatty livers and induces inflammatory markers in an in vitro model of hepatic steatosis. J Hepatol 2012; 56: 647-55
IF 9.264

Ruijter HM den, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engström G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML -
Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012; 308: 796-803
IF 30.026

A.5 OUTPUT

A.5.1 Number of publications

The results of CARIM's scientific output (academic publications, professional publications and PhD theses) both at School and Theme level between 2007 and 2012 are presented in Table 10. The number of publications has increased annually from 498 publications (refereed articles with IF (SCI-SSCI) (WI-1), other refereed articles and letters to the editor) in 2007 to over 600 publications in 2012, 556 of which appeared in peer-reviewed journals. These articles had on average a significantly higher impact than the average publication in the relevant scientific fields (see previous chapter). In recent years, the average impact factor of the journals in which these articles were published has shown a clear increase to an average IF of 5.5 in 2012. More than 30% of the articles that are produced by CARIM are published in international journals that are in the top 10% of their research field.

For CARIM, the average number of refereed publications per year FTE academic tenured researcher in the period of 2007-2012 was 12.1. This number has remained relatively stable over the years but increased in 2011 and 2012, with 15.7 refereed publications per year FTE in 2012.

Table 10: Main categories of research output at School and Theme level

School	2007	2008	2009	2010	2011	2012
Refereed articles with IF (SCI-SSCI) (WI-1)	454	407	476	497	495	556
Other refereed articles	40	45	10	18	29	41
Letter to the editor	4	14	28	29	47	38
Non-refereed articles (1) (National scientific journals)	13	22	18	16	16	17
Books, book chapters, conference papers	28	25	19	17	34	62
PhD theses	37	30	32	35	39	50
Professional publications (2)	5	6	8	4	3	1
Publications aimed at the general public (3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other research output (4)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total publications*	**544**	**519**	**559**	**581**	**624**	**715**

Theme I	2007	2008	2009	2010	2011	2012
Refereed articles with IF (SCI-SSCI)	77	70	87	84	90	88
Other refereed articles	2	5	0	6	6	13
Letter to the editor	1	2	2	5	11	7
Non-refereed articles (1) (National scientific journals)	2	5	6	2	1	7
Books, book chapters, conference papers	2	1	1	4	9	5
PhD theses	9	6	9	5	8	8
Professional publications (2)	3	3	2	0	2	0
Publications aimed at the general public (3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other research output (4)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total publications	**87**	**86**	**98**	**101**	**119**	**112**

Theme II	2007	2008	2009	2010	2011	2012
Refereed articles with IF (SCI-SSCI)	133	114	147	174	183	221
Other refereed articles	14	22	2	4	9	13
Letter to the editor	0	5	4	12	22	22
Non-refereed articles (1) (National scientific journals)	4	1	2	1	1	2
Books, book chapters, conference papers	10	7	5	4	11	23
PhD theses	10	11	8	9	14	20
Professional publications (2)	0	2	4	1	1	0
Publications aimed at the general public (3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other research output (4)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total publications	**161**	**151**	**164**	**196**	**227**	**262**

Theme III	2007	2008	2009	2010	2011	2012
Refereed articles with IF (SCI-SSCI)	246	251	289	284	274	316
Other refereed articles	25	19	9	11	16	20
Letter to the editor	3	5	23	17	19	17
Non-refereed articles (1) (National scientific journals)	7	17	11	13	14	9
Books, book chapters, conference papers	16	17	13	9	14	35
PhD theses	18	15	15	21	17	22
Professional publications (2)	2	1	2	3	0	1
Publications aimed at the general public (3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other research output (4)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total publications	**299**	**310**	**347**	**337**	**337**	**398**

* Please note that the sum of WI-1 publications in Themes I, II and III exceeds the total number of publications at School level, due to a double counting of publications with authors from different themes

1) Articles in journals that are non-refereed, yet deemed important for the field
2) Exclusively patents
3) Also known as 'populariserende artikelen' > Not available from our school
4) Other types of research output, such as abstracts, editorships, inaugural lectures, designs and prototypes and media appearances > Not registered within our school

A.5.2 Number of PhDs

In 2012, the number of PhD students at CARIM equalled approximately 100 FTE compared with 80 FTE in 2007 (see Chapter 2). Table 11a shows an overview of the number of regular PhD candidates who started between 2004 and 2010. The primary aim of those PhD students with an employee status at CARIM is to conduct research and they have an obligation to graduate. The enrolment of new PhD students in 2009 and 2010 was significantly higher than in other years. The most important reason for this increase is the Maastricht Study which started in 2009. In 2011 enrolment returned to its normal level. During the whole evaluation period, the ratio male/female PhD students was about 50/50. On average 17% of the PhD students who enrolled in 2004-2009 have discontinued their PhD track. Based on the cohorts 2003-2007 (count of 31-12-2012), the duration of a PhD training program at CARIM varies between 60 and 69 months, 5 to 6 years, which is substantially longer than the four years originally set for a PhD student. One of the reasons for this longer duration is the integration of the PhD period into the clinical education track. Another reason is a lack of a strict schedule to finish the PhD training or the wish to obtain extra data in order to publish in higher ranked journal. With the already implementation of the CaRES plan and the future TRACK.2 program (see Chapter 10.1), CARIM plans to reduce the average time it takes to obtain a PhD.

Table 11a: Standard PhD candidates with employee status and conducting research with the primary aim/obligation to graduate; (doctoral student)

	Enrolment			Success rates				Total		
Starting year	Enrolment (male/female)		Total (male + female)	Graduated after (≤) 4 years	Graduated after (≤) 5 years	Graduated after (≤) 6 years	Graduated after (≥) 6 years	Total graduated	Not yet finished	Discontinued
T-10 = 2004	9	8	17	0/0%	6/35%	8/47%	10/59%	10/59%	3/18%	4/24%
T-9 = 2005	15	10	25	0/0%	7/28%	11/44%	20/80%	20/80%	1/4%	4/16%
T-8 = 2006	6	12	18	3/17%	8/44%	14/78%	14/78%	14/78%	0/0%	4/22%
T-7 = 2007	14	10	24	3/13%	11/46%	13/54%	16/67%	16/67%	6/25%	2/8%
T-6 = 2008	10	10	20	0/0%	5/25%	8/40%	8/40%	8/40%	8/40%	4/20%
T-5 = 2009	18	16	34	2/6%	7/21%	8/24%	8/24%	8/24%	21/62%	5/15%
T-4 = 2010	12	19	31	0/0%	0/0%	0/0%	0/0%	0/0%	28/90%	3/10%

In addition to these regular PhD candidates, CARIM has a number of contract PhD candidates with an employee status conducting research under the authority of the institute with the primary aim of graduating (Table 11b); EuCAR PhD students, Marie Curie Fellows, PhD students in the University Hospital and other guest PhD students.

Table 11b: Contract PhD candidates with employee status, receiving external funding or university scholarship, conducting research under the authority of the institute with primary aim of graduating

Enrolment			Success rates				Total		
Starting year	Enrolment (male/female)		Total (male + female)	Graduated after (≤) 4 years	Graduated after (≤) 5 years	Graduated after (≤) 6 years	Graduated after (≥) 6 years	Total graduated	Not yet finished	Discontinued
T-10 = 2004	3	3	6	1/17%	2/33%	2/33%	1/17%	3/50%	0/0%	3/50%
T-9 = 2005	4	1	5	2/40%	2/40%	2/40%	0/0%	2/40%	1/20%	2/40%
T-8 = 2006	2	3	5	1/20%	3/60%	4/80%	0/0%	4/80%	0/0%	1/20%
T-7 = 2007	2	2	4	0/0%	0/0%	3/75%	0/0%	3/75%	0/0%	1/25%
T-6 = 2008	4	2	6	0/0%	4/67%	4/67%	0/0%	4/67%	2/33%	0/0%
T-5 = 2009	5	2	7	0/0%	1/14%	2/28%	0/0%	2/28%	5/72%	0/0%
T-4 = 2010	5	4	9	1/11%	1/11%	1/11%	0/0%	1/11%	8/89%	0/0%

Finally, Table 11c shows the number of CARIM's external PhD candidates. Due to the manner of registration of these PhD students at CARIM, the starting year is mostly unknown. For this reason, the year of the PhD conferral is presented instead.

Table 11c: External PhD candidates

Year of PhD Conferral	Male	Female	Total (male + female)
2007	n.a.	n.a.	n.a.
2008	n.a.	1	1
2009	4	1	5
2010	2	3	5
2011	2	2	4
2012	1	2	3

A.5.3 Research facilities

Several research groups within CARIM manage or participate in unique core facilities, such as the Thrombosis Expertise Centre, the Centrale Proefdier Voorzieningen (CPV, animal facility), the NMR spectroscopy facility, the Microscopic Imaging Unit, the small animal laboratory for imaging (ultrasound, MRI and PET), and make use of the Biobank, which is a central research facility. CARIM is a major initiator of the Maastricht Study (developed in 2008, started in 2011); an epidemiological study in 10,000 individuals that focuses on the causes and consequences of the metabolic syndrome, type 2 diabetes and cardiovascular disease, and uses deep phenotyping of the microcirculation, the macrocirculation and the heart.

Until relatively recently there was very little knowledge of, facilities for or interest in the area of complex cardiovascular genetics. Measures have been taken to change this in the form of collaborative projects with GIGA Liège, the University of Münster, and Radboud University Medical Centre, Nijmegen. The engagement by CARIM of Professor Monika Stoll with a 0.2 FTE professorship is a major step towards solving the problem (see 1.3, p 12). A CARIM platform for cardiogenetic and -genomic research is currently being created in collaboration with the department of Clinical Genetics and the CVC.

In general, CARIM strives for integrated laboratory facilities and service platforms together with the CVC and the Schools of Maastricht University. Some have already been established (thrombosis and cardiac arrhythmias). A high priority is to establish others in the near future. Among them are a systems biology unit that is dedicated to cardiovascular themes to maintain international competitiveness, and the establishment of the VivariUM, a new animal facility, to be built on the premises. More detailed information on some of the research facilities is discussed in Chapter 9.2 (Infrastructure).

A.6 EARNING CAPACITY

A number of CARIM researchers have received worldwide recognition. CARIM researcher Prof. Harald Schmidt was awarded the prestigious Advanced Grant (2011) and Prof. Leon de Windt the Starting Grant (2012) by the European RC (ERC). Over the past 7 years, CARIM researchers have successfully obtained 4 VENI grants (Dr Blanche Schroen and Dr Koen Reesink in 2007, Dr Judith Sluimer in 2010 and Dr Kristiaan Wouters in 2011), 7 VIDI grants (Dr Esther Lutgens and Prof. Uli Schotten in 2007, Prof. Stephane Heymans in 2008, Dr An Moens and Dr Paul Volders in 2009, Dr Dietbert Neumann in 2010, Dr Rory Koenen in 2012), and 1 VICI grant (Prof. Christian Weber in 2009) awarded by NWO.

These grants have resulted in 7 post-doc positions, 1 junior staff position and 1 established investigatorship within the Dekker program of the Dutch Heart Foundation (NHS). In 2007 Dr Menno de Winther received an Established Investigatorship, Dr Paul Volders a junior staff position, and Dr Marjo Donners a Dr E. Dekker Post-doc stipendiary. Prof. Esther Lutgens was granted an Established Investigatorship in 2009 and in 2011 Dr Isabel Ferreira, Dr Bas de Laat, and Dr Judith Cosemans received a Post-doc stipendiary. Also in 2011, Dr Kevin Vernooy obtained a ZonMW Clinical Fellowship and Drs Siamack Sabrkhany was granted a NWO Mozaiek Grant. Prof. Coen Stehouwer received an EFRO grant (8 M€) and a Weijerhorst grant (3 M€) to set up the Maastricht Study (2009 and 2011). In 2012, a Post-doc stipendiary was received by Dr Joost Lumens. Dr Paula da Costa Martins received an NWO MEERVOUD grant in this year. An overview of the total of external funds that were obtained from 2007-2012 is given in Table 4a, paragraph 2.2. Addendum 1 provides the list of all granted projects in this period.

The amount of money from the externally financed projects (Table 12) is under severe pressure, because in the upcoming years the first round of prestigious Technological Top Institute projects (TTI projects) will be terminated and no new public-private initiatives such as the former successful TTIs are as yet foreseen. BMM, however, will be continued within Chemelot InSciTe in wich cardiovascular is a prominent theme.

Table 12: Participation CARIM in TTI projects

	In cash	In kind	Total project costs
Overview CTMM-projects			
TRIUMPH	1,439,633	687,890	2,127,523
PREDICCT	1,690,000	921,300	2,611,300
CIRCULATING CELLS	1,069,347	939,180	2,008,527
PARISk	1,942,746	1,054,498	2,997,244
INCOAG	1,704,800	1,608,054	3,312,854
EMINENCE	859,200	1,070,400	1,929,600
COHFAR	1,504,386	480,249	1,984,635
Subtotal	**10,210,112**	**6,761,571**	**16,971,683**
Overview TI Pharma-projects			
T2-108	1,005,350	400,000	1,405,350
D1-101	430,344	289,656	720,000
T2-301	617,400	360,000	977,400
Subtotal	**2,053,094**	**1,049,656**	**3,102,750**
Overview BMM-projects	-		
PENT	531,000	314,500	845,500
IDiDAS	232,000	338,550	570,550
iValve	638,500	348,000	986,500
Subtotal	**1,401,500**	**1,001,050**	**2,402,550**
Total	**13,664,706**	**8,812,277**	**22,476,983**
Overview TFIN-NEXT			
Relevance of Vascular Function	**1,294,252**	**528,638**	**1,822,890**

In 2008, one of the recommendations of the ERC was that CARIM should strive for funding, which might be achieved by creating and stimulating a more competitive environment and approach within CARIM. This is even more relevant, considering the reduction of CARIM's annual Faculty budget by 8-10% from 2011 onwards. The main policy to cope with this reduction is to lower the ratio of Scientific Personnel/Technicians from 1:0.9 FTE to 1:0.7 FTE. Although the landscape of the grant system in which CARIM operates is becoming more and more competitive, the main focus for the coming years will be receiving NWO grants and participation in European grant programs such as Horizon 2020.

A.7 ACADEMIC REPUTATION

Table 13: Hirsch-index and m-index of CARIM's Scientific Director, theme leaders and program leaders (as per March 2014, source: ISI Web of Science, * = Google Scholar)

Name	Department	h-index	Years of publication	m-index
Prof. Uli Schotten	Physiology	30	17	1.76
Prof. Frits Prinzen	Physiology	38	24	1.58
Prof. Matthijs Blankesteijn	Pharmacology	22	25	0.88
Prof. Hugo ten Cate	Biochemistry	46	25	1.84
Prof. Tammo Delhaas	BME	23	21	1.10
Prof. Erik Biessen	Pathology	43	24	1.79
Prof. Jan Glatz	Genetics and Cell Biology	58	25	2.32
Prof. Harry Crijns	Cardiology	76	25	3.17
Prof. Tilman Hackeng	Biochemistry	35	24	1.46
Prof. Johan Heemskerk	Biochemistry	41	25	1.64
Prof. Stephane Heymans	Cardiology	29	13	2.23
Prof. Hans Peter Brunner-La Rocca	Cardiology	34	20	1.70
Prof. Leo Koole	Biochemistry	28	25	1.12
Prof. Jos Maessen	CTC	26	25	1.04
Prof. Robert van Oostenbrugge	Neurology	20	12	1.70
Prof. Mark Post	Physiology	40	25	1.60
Prof. Bert Smeets	Genetics and Cell Biology	42	25	1.68
Prof. Coen Stehouwer	Internal Medicine	80	23	3.50
Prof. Thomas Unger	Scientific Director	83*	34	2.44
Prof. Harry Struijker Boudier	Pharmacology	38	25	1.52
Prof. Hans Vink	Physiology	31	20	1.55
Prof. Christian Weber	Biochemistry	72	20	3.60
Dr Paul Volders	Cardiology	25	13	1.92
Prof. Joachim Wildberger	Radiology	35	20	1.75
Prof. Leon de Windt	Cardiology	39	16	2.44
Prof. Peter de Leeuw	Internal Medicine	51	25	2.00
Dr Bram Kroon	Internal Medicine	29	22	1.32
Prof. Chris Reutelingsperger	Biochemistry	47	24	1.96
Prof. Harald Schmidt	Pharmacology	68*	25	2.72

The Hirsch-index (Hirsch J., Proc Natl Acad Sci USA 2005;102: 16569) is a strong indicator of the academic reputation of individual scientists and is being used in the yearly Planning & Control talks with the PIs. Table 13 shows an overview of the Hirsch-index for all CARIM PIs and the Scientific Director for the time span between 1988-2012 (with exception of the Scientific Director; as per March 2014). Only the researcher's articles and reviews were included in the calculation; letters to the editor and other publications were not taken into account. As an additional parameter, the m-index (h-index divided by the number of years starting with the year of the first publication, counting from 1988, used to calculate the h-index) is also presented to compare scientists of differing seniority. It should be kept in mind that the Hirsch-index was only calculated from 1988 and 'older' researchers, researchers with a higher publication age, could have published before this time. However, to even this out the m-index was also calculated from 1988.

Furthermore, to illustrate the academic reputation of the CARIM research staff, a list of important signs of recognition is provided in Annex 4. These include awards and prizes, invitations to present at major national and international meetings and congresses, memberships of editorial boards, as well as memberships of national and international scientific boards. CARIM researchers are represented in such influential committees as the NWO VENI committee (Dr Gerry Nicolaes, Prof. Jan Glatz), the NHS CVON committee (Prof. Erik Biessen) and the ZonMW TOP grant selection committee (Prof. Jan Glatz, Prof. Erik Biessen), and have had positions in international and national boards. For example, Prof. Tilman Hackeng is chair of the Dutch Society of Thrombosis and Haemostasis (NVTH) and Prof. Hugo ten Cate was elected as Chairman for the Dutch Federation of Anticoagulation Clinics in 2011. CARIM scientists are editors or reviewers for international top journals, such as Hypertension, Diabetes, Journal of Hypertension, Haemostasis, Circulation, New England Journal of Medicine. Finally, CARIM members have been involved in the organisation of several national and international conferences.

A.8 SOCIETAL RELEVANCE

A.8.1 Societal impact

On average, cardiovascular disease is the major cause of mortality and morbidity in Europe, although substantial regional differences have to be appreciated. In the Netherlands, cardiovascular disease is the major cause of death in women and the second largest cause of death in men (Dutch Heart Foundation, 2013). The higher mortality in women can probably be explained by the fact that they live longer than men (average age of death: 84 years in women and 77 years in men).

In its research CARIM focuses on the particular cardiovascular diseases and mechanisms that substantially contribute to this mortality and morbidity, such as atherosclerosis and plaque identification, atherothrombosis, heart failure, cardiac arrhythmias and hypertension. An important aim is to unravel the underlying mechanisms of these diseases with the intention of improving diagnosis and treatment. If successful, it will certainly benefit patient care. This endeavour requires good interaction between basic scientists and clinicians. A major advantage in this exercise is the fact that a relatively large number of scientists actively facilitating this interaction in CARIM are clinicians.

To strengthen the collaboration between basic scientists and clinicians in most of the diseases studied translational platforms have been set up or are under construction. Existing platforms are those on cardiac arrhythmias, thrombosis, plaque identification and hypertension. The platform on heart failure is about to start. Findings and observations from these platforms are exchanged and basic findings are tested in clinical cohorts.

The Maastricht Study is likely to make an important contribution to society. This highly ambitious study comprises an unparalleled combination of approaches to investigate the ageing process in a large population both with and without type 2 diabetes. The study focuses on cardiovascular disease, but also explores vision, mobility and cognition. The study uses sophisticated questionnaires, biological samples (including DNA) and cutting edge imaging techniques (Prof. John Yudkin, London). Epidemiologists, clinicians and basic scientists are closely collaborating in this study. Relationships observed in this population study can be evaluated on causality in pre-clinical models available within CARIM. Recognising its potential for translation, industrial partners are participating in the Maastricht Study.

Right from its beginnings in 1988, CARIM has always executed programs in collaboration with industry, sharing its expertise but maintaining its independence as reflected by the right to publish, for example. These collaborations also generated questions leading to new research lines. Several of these collaborations are long-lasting and have brought in revenues such as royalties. Collaboration with industry was intensified in programs such as CTMM, and BMM. In these programs, heavily supported by the Dutch government, Research Centres and Academic Hospitals closely collaborate with industry. Especially in CTMM, CARIM has been very successful in acquiring grants. It makes important contributions to four programs and has delivered the Principle Investigator to three others (see Table 12). These close collaborations with industry will lead to timely applications which the patient will benefit from.

CTMM: COHFAR Cardiac Resynchronisation Therapy (CRT) is a therapy for about 25% of the patients with heart failure who have abnormal impulse conduction in the ventricles. CRT resynchronises the electrical activation and contraction of the ventricles by pacing the right ventricle (RV) and left ventricle (LV) almost simultaneously. The benefit of CRT can be further improved by better programming of the stimulation delays between atrium and ventricles (AV interval) and between RV and LV (VV interval). Currently this tailoring of CRT to the individual patient is too complicated for standard clinical practice.

CARIM's societal relevance is recognised by the Dutch Heart Foundation (see Annex 6 for the full document provided by the DHF in March 2014):

The DHF finds it encouraging that CARIM seeks the growing involvement and participation of patient organisations in their research efforts. Another chance to provide patients with the most effective treatment available lies in the public – private research cooperation combining the innovative capabilities of the industrial and academic sectors. Such partnerships are firmly focused on the translational aspects of research. CARIM is the main author of the CTMM, a national example, also supported by the DHF. In this way CARIM's ideas are brought to the national science policy level. The DHF also appreciates CARIM's role in the formulation of the report of the CardioVascular Profiling Commission (March 2010).

A.8.2 Valorisation

CTMM: ENGINE Maastricht University and the Dutch company ACS Biomarker have discovered a series of new very small biomarkers called "microRNAs" that can be used for diagnosing heart failure and, at the same time, give information about the prognosis of the disease. This new approach allows the doctor to get a quick and complete picture of the cardiac condition of a patient. To make this new invention available to doctors and patients, extensive testing of the new biomarkers and of the new technology measuring the microRNAs is required. In **ENGINE** we will develop a proof-of-concept test on a novel biomarker detection instrument developed with the support of Biocartis. The DHF will play an overarching role in the project and install a committee of end-users consisting of patients, nursing staff and clinicians. The societal and economic impact encompasses the delivery of a new diagnostic device that enables personalised patient care.

Earlier clinical and pre-clinical research in the group of Prof. Prinzen showed that the vector cardiogram (VCG), measured on the body surface, can be used to find the optimal AV- and VV intervals and that a VCG-like signal (D-VCG) can be derived from the electrodes of implanted CRT devices.

In the Tailor-CRT valorisation project within COHFAR-CTMM, a system has been developed comprising novel pacing leads for D-VCG measurements and a novel algorithm that will be built into Medtronic CRT devices. The D-VCG signals serve as input for the algorithm to automatically adjust AV- and VV intervals. The algorithm can automatically adjust these intervals on a regular basis, ultimately even allowing the optimising of settings during exercise. This project is executed in close collaboration with Medtronic.

The scientists at CARIM have always been on the alert for valorisation of their findings, and this was noticed by the ERC in 2007. The committee stated that CARIM has an excellent record of valorisation (particularly from Theme I). The School continued to stimulate this, which is demonstrated by the number of patents obtained between 2007 and 2012. Over this period CARIM collaborators published or filed 28 patents. An overview of these patents is provided in Annex 7. The MUMC+ based technology transfer office BiomedBooster assists individual scientists and the board of CARIM in patenting and valorisation of inventions.

CARIM collaborators were also successful in acquiring grants in CTMM's competitive valorisation program. In collaboration with industry, three proposals were granted: COHFAR, ENGINE and PREBAT. Two of these proposals, COHFAR and ENGINE and their predicted societal impact are presented in the frames. Important industrial partners of CARIM in the TTIs (CTMM, TI Pharma and BMM) are e.g. Philips, Medtronic, Bayer Pharma and Boehringer Ingelheim.

Based upon newly-developed technologies or new valuable findings by CARIM, several new companies have been started. In addition to the existing ones, eight new start-up companies were founded between 2007 and 2012: VitaK BV, Pharma Target BV, ACS Biomarker BV, FABPulous, Synapse BV, Glycocheck BV, Mirabilis BV, YourRhythmics BV and MirNext BV. See Annex 7 for an overview and company profile of the CARIM spin-off companies.

A.8.3 Societal quality

To illustrate the interaction of CARIM and its research groups, an inventory of invitations to give lectures, symposia organisational activities, media coverage and national and international collaborations of CARIM researchers was carried out. The results of this inventory are presented in Annex 3 and Annex 5. A good example of productive interaction between CARIM researchers and society is the Vitamin K Cookbook ("*Het vitamine K kookboek – gezond en lekker koken voor thrombosepatiënten"* by Prof. Hugo ten Cate and Dr Leon Schurgers), published in 2012. The main idea of this cookbook is to give people with thrombosis more grip on the process of blood coagulation by providing them with knowledge on the level of vitamin K in their diet.

A.9 VIABILITY

A.9.1 Resource management

CARIM is a strong, viable research school with a long tradition of cardiovascular research. It is organised in a multi-disciplinary and bottom-up way around three main research themes which comprise 27 basic and clinical programs, led by a PI:

- Thrombosis and Haemostasis
- Cardiac Function and Failure
- Vascular Biology

Each PI is responsible for the scientific progress of the program, mentoring the PhD students and post-docs as well as the financial basis of the program. PIs are tenured scientific staff from various departments, performing their research within the School, based on longstanding financial arrangements with the departments. The performance of the PIs is monitored in a periodic Planning & Control cycle in order to maintain and improve high quality output. Each program/PI is expected to meet a set of scientific output criteria. The main criteria are based on: 1) number of scientific publications, 2) impact factor of the publications, 3) fund acquisition, and 4) number of PhD supervisions.

The output scoring tool is under revision. Based on experience in the Academic Medical Centre Amsterdam (AMC), we will add H-factor/M-index, societal impact and viability of the program to the tool citations. The PIs are a selected group of high quality researchers. We stimulate competition between them. Note that non-tenured scientific staff, such as PhD students and post docs, are not individually evaluated in the scoring exercise but as part of the PI program to which they contribute.

Next generation

CARIM values an efficient human resource management (HRM) policy and is willing to invest in it. Part of the policy is to recognise, stimulate and support talented students and staff and retain them by offering suitable career opportunities. The process starts at the level of Master's students and does not stop until the level of established researchers. The tenure track system we introduced a few years ago is an essential element in this regard. Further we are part of the Dean's central policy in recruitment of young talents on faculty level. Notably 5 out of 11 young researchers that have recently been selected from the six schools for the "*Toptalenten*" program of the Faculty are CARIM staff members.

CARIM is constantly scouting for new talent. This process starts during the Bachelor's program, where electives are offered in our laboratories. Thereby, we actively participate in the WESP program where talented medical students are selected. To facilitate medical students in research we opened up the opportunity to combine medical teaching with research (the so-called Stud-AIOs).

We also help talented young researchers by awarding travel grants or by providing support in their applications for junior Kootstra Fellowships (appointment to bridge a Master's to a PhD position) and senior Kootstra Fellowships (appointment to facilitate PhDs to prepare a successful Veni grant or Dekker Fellowship). Over the past 6 years, 16 Kootstra Fellowships were granted to CARIM talents.

A.9.2 Available infrastructure

CARIM provides researchers with valuable resources for an effective research environment by operating facilities in which equipment expertise and methods are made available. Some of these facilities are built on CARIM's efforts, other are built on joint efforts between the Schools, School and Faculty or via external grants. A few examples have already been discussed in Chapter 5.3 (Biobank, Maastricht Study). A few highlights are further presented in this paragraph.

CARIM platform for animal research
At present, much of CARIM's animal research takes place in peripheral laboratories which are allocated within the departments. In the new VivariUM, this will change into a situation where laboratories and equipment are shared by multiple users. To anticipate this development, we are integrating CARIM's animal research in a research platform. This platform will be open to all researchers from CARIM and –when capacity permits- from other research schools. The major advantages are that this will allow us to combine our expertise on animal research and make more efficient use of the existing staff and equipment. This will also allow us to better facilitate temporary research support required for grants or projects in collaboration with industry. Moreover, this development offers opportunities for combining experiments, e.g., by using multiple organs/tissues from single animals by different research groups, thereby responding to the societal need for replacement, reduction and refinement of animal experiments.

Imaging
Recently, the invasive and non-invasive imaging site in Maastricht was granted EuroBioImaging status. The final decision was motivated as follows:

The IEB panel saw this is a very strong Expression of Interest from a very accomplished core capability. The facility is clearly operating at the cutting edge and offers some unique infrastructure and capabilities. The facility has also established some very strong industry linkages. There is a strong cardiovascular focus, which largely reflects the proximity to the world class Cardiovascular Institute of Maastricht. The research outputs underpinned by this core capability are excellent and the facility clearly has strong national significance as well as broad European and beyond outreach and engagement. The facility offers excellent training opportunities for internal and external

users. The facility enjoys strong institutional and industry support, though the plan for longer-term sustainability is not particularly well articulated. The budget/cost concept was both balanced and well justified. In summary, this is a very strong Expression of Interest from a very accomplished research facility that is providing excellent support for the local, national and international research communities.

The EuroBioImaging unit in Maastricht consists of an Electron Microscopic (EM), an Advanced Optical microcopy, and a non-invasive imaging unit. See Annex 8 for a full description of each unit. All the equipment is embedded in central facilities within the same building, with easy transport between the facilities, and supported by personnel with a thorough schooling in the relevant techniques. The equipment is installed in and surrounded by an excellent infrastructure. This includes dedicated facilities for cell culture, animals, contrast agents, precursor radio chemicals, histopathology, genomics, and proteomics. For coordination of EM and optical microscopy, a Microscopic Imaging Unit is in place. New external and internal researchers are individually trained in imaging and data analysis, using the expertise of the technical experts on the equipment.

NMR Facility

In 2010, the decision was made to invest in protein structural analysis through NMR studies as part of the VICI grant awarded to Prof. Christian Weber and through investments from the FHML. Recently The Paul Martin Pavillion for Protein NMR studies was opened at the Biochemistry department of CARIM. Here, the latest generation Bruker HD 700 MHz NMR spectrometer with cryo probe was installed. NMR stands for Nuclear Magnetic Resonance and relies on a large superconducting magnet (in this case with a magnetic field of 16.4 Tesla) for the study of a large variety of molecules in solution. Biochemical NMR samples typically contain a dilute water solution of 0.2 to 0.5 ml volume, put into in a glass tube and placed inside the strong magnetic field of the spectrometer. Spectral information relies on the absorption of radio waves by proton (and other) nuclei after emitting short radio pulses into the sample that display similar radiofrequencies to those present in GSM phones. NMR spectra can be used to display chemical abnormalities in blood and urine samples for example, but also easily confer the purity of a drug and where exactly a drug molecule binds structurally to its biological target protein.

The special feature of NMR is that it is a so-called non-destructive measurement technique. The NMR samples are not subjected to damage by the observation method and compounds are left chemically unaltered for subsequent research purposes. Furthermore, NMR spectroscopy and X-ray crystallography are the two main techniques that allow the three-dimensional structure determination of large bio molecules at the atomic level. In contrast to crystallography, NMR does not rely on having to grow single crystals to solve a structure. In principle, any soluble protein can be measured and analysed by NMR, although it is normally required to isotopically label the protein of interest uniformly with 13C and 15N stable isotopes. Detailed high-resolution structures of proteins are an important prerequisite to the understanding of protein function and protein-protein interactions, e.g. useful in the rationale development of new drug targets.

The NMR equipment at the CARIM institute is available to assist various researchers at Biochemistry, but is also accessible to other parties within MUMC+ and/or to biotech companies via the Enabling Technologies platform. In this way Enabling Technologies manages and shares various analytical instruments, which would otherwise be too costly to use by smaller local business in Maastricht and surrounding areas. See Annex 9 for NMR projects at CARIM.

A.9.3 Innovative capacity

At CARIM the interactions between the multidisciplinary research groups of the MUMC+, between scientists at each of the graduate schools, as well as with national and international collaborators, warrants the generation of innovative ideas and the development of innovative technologies and protocols. New junior and senior staff have joined CARIM in recent years. Furthermore, new promising research groups headed by high potential scientists have been attracted to replace scientists that have left CARIM. For example Prof. Tilman Hackeng was appointed head of department and leader of Theme I, and Prof. Leon de Windt and his research group at the Department of Cardiology have joined CARIM.

Interaction between CARIM and MH&NS has resulted in the newly-formed collaborative group 'Cardiovascular Research meets Neuroscience', led by the two school directors, Prof. Harry Steinbusch and Prof. Thomas Unger, together with Prof. Robert van Oostenbrugge (Chief of the Neurology Department), and Dr Pawel Namsolleck (pharmacologist). In recognition of the need to combine forces on vascular, microvascular and neurological research in the field of cerebral small vessel disease with its consequences of cognition deficits and dementia, this group was formed by two research schools to create synergies and optimally exploit existing resources. From this nucleus, the group is planning to expand into imaging and experimental psychology, thus crossing the borders of research schools and faculties at Maastricht University. This initiative fits in well with the perspectives of the EU program Horizon 2020 which pays special attention to dementia the rapidly increasing health problem in the elderly.

Another example is the Marie Curie ITN initiative between Maastricht, Aachen, London and Stockholm centered on the vulnerable patient. This interdisciplinary graduate school, too, takes care of the increasing needs of the medical community and society to address the increasing number of elderly, multimorbid patients, especially those with chronic kidney disease accentuated by diabetes and other cardiovascular-metabolic disorders. In this a substantial number of CARIM researchers contribute to four work packages: shared mechanisms of multimorbidity, drug development, imaging, intervention, and thus doing so provide PhD students with the abilities and skills to develop new strategies of dealing with the research challenges that these patients are already posing and certainly will in the future.

A third example which shows CARIM's innovative capacity is its vascular group that has recently been founded under the leadership of Dr Koen Reesink and Prof. Chris Reutelingsperger from the macrovascular section, and by Prof. Robert van Oostenbrugge and Prof. Hans Vink from the microvascular section. In view of the need to reorganise vascular research at CARIM, and also to combine basic and clinical research on the vascular theme within MUMC+, this group now addresses a wide range of vascular research themes in a translational way, which fits well together with the Complex Arrhythmia Unit and the Thrombosis Expertise Centre (TEC), into the perspective of the CVC.

These three examples may suffice to illustrate that CARIM meets the challenges of our time and is adapting to them as mentioned in the introduction. The major issues here are the demographic change with an ageing population and, associated with this, cardio-metabolic multimorbidity and dementia in this rapidly increasing patient population which requires interdisciplinary, translational research approaches. Because of the close connection with the clinic, CARIM creates a climate where innovative ideas can be directly translated into clinical application which distinguishes CARIM from other institutes.

Finally, from 2007 to 2012 a number of CARIM staff members have been inaugurated as new professors in their specific areas of expertise. Among these were Prof. Joachim Wildberger, Prof. Tilman Hackeng, Prof. Chris Reutelingsperger, Prof. Erik Biessen, Prof. Tammo Delhaas, Prof. Leon de Windt, Prof. Stephane Heymans, Prof. Bert Smeets, Prof. Cees Wittens, Prof. Geert Schurink, Prof. Uli Schotten, Prof. Casper Schalkwijk, Prof. Pieter Dagnelie and Prof. Robert van Oostenbrugge.

A.10 NEXT GENERATION

A.10.1 PhD Training

One of the research institute's main responsibilities is the training of PhD students. Accordingly, CARIM offers a graduate program to educate and train students in the field of cardiovascular research. Over the period 2007-2012 CARIM has improved the support and training of its PhD students. The quality and timeliness of the PhD program is subject to continuous evaluation by the Education Program Committee (EPC) composed of PhD representatives and pre-clinical and clinical researchers. The EPC meets on a monthly basis and reports to the CARIM board. The PhD coordinator, Dr Marc van Bilsen serves as a mentor for all CARIM PhD students and as a point of contact for their supervisors. The PhD coordinator is also Chairman of the EPC. CARIM's PhD coordinator works closely with the CARIM Office, policy advisor and Scientific Director. One of the recommendations of the ERC in 2007 was to create more flexibility in the standards for PhD theses (e.g. reducing the standard of at least four peer-reviewed publications). CARIM complied with this recommendation by changing the standard to 3 to 5 full papers. However, whether or not a dissertation is approved for defense is mostly decided on a case by case basis since the PhD standards are still being discussed (also university-wide) and no final decision has been taken yet.

In 2010 a new PhD program was developed. The plan was extensively discussed by the EPC and presented to the School Council. After approval by the CARIM board the new plan was implemented in January 2011. The cornerstone of the new program is to offer a more structured and transparent training program that is attractive and challenging for CARIM's next generation of researchers. It focuses on both the research component and the acquisition of knowledge, skills and competence, including those skills that will be of use in the next step in the career of the PhD (whether this is at CARIM or somewhere else), the so-called transferable skills. After having obtained their PhD degree, many of our alumni go on to become medical specialists. An overview of the field in which our PhDs continue their career is given in Table 14.

Table 14: Career after obtaining PhD degree (sum 2007-2012)

Field	Netherlands	Abroad	Total
Health Care	79	8	87
Industry	12	3	15
University General	0	1	1
University Research	39	27	66
Other	6	3	9
Total	136	42	178

CaRES plan

In 2007, the ERC advised the school to put more effort into monitoring the quality of supervision of PhD students. This aspect was subsequently included in the PhD training program, which has been formalised in the CARIM Research, Education and Supervision plan. The CaRES plan encompasses (1) a general section describing the rights, duties, and tasks of the PhD students and their supervisors. This section has to be signed by all parties, including the human resources manager, (2) the Research plan, in which the research aims, experimental approach, work plan and timeline of the project are specified, (3) the Education plan, which requires that the PhD students will invest in their training. In the Education plan, all courses and activities, including participation in scientific meetings, the supervision of interns, teaching activities, that will be followed to meet this goal, are specified, and (4) the Supervision plan, describing how the supervision of the PhD student is organised, specifying the role of each supervisor. Also, the three members of the mentoring committee are appointed. The mentoring committee meets with the PhD student on an annual basis to assess the progress of the research and the scientific performance of the PhD. The CaRES plan has to be drafted during the first few months after the start of the appointment and is designed to be a tailored and flexible plan, allowing adjustment during the course of the PhD trajectory. An important additional goal of the CaRES plan is to increase the transparency among all stakeholders, which is the PhD student, their supervisor(s) and CARIM.

National guidelines for PhD programs

In the second half of 2011 two guidelines for PhD programs were issued, one by the Netherlands Federation of University Medical Centres (NFU) and the other by

ORPHEUS (Organisation for PhD Education in Biomedicine and Health Sciences in the European System). It is worthy of note that the CaRES PhD program was already in line with their recommendations, both in terms of total load of the educational program (25 ECTS), the emphasis on transferable skills, and the transparency and flexibility of the PhD training program. This strengthens our feeling that the new CARIM PhD program is up to date and meets the current criteria for a high quality PhD training program.

As a collaborative effort by the six research schools within the FHML, along with CARIM, a new web-based PhD monitoring program has been developed in collaboration with an IT company. This program, known as TRACK.2, will be implemented in 2014 and allows adequate monitoring of the research progress and the development of the PhD during his/her entire PhD trajectory. In addition, questionnaires that also enable the PhD to reflect on the quality of his/her supervision and the training program have been incorporated.

CARIM courses

Along with the shaping of our new PhD training program, the set-up and contents of CARIM's cardiovascular courses have been drastically revised. The Course Week is a collaborative effort from many of our PIs and was shaped by the valuable input of members from the Department of Educational Development & Research. The Course Week takes place in June/July and consists of five parallel courses, covering all aspects of CARIM's research, alternating with a combined scientific program and a social program organised in part by I'MCARIM, the organisation of CARIM's PhDs. Over past years 40-60 PhDs have participated and very much appreciated the high quality and instructiveness of the courses and the opportunity to interact with fellow PhDs and staff members. Together with the national courses organised by the Netherlands Heart Foundation, this enables the PhDs to get acquainted with all aspects of cardiovascular research during their four-year appointment. Annex 10 provides an overview of the CARIM PhD courses 2007-2012.

A.10.2 Tenure Track System

In November 2008, the CARIM EB decided to implement a tenure track system for talented researchers at the school. Following a three- or five-year program, young researchers are given the opportunity to obtain a permanent employment contract if they meet certain criteria, based on input, independence, funding, personal development, and recognition. In the context of improving scientific quality, an independent assessment of the tenure trackers is institutionalised, before they are offered a staff member at the institute. In January 2012, Dr Blanche Schroen, was the first 'tenure tracker' to meet the standard and therefore obtained a permanent position at CARIM. See Annex 11 for a full overview of the completed and ongoing tenure tracks.

By implementing the tenure track system, CARIM has shown that it is already working on the future of CARIM and its potential leading scientists. By creating a balanced pool of tenure trackers and by focusing on expertise and gender, CARIM is taking care of its problem of having too few female researchers/PIs and guarantee its research quality. Between 2008 and 2012, the male/female ratio of finished and ongoing tenure track candidates was 50/50.

The guidelines for the tenure track are currently being revised and the SB is working on a new proposal in which the criteria to enter and to finish the tenure track are elaborated on.

A.10.3 Master's program

CARIM's interest in developing a cardiovascular research-training program for graduate students has led to the development of the Research Master's degree 'Cardiovascular Biology & Medicine' (CBM), which was officially started in 2006. The Master's allowed graduates to start a national or international cardiovascular research career in academia or industry. However, in 2011 the Faculty of Health, Medicine and Life Science (FHML) decided to end the individual school research Master's programs and to integrate these programs into a newly designed FHML Master's of Biomedical Sciences. This new Master's degree still allows specialisation in the research disciplines of the individual FHML Schools. As a consequence, in September 2011, no new first year students could any longer enrol in the CARIM research program. Students then entering the second year of the CBM Master's program were allowed to finish their CBM Master's.

In the new Biomedical Sciences program, Master's students are informed about the FHML Research School programs in the first half year by attending school-specific lectures and parallel programs organised by School researchers. In the second half year, students may get acquainted in more detail with school-specific practical research. In this phase CARIM offers students the opportunity to participate in the CARIM course week program and to do a CARIM junior research internship at one of CARIM's laboratories. This allows students to make up their mind about the school of choice in which to receive their practical research training. When students choose CARIM, they can follow a CARIM senior research internship in their second year. This will lead to a notification of cardiovascular specialisation on their Master's certificate.

A.11 SWOT ANALYSIS

This analysis of CARIM's strengths, weaknesses, opportunities and threats is based on two sources of information. First of all, interviews with all CARIM's PIs were commissioned by the Board of MUMC+ in February 2012.

Secondly, in February 2013, a request for input for a SWOT analysis was sent to all scientific staff (including post-docs) at the request of the SB. The combined outcome of these two SWOT analyses is presented in the following figure:

Figure 3: SWOT analysis

STRENGTHS
1. Internationally recognised centre of excellence in cardiovascular research
2. Integrative scientific approach: the research programs within CARIM cover a range of different and relevant topics in the field and present basic science, clinical and translational research
3. Close contact with clinical departments (notably Cardiology)
4. Strong individual research lines and groups
5. The Maastricht Study is the largest diabetes study in the world, in terms of deep (metabolic, cardiovascular and other) phenotyping
6. Collaborative projects with related institutes of MUMC+, such as NUTRIM, MH&NS and CAPHRI
7. Collaboration with industrial partners such as DSM, Chemelot (InSciTe: Institute for Science and Technology), pharma and devices (e.g. Medtronic in Maastricht)

WEAKNESSES
1. Relative lack of immunological expertise
2. Limited facilities for animal experiments although new facilities have been planned. Animal experiments are increasingly performed extra muros
3. Collaboration with other institutes of FHML of Maastricht University is under-utilised
4. Recent leave of several top scientists of CARIM leading to a gap in the theme of Vascular Biology
5. Lack of funds endangers acquisition of latest medical devices (e.g. for imaging techniques)
6. The lack of a true systems biology group
7. Solving the gender problem, notably among PIs
8. Average during of the PhD period within CARIM

OPPORTUNITIES
1. More interaction between the Maastricht Study and all types of research in CARIM to create translational research
2. Collaboration with GIGA (University of Liege) to utilise specific genetic expertise and animal models (such as zebra fish)
3. Collaboration with NUTRIM, CAPHRI and MH&NS to create the profile of a national centre of excellence in cardiovascular metabolic studies
4. Clinical studies in patients with thrombosis, heart failure, cardiac rhythm abnormalities and diabetes mellitus type 2. The 'Vascular complications of metabolic diseases' program is a good example
5. BMM will be continued within Chemelot InSciTe in which cardiovascular is a prominent theme.
6. Maastricht Health Campus offers opportunities to profile faculty broad metabolic program.
7. Vacancies to recruit top scientists (e.g. immunology, stem cell research)
8. Change in organisational structure and delegation of tasks
9. Strengthen Dutch-German collaboration through joint professorships and bi-national PhD student Consortia (NWO-DFG) (in progress: Aachen, Mainz, Münster)
10. Increasing the CARIM tradition of multi- and interdisciplinary research, i.e. to promote and facilitate cross-theme and cross-school developments to make Theme III and CARIM a stronger leader in translational vascular biology research
11. Increasing focus of UM towards the β sciences offers CARIM the opportunity to collaborate with the new formed institutes M5I (institute for molecular imaging) and MERLN (institute for technology inspired regenerative medicine)

THREATS
1. Competition for large funding by large research consortia in the Netherlands
2. Interest of NUTRIM and CAPHRI in structurally collaborating with CARIM may be low, notably when the metabolic program carries a putative "CARIM stamp"
3. Reduced funding (notably when in 2014/2015 the TTI and CTMM subsidies will cease
4. The animal facilities are still in a non-competitive state and the pace of development of the new Vivarium is too capricious to assure quick wins
5. Budget cuts on a national level and also within the Maastricht University community
6. Funding of scientific research in the Netherlands is changing from projects and modest program grants to funding of large, multidisciplinary consortia in which top scientists from various university medical centres participate

A.12 STRATEGY

Based on the first results of the fully open SWOT questionnaire, the Strategic Board decided to schedule two workshop days in January 2014 (see Annex 12 for the program of these days) to discuss the analysis and to define short- and long- term measures. Four topics that received either the most comments or had the highest ratio of negative comments were chosen for further analysis and solution-finding at these workshops: 1) Infrastructure, e.g. shared infrastructure in CARIM, 2) culture (communication and internal collaboration, including with research schools), 3) scientific excellence (talent and funding), and 4) funding (external, e.g. EU, and internal support). For each of these topics several action items were identified which were further discussed at a Strategic Meeting on March 17, 2014.

This chapter, which discusses the CARIM strategy for the coming years, is based on the SWOT analysis described in the previous chapter and its follow-up strategic meeting. As a result of this process, the strategy has been divided into the following areas: research, collaboration, infrastructure, funding, CVC (translation to the clinic), education and publication strategy. Furthermore, a regular series of strategic meetings specifically addressing the question of how CARIM has to respond to the changes in the scientific landscape will be installed. This will not only include scientific exchange, but also strategic consideration on training of scientific staff, new technologies and allocation of personnel.

Research

- Investigate cardiovascular diseases as pathophysiological processes involving various cell types, tissues, and multiple organs. Explore the interfaces between different research domains as an important part of innovation within the cardiovascular field.
- Install a task force for systems biology and computational medicine.
- Further reinforce complex genetics expertise in CARIM. Because of its relevance to the research lines of many PIs (many of them deal with complex multifactorial diseases with some heritable factors) and as explained in the mid-term review 2007-2011, CARIM decided to invest in complex genetics and appointed Prof. Monika Stoll for 0.2 FTE. Additional support for bioinformatical expertise is needed here.
- To support the redefinition and restructuring of a coherent vascular research program within CARIM including interactions with the other research lines.
- Terminate research lines with a low scientific output.

Collaboration

- Intensify integration into international collaborative projects. The Horizon 2020 program offers significant opportunities. The previous funding of the Netherlands' large research programs (e.g. CTMM, BMM, TI Pharma, TIFN) had a strong emphasis on the development of new diagnostic tools and technology. An important element of the Horizon 2020 program is improvement of diagnosis and patient characterisation, a call to which many researchers of CARIM are well prepared to respond.

- Intensify projects with NUTRIM, CAPHRI and MH&NS to create research profiles of international visibility on the multidisciplinary interfaces between these schools.

Infrastructure

- Actively support and influence planning, construction and launch of the VivariUM.
- Establish a number of core units. Examples are a small animal facility a histology and immunohistochemistry unit, and a microscopic imaging unit.

Funding

- Explore interfaces between traditionally separate lines of research and disciplines and implement them in large collaborative research consortia (e.g. Horizon2020).
- Continue to actively scout for and support potential candidates for personal grants. We also will expand this evaluation and optimisation process to conceptual outlines of collaborative applications.

CVC

- Install CVC expertise centres as the crystallisation points of a new CVC structure. Examples are the TEC and a Complex Arrhythmia Unit.
- Protect CARIM's independence and interests as a scientific institute in the CVC structure. Actively discuss governance structure, HRM strategies and IP regulations.

Education

- Develop common, standardised guidelines for PhD training programs applicable to all PhDs across the FHML.
- Reduce the average time it takes to obtain a PhD by monitoring the PhD student's personal research plan (CaRES plan) and implementing the TRACK.2 program.

Publication strategy

- Focus on high quality research rather than dividing capacity on too many projects.
- Aim at larger collaborative articles with combined data sets to maximise the quality rather than the quantity of research articles.
- Discuss the consequences of new publication culture at all levels.

CARIM

School for Cardiovascular Diseases

Self-Evaluation 2007-2012

B_ DOCUMENTATION AT THE LEVEL OF THEMES

B.1 THEME I THROMBOSIS AND HAEMOSTASIS

B.1.1 Objectives and research area

The focus of Theme I is directed towards deciphering impairments of proteins, platelets, and the vessel wall in relation to the development of venous and arterial thrombosis. Reflecting on the blueprint of Virchow's triad which defines thrombosis as an imbalance between blood composition, vessel wall and components of flow, Theme I explores the multifactorial cause of thrombosis which in the case of venous thrombosis has a high societal impact on the population (oral contraceptive use; pregnancy), and as in the case of arterial thrombosis is the biggest cause of mortality worldwide.

Because of the multifactorial nature of thrombosis, Theme I covers a broad spectrum of disciplines and technologies to tackle crucial research questions in understanding how thrombosis develops and progresses, taking into account the rapidly evolving knowledge on thrombosis and haemostasis and by using state of art technology platforms.

Aiming at knowledge utilisation and valorisation, we are strengthening our current network and translational activities towards the clinic, exploring novel clinical interfaces to feed the clinical-preclinical axis resulting in a more efficient and rapid application of basic research results in diagnostics and therapeutics. As a part of this aim, official collaborations have been established with universities of Aachen, Mainz, Münster and Munich, in which active exchange of researchers, projects and ideas are ongoing.

As the clinical use of imaging agents and drugs requires full understanding of the structure and activity of molecules and small molecules and their interactions with proteins, we have recently invested in infrastructure and expertise for structural molecular analysis of proteins and small molecules.

In addition to gaining access to the molecular side of the translational axis, the clinical side has been strengthened by the establishment of the Thrombosis Expertise Centre between CARIM Theme I and the clinical Heart and Vascular Centre (HVC) of the Academic Hospital Maastricht, in which two out of four of our programs are embedded with financial support to improve knowledge on the origin of thrombosis and to apply personalised medicine to thrombosis management.

In all, Theme I is on track to employ the full translational spectrum from 'molecule to men' and vice versa on unravelling the pathophysiology of thrombosis, guided by clinical practice, and with a firm outlook on applying basic tools to personalised patient management.

B.1.2 Composition

Theme I 'Thrombosis and Haemostasis' is led by Prof. Tilman Hackeng and is divided into four programs. An overview of these programs is provided below with the principal investigators (PIs) of the programs indicated in brackets.

Programs

1. Blood proteins & engineering (Prof. Tilman Hackeng)
2. Vascular aspects thrombosis and haemostasis (Prof. Chris Reutelingsperger)
3. Cell biochemistry of thrombosis and haemostasis (Prof. Johan Heemskerk)
4. Clinical thrombosis and haemostasis (Prof. Hugo ten Cate)

In Theme I the focus is currently directed at impairments of coagulation proteins (Prof. Tilman Hackeng), blood cells (Prof. Johan Heemskerk), and the vessel wall (Prof. Chris Reutelingsperger) in relation to the development of venous and arterial thrombosis (Prof. Hugo ten Cate). Theme I covers the broad spectrum from 'molecule to men', which has been strengthened in recent years by investments in molecular research, protein engineering, platelet biology, and translational clinical activities.

B.1.3 Research environment and embedding

Infrastructure

In 2007, the external review committee advised that investment into this theme should be kept at the same high level or even more should be invested in it. In addition, they particularly recommended investment in the clinical translation of the fundamental mechanisms.

Protein engineering investments have been made in the laboratory for chemical protein synthesis in which parts of coagulation proteins are synthesised for structure-function analysis and where total chemical protein and peptide-based imaging agents are designed and made for in vivo imaging of angiogenesis, arteriogenesis, atherosclerosis, and thrombus formation. These contrast agents are tailor-made for applications within CARIM, which will also strengthen the translational axis between basic research departments, clinical research departments, and the clinic. To improve synthesis facilities and quality control, UPLC-ESI-TOF mass spectrometry has been acquired by CARIM's chemical synthesis labs (Prof. Tilman Hackeng). To focus more on molecular structure and to add a cardiovascular background to a 700 MHz protein NMR for determination of protein structure and protein/protein or protein/drug interactions has been acquired (Prof. Tilman Hackeng).

In addition, we have invested in a recombinant protein production facility which in combination with our molecular biology facility allows structure-function relationship studies of key proteins in simple and complex biological systems ranging from cell-free systems to cultured cells and animal models (Prof. Chris Reutelingsperger). For this purpose, our cell culture facility has been equipped with two xCELLigence systems.

To invest in our drug design unit, new facilities have been established for the in silico drug design group (Dr Gerry Nicolaes) that has proven to be very successful in the rapid, low cost identification of small molecules to target the function of many coagulation and inflammatory proteins.

Articles on two examples of difficult targets successfully approached by in silico design (i.e. small molecules inhibiting the binding of factor VIII to phospholipids limiting thrombotic situations and on small molecules targeting TRAF6 inhibiting CD40-dependent signalling as a therapeutic target in obesity-associated insulin resistance) have recently been

published in the high ranking journals Blood and PNAS, respectively.

In this context, the platform for direct binding analysis of biomolecules, including small molecules, has been expanded by upgrading the existing Biacore T100 system to a T200 system and by the purchase of a microcalorimetry setup, comprising nanoITC and nanoDSC equipment. This was facilitated by the successful applications for an investment grant from the Netherlands Scientific Organisation (NWO, to Dr Gerry Nicolaes).

For the studies involving blood, blood cells, and blood proteins in thrombosis and haemostasis, a fast line-scanning multicolour confocal microscope has been acquired which has proved to be indispensable to the studies of thrombus formation in vitro and in vivo (Prof. Johan Heemskerk). To extend the multidisciplinary approach to studying cardiovascular disease, a Roche LightICycler 480 has been installed to aid our research into the genetic factors that cause cardiovascular disease (Dr Elisabetta Castoldi).

Translation

In 2007, the ERC strongly advised that access to the clinical setting in order to facilitate translational research be organised. To this end, the development of the Thrombosis Expertise Centre (TEC) headed by Prof. Hugo ten Cate was started in 2008. The TEC spans clinical and translational research dedicated to post-thrombotic syndrome and operates in collaboration with the departments of Vascular Surgery, Radiology and Clinical Epidemiology and Medical Technology Assessment (KEMTA). The TEC is the leading centre in two multicentre efficacy studies (*Doelmatigheidsstudies*) (Netherlands Organisation for Scientific Research [*NWO-ZonMW*]) on post-thrombotic and catheter-based thrombolytic therapy of thrombosis, and on tailored stocking therapy in relation to anticoagulant and antiplatelet drugs. In addition, a collaboration on peri-operative haemostasis exists between the departments of Clinical Chemistry, Haematology (transfusion), and Anaesthesiology, and the TEC participates in public-private networks such as the CTMM-INCOAG program (Prof. Hugo ten Cate; Prof. Johan Heemskerk) and CTMM-PREBAT validation grant (Prof. Hugo ten Cate; Prof. Tilman Hackeng). By collaborating with Clinical Chemistry (Dr Yvonne Henskens) and Clinical Genetics (Dr Irene Keularts) of the academic hospital, a standardised structure has been created for inclusion of patients from the region with rare haemostatic or thrombotic diseases into the research programs (Prof. Johan Heemskerk, Prof. Hugo ten Cate). More recently, initiatives were taken to address specific questions related to efficacy and safety of complex antithrombotic therapy in patients with coronary artery disease.

On the molecular side of the translational axis, Theme I is involved in multiple CTMM consortia. As a part of CTMM-Triumph, Theme I is participating in the quest for a prognostic multimarker platform for heart failure (Prof. Tilman Hackeng). As a part of CTMM-Circulating cells, Theme I participates in analysis of genes and proteins involved in the development of atherosclerosis (Prof. Tilman Hackeng), in CTMM-Eminence, Theme I is involved in design and total chemical synthesis of molecular imaging agents for the detection of angiogenesis and arteriogenesis (Prof. Tilman Hackeng), and in the CTMM-INCOAG, Theme I is involved in the development of a bedside thrombin generation test (Prof. Hugo ten Cate, Prof. Johan Heemskerk).

Theme I has connected its fundamental research on proteins and vascular cells to the translational and societal contexts by actively pursuing and establishing collaborations with clinical programs (Nutraceutical reduction of vascular calcification in CKD patients, the VitaVask study of ETA-EDTA and Nutraceutical reduction of vascular calcification in CAC patients, the vitaCAC study of the Dutch Heart Foundation) (Dr Leon Schurgers and Dr Bram Kroon (Theme III)) and European Networks (WHRI-ACADEMY, the FP7 Marie-Curie COFUND) (Prof. Chris Reutelingsperger).

Valorisation and spin-off companies

Theme I is actively involved in spin-off companies. Established companies and those formed more recently are either based on out-licensed intellectual property or technology platforms, and indirectly or directly provide revenues to CARIM and Biochemistry through royalty contracts and exit strategies. Examples are shown in Annex 7 and include ACS Biomarker BV (Prof. Tilman Hackeng, Prof. Yigal Pinto, Prof. Mat Daemen); Vitak BV (Dr Cees Vermeer); Synapse (Dr Bas de Laat, Prof. Coen Hemker); Mosamedix (Prof. Chris Reutelingsperger) and Pharmatarget (Prof. Chris Reutelingsperger). In addition to IP valorisation,

SMEs from Theme I actively participate in public-private consortia such as CTMM and FP7, and are also involved in local collaboration with Theme I research.

Research management

Each of the four programs has weekly two-hour research meetings of 2 hours (Prof. Johan Heemskerk, Monday 9.00-11.00; Prof. Hugo ten Cate, Tuesday 9.00-11.00; Prof. Chris Reutelingsperger, Wednesday 10.00-12.00; Prof. Tilman Hackeng, Thursday 9.00-11.00). During these meetings, the day-to-day experiments of PhD students, technicians, and postdocs are discussed in detail and general lab issues are dealt with. In addition a weekly theme meeting, open to all CARIM personnel, is held in the auditorium. At these meetings Theme I researchers take turns to present a large part of their research objectives (45 min, followed by 15 min of discussion). There are extra dedicated meetings on design and synthesis of proteins and imaging agents (Prof. Tilman Hackeng, Friday 9.00-11.00), and on in silico drug design (Dr Gerry Nicolaes, Monday 11.00-13.00). To stimulate inter-theme interaction, monthly scientific meetings are organised between Themes I and III on atherothrombosis and micro- and macrovascular issues.

International collaboration

Collaboration with the Universities of Aachen (Dr Leon Schurgers, Prof. T. Hackeng) and Mainz (Prof. Hugo ten Cate, Prof. Johan Heemskerk) have been initiated and established. Collaboration with RWTH Aachen has led to a successful IRTG/NWO application (Daemen-Hackeng-Weber-Bernhagen) for 15 PhD students resulting in the recent delivery of the first joint PhD students between Aachen and Maastricht. A recent extension of collaborative, translational studies has been established with Gutenberg University in Mainz through a Gutenberg Research College visiting professorship grant to Prof. Hugo ten Cate.

In addition Theme I (Prof. Johan Heemskerk) has a strong presence in international consortia on thrombosis and haemostasis, i.e. the European Platelet Network (EUPLAN), the Platelet Proteomics Working Group (collaboration Dortmund, Mainz, Würzburg, Birmingham), and the BRIDGE consortium on full sequencing and gene discovery of patients with haemostatic related diseases, acting as an umbrella for NIHR BioResource funded Next Generation Sequencing (Cambridge, UK).

B.1.4 Quality and scientific relevance

Theme I has invested in research on vascular calcification and nutraceutical intervention strategies. The vascular calcification program (Dr Leon Schurgers) aims to elucidate molecular mechanisms regulating ectopic calcification and to translate knowledge into diagnostic and therapeutic concepts for cardiovascular patients (CVON junior grant application), CKD patients (VitaVask) and CAC patients (VitaCAC). In the light of current debate about novel oral anticoagulants, this research line adds to the scientific and social debate about implementation of NOACs.

In addition, Theme I has expanded to include atherothrombosis. The atherothrombosis focus is twofold, both in basic experimental and translational aspects. The role of coagulation and anticoagulation in the onset and progression of atrial fibrillation (AF) will be deciphered in collaboration with the Department of Cardiology (Theme II), and in multicentre collaboration (CVON grant application). In addition, the fundamental and translational studies of blood platelet research will include atherothrombotic complications in patients with coronary artery disease (CAD) focusing on platelet function and dysfunction, inflammation-coagulation interactions and individually tailored therapy to prevent thrombosis in high-risk individuals. Not only atherothrombosis has a high societal impact; Theme I is currently working on understanding how coagulation proteins (factors traditionally involved in venous thrombosis) are now also indicated in the initiation and development of arterial thrombosis. This opens up a new line of research.

To further move into the translational field of experimental medicine, four research lines involving thrombosis-related topics are distinguished in the Cardiovascular Centre (CVC)-TEC concept:

1) Mechanisms of arterial and venous thrombosis: diagnostics, imaging, drug development
2) Prevention of venous thromboembolism and its recurrence, and post-thrombotic syndrome (PTS)
3) Individually tailored antithrombotic therapy/peri-operative haemostasis
4) Tailored imaging agent and drug design

Within the CVC framework, patients and clinical/basic scientists interact, addressing specific research questions in the course of cohort and intervention studies. An example

of a new diagnostic tool used in Theme I is the testing and clinical validation of whole blood thrombin generation and thrombus formation in patients on anticoagulant therapy and the application of a novel heat-stable inhibitor of contact activation (P6036535PCT). This is carried out in collaboration with Synapse, ZonMW and the Anticoagulation clinic - all partners in TEC. Another example of a novel interventional technique is catheter-guided thrombolysis, applied in patients with proximal deep vein thrombosis. This is acollaboration between vascular medicine, radiology and vascular surgery. These examples illustrate how bench-side techniques can be transferred to a clinical setting. Finally, Theme I actively participates in initiatives to reduce and replace animal experimentation in atherothrombosis studies in a translational way (Willy van Heumen Award, ZonWM, Landsteiner Foundation for Blood Transfusion Research, collaboration Synapse).

Over recent years the output parameters from Theme I have been above world average, and have continued to increase since the previous external review in 2007. Information extracted from the CWTS (Centre for Science and Technology Studies Leiden) output analysis is shown in Table 1.

B.1.4.1 Programs and Highlights

BLOOD PROTEINS & ENGINEERING (PROGRAM 1)

PI	Prof. Tilman Hackeng (VIDI 2002)
STAFF	Prof. Jan Rosing (em)
	Dr Guido Tans
	Dr Gerry Nicolaes (VIDI 2003)
	Dr Elisabetta Castoldi (VIDI 2006)
	Dr Rory Koenen (VIDI 2012)
	(1 postdoc; 5 PhD students; 5 technicians)

Prof. Tilman Hackeng studied chemistry and biochemistry at the University of Utrecht where he obtained his Master's degree in 1988. After his military service he finished his PhD in 1993, and left for The Scripps Research Institute, La Jolla, CA, USA, where he worked in the laboratories of Prof. Griffin (Mol & Exp. Medicine) and Prof. Kent (Cell Biology/ Chemistry). In 1998 he was granted a position as a Research Fellow of the Royal Netherlands Academy of Arts and Sciences (KNAW) at the Department of Biochemistry (Prof. Jan Rosing) at the University Maastricht, the Netherlands. In 2002 he received a personal VIDI grant from the Netherlands Organisation for Scientific Research (NWO). Currently, he

Table 1: Bibliometric analysis CARIM Theme I 2007-2010

Theme I Thrombosis and Haemostasis	P	CPP	MNCS	MNJS
2004-2007	238.25	8.34	1.10	1.15
2005-2008	252.00	7.93	1.14	1.16
2006-2009	269.75	8.79	1.40	1.27
2007-2010	303.25	9.92	1.46	1.35

P: Number of articles. **CPP**: Average number of citations per publication (p), without self-citations. **MNCS**: The impact of a research unit's articles, compared to the world citation average in the subfields in which the research unit is active. **MNJS:** the impact of the journals in which a research unit has published compared to the world citation average in the subfield covered by these journals.

is head of the Department of Biochemistry were he studies the anticoagulant protein C/protein S/TFPI pathways and applies total chemical protein synthesis to the development of peptide/protein-based contrast agents for imaging of cardiovascular disease. He is a board member of CARIM, and President of the Netherlands Society on Thrombosis and Haemostasis.

Within Program 1 Prof. Tilman Hackeng studies structure-function relationships of anticoagulant coagulation proteins and leads the chemistry lab of synthesis of tailored imaging agents; Prof. Jan Rosing and Dr Guido Tans study coagulation enzyme kinetics, Dr Gerry Nicolaes applies structural bioinformatics and in silico drug design to cardiovascular disease, Dr Elisabetta Castoldi studies the genetics of venous thrombotic disease and bleeding disorders, and Dr Rory Koenen is specialised in experimental and molecular atherothrombosis.

Highlight: When antisense makes sense: RNA therapy of factor V deficiency

Coagulation factor V (FV) acts as an essential cofactor in prothrombin activation. We investigated a patient with undetectable FV and multiple life-threatening bleeding episodes. This patient was homozygous for a deep-intronic splicing mutation (c.1296+268A>G) causing the retention of a pseudo-exon with an in-frame stop codon in the mature mRNA. This mutation was targeted with two different antisense molecules (a morpholino oligonucleotide and an engineered U7snRNA) designed to anneal to the mutant pre-mRNA and hide the incorrect splicing signal. Both antisense molecules specifically and dose-dependently corrected the splicing pattern in an in vitro minigene model. Moreover, they restored FV protein synthesis in the patient's megakaryocytes differentiated ex vivo from circulating haematopoietic progenitor cells. These findings hold promise for the treatment of severe FV deficiency.

Highlight: A sweet solution to a bitter disease: heparin to treat systemic inflammation and sepsis

Recent progress in the treatment of sepsis has shown that anticoagulant protein C can improve survival of sepsis patients which may be explained by the proteolytic inactivation by APC of extracellular histones. While APC therapy has been discontinued due to the side effect of bleeding, we have found that a variant of heparin, a sugar-based natural glycan, is able to neutralise histone-induced cytotoxicity. A specific and safe sub fraction of heparin has been manufactured that retains the anti-inflammatory properties but that is devoid of virtually all anticoagulant activity. While research is ongoing, we have provided evidence that the use of this heparin can protect mice from death in an in vivo model of sterile inflammation and in models of sepsis. A patent, "Method for the prevention and treatment of Sepsis" (WO2013007771A1) was successfully filed in 2011.

VASCULAR ASPECTS THROMBOSIS AND HAEMOSTASIS (PROGRAM 2)

PI Prof. Chris Reutelingsperger
STAFF Dr Leon Schurgers
(1 postdoc; 3 PhD students; 4 technicians)

Prof. Chris Reutelingsperger studied biochemistry at the University of Utrecht and received his PhD from the Faculty of Medicine at Maastricht University in 1987. He was awarded the 5 year Senior Fellowship of the Royal Dutch Academy of Sciences (KNAW) in 1987. Currently he is Professor of Biochemistry of Apoptosis at CARIM, Maastricht University. He is Principal Investigator and member of the Strategic Board of CARIM. He supervises research on molecular and cellular mechanisms of vascular ageing, including atherosclerosis and vascular calcification. His interests focus on inflammation, cell death, phagocytosis, autophagy, vitamin K-dependent proteins and annexin A5. His strategy encompasses establishing collaborations with clinical research and industry. He has published over 160 peer-reviewed scientific papers and his inventions have resulted in more than 10 patents being granted. He is considered one of the leading experts in the field of annexin A5 and imaging.

Within Program 2, Prof. Chris Reutelingsperger studies vascular biology and imaging, and Dr Leon Schurgers explores mechanisms of arterial calcification.

Highlight: Vascular calcification: Filling the translational gap

Vascular calcification is increasingly prevalent in the ageing population. Systemic disorders such as metabolic disease and chronic kidney disease are associated with chronic vascular inflammation and concurrent calcification. Vascular calcification contributes to acute arterial events and chronic systemic conditions such as hypertension. This program explores the cellular and molecular mechanisms driving vascular calcification in order to offer concepts and targets for diagnosis and pharmaceutical and nutraceutical intervention. In order to be able to translate in vitro results of the calcification program to relevant clinical applications, we have designed a unique Biohybrid-system. The BioHybrid, a Theme I and III enterprise, is an innovative multi-tethered and versatile high-content-analysis (HCA) translational technology platform measuring a range of key functions of vascular cells (endothelial cells, macrophages and vascular smooth muscle cells) in vitro (ZonMW project MKMD, Theme III (Prof. Erik Biessen) and Theme I (Prof. Chris Reutelingsperger). The BioHybrid program proposes a logical step, feeding on the experience with animal studies. Animal studies have long been viewed as an inevitable step in research to capture understanding of aetiology and pathogenesis of human disease and in pharmaceutical, toxicological and nutritional research to test efficacy of compounds in treating human disease. However, humans are not simply 70 kg rodents and support for the low predictive value of rodent models of human disease is overwhelming. In fact, the predictive power of mouse models was estimated to be only 40%, a notion confirmed in numerous studies, showing a shocking lack of correlation between mouse and human post-trauma and sepsis responses, and in cardiovascular disease. The BioHybrid is designed to fill this gap and to support diagnosis (disease risk score), monitor treatment efficacy, predict efficacy in patients of lead drug candidates from discovery platforms and support hypothesis-generating fundamental and evidence-based clinical research.

CELL BIOCHEMISTRY OF THROMBOSIS AND HAEMOSTASIS (PROGRAM 3)

PI Prof. Johan Heemskerk
STAFF Dr Edouard Bevers
Dr Judith Cosemans (Dekker NHS, 2010)
Dr Paola van der Meijden
(1 postdoc; 5 PhD students; 2 technicians)

Prof. Johan Heemskerk studied chemistry and biology at the Radboud University of Nijmegen. There he started his PhD study on biochemical research into plant lipid biosynthesis in 1981. He carried out postdoctoral studies at the Universities of Hamburg (Germany), Cambridge (UK) and the Wihuri Research Institute in Helsinki (Finland). In 1986, he joined the Department of Biochemistry of Maastricht University to study the effects of dietary fats on blood platelet activation. Prof. Johan Heemskerk holds the chair of Cell Biochemistry in Thrombosis and Haemostasis, and is a Principal Investigator at CARIM. He heads the laboratory and its affiliated microscopic imaging facilities. He is author of numerous articles in the fields of signal transduction, experimental thrombosis and coagulation. Prof. Johan Heemskerk is a member of the Advisory Board of the CVC and of several national and international Scientific Advisory Boards in the field of thrombosis and haemostasis. He is associate editor of the Journal of Thrombosis and Haemostasis and member of the editorial advisory board of several other journals. He is a member of the International Advisory Board of the International Society on Thrombosis and Haemostasis. He has chaired the Section Biorheology of the Scientific & Standardisation Committee of the International Society on Thrombosis and Haemostasis. He is an elected member of several scientific societies both in the Netherlands and abroad.
Within Program 3, Prof. Johan Heemskerk studies complex platelet phenotyping in thrombosis and haemostasis, Dr Edouard Bevers studies mechanisms of platelet phospholipid asymmetry, Dr Judith Cosemans studies the role of platelets in vascular function and remodelling, and Dr Paola van der Meijden covers translational thrombosis and haemostasis.

The group performs state-of-the-art studies on basic and clinically related aspects of functions of platelets and

other blood cells in a physiological and pathophysiological context. Highlights are discoveries in signal transduction and cell-cell communication in blood cells in relation to thrombus formation. There is particular focus on studies of the functions of blood platelets in atherothrombosis and haemostasis, in vascular responses, in coagulation and inflammation (acute plaque rupture, multiparameter thrombus formation, complex platelet phenotyping). Currently progress is being made in the study of platelet interactions with neutrophils and monocytes in atherothrombosis, inflammation and NET formation. Functional studies are performed in relation to big-data expression analyses (quantitative platelet proteomics, second generation sequencing). Experimental work extends from humans to mice, with new focus on post-thrombotic modulation of the diseased vasculature. Clinically related work concentrates on patients with bleeding disorders or a prothrombotic propensity, on acquired coagulopathy, and on basic studies to the efficacy of antiplatelet medication. Microfluidic devices for preclinical screening of thrombus formation and thrombin generation have recently been developed and validated. The major progress in research is highly driven by the large international networks of the group.

CLINICAL THROMBOSIS AND HAEMOSTASIS (PROGRAM 4)

PI	Prof. Hugo ten Cate
STAFF	Dr Henri Spronk
	Dr Jose Govers-Riemslag
	Dr Paola van der Meijden
	Dr Arina ten Cate-Hoek
	(2 postdoc; 7 PhD students; 4 technicians)

Prof. Hugo ten Cate studied medicine at the University of Amsterdam where he obtained his Master's degree in 1987. The same year he obtained a PhD degree with his thesis "Low molecular weight heparinoids" and spent a postdoc period at the Division of Hematology-Oncology, Beth Israel Hospital, Harvard Medical School, Boston, USA, under Prof. Robert D. Rosenberg (1988-1990). He specialised in internal medicine at the Slotervaart Hospital and Academic Medical Centre in Amsterdam and was awarded a Clinical Established Investigatorship on behalf of the Dutch Heart Foundation (1996-2002). This supported further experimental work at the AMC (Experimental Internal medicine, head: Prof. Pieter Reitsma). In 1996, he obtained his license to practice internal medicine and in 2002 he was appointed Professor of Medicine, in particular Clinical Thrombosis and Haemostasis at the Maastricht University Medical Centre and CARIM, Maastricht. He is a member of the Strategic Board of CARIM, a scientific board member of the recently established CVC at the MUMC+, and chairman of the board of the Dutch Federation of Anticoagulation Clinics (FNT).

Within Program 4, Prof. Hugo ten Cate covers clinical thrombosis and haemostasis, Dr Henri Spronk studies coagulation effects beyond thrombin generation, Dr Paola van der Meijden covers translational thrombosis and haemostasis and Dr Arina ten Cate studies the pathophysiology of venous thrombosis and post-thrombotic syndrome. The role of coagulation proteases in onset and progression of atherosclerosis and thrombosis is being studied in a large cohort of participants in the Gutenberg Health Study, Gutenberg University, Mainz (5000 individuals at risk of CVD, follow-up over 5 years completed in 2013; GFK grant, starting 2013).

Highlight: Novel diagnostic tools: towards individualised risk assessment

Within the framework of the CTMM INCOAG program, a panel of novel tests and novel test applications is being developed. The first product to enter the stage of validation is the whole blood thrombin generation test, in a close to point of care (POC) application. In the PREBAT validation study, a whole blood thrombin generation POC test is being further developed and validated in studies with clinically relevant outcomes (bleeding, thrombosis). The combination of clinical risk assessment in conjunction with selected new laboratory tests was addressed in the LETS venous thromboembolism study in Leiden. Based on the successful combination of risk factors and selected laboratory biomarkers, further studies were devised. This principle is also the main instrument in a recently submitted Horizon 2020 grant pre-application, (PRIMETOPIC) in which the main objective is to develop a PoC device for thrombin generation in whole blood to detect a prothrombotic phenotype in cancer patients. This is done in conjunction with a risk assessment model (RAM) that translates in vitro test results

and clinical patient characteristics into an accurate VTE risk score (collaboration with Synapse, Philips and Biocyntex). Ongoing validation studies assess the potential of the entire spectrum of developed assays in plasma and whole blood in patients with manifestations of arterial vascular disease (peripheral artery disease, acute coronary syndrome), or venous vascular disease (VTE).

Highlight: Pleiotropy of coagulation proteases

Another avenue that is being explored is the clinical relevance of coagulation proteases such as thrombin in relation to arterial vascular disease, AF, and ischaemic reperfusion injury. In collaboration with the Department of Cardiology (Prof. Uli Schotten, Prof. Harry Crijns), the Erasmus University (Prof. Felix Zijlstra, Dr Moniek de Maat, Dr Heleen van Beusekom), the Antonius Hospital, Nieuwegein (Dr Chris Hackeng, Prof. Jurrien ten Berg) and Gutenberg University Mainz, several research programs are aiming to decipher how coagulation proteases drive inflammatory processes that tend to aggravate atherosclerosis, AF and ischaemic organ damage. Existing and novel anticoagulants that reverse these processes in animal studies may also have the potential to influence these CV disorders in humans. In submitted CVON grant applications as well as commercial contract research, we aim to further deepen our understanding of the mechanisms involved and to explore the clinical relevance of these mechanisms. In a British Heart Foundation program, we additionally investigate the specific role of contact inhibition with novel FXIIa inhibitors on the above-mentioned CV processes in mouse experiments (collaboration with Dr Helen Philippou and Prof. Robert Ariens, Leeds, UK).

B.1.4.2 Key publications

2007

Prinzen L, Miserus RJ, Dirksen A, Hackeng TM, Deckers N, Bitsch NJ, Megens RT, Douma K, Heemskerk JW, Kooi ME, Frederik PM, Slaaf DW, van Zandvoort MA, Reutelingsperger CP -
Optical and magnetic resonance imaging of cell death and platelet activation using annexin a5-functionalized quantum dots. Nano Letters 2007; 7(1): 93-100
IF 13.05

Sarai M, Hartung D, Petrov A, Zhou J, Narula N, Hofstra L, Kolodgie F, Isobe S, Fujimoto S, Vanderheyden JL, Virmani R, Reutelingsperger C, Wong ND, Gupta S, Narula J -
Broad and specific caspase inhibitor-induced acute repression of apoptosis in atherosclerotic lesions evaluated by radiolabeled annexin A5 imaging. J Am Coll Cardiol 2007; 50(24): 2305-12
IF 14.09

Van de Walle G, Schoolmeester A, Iserbyt BF, Cosemans JMEM, Heemskerk JWM, Hoylaerts MF, Nurden A, Vanhoorelbeke K, Deckmyn H -
Activation of allbb3 is sufficient but also an imperative prerequisite to activate a2b1 on platelets. Blood 2007; 109: 595-602
IF 9.90

2008

Cleutjens CBJM, Faber BC, Rousch M, van Doorn R, Hackeng TM, Vink C, Geusens PPMM, ten Cate H, Waltenberger JL, Tchaikovski V, Lobbes M, Somers V, Sijbers A, Black D, Kitslaar PJEHM, Daemen MJAP -
Noninvasive diagnosis of ruptured peripheral atherosclerotic lesions and myocardial infarction by antibody profiling. J Clin Invest 2008; 118(8): 2979-85
IF 16.915

Van den Borne SWM, Isobe S, Verjans JW, Petrov A, Lovhaug D, Li P, Zandbergen HR, Ni Y, Frederik PM, Zhou J, Arbo B, Rogstad A, Cuthbertson A, Chettibi S, Reutelingsperger CPM, Blankesteijn WM, Smits JFM, Daemen MJAP, Zannad F, Vannan MA, Narula N, Pitt B, Hofstra L, Narula J -
Molecular imaging of interstitial alterations in remodeling myocardium after myocardial infarction. J Am Coll Cardiol 2008; 52(24): 2017-2028
IF 11.054

Van den Borne SWM, Narula J, Voncken JW, Lijnen PM, Vervoort-Peters HT, Dahlmans VE, Smits JFM, Daemen MJAP, Blankesteijn WM -
Defective intercellular adhesion complex in myocardium predisposes to infarct rupture in humans. J Am Coll Cardiol 2008; 51(22): 2184-92
IF 11.054

Shroff RC, McNair R, Figg N, Skepper JN, Schurgers LJ, Gupta A, Hiorns M, Donald AE, Deanfield J, Rees L, Shanahan CM -
Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. Circulation 2008; 118(17): 1748-57
IF 15.202

Maurissen LF, Thomassen MC, Nicolaes GA, Dahlback B, Tans G, Rosing J, Hackeng TM -
Re-evaluation of the role of the protein S-C4b binding protein complex in activated protein C-catalyzed factor Va-inactivation. Blood 2008; 111: 3034-41
IF 9.90

Key publications

2009

Koenen RR, von Hundelshausen P, Nesmelova IV, Zernecke AET, Liehn EA, Sarabi A, Kramp BK, Piccinini AM, Paludan SR, Kowalska MA, Kungl AJ, Hackeng TM, Mayo KH, Weber C -
Disrupting functional interactions between platelet chemokines inhibits atherosclerosis in hyperlipidemic mice. Nature Medicine 2009; 15(1): 97-103
IF 27.553

Sluimer JC, Kolodgie FD, Bijnens AP, Maxfield K, Pacheco E, Kutys B, Duimel H, Frederik PM, van Hinsbergh VW, Virmani R, Daemen MJAP -
Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. J Am Coll Cardiol 2009; 53(17): 1517-27
IF 11.438

Rensen SSM, Slaats Y, Driessen ALC, Peutz-Kootstra CJ, Nijhuis JG, Steffensen R, Greve JW, Buurman WA -
Activation of the complement system in human nonalcoholic fatty liver disease. Hepatology 2009; 50(6): 1809-17
IF 11.355

Saller F, Brisset AC, Tchaikovski SN, Azevedo M, Chrast R, Fernandez JA, Schapira M, Hackeng TM, Griffin JH, Angelillo-Scherrer A -
Generation and phenotypic analysis of protein S-deficient mice. Blood 2009; 114: 2307-2314
IF 9.90

2010

Borissoff JI, Heeneman S, Kilinc E, Kassak P, van Oerle R, Winckers K, Hackeng TM, Spronk HMH, Govers-Riemslag JWP, Hamulyak K, Daemen M, Ten Cate H -
Early Atherosclerosis Exhibits an Enhanced Procoagulant State. Circulation 2010; 122(8): 821-30
IF 14.816

Oostendorp M, Douma K, Wagenaar A, Slenter J, Hackeng TM, van Zandvoort M, Post MJ, Backes WH -
Molecular Magnetic Resonance Imaging of Myocardial Angiogenesis After Acute Myocardial Infarction. Circulation 2010; 121(6): 775-83
IF 14.816

Parker BD, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, Shlipak MG, Whooley MA, Ix JH -
The Associations of Fibroblast Growth Factor 23 and Uncarboxylated Matrix Gla Protein With Mortality in Coronary Artery Disease: The Heart and Soul Study. Annals of Internal Medicine 2010; 152: 640-648
IF 13.976

Key publications

2011

Borissoff JI, Spronk HMH, ten Cate H -
The Hemostatic System as a Modulator of Atherosclerosis. New England Journal of Medicine 2011; 364(18): 1746-60
IF 53.486

Laeremans H, Hackeng TM, van Zandvoort M, Thijssen V, Janssen BJA, Ottenheijm HCJ, Smits JFM, Blankesteijn WM -
Blocking of Frizzled Signaling With a Homologous Peptide Fragment of Wnt3a/Wnt5a Reduces Infarct Expansion and Prevents the Development of Heart Failure After Myocardial Infarction. Circulation 2011; 124(15): 1626-35
IF 14.432

Strijkers RHW, ten Cate-Hoek AJ, Bukkems S, Wittens CHA -
Management of deep vein thrombosis and prevention of post-thrombotic syndrome. British Medical Journal 2011; 343: 8
IF 13.471

Van den Boezem PB, Klem T, d'Armandville EL, Wittens CHA -
The management of superficial venous incompetence. British Medical Journal 2011; 343: 6
IF 13.471

Panizzi P, Nahrendorf M, Figueiredo JL, Panizzi J, Marinelli B, Iwamoto Y, Keliher E, Maddur AA, Waterman P, Kroh HK, Leuschner F, Aikawa E, Swirski FK, Pittet MJ, Hackeng TM, Fuentes-Prior P, Schneewind O, Bock P, & Weissleder R -
In vivo detection of Staphylococcus aureus endocarditis by targeting pathogen-specific prothrombin activation. Nature Medicine 2011; 17: 1142-1146
IF 27.553

2012

Doring Y, Manthey HD, Drechsler M, Lievens D, Megens RTA, Soehnlein O, Busch M, Manca M, Lutgens E, Koenen RR, Pelisek J, Daemen MJ, Zenke M, Binder CJ, Weber C, Zernecke A -
Auto-Antigenic Protein-DNA Complexes Stimulate Plasmacytoid Dendritic Cells to Promote Atherosclerosis. Circulation 2012; 125(13): 1673-83
IF 14.739

Nazari-Jahantigh M, Wei YY, Noels H, Akhtar S, Zhou Z, Koenen RR, Heyll K, Gremse F, Schober A, Kiessling F, Grommes J, Weber C -
MicroRNA-155 promotes atherosclerosis by repressing Bcl6 in macrophages. Journal of Clinical Investigation 2012; 122(11): 4190-4202
IF 13.069

Grommes J, Alard JE, Drechsler M, Wantha S, Morgelin M, Kuebler WM, Jacobs M, von Hundelshausen P, Hackeng TM, Markart P, Wygrecka M, Preissner KT, Koenen RR, Weber C -
Disruption of Platelet-derived Chemokine Heteromers Prevents Neutrophil Extravasation in Acute Lung Injury. American Journal of Respiratory and Critical Care Medicine 2012; 185(6): 628-36
IF 11.08

Van de Vijver P, Schmitt M, Suylen D, Scheer L, Thomassen MC, Schurgers LJ, Griffin JH, Koenen RR, Hackeng TM -
Incorporation of disulfide containing protein modules into multivalent antigenic conjugates: generation of antibodies against the thrombin-sensitive region of murine protein S. Journal of the American Chemical Society 2012; 134:19318-21
IF 10.677

Weijs B, Blaauw Y, Rennenberg RJ, Schurgers LJ, Timmermans CC, Pison L, Nieuwlaat R, Hofstra L, Kroon AA, Wildberger J, Crijns HJ -
Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients. Eur Heart J. 2011 Jul 20
IF 14.097

B.3.4.3 Strategy based on SWOT analysis

The SWOT analysis below is based on the CARIM Midterm 2007-2011 and the CARIM future research strategy evaluation in 2012. It defines Theme I's key strategy, which is to form the solid basic foundation of the translational axis, and to stimulate inter-theme collaboration through multidisciplinary approaches.

STRENGTHS

1. Many collaborative projects have been established with CARIM Themes, related departments and institutes such as NUTRIM, GROW, KEMTA, Dept. of Neurology, Dept. of Cardiology (Theme II), Dept. of Physiology (Theme III), Dept. of Rradiology, Dept. of Internal Medicine (Theme III), and the Dept. of Clinical Chemistry. These projects have been initiated through a bottom-up fashion, by applying clinical research questions to a firm understanding of the underlying mechanisms of disease, and vice versa by applying molecular design and synthesis as well as protein function to the physiological environment of the clinical sciences.
2. The basic and molecular Theme I is in close contact with the clinical departments, notably Cardiology, Neurology, and Radiology.
3. Strong individual programs in Theme I are being maintained, with each program having its own original signature specialism that stand out and are internationally well recognized.
4. Two strong Theme I specialisms vascular biology and arterial thrombosis have intiated cross activities with Theme III, in which interdisciplinary projects based on the subjects are performed on a background of scientific meetings and PhD student exchanges.
5. Successfull spin-offs have been established, and currently joint research programs with the spin-offs are being initiated.

WEAKNESSES

1. Limitations in the facilities for animal experimentation.
2. Lack of CARIM inter-theme scientific meetings and exchange.
3. Underperformance in the national arena of organisation/ committees of thrombosis and hemostasis.

OPPORTUNITIES

1. Increasing the CARIM cross-theme interdisciplinary research even more will make Theme I and CARIM stronger in translational cardiovascular research. Currently initiatives are deployed to couple CARIM to the clinical Heart and Vessel institute to create a full spectrum translational axis between molecules and treatment of men (population).

THREATS

1. The change in gravity towards arterial thrombotic disease research at the cost of venous thrombotic disease research due to societal needs and granting agencies poses a serious threath on the high level of venous thrombosis research that is maintained by Theme I*.

* Many do not realize that acquired venous thrombosis is seen relatively often in young people, and can have a major social impact. Just as little one realizes that the annual European mortality rate as a result of complications of venous thrombosis is more than twice the number of deaths as a result of traffic accidents, AIDS, breast and prostate cancer together (Cohen et al., Thrombosis and Haemostasis 2007).

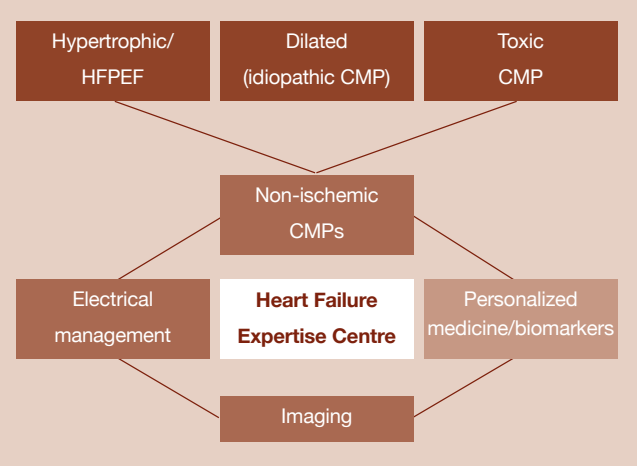
B.2 THEME II CARDIAC FUNCTION AND FAILURE

B.2.1 Objectives and research area

Research within Theme II 'Cardiac Function and Failure' ranges from mechanistic studies to clinical trials and surveys of specific cardiac diseases. It focuses on heart failure, ventricular arrhythmias and AF. The main aims of the programs in this theme are to gain insights into the basic biology of heart failure and arrhythmias, and to develop early diagnostic and therapeutic strategies based on concepts developed in the laboratory, and vice versa.

The future of care for patients with cardiac failure and arrhythmias will be significantly individualised by applying in-depth clinical, molecular and genetic phenotyping including versatile biomarkers and advanced imaging, supported by computer sciences.

Figure 1: Schematic overview Heart Failure Expertise Centre



In heart failure research, both the *thick* and the *thin* heart are studied to unravel basic and clinical heart failure mechanisms with the aim of enhancing diagnosis and treatment. *Thick heart* research – studying left ventricular hypertrophy - has produced significant experimental outcomes and is about to go clinical (microRNA based). *Thin heart* research, i.e. on cardiomyopathies, has developed into a significant translational research line with branches in the areas of inflammatory and non-inflammatory and non-ischaemic cardiomyopathies. Above all, it is the basis for an established clinical treatment algorithm and a pivotal clinical trial. Multidimensional biomarking research in clinical populations is fed by the preclinical findings and aims to find novel diagnostic algorithms which may impact on management of heart failure patients.

Electrical heart failure is being extensively studied in a translational bench-to-bedside program, encompassing novel technology, heart failure models including innovative multidimensional modelling and molecular biological characterisation, and cutting edge innovative patient management. Modelling electrical heart failure is an important topic of research aimed at understanding new treatment algorithms and understanding success and failure of the electrical management of heart failure. A strong systems biology approach towards understanding electrical heart failure is being undertaken.

Thick heart ventricular tachycardias and sudden death due to fibrillation (VT/VF) are being studied in a translational experimental- to-clinical program with a focus on unravelling ion channel pathology as the basis for ventricular arrhythmias, and also its modulation by the autonomic nervous system. In addition, inherited ventricular arrhythmias and sudden cardiac death are being studied in patients applying extensive molecular-to-clinical phenotyping in an effort to disentangle their mechanisms and to enhance treatment. A systems biology approach is taken in modelling molecular and cellular arrhythmia mechanisms.

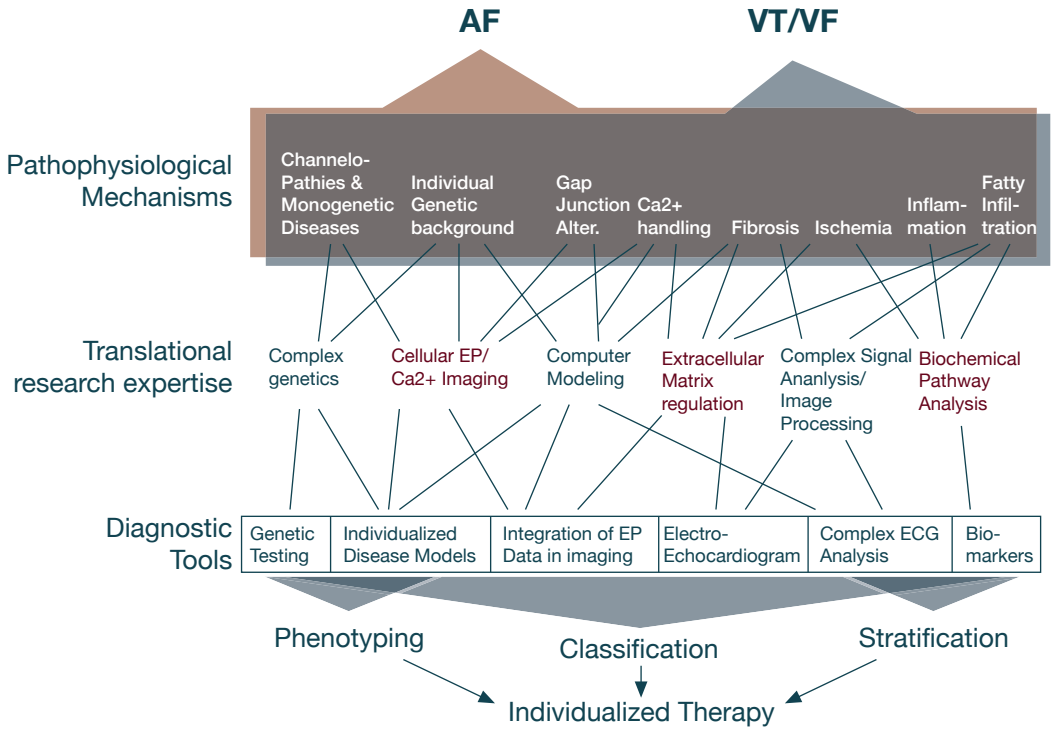


Figure 2: Schematic overview Arrhythmia Research Program

AF and ventricular tachycardia and fibrillation (VT/VF) share many mechanisms, research expertise and diagnostic tools. Maastricht has a long history of research on arrhythmias. The AF program spans molecular and experimental electrophysiology to clinical electrophysiological analyses with mapping, ablation and hybrid ablation. The programs in this area concentrate on characterising all types of AF at its various pathophysiological layers (Figure 2) and translating these into treatment algorithms. Thus, physiology (Prof. Uli Schotten), cardiology (Prof. Harry Crijns) and cardiac surgery (Prof. Jos Maessen) cooperate to improve diagnosis and treatment of AF. Translational reach-outs have been made to the CARIM Theme 'Thrombosis and Haemostasis', i.e. the Clinical Thrombosis and Haemostasis program (Prof. Hugo ten Cate) in order to understand the role of hypercoagulation in worsening of AF (AF progression) as well as the enhanced risk of thrombosis. The VT/VF program focuses on electrophysiological phenotyping of arrhythmia substrates in inherited channelopathies and cardiomyopathies, as well as acquired cardiac overload. The experimental part of the program encompasses studies ranging from cell to intact-animal and translates directly into patient care due to the strong integration of knowledge concerning ion-channel related signalling pathways, genetics and genomics of cardiac arrhythmias and functional determinants of arrhythmia syndromes.

B.2.2 Composition

Theme II 'Cardiac Function and Failure', led by Prof. Harry Crijns, is divided into twelve programs. An overview of these programs is provided below, with the program leaders (PIs) in brackets.

Programs:

1. Cardiomyopathy (Prof. Stephane Heymans)
2. Mitochondrial disease (Prof. Bert Smeets)
3. ECM + Wnt signalling (Dr Matthijs Blankesteijn)
4. Arrhythmogenesis and cardiogenetics (Dr Paul Volders)
5. Clinical heart failure (Prof. Hans Peter Brunner-La Rocca)
6. Intermediate cardiac metabolism (Prof. Jan Glatz)
7. Gene regulation (Prof. Leon de Windt)
8. Electro mechanics (Prof. Frits Prinzen)
9. Cardiovascular system dynamics (Prof. Tammo Delhaas)
10. Clinical atrial fibrillation (Prof. Harry Crijns)
11. Experimental atrial fibrillation (Prof. Uli Schotten)
12. Surgical intervention (Prof. Jos Maessen)

The programs in 'Cardiac Function and Failure' focus mainly on the early diagnosis and treatment of cardiac disease, and mainly take a translational approach. Collaborations between programs in theme II are strong, not only sharing common facilities but also common ideas and themes. Likewise, common research themes, clustered around hypercoagulation, vascular dysfunction and inflammation represent the cooperation between Theme II and the other two themes within CARIM (see below Programs and Highlights).

B.2.3 Research environment and embedding

One of the main suggestions made by the previous ERC was to strengthen the heart failure profile both in the clinical and basic research lines. During the last five years the heart failure (HF) basic research line has gone through a major remodelling phase. Before 2008, PIs in the area of cardiology worked separately in different small labs. Since 2008 heart failure research has been strengthened through an alliance between the HF-PIs in Cardiology, including Prof. Leon de Windt, Dr Paul Volders, Prof. Hans Peter Brunner-La Rocca and Prof. Stephane Heymans. Together they have formed the 'Greater Cardiology Lab' (GLC), sharing space, facilities and expertise, leading to a lab staffed by over 40 people. Future growth has been assured by the assignment of tenure tracks to Dr Blanche Schroen and Dr Paula da Costa Martins. This has led to an increase in grants and scientific output as well as the development of new programs, including RNA and sarcomeres in HF (Prof. Leon de Windt), sudden death in HF (Dr Paul Volders), and inflammation and extracellular matrix (Prof. Stephane Heymans). In line with the suggestions of the ERC, the clinical program of HF has grown and has a particular focus on non-ischaemic, non-valvular cardiomyopathies, a multidisciplinary approach to heart failure management, and database implementation (Prof. Hans Peter Brunner-La Rocca). This development has guaranteed fertile ground on which to develop the translational axis in heart failure. Database management and biobanking is growing towards maturity under the supervision of our HF specialist, Prof. Hans Peter Brunner-La Rocca. Clinical heart failure has been further strengthened by attracting a clinical cardiologist with expertise in the pathology of the thick heart, i.e. diastolic heart failure (Dr Vanessa van Empel).

The ventricular arrhythmia program of Dr Paul Volders has developed into a full translational program including biophysical, molecular and cellular electrophysiology studies, modelling studies as an integrated program with the Department of Knowledge Engineering (DKE), a translational program in the Electro Physiology lab investigating completely novel diagnostic electromechanical TDP mechanisms (also linking to the AF program), and a clinical cardiogenetics program with national coverage (ICIN) as well as local integration with clinical and molecular genetics. The latter is now reinforced by the acquisition of Prof. Monika Stoll (CARIM) and Prof. Han Brunner (Dept. of Clinical Genetics) with several postdocs devoted to cardiogenetics including genetics of monogenetic cardiac diseases as well as complex genetics.

The clinical EP program includes advanced mapping and ablation of AF and ventricular arrhythmias VT/VF, implementation of new technologies and imaging of the atrial anatomy and vascular disease using CT angiography (Prof. Joachim Wildberger and Prof. Harry Crijns) and ventricular substrate using cardiac MRI (Prof. Joachim Wildberger, Radiology and Dr Bas Bekkers, Cardiology)

The dyssynchrony program has developed into a robust translational research line - Electrical Management of Heart Failure - headed by Prof. Frits Prinzen of the Physiology Department in cooperation with Prof. Tammo Delhaas of the Department of Biomedical Engineering and the Department of Knowledge Engineering. This axis has been reinforced significantly, focusing on biomedical modelling. In addition, the translational axis has been installed through a connection with molecular biology (Prof. Leon de Windt). Above all, in line with a long tradition, extensive mechanistic clinical studies as well as translational clinical trials are embedded in the Department of Cardiology (Prof. Harry Crijns).

The AF program has been further developed in a robust integrated fashion with Physiology as the central department (Prof. Uli Schotten), and embedded in Cardiology (Prof. Harry Crijns) and Cardiothoracic Surgery (including a hybrid operating room, for extensive electrical mapping and ablation studies including biobanking opportunities, Prof. Jos Maessen) and linked to the Departments of Biomedical Technology and Knowledge Engineering. In addition, it has been firmly embedded in the Maastricht Study, focusing on prediction of atrial instability and AF in a patient population at vascular risk. The AF research group is now fully integrated into the international and national scientific community. As mentioned above, clinical and preclinical research centres on non-invasive characterisation of the atrial substrate in AF operate in an integrated fashion. Epidemiological research and the construction of patient cohorts including a blood and CT angiography bio-bank (Prof. Marja van Dieijen, Prof. Joachim Wildberger and Prof. Harry Crijns) form the clinical basis of the integrated clinical/preclinical research program. Imaging facilities are also being used for atrial imaging (scintigraphic, Prof. Joachim Wildberger and Prof. Felix Motthagy) and MRI (Prof. Joachim Wildberger) but need further development. The translation of AF knowledge to patient care has been accommodated in the newly-built outpatient department of the HVC. Integrated catheter and surgical ablation of AF has been developed on the opening of our hybrid operating theatre (Prof. Jos Maessen, Prof. Michael Jacobs and Prof. Harry Crijns), leading to a unique hybrid approach to AF ablation which has been the subject of extensive international interest.

The clinical research facility CardioResearch MUMC+ within Theme II is headed by Dr Bas Kietselaer, general and imaging cardiologist responsible for all clinical trials both investigator-initiated as well as industry-driven studies. At our CVC, both the inpatient and outpatient departments accommodate the patient flows needed for such trials providing uniformity of diagnosis and management through care pathways. The Clinical Trial Centre Maastricht (CTCM) embeds all clinical research activities ensuring that research is performed according to GCP and GLP norms, and providing state-of-the-art research facilities.

B.2.4 Quality and scientific relevance

Quality and scientific relevance are apparent from the scientific output and earning power (publications in top journals, the number of large grants and grants, honours, patents) reported in part A of this self-evaluation report.

In the most recent CWTS analysis (2007-2010) the publications of CARIM line II 'Cardiac Function and Failure' are cited 1.95 times more frequently than the world average. In the fields of cardiology and the cardiovascular system, Maastricht UMC+ scores the highest MNCS of all Dutch UMCs (1.90). Articles from the CARIM's Department of Cardiology are even cited 2.67 times more often than the world average.

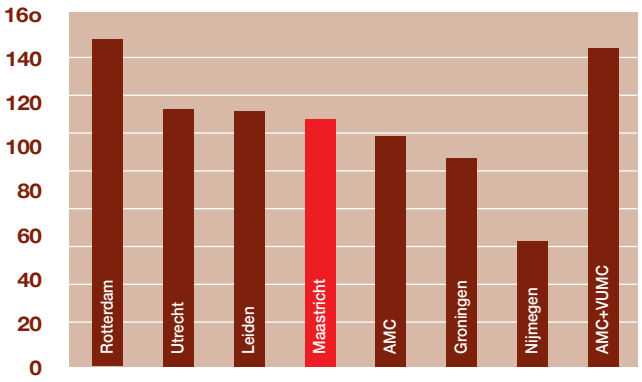
Table 2: Bibliometric analysis CARIM Theme II 2007-2010

Theme II Cardiac Function and Failure	P	CPP	MNCS	MNJS
2004-2007	457.50	9.68	1.37	1.34
2005-2008	465.00	11.10	1.46	1.37
2006-2009	472.75	12.90	1.71	1.49
2007-2010	518.75	12.55	1.95	1.51

P: Number of articles. **CPP**: Average number of citations per publication (p), without self-citations. **MNCS**: The impact of a research unit's articles, compared to the world citation average in the subfields in which the research unit is active. **MNJS:** the impact of the journals in which a research unit has published compared to the world citation average in the subfield covered by these journals.

Quality parameters for the research staff within Cardiac Function and Failure, such as the Hirsch-factor and m-index have also been analysed and indicate that most PIs in Cardiac Function and Failure rank highly. A Web of Science benchmark for item Cardiac/Cardiovascular (the main publication area for theme II) shows that Maastricht UMC+ ranks higher concerning number of publications and h-index per UMC than 4 other UMCs (AMC, Groningen, VUMC and Nijmegen), and is equal to Utrecht and Leiden. Only Rotterdam scores higher.

Figure 3: H-index in Web of Science for 'Cardiac/Cardiovascular Systems' per Dutch UMC



B.2.4.1 Programs and Highlights

Cardiomyopathy (Program 1)
PI: PROF. STEPHANE HEYMANS

Prof. Stephane Heymans heads a trans-disciplinary clinical program on viral and inflammatory cardiomyopathies. In the clinic, cardiologists, immunologists, microbiologists, and pathologists are brought together to study the role of inflammation, matrix remodelling and cardiomyocyte biology in non-ischaemic cardiomyopathies (also dilated or idiopathic cardiomyopathies). On the experimental level, a strong molecular program examines the contribution of matrix proteins and non-coding RNAs in inflammation and cell-to-cell communication in these diseases.

Knowledge obtained from basic research is continuously translated to human pathology and vice versa, in order to relate preclinical findings to molecular, functional and structural observations in human hearts. Strategic strengthening of the program lies in further collaboration with bordering fundamental programs to exchange materials and techniques to study cell-to-cell communication (Dr Matthijs Blankesteijn), and microRNA biology (Prof. Leon de Windt).

Prof. Stephane Heymans's translational work within this field of non-ischaemic CMPs has resulted in an increasing number of personal, national and European collaborative projects (2012 and 2013). He has become principal investigator and work package leader in 5 FP7 European projects, and in 1 national CVON-NHS collaborative project. Importantly, these EU projects and personal grants are all translational projects allowing him to collect patient data and cardiac samples in metabolic risk-induced HFpEF (FP7-MEDIA 2011 and FP7-Homage 2013), toxic (FP7-Hecatos 2013) and viral CMP (VIDI and FP7-Homage).

Highlight: idiopathic and non-ischaemic CMPs
A strong computational-biology environment serving the ambitions of systems biology of the topic of idiopathic cardiomyopathies will be developed (Prof. Stephane Heymans, Dr Paul Volders). One major challenge of this program will lie in translating the new fundamental insights into new clinical treatment avenues for patients with viral myocarditis and cardiomyopathies by regional, national, and international collaboration by means of starting a multicentre clinical trial aimed at achieving personalised treatment for this patient group. Existing local expertise in designing multicentre trials is present in the clinical heart failure program (Prof. Hans Peter Brunner-La Rocca). A cohort of over 600 patients with a long-term follow-up, and a biobank including blood, DNA and cardiac samples, is the growing result of this work. As such, knowledge obtained in basic research is continuously translated to human pathology and vice versa, in order to relate preclinical findings to molecular, functional and structural data in human hearts.

Highlight: Matricellular proteins and heart failure
Two important systems in the matrix are the structural proteins such as collagens, and the non-structural proteins, the matricellular proteins. The primary aims of this program include the unravelling of the implication of the matricellular proteins at the level of each individual cardiac cell: inflammatory cells, fibroblasts, cardiomyocytes and endothelial cells. The molecular mechanisms by which these matricellular proteins alter cardiomyocyte survival/hypertrophy, promote matrix maturation, and prevent adverse inflammation will be addressed. We aim to find out which are the molecular partners on the cell membrane that regulate protective effects on cardiomyocyte survival, the downstream signalling cascade and the resulting changes in hypertrophy, inflammatory and fibrotic targets.

Highlight: Inflammation-mediated microRNAs and cardiac disease (Senior Investigator Dr Blanche Schroen)
Over the last 3 years, because of her interest in cardiac inflammation and heart failure, Dr Blanche Schroen has opened a completely new area of research, investigating the as yet unknown role for inflammation-related, non-coding RNAs in heart failure in general, and viral myocarditis in particular. A major microarray analysis of microRNAs was performed at varying time points during the course of viral myocarditis, pressure overload and dilated cardiomyopathy in both mice and humans; in this way major inflammation microRNA signals were unravelled, and novel microRNA targets implicated in cardiac inflammation and heart failure identified. The overall objective of this research line is to unravel the precise biological role of specific inflammation-mediated microRNAs and their regulation

in cardiac injury and dysfunction following viral infection, and in hypertrophy and fibrosis during hypertensive heart disease. Whereas recent studies have mainly focused on the role of cardiomyocyte- and fibroblast-derived microRNAs in hypertrophy, fibrosis and arrhythmias, this program will unravel the biological role of the inflammation-derived microRNAs in cardiac disease. By combining microRNA knockout animal experiments, the use of antagomirs, and in vitro studies, this program *is currently addressing* the role of particular inflammation-derived microRNAs in both hypertensive heart disease and viral myocarditis. It is expected that inflammation-mediated microRNAs play a crucial role in the susceptibility to cardiac injury following viral infection of the heart, and mediate hypertrophy and fibrosis during hypertension.

Mitochondrial disease (Program 2)
PI: PROF. BERT SMEETS

Prof. Bert Smeets heads the Genome Centre Maastricht and his research in clinical genomics focuses on mitochondrial disorders (research schools CARIM and GROW). His group Clinical Genomics, consists of more than 60 FTE, two-thirds of whom are involved in diagnostics and one-third in scientific research and activities of the Genome Centre, embedded in CARIM, GROW and MH&NS. A number of staff members play a key role in the CARIM research line. First, Dr Arthur van den Wijngaard is responsible for the multiple parallel sequencing of cardiomyopathy genes, explaining the genetic variation with respect to RNA levels and processing, protein function (lamin A/C) and phenotypic manifestation and establishing iPS technology. Dr Patrick Lindsey is a bioinformatician and responsible for data handling and analysis of transcriptomics, CHIP-based and next generation sequencing experiments to convert huge data sets into relevant biological and clinical information. Finally, Dr Jos Broers, cell biologist from the group of Prof. Frans Ramaekers, is an expert on cellular studies of normal and mutated lamina A/C and other interfilament proteins, and is involved in the follow-up studies of the patients with mutations.

The cardiogenetics team consists of the clinical molecular geneticists Dr Arthur van den Wijngaard and Prof. Bert Smeets, the clinical geneticist Dr Ingrid Krapels, and the cardiologists Prof. Stephane Heymans and Dr Paul Volders.

Highlight: full power genomics
The full power of genomics technology is implemented to elucidate the role of quantitative (sequence analysis) and qualitative (RNASeq and copy number variants) genetic defects in mitochondrial and structural heart genes in mitochondrial syndromes and inherited cardiomyopathies. The pathophysiological processes are characterised in further detail by transcriptomics, bioinformatics and functional studies, using patient-derived cell lines (fibroblasts and iPS cells) and Zebrafish models. Novel treatment strategies are being developed based on gene-specific compounds and stem cells (pericytes). MUMC+ is a national reference centre that each year carries out an ever increasing number of tests for mitochondrial diseases (600-700) and cardiovascular diseases (2500-3000), resulting in unique large and available patient cohorts in Maastricht. Advances in molecular and clinical genetics have yielded large numbers of genes involved in hereditary mitochondrial diseases, cardiomyopathies and heart failure. Key pathological mechanisms are related to defects in mitochondrial energy production and structural proteins (sarcomeric proteins or intermediate filaments). It has been demonstrated that these mechanisms interact and defects in structural heart proteins can also have a negative secondary effect on mitochondrial function. Rapid progress in genomics technologies allows screening of multiple genes in parallel, enabling characterisation of the genetic background of complete systems (mitochondria, sarcomere) rather than single proteins. Elucidation of often multiple highly penetrant genetic defects and the pathophysiology in relatively rare genetically affected patients will also generate new concepts to explain more common forms of cardiomyopathy and heart failure.

ECM + Wnt signalling (Program 3)
PI: DR MATTHIJS BLANKESTEIJN

Dr Matthijs Blankesteijn is Assistant Professor of Pharmacology at CARIM. His main research interests are the identification of novel pathological mechanisms for cardiovascular diseases and the development of intervention in these targets.

As an example, expansion and thinning of the infarct area is one of the major causes of heart failure as it results in excessive dilation of the entire ventricle. The

current pharmacotherapy focuses more on the surviving myocardium than on the infarcted area itself, leaving opportunities for targeted interventions to prevent infarct thinning. To address this issue, we have extensively studied the process of wound healing after myocardial infarction and found a pivotal role for the myofibroblast in the prevention of excessive dilatation of the infarct area. These cells are capable of generating a sustained contractile force in the scar and subsequently can deposit extracellular matrix to replace fibres that were damaged due to the repetitive stress imposed on the infarct. When studied in time, myofibroblast numbers peak at 1-2 weeks post-MI and decline over subsequent weeks. We have recently studied signalling pathways that can preserve the myofibroblasts in the infarcted area.

A promising signalling pathway is the Wnt/frizzled pathway. This pathway is known to be active in cardiac development but is silent in the adult heart. The pathway is reactivated during myocardial remodelling, particularly after infarction. In collaboration with the Biochemistry department (Prof. Tilman Hackeng) and Pepscan N.V. in Lelystad (Prof. Peter Timmerman) we are working on peptides that can modulate the activity of the Wnt/frizzled signalling pathway. The first peptide, UM206, significantly improved the outcome of infarct healing in mice and rats and was able to prevent the development of heart failure, which was paralleled by higher myofibroblast numbers in the infarct area. Apart from Wnt/frizzled signalling, other interventions that have similar effects on infarct dilatation were also found to have a positive effect on myofibroblast numbers, including intermittent pacing (collaboration with Prof. Frits Prinzen, CARIM and Prof. Dirk Duncker, Erasmus Medical Centre, Rotterdam) and administration of growth hormone in a biodegradable alginate matrix (Prof. Theofilos Kolettis, University of Ioannina, Greece). We are currently investigating a role for miRNAs in this process (collaboration Prof. Leon de Windt).

Highlight: Cytokine biomarkers

One of the lessons learned in the development of novel therapeutic strategies is that biomarkers should be available to monitor the effect of the therapy on the disease process. This is particularly relevant in heart failure, as the disease progresses relatively slowly and trials have to run for many months or even years. To this end, we initiated a biomarker discovery project with specific focus on biomarkers for inflammation, a hallmark process of cardiac remodelling. We identified a family of related cytokines that is upregulated in animal models of myocardial infarction and pressure overload-induced hypertrophy. In subjects with left ventricular dysfunction, obtained from the FLEMENGHO cohort (collaboration Prof. Jan Staessen, KU Leuven and UM), the circulating levels of the cytokines were proportional to the severity of the condition. We are currently planning to expand these observations in HFpEF vs. HFrEF patients (collaboration with Dr Vanessa van Empel and Prof. Hans Peter Brunner-La Rocca).

Arrhythmogenesis & Cardiogenetics (Program 4)

PI: DR PAUL VOLDERS

Dr Paul Volders, MD, PhD, FESC is cardiologist and Principal Investigator at CARIM. He is a clinician-scientist with a focus on translational cardiology. He coordinates the cardiogenetic care of patients with inherited heart disease, notably inherited arrhythmias and structural cardiomyopathies. Within this clinical-experimental environment he leads an active research program to gain novel pathogenic insights into ventricular arrhythmias and sudden cardiac death. As PI, he leads a team of 10 people with a special interest in translational cardiology, notably ventricular arrhythmogenesis and sudden cardiac death. He has coached 4 PhD candidates to their doctorate, and currently supervises numerous other postdoctoral and PhD projects. To date, Dr Paul Volders is first or co-author on >70 peer-reviewed original papers, reviews and book chapters.

Traditionally, the Volders team has focused on the electrophysiological characterisation of arrhythmia substrates in inherited channelopathies and cardiomyopathies, and acquired cardiac overload. While these studies continue at the cellular, intact-animal and patient level, research activities are increasingly being directed at (1) intracellular signalling pathways determining ion channel function; (2) the genetic and genomic basis of cardiac arrhythmias; and (3) systems biology to integrate the basic molecular and functional determinants of arrhythmia syndromes with the clinical characteristics of individual patients, in order to provide better risk management and treatment.

Highlight: Predicting sudden death
The project Predicting Sudden Cardiac Death (CVON) focuses on new molecular genetic causes of ventricular fibrillation and sudden death. It will lead to advanced diagnosis and treatment of patients and family members harbouring mono- or polygenetic VF mechanisms. The South-Limburg founder population on SCN5A-mutatin delPhe1617 with a high incidence of sudden death provides the opportunity to study new genetic modifiers for VF and sudden death.

Clinical heart failure (Program 5)
PI: PROF. HANS PETER BRUNNER-LA ROCCA

Prof. Hans Peter Brunner-La Rocca heads the clinical HF program and is Vice Chairman of the Department of Cardiology, where he is responsible for the organisation of the clinic. He was trained as a specialist in internal medicine and Cardiology in Switzerland, spent a postdoc period in Melbourne, Australia and headed the HF and heart transplant program in Basel, Switzerland. There, he led the TIME-CHF study, a multicentre trial investigating the effects of NT-proBNP guided therapy in HF (>15 publications as first/senior author, i.e. JAMA 2009). Moreover, he performed several investigator-initiated clinical trials on pathophysiology and on prognosis in cardiovascular disease, mainly HF, as well as several clinical research activities in interventional cardiology and echocardiography. In September 2009, he was appointed as full professor of clinical HF at Maastricht University.

The research interest of his group is focused on personalised medicine in patients with HF. The group is developing new means to use biomarkers to more specifically target medical therapy in patients with HF, by using mathematical modelling based on data including multiple biomarkers from TIME-CHF. The group is collaborating with the Department of Knowledge Engineering at Maastricht University. The findings are validated on data from other biomarker-guided trials, with the aim of developing new concepts that can be tested first in a phase II study (beginning 2015), and, if positive, later in a phase III study using a multiple biomarker approach to personalise HF care. In this regard, the group is collaborating locally with several groups in CARIM (see below) and internationally with most groups that have conducted (NT-pro) BNP guided trials in HF and with large European consortia (fp7-HOMAGE, fp7-MEDIA). The group is also investigating telemedicine in HF (INTERREG IVb program).

Since personalised medicine in a complex chronic disease such as HF should address different aspects of care – an often neglected part of HF care – the second main research topic of the group is investigating current practice in HF care. This includes investigation of co-morbidities such as cognitive impairment, which is conducted with four other centres in the Netherlands and, locally, with neurology (Prof. Robert van Oostenbrugge) as part of a CVON-NHS project (HBC).

The group is currently developing a new approach to clinically diagnosing and treating patients with HF and preserved ejection fraction. Our hypothesis is that a broad range of disorders may result in HFpEF. Within the comprehensive database to be built, clinical (Prof. Harry Crijns, Marc Spaanderman) and preclinical researchers (e.g. Prof. Leon de Windt, Prof. Stephane Heymans, Dr Matthijs Blankesteijn, Prof. Harald Schmidt) will collaborate. A special cooperative project has been started with gynaecology (Marc Spaanderman) for investigating preeclampsia patients (which may be at risk for HFpEF).

Intermediate cardiac metabolism (Program 6)
PI: PROF. JAN GLATZ

Prof. Jan Glatz was trained in chemistry, biochemistry and physiology and has ample experience in studying cardiac energy metabolism in the healthy and diabetic heart, with a focus on membrane substrate transporters and their application for so-called metabolic modulation therapy. With his group he has disclosed the pivotal role of protein-mediated substrate (glucose, fatty acids) uptake in regulating myocardial substrate utilisation and the need for a proper balance of these substrates for optimal energy production and cardiac functioning. Malfunctioning of this balance is associated with chronic cardiac disease (and vice versa).

The aim of the intermediate cardiac metabolism program is to disclose the mechanisms underlying the process of

metabolic adaptation and maladaption and its relation to cardiac dysfunction in pathophysiological conditions such as diabetic cardiomyopathy (DCM) and Wolff-Parkinson-White (WPW) syndrome (glycogen storage disease). DCM is common in type 2 diabetes and results from the adaptation of the insulin-resistant heart towards an increased utilisation of fatty acids for energy production, at the expense of glucose. The increased fatty acid uptake rate leads to intracellular accumulation of lipids and toxic lipid intermediates (lipotoxicity) which aggravate insulin resistance (further diminished glucose uptake) and mitochondrial function, leading to severe cardiac dysfunction. Central to the research program are (i) the roles of external and environmental factors (cytokines, high-fat diet, etc.) in the development of DCM, and (ii) the development of strategies to normalise the substrate balance in the diabetic heart, i.e., lower fatty acid uptake and increase glucose utilisation ('metabolic modulation'), by manipulating the sarcolemmal presence and activity of substrate transporters for fatty acids and for glucose, and by reducing the adverse effects of substrate intermediates on mitochondrial function. In the WPW syndrome glycogen utilisation is impaired which becomes manifest in a markedly reduced flexibility of cardiac function. The hypothesis that this is the result of a defect in the interaction between AMP kinase and glycogen is being studied.

Highlight: genes, mitochondria and heart failure
Future aspects relate to (i) genetic and epigenetic control of cardiac metabolism (e.g. cytokines, microRNAs), and (ii) elucidating the derailment of cardiac energy metabolism (especially mitochondrial function) in heart failure and applying interventions to improve cardiac mitochondrial function in heart failure. Studies will be performed in isolated cells, perfused hearts, (transgenic) rodents and humans.

Gene regulation (Program 7)
PI: PROF. LEON DE WINDT

Prof. Leon de Windt obtained a Master's degree in Molecular Biology and biochemistry at Utrecht University in 1994 and a PhD in Cardiovascular Physiology at Maastricht University in 1999. Subsequently, he received an American Heart Association Fellowship for a postdoctoral residence at the Howard Hughes Medical Institute of Prof. Jeffery D. Molkentin in Cincinnati OH, USA where he studied various signalling mechanisms in cardiac remodelling. In the early phase of his career as group leader at the Hubrecht Institute in Utrecht (Director Prof. Hans Clevers), his research interests shifted to the pro-hypertrophic mechanisms of calcineurin-responsive transcription factors. In mid-2010, he was appointed as full professor of Molecular Cardiology at CARIM. His research lines (www.dewindtlab.com) provide fundamental explanations for altered gene expression profiles during pathological left ventricular hypertrophy (LVH) as the main biologically pathogenic process in heart failure by studying transcriptional regulators in heart muscle.

Additionally, his laboratory has demonstrated interest in microRNAs (miRNAs), a class of endogenous, small non-coding RNAs, which suppress protein expression by either messenger RNA degradation or translational inhibition. Each miRNA potentially targets multiple transcripts, suggesting that miRNAs, not unlike transcription factors, play a fundamental role in regulating gene expression. Using a functional genomics platform with cellular imaging and automated segmentation analyses, his laboratory has recently extended the discovery pipelines for miRNAs and its direct target genes as regulators of agonist-induced cardiomyocyte hypertrophy, cardiomyocyte autophagy and cardiac endothelial cell proliferation/migration as disease processes in LVH. RNA-seq and analytical pipelines are used to detect direct target genes in these new disease processes. The validity of the identified candidates for the complexity of heart disease in vivo is being studied using genetically modified animals for miRNAs and their target genes. Examples of this work were published in Nat Cell Biol and Cell Metab in 2013. Apart from fundamental, posttranscriptional gene regulatory mechanisms, miRNAs also provide excellent drug-able disease targets by their central function in disease mechanisms and their evolutionary conservation.

As scientific objectives in this research program, a multidisciplinary approach is used, combining diagnostics, (RNA) sequencing and genome-wide association studies in (heart failure) patient cohorts, computer modelling, bioinformatics, cellular biology, mouse genetics, in vivo imaging tools and physiological techniques to provide in-depth molecular information on the role of several embryonic transcription factors in adult onset cardiac remodelling and

heart failure (research line 1); to perform a multidisciplinary, systems biology approach to provide mechanistic insight into the role of non-coding RNA in the genesis of heart failure with specific attention to heart failure with preserved ejection fraction (HFpEF) (research line 2); and to use a multidisciplinary approach to obtain mechanistic insight in the control of microRNAs on mitochondrial function in heart failure and skeletal muscle disorders (research line 3).

Highlight: microRNAs as modulators of mitochondrial function in heart failure and skeletal muscle disorders (cf. research line III above)
MicroRNA mechanisms regulate mitochondrial biogenesis and cardiac function (el Azzouzi et al. Cell Metabolism 2013) through influencing mitochondrial respiration, energy production and/or redox potential in skeletal muscle and potentially also in heart muscle (cooperation with NUTRIM, Dr Patrick Schrauwen). We aim to uncover the intracellular mechanisms of how mitochondria are influenced by non-coding RNAs. In addition, chemically modified antisense oligonucleotides will be used as silencers of endogenous microRNA genes for “mitochondrial” microRNAs which may yield novel therapeutic treatments in experimental mouse models of cardiac or skeletal muscle disorders.

Electro mechanics (Program 8)
PI: PROF. FRITS PRINZEN

Prof. Fritz Prinzen is recognised as world expert on the pathophysiology and physiology of pacing therapies. His papers in the 1990s on the mechanical consequences of electrical asynchrony paved the way to the development of Cardiac Resynchronisation Therapy (CRT) and to the search for better pacing sites. Likewise, the articles on ventricular remodelling induced by asynchronous activation are a basis for understanding of the molecular abnormalities in asynchronous hearts and the long-term benefits of CRT. More recent work provided the first evidence of the benefits of endocardial CRT, LV apical and LV septal pacing and of pacing pre- and post-conditioning.

In the research group, Prof. Frits Prinzen collaborates with Prof. Tammo Delhaas, paediatric cardiologist and currently Chairman of the Department of Biomedical Engineering (BME). Prof. Tammo Delhaas is a renowned expert on paediatric pacing. A collaborative article on LV apical pacing by Prof. Tammo Delhaas and Prof. Frits Prinzen was published in 2007 in the New England Journal of Medicine and convinced many implanters of pacemakers in children to position the pacing lead at the LV apex. In collaboration with Prof. Janousek (Prague), Prof. Tammo Delhaas has conducted a worldwide multicentre study on the optimal pacing site in children. Within his BME group he is also heavily involved in studies on mathematical modelling of the heart and circulation. An important and innovative approach that has been developed is the CircAdapt model. This is a multi-scale model that simulates beat-to-beat cardiovascular mechanics and haemodynamics, using physical/physiological principles.

Current research
Abnormal, asynchronous electrical activation of the ventricles originates from intrinsic conduction abnormalities, such as left bundle branch block, and from ventricular pacing. Such electrical abnormalities (dyssynchrony) lead to a variety of derangements: local differences in myofibre shortening and workload, reduced pump function, local and global remodelling. The research in this program pays attention to scientific applications and clinical problems and opportunities of these consequences of asynchrony: (1) Improve CRT for patients with reduced pump function; (2) Search for pacing site(s) that are best for adult and paediatric patients requiring anti-bradycardia pacemaker therapy ; (3) Consequences of conduction abnormalities developing during Transcatheter Aortic Valve Implantation (TAVI); (4) Electrical remodelling due to mechano-electrical feedback in normal and failing hearts; (5) Intermittent ventricular pacing for cardioprotection: mechanisms and applications.

Highlight: Improving TAVI (see research line 3 above)
TAVI is a novel way to replace a dysfunctioning aortic valve that does not require open chest surgery. For this reason it is extremely promising. However, one of the frequently occurring complications is the development of left bundle branch block (LBBB) or AV-block during TAVI. In 2012, our research group has demonstrated that TAVI-induced LBBB is an independent determinant of mortality during follow-up

after TAVI. Currently, the group investigates the cause of this increased mortality (heart failure, arrhythmias) and how conduction abnormalities can be prevented.

Highlight: Heart memory to improve CRT
In a combination of animal experimental, clinical and computer simulation studies we are investigating the idea that local action potential duration is regulated by local stretch or workload. Such a regulation by mechano-electrical feedback (MEF) could explain phenomena such as the T-wave being concordant with the QRS complex and the T-wave memory after stopping ventricular pacing. Implications for the presence or absence of MEF for cardiac function and arrhythmia are being investigated. Moreover, recent results indicate that the T-wave morphology is an independent predictor of response to CRT, indicating also implications of abnormal action potentials for pump function.

Cardiovascular system dynamics (Program 9)
PI: PROF. TAMMO DELHAAS

Prof. Tammo Delhaas obtained his MD at the University of Groningen in 1988. He received his PhD degree from Maastricht University in 1993 on the basis of a thesis on cardiac mechanics under normoxic and ischaemic circumstances. He was trained in Paediatrics at the University Hospital Maastricht and at the Wilhelmina Children's Hospital in Utrecht and qualified as a paediatrician in 1997. He received a Fulbright grant and an ICIN Fellowship to spend one year in 1996/1997 at the Departments of Bioengineering and Medicine at the University of California at San Diego, USA. In 1997 he joined the Department of Physiology on a part-time basis. In the remaining time he was trained in paediatric cardiology at the University Hospital Aachen, Germany, and the Royal Children's Hospital in Melbourne, Australia. In 2000 he qualified as a paediatric cardiologist, was appointed as a clinical fellow of the Netherlands Heart Foundation, and got a full-time appointment at the Departments of Paediatrics and Physiology. In 2009 he was appointed professor and chair of Biomedical Engineering at Maastricht University. Prof. Tammo Delhaas is heading the CardioVascular Systems Dynamics Research Group (CVSDRG) and as such he is involved in projects related to cellular, vascular and cardiac mechanics, cardiac pacing, and mathematical modelling of the heart and circulation.

With clinical questions regarding acquired and congenital heart disease in mind, research in the CVSDRG focuses on the following subjects: asynchronous electrical activation, aortic stenosis, vascular and myocardial structure-function relation, myocardial adaptation, and computer-model assisted diagnosis and treatment of cardiac failure, pulmonary hypertension and congenital heart diseases. Besides standard expertise, the CVSDRG uses the following techniques / models in which according to international standards it has expertise of extraordinary quality.

Highlight: CircAdapt, science and education
CircAdapt is a lumped parameter mathematical model of the human heart and circulation. It enables real-time simulation of cardiovascular system dynamics in a wide variety of physiological and pathophysiological situations. The entire cardiovascular system is modelled as a concatenation of modules representing cardiac chambers, valves, blood vessels, and peripheral vascular beds. A unique feature of the CircAdapt model is that it includes structural adaptation of the vascular and myocardial tissues to the mechanical load generated by the model itself. Using this model we can: a) derive information that otherwise could only be obtained invasively, e.g. pulmonary artery pressure; b) evaluate the effect of induced and non-induced electrical asynchrony in the normal heart as well as in pathological conditions such as pulmonary hypertension; c) explore mechanisms of dyssynchronous heart failure and of its treatment with CRT; and d) evaluate the effectiveness of proposed surgical and drug treatment in acquired and congenital heart disease beforehand thus enabling the best decisions to be made.

Clinical Atrial fibrillation (Program 10)
PI: PROF. HARRY CRIJNS

Prof. Harry Crijns is head of the Department of Cardiology of the MUMC+ in Maastricht. He heads the clinical electrophysiology group focusing on atrial fibrillation and ventricular arrhythmias and sudden death. The clinical department is an internationally renowned AF referral centre and a training centre for AF management. Over the past decade his group has introduced innovative concepts for

the diagnosis and treatment of the vascular risks of patients with AF. Quite contrary to longstanding beliefs, the group has shown that electrical management of AF may not be beneficial at all. This has revolutionised management of the arrhythmia worldwide with the effect that major interventions such as electrical cardioversion, catheter ablation and antiarrhythmic drug therapy are being applied in a much more personaliszed fashion. Subsequently, his group has shown that rate control in AF can be individualised thereby removing the previously used strict heart rate targets from the international guidelines. He also carried out the Euro Heart Survey on AF and has made many contributions to the field of stroke management in AF, such as the construction of well-recognised AF specific-risk stratification scores for AF progression (HATCH), ischaemic stroke (CHA2DS2-VASc) and major bleeding (HAS-BLED). These scores have practically conquered the medical AF community and improved patient care whilst boosting new clinical research throughout the world. Within his international network he has studied stroke prevention in AF using non-antithrombotic antiarrhythmic medication.

Highlight: AF a vascular disease

Clinical AF research in MUMC+ now focuses on comprehensive AF management, hybrid AF ablation and vascular mechanisms for AF progression in AF. A firm collaboration exists with Prof. Uli Schotten at physiology and Prof. Hugo ten Cate (Theme I, Clinical Thrombosis and Haemostasis) and research on *AF a vascular disease* concentrates on the role of thrombin activation in electrical and structural remodelling in patients with lone AF or AF associated with minimal heart disease (early AF). National collaboration on this topic exists with Prof. I. van Gelder at UMCG, and internationally with Münster (G. Breithardt), Birmingham (P. Kirchhof) and Hamburg (K-H. Kuck, K. Wegscheider).

Highlight: Early and comprehensive management of AF

Following a pilot study which showed decreased morbidity and mortality in AF patients when managed within an integrated chronic care program, a national multicentre clinical trial (RACE-5) including a biobank, will corroborate these results and show that AF progression, mental deterioration and MACCE will be ameliorated in this innovative care program. In a multicentre international trial (EAST), early comprehensive rhythm control is being compared with standard rate or rhythm control in complex AF patients. These landmark trials may help improve patient management and at the same time form a platform for extensive phenotyping patients and enhance personalised AF therapy.

Experimental Atrial Fibrillation (Program 11)

PI: PROF. ULI SCHOTTEN

Prof. Uli Schotten studied medicine at the universities of Aachen, Glasgow and Valetta. He graduated from Aachen University in 1995. After training in cardiology for 4 years he joined the Dept. of Physiology at Maastricht University in 1999. He received a PhD in physiology at Maastricht University in 2003 and the Venia Legendi in Experimental Cardiology in 2004 (title: “Adaptive mechanisms of excitation-contraction coupling in the heart”). In 2004, he worked as research fellow at the Dept. of Cardiology of the Cleveland Clinic, Ohio, USA where he was trained in cellular electrophysiology. Since 2007 he has been principal investigator of the research line “Pathophysiology of atrial fibrillation”. In 2011, he was appointed a full professor of cardiac electrophysiology. Main research topics are: Adaptation processes of excitation-contraction coupling in ventricular and atrial myocardium, development of antiarrhythmic drugs, regulation of ion channel activity by intracellular signalling pathways and local microdomains, substrates for the perpetuation of atrial fibrillation, and non-invasive techniques for classification of atrial fibrillation.

Highlight: Classification of AF based on invasive and non-invasive quantification of the AF substrate complexity

The objective of this research line is to develop new diagnostic tools allowing for classification of AF. In order to enable patient-tailored treatment of AF with antiarrhythmic drugs and catheter ablation, algorithms for fully automated quantification of the AF substrate complexity based on direct contact fibrillation electrograms are being developed. The clinical relevance of this complexity quantification is validated in patients undergoing cardiac surgery by comparison to established scoring methods such as clinical risk profiles and rhythm follow-up of the patients. The

development of non-invasive or semi-invasive surrogate parameters for the complexity of the AF substrate will allow for broad scale use of the AF classification in clinical practice and has become a central research activity of the group. In order to valorise this research activity, Ulrich Schotten obtained a research grant from the Netherlands Genomic Initiative with the goal to launch a spin-off company (YourRhythmics BV) offering hardware and software solutions for non-invasive quantification of the AF complexity using complex signal analysis of an extended set of ECG recording including several oesophageal leads.

Surgical intervention (Program 12)
PI: PROF. JOS MAESSEN

Prof. Jos Maessen heads the department of Cardiothoracic Surgery and is full professor at the MUMC+. His major research goal is to give as many of the CARIM disciplines access to the opportunities cardiac surgery has to offer to collect tissue or blood samples and follow-up data as well as to allow direct measurements of heart function during surgery. Electrophysiologists, heart failure physicians and haematologists are among the most frequent users of these opportunities. The focus of his cardiac surgery-initiated research is in atrial fibrillation, short-term support of the failing heart and minimal trauma surgery.

In addition to drug therapy, patients with severe atrial fibrillation can be offered either a percutaneous, catheter-based ablation procedure or a surgical procedure. Despite many improvements the success rate of these approaches was limited. Some ten years ago, the idea was raised that combining them in a single and simultaneous endo- and epicardial ablation procedure would abolish the shortcomings of both these approaches. To this end, the invasive surgical procedure had to be scaled down first to a minimally invasive, thoracoscopic approach that would not involve much additional trauma to the percutaneous endocardial approach. By testing many tools and ways of access to the left atrium, MUMC+ cardiac surgeons eventually succeeded in developing a procedure that met these requirements. As a result, in 2008 a clinical, so-called hybrid AF ablation program was launched. This program is now carried out routinely, and uniquely, at the MUMC+ by electrophysiologists and surgeons working together as a team and up to now its results have been unsurpassed. Clinical follow-up studies have been complemented by epi-endo mapping studies and atrial tissue biochemical and genetic analysis.

Highlight: Heart-lung machine technology
This technology has long been exclusively the domain of intraoperative cardiac surgery. Recently, its advantages over LVADs were recognised as it is readily available, cheap and in addition to circulatory support offers pulmonary support for metabolic resuscitation. Major steps in improved biocompatibility allow extracorporeal use for weeks up to more than one month. Thus it may become first-line therapy as a bridge to recovery or definitive therapy in patients with heart failure or combined heart and lung failure. From a research standpoint important challenges still remain, i.e. the adequate selection of patients and the development of appropriate weaning strategies. It offers a clinical model for translational research in cardiac remodelling at a functional and biochemical level.

Highlight: Education
A continuous program to educate electrophysiologists-ablationists and cardiothoracic surgeons from all over the world in the background and technique of hybrid AF ablation is carried out together with the Department of Cardiology. In addition, an annual Hybrid AF ablation course is held in the MUMC+.

B.2.4.2 Key publications

2007

Singh BN, Connolly SJ, Crijns HJ, et al. -
Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Eng J Med 2007; 357: 987-99
IF 51.296

Schellings MWM, Lowenberg B, Pinto YM -
Another look at imatinib mesylate. New Engl J Med 2007; 356(11): 1183
IF 51.296

Vanagt WY, Prinzen FW, Delhaas T -
Single site LV apical pacing cures overt RV pacing-induced heart failure. New Engl J Med 2007; 357(25): 2637-38
IF 51.296

Schroen B, Leenders JJ, van Erk A, Bertrand AT, van Loon M, van Leeuwen REW, Kubben N, Duisters RFJJ, Schellings MWM, Janssen BJA, Debets JJM, Schwake M, Hoydal MA, Heymans SRB, Saftig S, Pinto YM -
Lysosomal integral membrane protein 2 is a novel component of the cardiac intercalated disc and vital for load-induced cardiac myocyte hypertrophy. J Exp Med 2007; 204(5): 1227-35
IF 14.484

Vanhoutte D, Schellings MW, Gotte M, Swinnen M, Herias V, Wild MK, Vestweber D, Chorianopoulos E, Cortes V, Rigotti A, Stepp MA, Van de Werf F, Carmeliet P, Pinto YM, Heymans S –
Increased expression of syndecan-1 protects against cardiac dilatation and dysfunction after myocardial infarction. Circulation 2007; 115(4): 475-482
IF 14.595

2008

Ahmed S, Rienstra M, Crijns HJ, et al. -
Continuous versus episodic prophylactic treatment with amiodarone for the prevention of AF: a randomized trial. JAMA 2008; 300: 1784-92
IF 28.9

2009

Nieuwlaat R, Crijns HJ -
Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of AF. J Am Coll Cardiol 2009; 53: 1690-8
IF 14.156

Hohnloser SH, Crijns HJ, van Eickels M, et al.; ATHENA Investigators -
Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009; 360: 668-78
IF 51.296

Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-La Rocca H -
BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009; 301(4): 383-92
IF 31.718

Schellings MWM, Vanhoutte D, Swinnen MIPH, Cleutjens JPM, van Leeuwen REW, d'Hooge J, van de Werf F, Carmeliet P, Pinto YM, Sage EH, Heymans SRB -
Absence of SPARC results in increased cardiac rupture and dysfunction after acute myocardial infarction. J Exp Med 2009; 206(1): 113-23
IF 15.219

Swinnen MIPH, Vanhoutte D, van Almen GC, Hamaekers

AEW, Hamdani N, Schellings MWMJ, D'hooge J, van der Velden MS, Weaver EH, Sage P, Bornstein P, Verheyen FK, VandenDriessche T, Chuah MK, Westermann D, Paulus WJ, van de Werf F, Schroen BLM, Carmeliet P, Pinto YM, Heymans SRB -
Absence of thrombospondin-2 causes age-related dilated cardiomyopathy Circulation 2009; 120(16): 1585-97
IF 14.595

Lumens J, Delhaas T, Kirn B, Arts T –
Three-wall segment (TriSeg) model describing mechanics and hemodynamics of ventricular interaction. Ann Biomed Eng 2009 Nov; 37(11): 2234-55.
IF 2.605

2010

Van Gelder IC, Groenveld HF, Crijns HJ, et al.; the RACE II Investigators -
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. N Engl J Med 2010; 362: 1363-73
IF 51.296

Glatz JF, Luiken J, Bonen A -
Membrane Fatty Acid Transporters as Regulators of Lipid Metabolism: Implications for Metabolic Disease. Physiological Reviews 2010; 90(1): 367-417
IF 37.726

Da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, Bierhuizen MF, de Weger R, Hansen A, Coenen-de Roo CJ, van der Nagel R, van Kuik J, Condorelli G, Arbones ML, de Bruin A -
MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signaling. Nature Cell Biology 2010; 12(12): 1220-27
IF 19.527

De Groot NMS, Houben RPM, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allessie MA -
Electropathological Substrate of Longstanding Persistent Atrial Fibrillation in Patients With Structural Heart Disease Epicardial Breakthrough. Circulation 2010; 122(17): 1674-82
IF 14.816

2011

Schotten U, Verheule S, Kirchhof P, Goette A -
Pathophysiological Mechanisms of Atrial Fibrillation: A Translational Appraisal. Physiological Reviews 2011; 91(1): 265-325
IF 28.417

Laeremans H, Hackeng TM, van Zandvoort M, Thijssen V, Janssen BJA, Ottenheijm HCJ, Smits JFM, Blankesteijn WM -
Blocking of Frizzled Signaling With a Homologous Peptide Fragment of Wnt3a/Wnt5a Reduces Infarct Expansion and Prevents the Development of Heart Failure After Myocardial Infarction. Circulation 2011; 124(15): 1626-35
IF 14.432

Wellens HJ, Gorgels APM -
How Important Is the Electrocardiogram in Protecting and Guiding the Athlete? Circulation 2011; 124(6): 669-97
IF 14.432

Weijs B, Crijns HJ -
Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk AF patients. Eur Heart J 2011, July
IF 11.5

2012

Houthuizen P, van Garsse L, Poels TT, de Jaegere P, van der Boon RMA, Swinkels BM, ten Berg JM, van der Kley F, Brueren GRG, Schalij MJ, Baan J, Cocchieri R, van Straten AHM, den Heijer P, Stella PR, Bentala M, van Ommen V, Kluin J, Prins MH, Maessen JG, Prinzen FW -
Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. Circulation 2012; 126(6): 720-28
IF 14.739

Kappert K, Bohm M, Schmieder R, Schumacher H,

Key publications

Teo K, Yusuf S, Sleight P, Unger T -
Impact of Sex on Cardiovascular Outcome in Patients at High Cardiovascular Risk Analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation 2012; 126(8): 934-41
IF 14.739

Weijs B, Pisters R, Crijns HJ -
Patients originally diagnosed with idiopathic AF more often suffer from insidious coronary artery disease compared to healthy SR. Heart Rhythm 2012(12): 1923-9
IF 4.102

Pluijmert M, Kroon W, Rossi AC, Bovendeerd PH, Delhaas T -
Why SIT Works: Normal Function Despite Typical Myofiber Pattern in Situs Inversus Totalis (SIT) Hearts Derived by Shear-induced Myofiber Reorientation. PLoS Comput Biol. 2012 Jul; 8(7): e1002611
IF 5.215

Arts T, Lumens J, Kroon W, Delhaas T -
Control of Whole Heart Geometry by Intramyocardial Mechano-Feedback: A Model Study. PLoS Comput Biol. 2012 Feb; 8(2): e1002369.
IF 5.215

Corsten MF, Papageorgiou A, Verhesen W, Carai P, Lindow M, Obad S, Summer G, Coort SL, Hazebroek M, van Leeuwen R, Gijbels MJ, Wijnands E, Biessen EA, De Winther MP, Stassen FR, Carmeliet P, Kauppinen S, Schroen B, Heymans S -
Microrna profiling identifies microrna-155 as an adverse mediator of cardiac injury and dysfunction during acute viral myocarditis. Circ Res 2012; 111: 415-425
IF 9.489

B.2.4.3 Strategy based on SWOT analysis

Based on the SWOT analysis presented in the CARIM Midterm 2007-2011 and the CARIM future research strategy evaluation in 2012, the main strategy within Theme II is the obvious reinforcement of the cooperation between programs in CARIM, but especially in the areas of imaging and the Maastricht Study. In addition, within Theme II we increase focus of research by reducing the number of research spearheads to four or five, which means combining programs in the future.

Concerning enhancing infrastructure: we are in the process of further defining the research infrastructure by describing and forming the expertise centres for arrhythmias (Complex Arrhythmia Unit) and heart failure (heart failure expertise centre) (cf. Thrombosis Expertise Centre in Theme I). Since these centres include infrastructure in both the clinic (HVC) as well as the CARIM, premises one natural line for performing translational research is formed. In other words, the opportunity of opening up hidden research infrastructure is now at our feet.

Excellent examples include mapping of the same arrhythmias in CARIM as well as in the cath lab, or the formation of a large clinical database on diastolic heart failure including complex genetic analyses. This centre formation still needs appointments of several specialists among which an experimental electrophysiologist and a systems modelling expert. For this we may join forces with the Cardiovascular Centre of Excellence since main activities of the people to be appointed are in the area of top referral care. Yet, an inventory of available expertises needs to be made and taken into consideration.

Valorisation is being promoted through start-up companies like YourRhythmics and Mirabilis. The links of Theme II programs with the Maastricht Study are quite strong and will be kept so by promoting PhD projects and comply with the rules and standards of the Study. In imaging we have chosen for and will further promote appointments across departments. With the success of the CT-biobank in mind many translational bio-imaging projects are now under way. A fine example includes the CARMENTA trial representing a combined effort of all parties to investigate urgently needed cardiovascular imaging in the setting of chest pain in the hs-TnT era.

Important areas to further develop are genetics and modelling. For genetics we seek cooperation with the newly appointed Prof. Han Brunner and are confident that we can build on his expertise to enhance our monogenetic program and cutting edge techniques such as iPS technology for our spearheads arrhythmia, sudden death and heart failure. The complex genetics is now covered by Prof. Monika Stoll and we have recently seen very reassuring and promising cooperations which now wing several research programs, also with a view to perform systems biology.

B.3 THEME III VASCULAR BIOLOGY

B.3.1 Objectives and research area

Until 2007, research within Theme III 'Vascular Biology' (theme leader: Prof. Coen Stehouwer) was focused around neovascularisation, vascular complications of metabolic diseases and hypertension and plaque instability. However over the past 6 years, relatively large personnel changes have occurred both in the PI group and in the group of associated researchers. First, Prof. Mark Post, who had been appointed theme leader in 2006, succeeded Prof. Mat Daemen as institute director for an interim period (2011-2012) until the appointment of Prof. Thomas Unger (2012), and thereafter decided not to return as theme leader. Prof. Mark Post was succeeded as initial theme leader (i.e. 2011-2012, on an interim basis) by Prof. Coen Stehouwer (2011-present day). Secondly, PIs Prof. Mat Daemen (Pathology), Prof. Jo De Mey (Pharmacology), Prof. Leo Hofstra (Cardiology), Prof. Johannes Waltenberger (Cardiology) and Dr Menno de Winther (Molecular Genetics) left. Prof. Jos van Engelshoven (Radiology) retired, and Prof. Erik Biessen (Pathology), Prof. Robert van Oostenbrugge (Neurology), Prof. Harald Schmidt (Pharmacology), Prof. Christian Weber (Cardiology) and Prof. Joachim Wildberger (Radiology) were newly appointed.

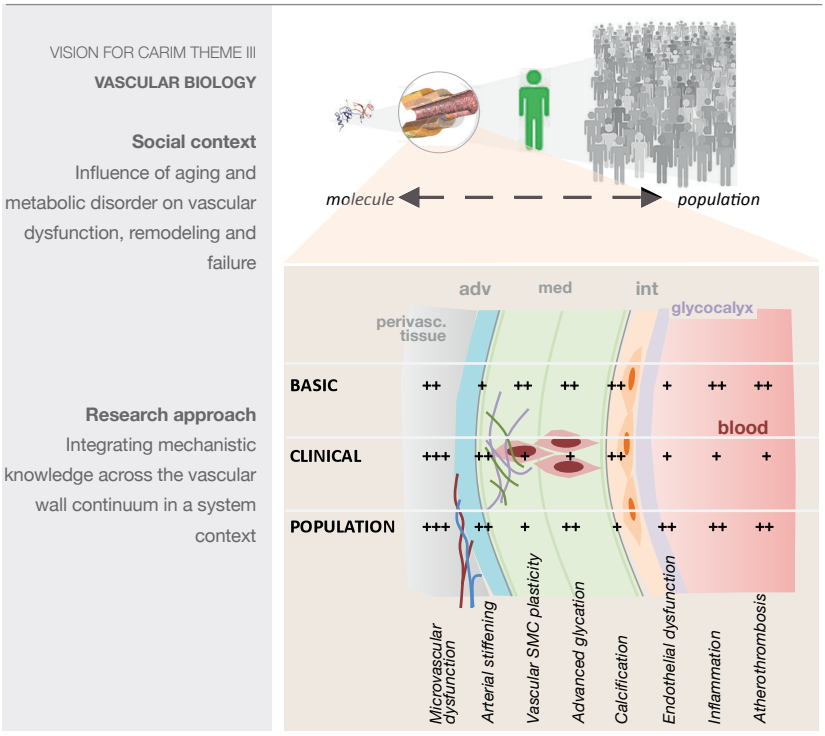
This, together with collaborative development across research groups and themes, has stimulated the redefinition of focus and organisation.

Research within Theme III is now centred around the following eight key processes underlying cardiovascular disease: 1) microvascular dysfunction;
2) atherothrombosis; 3) arterial stiffening;
4) vascular smooth muscle cell plasticity;
5) endothelial dysfunction; 6) calcification; 7) advanced glycation; and 8) inflammation.

These processes are studied in the context of specific cardiovascular diseases that pose major burdens to the ageing society, namely 1) diabetes and the metabolic syndrome;
2) hypertension and chronic kidney disease;
3) stroke and cognitive impairment; 4) acute coronary syndrome and heart failure; 5) aortic aneurysm; and 6) venous disease.

The interaction between these key processes and specific cardiovascular diseases is depicted in Figure 4. The upper part of the figure illustrates the enormous societal impact (disease burden and economic burden) that vascular dysfunction imposes, i.e. remodelling and failure, in the context of ageing and highly prevalent metabolic disorders, such as the metabolic syndrome and type 2 diabetes. The lower part of the figure shows, in a schematic and semi-quantitative manner, how the research approach in Theme III (left) is applied to specific vascular pathobiological processes (bottom) across the vascular wall (depicted schematically) in basic, clinical and population research. Abbreviations: perivasc, perivascular; adv, adventitia; med, media; int, intima. Symbols +, ++, +++: reasonably well-developed, well-developed, very well-developed, respectively.

Figure 4: Interactions between key pathobiological processes and specific cardiovascular diseases studies in Theme III



B.3.2 Composition

Theme III contains 11 programs. A brief overview of these programs is provided below, with the PIs in parentheses. The associated researchers are shown in Table 3. Current status and future prospects of the programs in Theme III are described in paragraph 3.4.1.

Programs:

1. Vascular complications of diabetes and the metabolic syndrome (Prof. Coen Stehouwer)
2. Hypertension and target organ damage (Prof. Peter de Leeuw - retired 2013; Dr Bram Kroon, Internal Medicine, interim)
3. Cerebral small vessel disease (Prof. Robert van Oostenbrugge)
4. Microvascular dysfunction and glycocalyx (Prof. Hans Vink)
5. Vascular remodelling in cardiovascular disease (Prof. Harry Struijker Boudier)
6. The vulnerable plaque: makers and markers (Prof. Erik Biessen)
7. Structure-function analysis of the chemokine interactome for therapeutic targeting and imaging in atherosclerosis (Prof. Christian Weber)
8. Regenerative and reconstructive medicine for vascular disease (Prof. Mark Post)
9. Cardiovascular biomaterials (Prof. Leo Koole)
10. Utilising network pharmacology and common mechanisms for cardiovascular target validation and drug discovery (Prof. Harald Schmidt)
11. Imaging (Prof. Joachim Wildberger)

Table 3: Researchers within Theme III

Associated	
Dr Walter Backes	Radiology
Dr Pieter Dagnelie	Epidemiology (principal embedding is in Theme II)
Dr Jan Damoiseaux	Clinical Chemistry/Immunology
Dr Adriaan Duijvestijn	Internal Medicine
Dr Isabel Ferreira	Clin Epidemiology & MTA (KEMTA)
Dr Marion Gijbels	Pathology
Dr Marleen van Greevenbroek	Internal Medicine
Dr Sylvia Heeneman	Pathology
Dr Boy Houben	Internal Medicine
Prof. Michael Jacobs	Surgery
Dr Carla van der Kallen	Internal Medicine
Dr Eline Kooi	Radiology
Dr Rory Koenen	Biochemistry (principal embedding is in Theme I)
Dr Bram Kroon	Internal Medicine
Prof. Chris Reutelingsperger	Biochemistry
Prof. Casper Schalkwijk	Internal Medicine
Dr Nicolaas Schaper	Internal Medicine
Dr Geert Schurink	Surgery
Dr Leon Schurgers	Biochemistry (principal embedding is in Theme I)
Dr Jan Staessen	Epidemiology
Dr Ronit Sverdlov	Genetics & Cell Biology
Prof. Hugo ten Cate	Internal Medicine (principal embedding is in Theme I)
Dr Marc van Zandvoort	Genetics & Cell Biology
Newly appointed	
Dr Ilja Arts	Epidemiology
Dr Jan Bucerius	Radiology
Prof. Tammo Delhaas	Biomedical Engineering
Dr Marjo Donners	Pathology
Dr Ronald Henry	Internal Medicine
Dr Jan Kooman	Internal Medicine
Dr Karel Leunissen	Internal Medicine
Dr Remco Megens	Biomedical Engineering
Dr Koen Reesink	Biomedical Engineering
Dr Carine Peutz	Pathology
Dr Miranda Schram	Internal Medicine
Dr Judith Sluimer	Pathology
Dr Jan Staals	Neurology
Prof. Cees Wittens	Surgery
Dr Kristiaan Wouters	Internal Medicine
Left institute/retired	
Prof. Jan Willem Cohen Tervaert	Internal Medicine
Dr Guillaume van Eys	Genetics & Cell Biology
Dr Arjan Griffioen	Pathology
Dr Arnold Hoeks	Biomedical Engineering
Dr Maya Huijberts	Internal Medicine
Dr Ferdi Le Noble	Surgery
Dr Esther Lutgens	Pathology
Prof. Mirjam Oude Egbrink	Physiology
Prof. Rob Reneman	Physiology

B.3.3 Research environment and embedding

Infrastructure, collaborations, and translation
In 2007 the external review committee advised 1) further integration with the newly-formed group on diabetes and the metabolic syndrome (Prof. Coen Stehouwer and Prof. Casper Schalkwijk) and 2) investment in clinical imaging. The former has been achieved through the CVC and the Maastricht Study, which has developed collaborations not only with PIs in Theme III (Prof. Peter de Leeuw/Dr Bram Kroon, Prof. Robert van Oostenbrugge, Prof. Hans Vink, Prof. Erik Biessen, Prof. Joachim Wildberger) but also with Theme I (Prof. Hugo ten Cate) and Theme II (Prof. Hans Peter Brunner-La Rocca, Prof. Harry Crijns, Dr Ton Gorgels, Prof. Uli Schotten). The latter has been achieved by attracting three leaders in clinical imaging (Prof. Joachim Wildberger, Dr Jan Bucerius, Dr Felix Mottaghy), which has given a strong impetus to heart failure and cardiac arrhythmia research (Theme II). Additional collaborations have been developed with Theme I on vascular calcification in chronic kidney disease patients; on vascular smooth muscle cell plasticity in aortic aneurysm and venous disease; and on atherothrombotic mechanisms in stroke. By their nature, these developments and collaborations have also given a strong impetus to translational research.

Thus, developments within Theme III, together with the wide range of research approaches and resources that have traditionally been available within this theme, have resulted in research programs that span the continua 1) across the vascular wall, 2) from molecule to population, and 3) dysfunction-remodelling-failure. The current research infrastructure is well-suited to adopt a systems approach to develop and integrate mechanistic knowledge from basic, clinical and population research into a translational program, within the emergent societal context of cardiovascular diseases associated with ageing, metabolic disorders, and other chronic diseases.

Both nationally and internationally, Theme III researchers collaborate in key consortia such as *Cardiovasculair Onderzoek Nederland* (CVON; Dutch Cardiovascular Research), Top Technological Institutes (Centre for Translational and Molecular Medicine, Top Institute for Food and Nutrition, BioMedial Materials and TI Pharma), the Leducq Transatlantic Network and EU Framework Programs. Because of the many links among PI programs within Theme III, between Theme III and Themes I and II, and indeed between Theme III and other research schools, Theme III has recently become a Vascular Network Group which convenes on a monthly basis and is rapidly becoming the main forum for further integration of research within Theme III. The Vascular Network Group is a semi-open organisational structure that has resulted from a research strategy analysis in 2012 and in-depth reviews of macrovascular and microvascular research within CARIM led by Dr Koen Reesink and Prof. Chris Reutelingsperger, and Prof. Robert van Oostenbrugge and Prof. Hans Vink, respectively.

Valorisation
In 2010 Prof. Hans Vink founded a spin-off company named GlycoCheck, which is based on monitoring glycocalix function. Patents were acquired by Theme III PIs on a coiled wire for the controlled release of drugs to the eye (Koole, 2007 and 2009), on a radio-opaque prosthetic intervertebral disc nucleus (Koole, 2007), on homogenous intrinsic radio-opaque embolic particles (Koole, 2008 and 2009), on a wire, tube or catheter with hydrophilic coating (Koole, 2008), on two-component cement for vertebroplasty (Koole, 2009) , on GAG-antagonising MCP-1 mutants (Weber, 2009), and on mIR-126 and tissue repair (Weber, 2009).

B.3.4 Quality and scientific relevance

Quality and scientific relevance are apparent from the scientific output and earning power reported in part A of this self-evaluation report. In addition, citation scores in the major areas of research, i.e. those areas that cover most of its publications, are far above average (see Table 4). Quality indicators for the research staff within Theme III, such as the Hirsch-factor and m-index, indicate that many researchers in Theme III rank highly (see Part A). Additional quality indicators include an EU Advanced Grant (Prof. Harald Schmidt, 2011); Veni grants (Dr Koen Reesink, 2008; Dr Kristiaan Wouters, 2011); a Vici grant (Prof. Christian Weber, 2009); an E Dekker grant (Dr Isabel Ferreira, 2011); and EFRO (8 M€, 2009) and Weijerhorst (3 M€, 2011) grants to set up the Maastricht Study (Prof. Coen Stehouwer).

Table 4: Bibliometric analysis CARIM Theme III 2007-2010

Theme III Vascular Biology	P	CPP	MNCS	MNJS
2004-2007	785.50	9.67	1.45	1.23
2005-2008	886.75	10.95	1.52	1.26
2006-2009	926.00	12.63	1.68	1.30
2007-2010	1,007.25	13.43	1.78	1.36

P: Number of articles. **CPP**: Average number of citations per publication (p), without self-citations. **MNCS**: The impact of a research unit's articles, compared to the world citation average in the subfields in which the research unit is active. **MNJS:** the impact of the journals in which a research unit has published compared to the world citation average in the subfield covered by these journals.

B.3.4.1 Programs and Highlights

The current status and future prospects of the 11 PI programs within Theme III are briefly described below.

Vascular complications of diabetes and the metabolic syndrome (Program 1)

PI: PROF. COEN STEHOUWER

Prof. Coen Stehouwer is Professor of Internal Medicine and Chair of the Department of Internal Medicine at MUMC+ in Maastricht, and Principle Investigator for diabetes and cardiovascular disease at CARIM (since 2004). He obtained his MD in 1985 (cum laude, Erasmus University Rotterdam); was registered as internist in 1990 and obtained his PhD in 1992 (Vrije Universiteit [VU] Amsterdam); did postgraduate training in epidemiology (1991-3, Erasmus University Rotterdam and VU Amsterdam) and molecular biology (1994-5, Gaubius Laboratory, Leiden); and was appointed associate professor of internal medicine in 1996 and full professor in 2000 (VU Amsterdam). From 1996 to 2002 he was Vice-Director, and from 2002 to 2004 Director, of the Institute for Cardiovascular Research, all at the VU Amsterdam. His research program focuses on the elucidation of how metabolic changes in pre-diabetes and diabetes cause micro- and macrovascular disease. A key element of the program is to combine epidemiology, clinical physiology and experimental approaches, in the conviction that these approaches should complement and mutually inspire each other. He is one of the principal investigators of the well-known Hoorn Study (since 1992). He also obtained national and European funding (16 million Euro) for, and is the Scientific Director of, the Maastricht Study (started 2010), He has been an author on more than 500 papers; his h-index is 80.

The program focuses on the elucidation of how metabolic changes in pre-diabetes and diabetes cause micro- and macrovascular disease. A key element of the program is to combine epidemiology, clinical physiology and experimental approaches in the conviction that these approaches should complement and mutually inspire each other. An important development is the funding and start (2010) of the Maastricht Study, which combines very detailed, state-of-the-art phenotyping with an 'omics' approach in 5,000 individuals with and 5,000 without type 2 diabetes to elucidate how diabetes lads not only to classic complications but also to so-called emerging complications such as cognitive dysfunction, mood disorders, liver disease, musculoskeletal disease, pulmonary disease, sleep-disordered breathing, and infectious diseases.

Highlight: Arterial stiffening in diabetes and the metabolic syndrome: a pathway to cardiovascular disease

We were the first to systematically investigate arterial stiffening in diabetes and the metabolic syndrome. In a series of papers (1995-present day), we showed 1) that arterial stiffness is increased in type 1 diabetes, and that this is an early phenomenon that occurs before the onset of clinically overt micro- or macrovascular complications; 2) that arterial stiffness is increased in type 2 diabetes and in the impaired glucose metabolism state; 3) that the presence of micro- and macrovascular complications is associated with a further increase in arterial stiffness; 4) that arterial stiffness is also increased in the metabolic syndrome and in insulin-resistant states; 5) that subtle changes in metabolic variables affect arterial stiffness from an early age; and 6) that estimates of arterial stiffness are associated with an adverse prognosis both in type 1 and type 2 diabetes. Thus, this research has firmly established diabetes as a disease of accelerated arterial ageing, and arterial stiffening as an important mechanism leading to cardiovascular disease in diabetes.

Hypertension and target organ damage (Program 2)

PI: PROF. PETER DE LEEUW (RETIRED 2013) AND DR BRAM KROON (INTERIM)

Until 2010 Prof. Peter de Leeuw headed the Vascular Medicine division at the Department of Internal Medicine. He studied medicine at the Erasmus University in Rotterdam and completed his training in internal medicine at the Zuider Hospital in Rotterdam. After he had obtained a doctorate in medicine at the Erasmus University, he spent a year as postdoc at The Peter Bent Brigham Hospital and Harvard Medical School in Boston (USA), where he worked on tachyphylaxis for angiotensin II. Thereafter, he set up his own research group, first in Rotterdam and later at Maastricht University, where he was appointed as full professor in

1991. His research interest covers the whole area from basic physiology to clinical trial. He has particularly concentrated on renal mechanisms in hypertension and various aspects of treatment. He has received several awards including the Björn Folkow Award of the European Society of Hypertension.

Dr Bram Kroon is Associate Professor of Medicine at MUMC+ and has been head of the vascular medicine section of the Department of Internal Medicine since 2010. He was certified as a general internist in 1990 and did his PhD thesis on regression of atherosclerosis in patients with familial hypercholesterolemia, both at the St. Radboud University Hospital of Nijmegen (NL). In 1995 he moved to the University Hospital of Maastricht and continued working as a general internist with special interest in hypertension. In 1997 he was appointed senior investigator in CARIM, Theme III. He was first registered as a clinical pharmacologist and some years later as a vascular medicine specialist. He was the first president of the Dutch Internal Vascular Medicine Society (IVG) and for many years now has been the treasurer of the Dutch Hypertension Society (NHV). In 2005 he was appointed fellow (Established Clinical Investigator) of the Dutch Heart Society for his research on 'ADMA and cardiovascular disease in hypertension'. He is a strong supporter of the Cardiovascular Centre at the Maastricht University Medical Centre, which is a major opportunity to further improve the quality of treatment and research for patients with cardiovascular diseases in a multidisciplinary context. In 2010 the Hypertension Clinic was awarded by the European Society of Hypertension (ESH) as European Centre of Excellence due to the outstanding scientific and clinical activities performed in close collaboration with Prof. Peter de Leeuw. His major research focus is on baroreceptor activation therapy in treatment-resistant hypertension, on renal haemodynamics in hypertension and renovascular disease. He has co-authored over 200 publications.

The program focuses on a) ambulatory and home blood pressure monitoring, b) hypertensive target organ damage, i.e. renal, cerebral, and vascular presentations, c) device-based treatment in resistant hypertension, i.e. baroreflex activation therapy and renal denervation, and d) renal haemodynamic studies in hypertension and renal artery stenosis. In coming years, the focus will be on a) ambulatory & home blood pressure measurements and their relationship with vascular target organ damage using data from the Maastricht Study and implementation studies in general practice, b) baroreflex activation therapy and renal denervation [investigator-initiated studies with new devices], and c) detection of and early intervention in renovascular hypertension in the prevention of target organ damage [Dutch randomised controlled multicentre study].

Highlight: Baroreflex activation therapy in treatment-resistant hypertension

Despite the availability of many antihypertensive drugs, a sizeable proportion of hypertensive patients remain resistant to treatment. In 2004 the hypertension research group in Maastricht started a program that utilised the so-called baropacer to treat these resistant patients. In hypertensive patients who did not respond adequately to medical treatment and in whom secondary hypertension, non-adherence and other forms of pseudo-resistance had been ruled out, a baropacing system was implanted at the level of the carotid baroreceptors. This device proved to be able to significantly lower the blood pressure. It also led to regression of left ventricular hypertrophy and was not associated with renal impairment. A number of physiological studies with the device have revealed important interactions with humoral systems (renin, BNP) and more recently shed more light on the importance of left-right differences in carotid barostimulation.

Cerebral small vessel disease (Program 3)

PI: PROF. ROBERT VAN OOSTENBRUGGE

Prof. Robert van Oostenbrugge (1965) is Chairman of the Department of Neurology and leader of the research program Vascular Neurology within CARIM. He studied Medicine at Maastricht University, the Netherlands. After his graduation in 1990 he was trained in neurology at the University Hospital Maastricht. Since 2000 he has been a staff member of the Department of Neurology at MUMC+ with special emphasis on Vascular Neurology. In November 2011, he was appointed as full Professor of Neurology. He is engaged in clinical research into the causes and consequences of cerebrovascular disease in general, and into molecular biological studies in cerebral small vessel disease in particular.

The program focuses on cerebral small vessel disease (cSVD), an umbrella term that covers different diseases of the small cerebral vessels, the most prevalent form relating to vascular risk factors such as age, hypertension and inflammation, which manifests itself by structural brain damage such as ischaemic white matter lesions, lacunar infarcts and brain microbleeds. cSVD may manifest itself acutely or in a slowly progressive manner. Cognitive impairment is one of the major consequences of the slowly progressive manifestation of cSVD. Increasingly, evidence suggests that vascular endothelial dysfunction leading to an increase in the permeability of the blood-brain barrier is the underlying initiating cause of cSVD. The program is directed towards the clinical consequences of cSVD with a particular emphasis on cognitive function, and to unravel the impact of endothelial dysfunction and blood-brain barrier dysfunction on the development and progression of cSVD. The focus for the coming years will be on these two aspects. With regard to endothelial dysfunction in cSVD, we will focus on the role of the glycocalyx and the AT2 receptor in the pathogenesis and progression of cSVD. This will be studied in humans as well as in animal models for cSVD. A second focus in the coming years will be on the role of blood-brain barrier permeability in cSVD by means of novel contrast-enhanced dynamic MR techniques to quantify blood-brain barrier permeability.

Highlight: Blood-brain barrier permeability in cerebral small vessel disease

Cerebral small vessel disease (cSVD) is an umbrella term which covers different types of disease of which vascular risk factors and age-dependent deep cerebral small vessel disease is the most prevalent. Our research program is aimed at unravelling mechanisms of disease that lead to the various structural lesions seen in this type of cSVD. Our contributions supported the idea that different types of lacunar stroke do exist and that endothelial dysfunction with subsequent increased blood-brain barrier permeability might play a pivotal pathogenetic role in the development and progression of structural lesions seen in patients with deep cerebral small vessel disease. Currently, means to interfere with this process are being studied.

Microvascular dysfunction and glycocalyx (Program 4)

PI: PROF. HANS VINK

Prof. Hans Vink received his physics degree in 1989 at the University of Amsterdam. After receiving his PhD in Medicine in 1994 and a postdoctoral fellowship at the Dept. Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA, USA, he returned to the University of Amsterdam and developed a research program on the endothelial glycocalyx (www.glycocalyx.nl), supported by grants from the Netherlands Organisation for Scientific Research (NWO 1997 – 1999) and a fellowship from the Royal Netherlands Academy of Sciences (KNAW 2000 – 2005). In 2006 he was awarded an Established Investigatorship by the Netherlands Heart Foundation and moved to Maastricht University as a PI at CARIM and he was appointed professor of Circulatory Physics at the University in Amsterdam in 2008. His research on the endothelial glycocalyx progresses towards clinically applicable tools for early diagnosis of cardiovascular risk and new therapeutic approaches to protect the vascular wall against atherogenic challenges, and is supported by program grants from the Centre for Translational Molecular Medicine, The Netherlands Heart Foundation, The Dutch Diabetes Research Foundation and the Netherlands Kidney Foundation. He has published more than 85 scientific publications and his H-factor is 31.

The program focuses on the innermost lining of blood vessels, i.e. endothelial cells and the endothelial glycocalyx. The glycocalix mediates many interactions between blood components and the vascular wall and consists of a complex mesh of proteoglycans, glycosaminoglycans and plasma proteins that is anchored to the plasma membrane of vascular endothelium. The glycocalyx protects the healthy vessel wall against transendothelial leakage of plasma molecules, endothelial adhesion of platelets and leukocytes, and mechanical damage by stimulating endothelial production of the vasodilator nitric oxide in response to increased levels of fluid shear stress. Central to the glycocalyx research program is the development of new methods to assess glycocalyx protective properties in experimental settings and to translate these methods into non-invasive clinical tools to test whether early glycocalyx modification identifies persons at risk for vascular

complications. At the basic science level, a new method is being developed to measure the impact of metabolic stimulation on glycocalyx barrier properties in the coronary and systemic circulation. It has been demonstrated that a healthy glycocalyx is essential for controlled metabolic regulation of coronary blood volume, exchange capacity and insulin-mediated glucose disposal. Recent clinical studies have demonstrated that monitoring glycocalyx damage identifies early vascular vulnerability in patients, for example those with early cognitive impairment (neurology), premature atherosclerosis and coronary microvascular disease (cardiology), impaired renal function (nephrology), insulin resistance (diabetes) and acute vascular vulnerability in critically ill patients (ICU). In the coming years we will focus on identifying the mechanisms contributing to the above-mentioned glycocalyx damage, on monitoring the effect of conventional therapies on repair of glycocalyx and vascular health, and on developing new glycocalyx-based therapies to optimise organ function.

Highlight: Sublingual microvascular glycocalyx dimensions in lacunar stroke patients

Cerebral small vessel disease is thought to result from endothelial dysfunction. The glycocalyx, lining the endothelium, is a major determinant of endothelial function. The glycocalyx is partially accessible to flowing red blood cells at its luminal side, called the perfused boundary region (PBR). Glycocalyx damage results in increased PBR, which can be measured in the sublingual microvasculature. We tested if PBR is increased in patients with cerebral small vessel disease, i.e. lacunar stroke patients, and further distinguished patients with presence of white matter lesions as a sign of extensive cerebral small vessel disease. We used intravital videomicroscopic imaging of the sublingual microcirculation in 31 lacunar stroke patients and demonstrated that lacunar stroke patients with white matter lesions had an increased PBR compared with both healthy controls and patients without white matter lesions. Thus, white matter lesions are associated with an increase in the red blood cell permeable part of the sublingual microvascular glycocalyx in lacunar stroke patients. This implicates compromised glycocalyx barrier properties, which is consistent with impaired endothelial function in lacunar stroke patients with white matter lesions.

Vascular remodelling in cardiovascular disease (Program 5)

PI: PROF. HARRY STRUIJKER BOUDIER

Prof. Harry Struijker Boudier has headed the experimental vascular remodelling program since 2012 following the departure of Prof. Jo De Mey. Prof. Harry Struijker Boudier was chairman of the Department of Pharmacology from 1984 – 1999 and Scientific Director of CARIM from 1999 – 2006. Since 2006 he has been a senior professor in the Department of Pharmacology. He was trained at the University of Nijmegen where he obtained his PhD degree in 1975. After that he spent a postdoc period in Prof. Guyton's group in Jackson, Miss., USA. In 1991 he spent a sabbatical year in the INSERM group led by Prof. Lévy in Paris, France. His research interests have focused on the role of both large vessels and the microcirculation in hypertension, the pharmacology of antihypertensive drugs, as well as advanced delivery forms of drugs. He is doctor honoris causa of the University of Liege and Officer in the Order of Oranje-Nassau of the Dutch Royal House. From 2003 – 2011 he served as member and Vice-chairman of the scientific council of the European Society of Hypertension.

The program focuses on vascular remodelling as well as therapeutic strategies to influence the remodelling process both at the level of large arteries and the microcirculation. In recent years the focus has been on two major paracrine control mechanisms, i.e. the endothelin and renin-angiotensin systems. In the next few years the focus will be on inflammatory and immune mechanisms underlying the remodelling process.

Highlight: Immune mechanisms in experimental hypertension

In a series of studies on renin-inducible forms of hypertension in rats it was shown that a specific adaptive immune response within the kidney, i.e. a shift from Th1 cells to regulatory T cells, is the underlying factor of the irreversible renal damage and sustained hypertension. This immune response is angiotensin type 1 receptor mediated. This finding may explain how repeated short periods of pressure elevation ultimately lead to irreversible hypertension.

The vulnerable plaque: makers and markers (Program 6)

PI: PROF. E. BIESSEN

Prof. Erik Biessen graduated in Biophysical Chemistry at Groningen University in 1989. He then joined the Division of Biopharmaceutics of Leiden University (Prof. T.J.C. van Berkel) as a postdoctoral fellow. In 1994 he was elected for a career development track of the Netherlands Heart Foundation (Molecular Cardiology Program) to become Established Investigator of this program in 2001. He received an innovational research incentive premium from the NWO in 2001 and acquired a second Established Investigatorship of the Taskforce Cardiovascular Genomics (NHS) in 2004. Prof. Erik Biessen was appointed Professor in Therapeutic Gene Modulation at Leiden University in 2005. Since 2007 he has headed CARIM's Experimental Vascular Pathology group (MUMC+). Prof. Erik Biessen has been board member of CCVON of the Netherlands Heart Foundation since 2010, of the Dutch Atherosclerosis Society (>2008), of the ZonMW TOP grant committee (>2010), of the EuCAR Program and of the cardiovascular unit of Roadmaps. He is scientific adviser to VantageView (St Louis, USA), work package leader in the Center of Translational Molecular Medicine (Circulating Cells), and regular reviewer of Journal of Clinical Investigation, Circulation, Circulation Research, and Arteriosclerosis Thrombosis and Vascular Biology. He has authored over 160 papers in peer-reviewed journals and is holder of >10 patent applications. His current H-factor is 43 (6251 citations).

The program focuses on advanced atherosclerosis, with special emphasis on intra- and extraplaque immune responses and the infrastructural conduits between both compartments (micro- and lymph vessels) (line 1) and on inflammation-associated hypoxia (line 2). We employ a three-step research pipeline involving: 1) advanced molecular pathology on human tissue (histology, advanced genomics and bioinformatics), both patient-derived plaque tissue and leukocyte subsets; 2) experimental gain/loss of function studies in in vitro and in vivo models of disease to address the impact of immunomodulatory and angiogenic cues identified by molecular pathology analysis; and 3) validation of the diagnostic potential of biomarkers extracted in the first step, for vulnerable plaque imaging and patient stratification. Over recent years, while maintaining our previous focus on the vulnerable plaque, we have adjusted our strategy, giving more weight to human molecular pathology approaches (omics, bioinformatics) for hypothesis generation, and to cell dynamics studies (e.g., multiphoton microscopy). In the coming years we will continue along this successful track, also embracing newly acquired technologies such as MS Imaging, STED and advanced reporter models, thus pushing our research to the next level. Conceptually, we will increasingly shift our focus to the cross-communication between the vulnerable plaque and other compartments within the vulnerable patient, tapping in on ongoing collaborations with Internal Medicine (Schalkwijk, Wouters, Stehouwer), Biochemistry (Reutelingsperger, Heemskerk), and Euregional partners (Floege, Tacke, Ludwig (RWTH), Stinissen (U Hasselt)).

Highlight: Plasmacytoid dendritic cells in cardiovascular disease - evidence for a protective role

Antigen-presenting cells by profession, dendritic cells are instrumental in adaptive immune responses relevant to atherosclerosis. Here we have investigated the contribution of a subset of dendritic cells (DCs), plasmacytoid DCs, to atherogenesis, in humans and mouse models of disease. Loss of function studies in mice suggested an overt protective activity of pDC, which as we show was probably mediated by promoting IDO mediated T cell tolerance under conditions of low grade inflammation. Molecular pathology studies in human plaque have confirmed this strong cross-interaction between plasmacytoid DCs and T cells, and allowed us to identify a specific LXR-regulated gene program that is orchestrating this interaction. In an effort to verify these findings we were able to demonstrate in vitro that oxidized LDL-exposed-pDC display a completely disrupted ability to produce type I interferons in response to TLR9 activation, which could have major implications for the host defence in patients with marked hyperlipidaemia or manifest as atherosclerosis (Daissormont et al., Circ Res, 2011; Christ et al., Circulation, 2013).

Structure-function analysis of the chemokine interactome for therapeutic targeting and imaging in atherosclerosis (Program 7)

PI: PROF. CHRISTIAN WEBER

Prof. Christian Weber is Director of the Institute for Cardiovascular Prevention and has the Chair in Vascular

Medicine at Ludwig-Maximilians-University (LMU) in Munich, Germany. After completing his training in internal medicine at LMU and Harvard Medical School, Boston, he was board-certified in clinical cardiology and appointed as Chair in Molecular Cardiology at RWTH Aachen University. As a VICI laureate, since 2010 he has also served as a professor at the CARIM at Maastricht University. His group has a strong interest in the molecular interactions and pathophysiological functions of chemokines and immune cells, as well as the role of microRNAs and their targets in vascular disease, namely atherosclerosis, while his clinical interests are focused on developing novel biomarkers and peptide-based biopharmaceuticals. Among many other awards, he is an ERC Advanced Investigator with > 380 publications and h-index of 72, Senior Editor of ATVB, Editor-in-Chief of Thrombosis & Haemostasis and co-founder of Carolus Therapeutics.

The program focuses on chronic inflammation of the arterial wall in atherosclerosis. Mononuclear cell recruitment is driven by chemokines that can be deposited e.g. by activated platelets on inflamed endothelium. Chemokines require oligomerisation and immobilisation for efficient function, and recent evidence supports the notion that heterodimer formation between chemokines constitutes a new regulatory principle amplifying specific chemokine activities while suppressing other activities. Although crucial to inflammatory disease, this functional role has been difficult to prove in vivo, primarily as chemokine heterodimers exist in equilibrium with their homodimer counterparts. We have introduced the paradigm that heteromerizsation of chemokines provides the combinatorial diversity for functional plasticity and fine-tuning, coining this interactome. Given the relevance of chemokine heteromers in vivo, we aim to exploit this in an anti-inflammatory approach to selectively target vascular disease. In a multidisciplinary project, we plan to generate covalently linked heterodimers to establish their biological significance. Obligate heterodimers of CC and CXC chemokines will be designed using computer-assisted modelling, chemically synthesised and cross-linked, structurally assessed using NMR spectroscopy and crystallography, and subjected to functional characterisation in vitro and reconstitution in vivo. Conversely, we will develop cyclic beta-sheet-based peptides to specifically disrupt such heteromers and we will generate mice with conditional deletion or knock-in of chemokine mutants with defects in heteromerisation to be probed in models of atherosclerosis. Peptides will be used for molecular imaging and chemokine heteromers will be quantified in cardiovascular patients.

Highlight: Two are better than one
Prof. Christian Weber has elucidated a new mechanism, by which endothelial apoptotic microparticles induce the atheroprotective chemokine CXCL12. Released during endothelial damage in atherosclerosis, these endothelial microparticles confer the microRNA-126-3p with the ability to unleash an autocrine loop, which enhances local CXCL12 expression and the recruitment of angiogenic cells to promote endothelial regeneration and protection against atherosclerosis. Further work could show that the passenger strand miR-126-5p prevents atherosclerotic lesion formation and promotes resident endothelial cell (EC) proliferation by suppressing the NOTCH1 inhibitor Dlk1. Reduced levels of miR-126-5p at pre-dilection sites with disturbed flow or in miR-126 deficiency rendered ECs susceptible to anti-proliferative and lesion-promoting effects of hyperlipidaemia by increasing Dlk1 expression. By contrast, miR-126-5p mimics conferred a proliferative reserve in ECs and limited atherosclerosis, establishing a promising therapeutic strategy. Both miR-126 strands form a dual system for athero-protection by combined effects on resident EC proliferation and angiogenic cell recruitment.

Regenerative and reconstructive medicine for vascular disease (Program 8)
PI: PROFESSOR MARK POST

Prof. Mark Post is a medical doctor who has had several appointments as assistant professor at Utrecht University, Harvard University, as associate professor at Dartmouth College, and as full professor and vice-Dean at Eindhoven University of Technology and Maastricht University. He currently holds the chair of the Physiology Department at Maastricht University. His main research interest is the engineering of tissues for vascular applications and for food. The medical applications focus on the construction of blood vessels that can be used as grafts for coronary artery bypass grafting. In addition, he coordinates a national program on early molecular imaging of neovascularisation. Tissue engineering for food has led to the culturing of beef from bovine skeletal

muscle stem cells in an effort to supplement and perhaps transform the traditional meat production through livestock. Prof. Mark Post has co-authored 160 papers in leading peer-reviewed scientific journals and during his career has received more than 48 million dollars in funding and awards from different sources including government, charity and industry. In August 2013, he presented the world's first hamburger made from cultured beef.

The program focuses on:

1). Surgical solutions for abdominal and thoracic arterial aneurysms. In this subprogram, biomarkers and other phenotypical criteria are being studied in order to understand the pathophysiology and, based on this understanding, to develop diagnostics and therapeutics.
2). Tissue engineering of blood vessels. Using biomaterials and stem cell technology, small diameter blood vessels that can serve as grafts for bypass or arteriovenous shunts are being tissue-engineered.
3). Early molecular diagnosis of neovascularisation. This is a national project, coordinated by the PI, which aims to identify novel markers for neovascularisation and novel non-invasive imaging technologies.

The aneurysm program will continue with the same focus it has had for the last 5 years. The regenerative medicine applications will greatly expand, and will also include prevascularisation of engineered tissues, using free-form fabrication technologies and novel biomaterials. The diagnostic program will probably be discontinued or incorporated into the prevascularisation project.

Highlight: Molecular imaging

From 2008 until 2011 Dr Walter Backes and Prof. Mark Post, in close collaboration with Prof. Tilman Hackeng and Dr Marc van Zandvoort, ran a molecular imaging program using MRI detectable ligands based on the tripeptide NGR in various tumour and cardiovascular models of angiogenesis. This resulted in successful non-invasive detection of angiogenesis in those models and led to 10 papers, published, among others, in Radiology, Cancer Research and Circulation. As a sequel to this program, the CTMM funded program EMINENCE started an extended collaboration including investigators from AMC, UMCU and the MUMC+ Departments of Cardiology. Two clinical trials have been initiated as a result of this funding.

Cardiovascular biomaterials (Program 9)

PI: PROF. LEO KOOLE

Prof. Leo Koole is the CARIM Professor for Cardiovascular Biomaterials Science. His research group is part of the Department of Biomedical Engineering at the Faculty of Health, Medicine & Life Science of Maastricht University. Prof. Leo Koole is co-author of >150 scientific publications and co-inventor of >20 international patents and patent applications. From 2004 to 2008 he was the scientific leader of the bilateral public-private partnership "Bioterials" in which Maastricht University and DSM Biomedical cooperated in the development of new polymer biomaterials. Prof. Leo Koole has also been heavily involved in the Top Technological Institute "Biomedical Materials" (BMM), through the project IDIDAS (2009-2014). Since 2011, Prof. Leo Koole has been responsible for the Interreg-IVA project "BioMiMedics", in which the Universities of Maastricht (Lead Partner), Liege, Hasselt and Aachen (RWTH and Fachhochschule Juelich) are cooperating on the development and commercialisation of bio-inspired and biomimetic polymer biomaterials. Prof. Leo Koole also participated in the project i-Nephron (funded by the Dutch Kidney Foundation), from 2009 to 2013. Finally, Prof. Leo Koole's group is taking part in a new LSH (Life Sciences & Health)-TKI project, which is called: KidneyPort. This 4-year project, which started in February 2014, is a consortium of the universities of Twente and Maastricht, along with four small Dutch high-tech companies and the Dutch Kidney Foundation.

The program focuses on design, synthesis and evaluation of new polymer biomaterials for use in contact with blood. Emphasis is laid on the interaction of polymer biomaterials and cells, particularly endothelial cells, with the aim of developing devices with long-term haemocompatibility (e.g. for vascular graft prostheses, or for surface coatings for endovascular stents). New surface coatings for percutaneous catheters which help to prevent complications due to coagulation and bacterial line infections have been developed. Furthermore, a unique new technology to manufacture radiopaque biocompatible polymer microspheres is being explored. Such particles are used in minimally-invasive strategies to treat uterine fibroids and hepatocellular carcinomas, using the strategy of combined targeted embolisation and controlled local release of a cytostatic or a pain-killing agent. Research in

the coming years will be focused on 1) further development of radiopaque microparticles to be used in minimally-invasive treatment strategies in oncology, particularly through combined embolisation & intratumoural release of cytostatic drugs; 2) development of new blood-contacting biomaterials that link excellent haemocompability to a high affinity for toxic molecules, and the use of these materials to enhance the efficacy of haemodialysis; 3) development of a new vascular access graft (for haemodialysis), based on the use of new materials with near-zero thrombogenicity and advanced computer modelling of blood flow.

Highlight: Development of haemocompatible biomaterials with intrinsic radio-opacity
Haemocompatible biomaterials with intrinsic radio-opacity can be localised in situ in a non-invasive manner, via X-ray fluoroscopy and computed tomography. This concept has proved to be highly valuable in the context of transarterial chemo-embolisation therapies. The group has developed entirely new radiopaque microspheres. These are the basis for a new CE-certified medical device, which is now being introduced into the clinic. There is growing evidence that these embolisation particles really help to improve accuracy and safety of embolisation procedures. This technique is rapidly gaining popularity in the treatment of uterine fibroids and certain solid cancers, such as hepatocellular carcinomas. See: Saralidze K, Knetsch ML, van der Marel C, Koole LH. Biomacromolecules 2010; 11: 3556-62.

Another very important branch of Prof. Leo Koole's research activities relates to central venous catheters. These devices are used frequently in the treatment of critically ill patients. It is known that use of these catheters is associated with substantial risks of complications, notably thromboembolism and bacterial infection. Prof. Leo Koole's group has developed new surface coatings for central venous catheters, which combine excellent haemocompatibility (no contact activation) and pronounced antimicrobial activity. This work aims at reducing the incidence of hospital-acquired infections. See: Stevens KN, Croes S, Boersma RS, Stobberingh EE, van der Marel C, van der Veen FH, Knetsch ML, Koole LH. Biomaterials 2011 32:1264-9.

Utilising network pharmacology and common mechanisms for cardiovascular target validation and drug discovery (Program 10)

PI: PROF. HARALD SCHMIDT

Prof. Harald Schmidt was recruited to Maastricht University from Monash University, Melbourne, Australia, in 2010. He is Professor of Pharmacology & Personalised Medicine at CARIM, co-leader of Maastricht University's Faculty of Health, Medicine and Life Sciences innovation platform and Board Member of the Maastricht Institute of Advanced Studies. As a European Research Council Advanced Investigator, he leads a EUROSTAR research program and has founded a European Science Foundation COST Action. He has previously worked in Australia, Germany and the USA where he held a number of different academic and business leadership positions. These include chair of Monash University's Centre for Vascular Health, chairs in pharmacology at the universities of Würzburg, Gießen, Melbourne, and as director of a drug discovery CRO at TransMIT, Giessen, Germany. He co-founded Vasopharm a drug discovery company now entering into phase III clinical development, which for two years he led as CEO. His research focuses on cardiovascular and neurological disease mechanisms, target validation, drug and biomarker discovery, personalised and network medicine. He has published over 160 peer-reviewed papers, reviews, books and patents (Hirsch-index of 67; Google-Scholar: tinyurl.com/q4july7). He is a member of the European Society of Cardiology Working Group on Cardiovascular Pharmacology and Drug Therapy, Section Editor of the Public Library of Science, and a Member of the Faculty of 1000 Medicine. He has been awarded the Roche Molecular Biochemicals Research Prize for Cell Biology, and, together with his team, the Phoenix Research Prize in Pharmacy and Pro Scientia Prize.

The program focuses on a new approach by moving away from our current organ- and symptom-based disease ontology. At its most radical, it challenges the notion that pure cardiovascular diseases exist at all. Instead, both genetic and metabolomic associations point to new, previously unrecognised disease families within an entire diseasome, some of which of course have a predominant, but not exclusive, cardiovascular phenotype. This program

will also leave the basic bench-to-bedside approach, and – together with international key collaborators - introduce an additional, reverse epidemiology-to-basic-to-clinic discovery and speed-validation approach, which will lead to novel diagnostics and evidence-based treatment suggestions, and – most importantly – immediate benefits to patient. The key links within the diseasome are hidden, common mechanisms. In the first instance the program will focus on oxidative stress interaction with nitric-oxide-cyclic-GMP signalling and its network with a particular focus on vascular dysfunction as a cause of diverse types of organ failure, e.g. stroke, Alzheimer Disease, vascular dementia, diabetic nephropathy and other diabetic end-organ damage, and heart failure with preserved ejection fraction.

Highlight: NADPH oxidases
Accompanied by three independent set of press releases in Netherlands, Switzerland and Australia, Prof. Harald Schmidt and his German and Australian collaborators identified different forms of the NADPH oxidase gene family as key disease triggers in stroke and diabetic nephropathy (both Nox4) and diabetic atherosclerosis and retinopathy (booth Nox1). A close collaborator - SME, GenKyoTex, Geneva, Switzerland - currently has a Nox1/4 inhibitor for diabetic nephropathy at phase II of clinical development. In 2013 another long-term collaboration with Bayer and the University of Gießen Lung Centre on modulators of soluble guanylate cyclaseresulted in a positive phase III trial in pulmonary hypertension and market entry. Other studies with sGC activators and eNOS decoupling are underway.

Imaging (Program 11)
PI: PROF. JOACHIM WILDBERGER

Prof. Joachim Wildberger heads the imaging program and is Chairman of the Department of Radiology and director of the Division of Clinical laboratories and Medical Imaging. He was trained as specialist in Radiology in Aachen (Germany), he received his PhD in Radiology in 2002, was appointed as Vice-chairman of the department in 2006 and received a professorship at the Technical University, Aachen in 2007. In July 2007 he became Head of Department of Diagnostic Radiology, HELIOS Klinikum Berlin-Buch, Charité Berlin, Campus Buch. In July 2008, he was appointed as full professor at Maastricht University. He is author and co-author of >230 scientific papers in peer-reviewed international journals (h-index: 35).

This program can be considered as an imaging platform with input from different core disciplines (radiology, nuclear medicine, optical imaging). From an imaging perspective as a motor of new cardiovascular research, imaging as such can be considered at three different levels of expertise: pure service for other researchers, the provision of expertise for a dedicated research project (employing new imaging procedures/techniques to answer a clinical or preclinical problem), and the development of new technologies. The main focus of the research line in terms of new technologies is still the development of new imaging techniques such as advanced MR, CT and SPECT (spectroscopy in the heart; functional cardiac assessment), the development of new tracers and the optimisation of contrast material delivery, the implementation of advanced imaging techniques that combine splendid anatomical display with functional information (PET-MR; post-processing) and the translation of imaging findings into clinical decision making (in terms of efficacy studies and benefits on a societal level). The program's excellence in the field of MR/imaging in general is generally acknowledged and this is critical for many projects.

Highlight: Diagnostic performance of non-invasive myocardial perfusion imaging for the detection of obstructive coronary artery disease
The diagnostic accuracy of the three most commonly used non-invasive myocardial perfusion imaging modalities, single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR), and positron emission tomography (PET) perfusion imaging for the diagnosis of obstructive CAD was determined. Additionally, the effect of test and study characteristics was explored. All yielded a high sensitivity, while a broad range of specificity was observed. SPECT is widely available and most extensively validated; PET achieved the highest diagnostic performance; CMR may provide similar diagnostic accuracy to PET but without ionising radiation. Since the publication of this study, referring physicians at our centre consider CMR more often as the imaging modality of choice.

B.3.4.2 Key publications

2007

Jonk AM, Houben AJHM, Jongh RT de, Serné EH, Schaper NC, Stehouwer CDA -
Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology 2007; 22: 252-60
IF 6.268

Verberk WJ, Kroon AA, Lenders JWM, Kessels AGH, van Montfrans GA, Smit AJ, van der Kuy PHM, Nelemans PJ, Rennenberg RJMW, Grobbee DE, Beltman FW, Joore MA, Brunenberg DEM, Dirksen C, Thien T, de Leeuw PW -
Self-measurement of blood pressure at home reduces the number of anti-hypertensive drugs: a randomized controlled trial. Hypertension 2007; 50: 1019-25
IF 6.007

Van Teeffelen JW, Brands J, Jansen C, Spaan JA, Vink H -
Heparin impairs glycocalyx barrier properties and attenuates shear dependent vasodilation in mice. Hypertension 2007; 50: 261-7
IF 6.007

Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, Dewor M, Georgiev I, Schober A, Leng L, Kooistra T, Fingerle-Rowson G, Ghezzi P, Kleemann R, McColl SR, Bucala R, Hickey MJ, Weber C -
MIF is a non-cognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. Nat Med 2007; 13: 587-596
IF 28.588

Mittal M, Roth M, König P, Hofmann S, Dony E, Goyal P, Selbitz A, Schermuly RT, Ardeschir Ghofrani H, Kwapiszewska G, Kummer W, Klepetko W, Hoda MAR, Fink L, Hänze J, Seeger W, Grimminger F, Schmidt HHHW, Weissmann N -
Hypoxia-dependent regulation of non-phagocytic NADPH oxidase subunit NOX4 in the pulmonary vasculature. Circ Res 2007; 101: 258-67
IF 9.854

2008

Cleutjens CBJM, Faber BC, Rousch M, van Doorn R, Hackeng TM, Vink C, Geusens PPMM, ten Cate H, Waltenberger JL, Tchaikovski V, Lobbes M, Somers V, Sijbers A, Black D, Kitslaar PJEHM, Daemen MJAP -
Noninvasive diagnosis of ruptured peripheral atherosclerotic lesions and myocardial infarction by antibody profiling. J Clin Invest 2008; 118(8): 2979-85
IF 16.915

Stehouwer CDA, Henry RMA, Ferreira I -
Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008; 51: 527-39
IF 5.822

2009

Koenen RR, von Hundelshausen P, Nesmelova IV, Zernecke AET, Liehn EA, Sarabi A, Kramp BK, Piccinini AM, Paludan SR, Kowalska MA, Kungl AJ, Hackeng TM, Mayo KH, Weber C -
Disrupting functional interactions between platelet chemokines inhibits atherosclerosis in hyperlipidemic mice. Nature Medicine 2009; 15(1): 97-103
IF 27.553

Kwee RM, Schreuder FHBM, Mess WH, van Oostenbrugge RJ, Triebels VHJM, van den Akker LH, Heeneman S, Hofman PAM, van Engelshoven JMA, Wildberger JE, Kooi ME -
Carotid intraplaque hemorrhage: a possible cause of stroke. Circulation 2009; 120: 1637-39
IF 14.595

Key publications

Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, van Oostenbrugge RJ -
Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomized trial. Lancet Neurol 2009; 8(4): 326-33
IF 14.27

Stevens KN, Crespo-Biel O, van den Bosch EE, Dias AA, Knetsch ML, Aldenhoff YB, van der Veen FH, Maessen JG, Stobberingh EE, Koole LH -
The relationship between the antimicrobial effect of catheter coatings containing silver nanoparticles and the coagulation of contacting blood. Biomaterials 2009; 30: 3682-3690
IF 6.646

Meurer S, Pioch S, Pabst T, Opitz N, Schmidt PM, Beckhaus T, Wagner K, Matt S, Gegenbauer K, Geschka S, Karas M, Stasch JP, Schmidt HHHW, Müller-Esterl W -
Nitric oxide-independent vasodilator rescues heme-oxidised soluble guanylate cyclase from proteasomal degradation. Circ Res 2009; 105: 33-41
IF 9.989

2010

De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, Grobbee DE, van Sambeek MR, Balm R, Blankensteijn JD, van Engelshoven JMA -
Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. New Engl J Med 2010; 362(20): 1881-9
IF 47.05

Hristov M, Gumbel D, Lutgens E, Zernecke A, Weber C -
Soluble CD40 Ligand Impairs the Function of Peripheral Blood Angiogenic Outgrowth Cells and Increases Neointimal Formation After Arterial Injury. Circulation 2010; 121(2): 315-24
IF 14.816

Oostendorp M, Douma K, Wagenaar A, Slenter J, Hackeng TM, van Zandvoort M, Post MJ, Backes WH -
Molecular Magnetic Resonance Imaging of Myocardial Angiogenesis After Acute Myocardial Infarction. Circulation 2010; 121(6): 775-83
IF 14.816

Lutgens E, Lievens D, Beckers L, Wijnands E, Soehnlein O, Zernecke A, Seijkens T, Engel D, Cleutjens J, Keller AM, Naik SH, Boon L, Oufella HA, Mallat Z, Ahonen CL, Noelle RJ, de Winther MP, Daemen MJ, Biessen EA, Weber C -
Deficient CD40-TRAF6 signaling in leukocytes prevents atherosclerosis by skewing the immune response toward an antiinflammatory profile. Journal of Experimental Medicine 2010; 207: 391-404
IF 13.21

Scheffers IJM, Kroon AA, Schmidli J, Jordan J, Tordoir J, Mohaupt M, Luft F, Haller H, Menne J, Engeli S, Ceral J, Eckert S, Erglis A, Narkiewicz K, Philipp T, de Leeuw PW -
Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. J Am Coll Cardiol 2010; 56: 1254-60
IF 12.64

2011

de Jager SC, Bermúdez B, Bot I, Koenen RR, Bot M, Kavelaars A, de Waard V, Heijnen CJ, Muriana FJ, Weber C, van Berkel TJ, Kuiper J, Lee SJ, Abia R, Biessen EA -
Growth differentiation factor 15 deficiency protects against atherosclerosis by attenuating CCR2-mediated macrophage chemotaxis. Journal of Experimental Medicine 2011; 208: 217-25
IF 13.21

Weber C, Noels H -
Atherosclerosis: current pathogenesis and therapeutic options. Nature Medicine 2011; 17(11): 1410-22
IF 25.43

Key publications

Weber C, Meiler S, Doring Y, Koch M, Drechsler M, Megens RTA, Fecher C, Binder CJ, Rowinska Z, Bidzhekov K, Ribechini E, van Zandvoort M, Lutz MB, Hristov M, Boon L, Jung S, Korn T, Jelinek V -
CCL17-expressing dendritic cells drive atherosclerosis by restraining regulatory T cell homeostasis in mice. Journal of Clinical Investigation 2011; 121(7): 2898-2910
IF 14.152

Emerging Risk Factors Collaboration -
Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829-41
IF 53.486

Daissormont IT, Christ A, Temmerman L, Sampedro Millares S, Seijkens T, Rousch M, Poggi M, Boon L, van der Loos C, Daemen M, Lutgens E, Halvorsen B, Aukrust P, Janssen E, Biessen EA -
Plasmacytoid dendritic cells protect against atherosclerosis by tuning T-cell proliferation and activity. Circulation Research 2011; 109: 1387-95
IF 9.504

2012

Bucerius J, Mani V, Moncrieff C, Rudd JHF, Machac J, Fuster V, Farkouh ME, Fayad ZA -
Impact of Noninsulin-Dependent Type 2 Diabetes on Carotid Wall F-18-Fluorodeoxyglucose Positron Emission Tomography Uptake. Journal of the American College of Cardiology 2012; 59(23): 2080-88
IF 14.156

Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, Nelemans PJ, Schalla S -
Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. Journal of the American College of Cardiology 2012; 59(19): 1719-28
IF14.156

Gaens KHJ, Niessen PMG, Rensen SS, Buurman WA, Greve JWM, Driessen A, Wolfs MGM, Hofker MH, Bloemen JG, Dejong CH, Stehouwer CDA, Schalkwijk CG -
Endogenous formation of N-epsilon-(carboxymethyl)lysine is increased in fatty livers and induces inflammatory markers in an in vitro model of hepatic steatosis. J Hepatol 2012; 56: 647-55
IF 9.264

Knottnerus I, Winckers K, ten Cate H, Hackeng T, Lodder J, Rouhl R, Staals J, Govers-Riemslag J, Bekers O, van Oostenbrugge RJ -
Levels of heparin-releasable TFPI are increased in first-ever lacunar stroke patients. Neurology 2012; 78: 493-498
IF 8.32

Vlahu CA, Lemkes BA, Struijk DG, Koopman MG, Krediet RT, Vink H -
Damage of the endothelial glycocalyx in dialysis patients. J Am Soc Nephrol 2012; 23: 1900-8
IF 9.663

B.3.4.3 Strategy based on SWOT analysis

The SWOT analysis below is based on the CARIM Midterm 2007-2011 and the CARIM future research strategy evaluation in 2012. It clearly defines Theme III's key strategy, which is to enhance synergy to improve performance and successfully adapt to changing societal needs.

STRENGTHS
1. The Maastricht Study is up and running
2. The Cardiovascular Centre of Excellence has been established
3. A strong imaging group has been developed, which is well-embedded in CARIM's early position as a reference center for both vascular ultrasound and microcirculatory imaging. Preclinical and clinical imaging expertise and infrastructure are continually being developed to both define and keep pace with the state-of-the-art
4. The Biomedical Engineering Department has been re-established. Physical modeling is an indispensable asset in translating basic research findings at micro-levels (i.e. molecule and cell) to macro-levels (i.e. organ/system and patient). Past developments in circulatory modeling are now finding their way to clinical application in cardiology, paediatrics and vascular medicine & surgery
5. The Maastricht Centre for Systems Biology has been established
6. A Vascular Network Group has been initiated to facilitate cross-theme and cross-school interactions between basic and clinical/epidemiological researchers with focus on ageing and metabolic disorders

WEAKNESSES
1. There is an as of yet insufficient critical mass of systems biology, bioinformatics/statistics, biomedical engineering and clinical physics approaches that are essential for developing and integrating mechanistic knowledge across system levels to translate findings into application for societal health benefit.

OPPORTUNITIES
1. Increasing the CARIM tradition of multi- and interdisciplinary research, i.e. to promote and facilitate cross-theme and cross-school developments will make Theme III and CARIM a stronger leader in translational vascular biology research. There are emerging structural collaborations between CARIM, CAPHRI, NUTRIM and MH&NS.

THREATS
1. The breadth of approaches within and the diverse composition of Theme III could lead to incoherent research and funding strategies that may endanger creativity and continuity.
2. The scattered appearance of expertises, resources and initiatives, if unaddressed, may create an unattractive outward image, hampering partnering with international research consortia and industry.

CARIM

School for Cardiovascular Diseases

Self-Evaluation 2007-2012

C_ ANNEXES

ANNEX 1
ABBREVIATIONS

AMC	Academic Medical Centre Amsterdam
BMM	BioMedical Materials
CAPHRI	School for Public Health and Primary Care
CaRES	CARIM Research Education and Supervision plan
CARIM	School for Cardiovascular Diseases
CPP	Average number of citations per publication, or citations per publication ratio. Self-citations are excluded
CPV	Centrale Proefdier Voorzieningen (animal facility)
CTCM	Clinical Trial Centre Maastricht
CTMM	Centre for Translational Molecular Medicine
CVC	Cardiovascular Centre of Excellence (CARIM/HVC)
CVON	Cardiovasculair Onderzoek Nederland (Dutch Cardiovascular Research)
CWTS	Centre for Science and Technology Studies
EB	Executive Board
ECOS-KNAW	Recognition Committee Research Schools-Royal Dutch Academy of Arts and Sciences
ECTS	European Credit Transfer and Accumulation System
EJD	European Joint Doctorate
Erasmus MC	Erasmus University Medical Centre Rotterdam
ERC	European Research Council or External Review Committee
EPC	Education Program Committee
EuCAR	Euregio Cardiovascular International Research Training Group GRK 1508 (RWTH Aachen/CARIM Maastricht)
FHML	Faculty of Health, Medicine and Life Sciences
FTE	Full-time equivalent
GROW	School for Oncology and Developmental Biology
HVC	Hart en Vaatcentrum (Heart and Vascular Centre)
ICaR-VU	Institute for Cardiovascular Research, Free University Amsterdam
IF	Impact Factor
ITN	Initial Training Network (Marie Curie action within Horizon 2020)
KNAW	Royal Dutch Academy of Arts and Sciences
LUMC	Leiden University Medical Centre
MH&NS	School for Mental Health and Neurosciences
MNCS	Mean normalized citation score. The average number of citations of the publications of a university, normalized for field differences, publication year, and document type.
MNJC	The impact of the journals in which a research unit has published (the research unit's journal selection), compared to the world citation average in the subfield covered by these journals
MUMC+	Maastricht University Medical Centre+
NFU	Dutch Federation of University Medical Centres
NHS	Dutch Heart Foundation
NUTRIM	School for Nutrition, Toxicology and Metabolism
NWO	Dutch Foundation for Scientific Research
ORPHEUS	Organisation for PhD Education in Biomedicine and Health Sciences in the European System
P	Number of publication
PI	Principle Investigator
RC	Research Council
SB	Strategic Board
SEP	Standard Evaluation Protocol
SHE	School for Health Professions Education
TEC	Thrombosis Expertise Centre
TTI	Technological Top Institute
UMC	University Medical Center
VENI/VIDI/VICI	Personal grants from the Dutch Foundation for Scientific Research (NWO) Innovational Research Incentives Scheme
VSNU	Association for Co-operating Dutch Universities
VUMC	VU University Medical Centre Amsterdam
WI-1	Peer-reviewed publication
ZonMW	Netherlands Foundation for Health Care Research

ANNEX 2
MASTERPLAN CVC

Foreword

The document ‘Cardiovascular Center Maastricht UMC+, blueprint for the realisation of an international center of excellence’ (hereinafter: blueprint) was written in May 2012. This document sets out a concept for an international cardiovascular center of excellence that is destined to become one of the best in Europe. The blueprint was well received by our stakeholders and the Executive Board. An effective and dynamic decision-making process is important to the Cardiovascular Center Maastricht UMC+ (hereinafter CVC Maastricht) being realised in the foreseeable future. The formalisation of the blueprint into a master plan, including financial impact report is essential in this context.

This master plan is presented here.
It corresponds exactly with the strategy recently plotted by Maastricht UMC+, which provided the contextual policy framework for the CVC Maastricht. This strategy is based on the following three pillars:

1. UMC development;
2. Development of centers of excellence and;
3. Operational excellence.

The joint and integrated further development of the Heart and Vascular Center (HVC) and the Cardiovascular Research Institute Maastricht (CARIM) into one center of excellence may in fact be considered the application of the process of UMC formation within the cardiovascular domain. The development of the CVC Maastricht as an international center of excellence is a direct response to the desire to create a small number of high quality centers of excellence which combine patient care, research and training at the highest level.

Operational excellence will take concrete shape by creating a truly patient centered organisation with excellent logistics. Building on a strong regional position and integration, the intended

CVC Maastricht seeks to acquire a top ranking position at national level. Furthermore, it has the express ambition to position itself internationally on the basis of a unique, distinctive profile. A profile based on five key focus areas, namely:

1. Thrombosis;
2. Arrhythmia;
3. Heart Failure;
4. Macro Vascular;
5. Micro Vascular.

In the period 2013-2018 CVC Maastricht should develop into an entrepreneurial organisation with excellent key players in the above key focus areas. At CVC Maastricht a high patient volume should go hand in hand with innovation. This innovation will be driven primarily by translational research. The research and health care chain will be organised and integrated for each of the focus areas. CVC Maastricht will be a financially robust organisation.

The high patient volume in combination with successful research projects will guarantee that. In this context, CVC Maastricht chooses expressly for a positive revenue model and a high level of self-responsibility. CVC Maastricht opts for an appropriate organisational independence and corresponding governance structure that does justice to the opportunities and possibilities available to CVC Maastricht.

This master plan is the result of the efforts, inspiration, diligent work and commitment of many. We would therefore like to extend our special thanks to everyone who contributed to this master plan.

Prof. Dr. Michael Jacobs MD
Executive Director HVC
Chair of the CVC Program Board

Prof. Dr. Thomas Unger MD
Executive Director CARIM

Drs. Ir. Henk Hoogervorst
Program Director CVC

Contents

Note to readers: in cases relating to the present situation the names CARIM and HVC are used. In all other cases the name CVC Maastricht is used.


WAT JE NIET KENT, HERKEN JE NIET!
Post operatief

1 CVC Maastricht: context and ambition

Context

CVC Maastricht should be considered as the joint and integrated further development of the Heart and Vascular Center[1] (HVC) and the Cardiovascular Research Institute Maastricht CARIM[2 3] into one center of excellence. Both institutes have developed strongly over the past decades and have built up a considerable track record accordingly. National and international peers recognise and acknowledge the position of CARIM and HVC as top institutes. Notably, an external visitation committee of international experts classified the research conducted by CARIM in 2009 as very good to excellent.

The quality of CARIM's scientific output has been consistently high for many years. With a turnover of over 77 million euros and 9500 cases[4] in 2011, HVC is among the larger cardiovascular centers in the Netherlands. Indeed, with regard to certain interventions and procedures HVC holds a leading position. Not only at national level, but also at European level. With a total staffing of 575 FTE, the combination of CARIM and HVC, is one of the *largest integrated cardiovascular centers* in both the Netherlands and Europe.

There is much interest from the national government, and increasingly also from the European government, for the activities of CARIM and HVC. CARIM and HVC collectively hold a prominent position in the (top sector) policy formulated by the Dutch government. The Hague considers both to be top centers.

For several ministries Maastricht UMC+ is synonymous to high quality, innovative cardiovascular care and research[5], and with good reason.

Companies that operate internationally in the field of medical technology also endorse the high standard of cardiovascular knowledge and expertise available in-house. Large scale and intensive public-private partnerships, such as CTMM and BMM form the basis for further growth and development in the cardiovascular domain. And this does not only apply to (long-term) contract research.

New initiatives, such as the realisation of joint high-quality training facilities in Maastricht, are currently being explored.

The cardiovascular research and patient care performed and provided by CARIM and HVC are of strategic importance to Maastricht UMC+. An importance which will further increase in the future. As such, Maastricht UMC+ also recognises and acknowledges the cardiovascular domain as one in which it can distinguish itself[6].

Ambition

As indicated earlier, CARIM and HVC have extensive and intensive knowledge in the cardiovascular field. Indeed, it is here that the cardiovascular competence of Maastricht+ is concentrated. To ensure continued success in the future an integral plan has been developed, based on a collective vision and ambition, to position CVC Maastricht as a center of excellence. Not only at national level, but also at international level. *CVC Maastricht has the ambition of developing into one of the top ten in Europe in the period up to 2020*. An ambitious yet most certainly realistic goal. CVC Maastricht aims to achieve this by focusing on a limited number of key focus areas. Areas in which the institutes already hold a strong to very strong position, from both a clinical and a research perspective.

Quantitative data to substantiate the stated ambition

There is no denying that the vision set out above, of an integrated cardiovascular center of excellence that aims to achieve a top 10 position in Europe, is an ambitious one. Over the past months a methodological sanity check was conducted to verify explicitly and with external support - ‘two heads are better than one’ - whether this ambition is realistic. To do justice to the inherently different natures of both clinical and research activities, a two-dimensional approach was adopted.

To do justice to the inherently different natures of both clinical and research activities, a two-dimensional approach was adopted.

HVC

With regard to HVC the number of procedures (volume of cases) representative of a specific key focus area was considered. A list of interventions and procedures was compiled, which is distinctive of HVC and which gives an objective indication of the type and number of interventions and procedures.

The conclusion is that benchmarked with 3600 European cardiovascular centers, in terms of volume (= number of procedures), HVC is in the top 100. In terms of the aforementioned procedures and in relation to the selected key focus areas, it is among the leading centers in Europe. In certain areas (TAA and AAA) it is even one of the largest centers in the 2nd and 8th positions respectively.

By focussing, CVC Maastricht satisfies the government strategy of centralising knowledge. This will also lead to increased patient flows within the five key focus areas.

Focusing specifically on a further increase in the number of procedures performed, such as ICDs and CRT-Ds, generates volume growth. A consequence of such volume growth is that the specific knowledge and expertise in relation to the focus area or areas also increases.

CARIM

In relation to CARIM, one of the key performance indicators for scientific research is the number and quality of scientific articles published. Every year, scientists associated with CARIM publish a large number of scientific articles in journals both within and outside their specialisms. This number increases every year; in 2011 there were 569 publications (495 of which in peer-reviewed journals).

Not only the number of publications is high, so too is their impact. The average impact factor (IF) of the journals in which these articles are published (determined by how often articles in the journal concerned are cited by other researchers) has risen significantly in recent years, with an average IF of 5.5 in 2011. More than 25% of the articles produced at CARIM are published in international journals ranked in the top 10% of the research field.

An analysis of data relating to these publications (quantity, impact, citations, etc.), a so-called bibliometric analysis, enables the comparison of groups of scientists with others, in either their own or other fields of specialisation, as any differences in scientific disciplines and fields are corrected. Every year, the Netherlands Federation of University Medical Centers (NFU) has the Center

for Science and Technology Studies (CWTS) analyse the bibliometric data of the eight Dutch UMCs. From the beginning of the analysis, CARIM has consistently maintained a level well above the world average. Remarkably enough however, CARIM has shown a particularly sharp increase in recent years. CARIM´s score has risen from 1.22 in 2006 to 1.79 in the most recent analysis, thus scoring well above the world average of 1.0. This means that CARIM´s publications are cited 1.79 times more often than average. In the most recent analysis Maastricht UMC+ scored 1.90 in the field of 'Cardiology and Cardiovascular System', the highest of all Dutch UMCs.

In fact, articles by CARIM´s Cardiology department are cited 2.7 times more often than the world average and other divisions of the Internal Medicine department (diabetes-cardiovascular, haematology, clinical immunology and nephrology) are cited more than twice as often as the world average.

CARIM's scientific output does not consist of articles alone: young PhD candidates write a PhD thesis.
At CARIM the number of these has remained constant over the last years, with an average of approx. 30 PhD theses per year. In addition, four patents were filed in 2011. CARIM researchers receive worldwide recognition. For example, the European Research Council (ERC) recently awarded CARIM researchers prestigious Advanced or Starting Grants, and CARIM has attracted various Veni, Vidi and Vici grants from the Netherlands Organisation for Scientific Research (NWO), various clinical fellowships, Mozaïek laureates and E. Dekker scholarships (at both senior and junior levels) from the Dutch Heart Foundation, and scholarships and grants from CVON and the Leducq Foundation. For years, CARIM has been a recognised training institute for researchers in the EU. Various institutional and individual Marie Curie grants from the EU support the international aspect of the training.

CARIM's income has grown steadily by the year to 22.8 million euros in 2011. Of this, 8.2 million euros is direct government funding, 1.4 million euros is indirect funding from such independent public organisations as NWO and KNAW [Royal Netherlands Academy of Arts and Sciences], and 13.2 million euros is project-related funding from charity funds, EU funding, business contracts, et cetera. Public-private collaboration has enabled CARIM to secure a prominent position among the Top Technological Institutes (TTI), CTMM and TI Pharma.

The knowledge and expertise developed at CARIM in the field of the diagnosis and treatment of cardiovascular conditions is increasingly used to generate spin-off companies (e.g.Vitak K, Synapse BV, Glycocheck BV, FABPulous BV Pharma Target BV, Mirabilis BV, YourRhythmics BV). These valorisation activities express a clear and identifiable relationship with the Maastricht Health Campus[7] currently under development.

International collaboration, partnerships and alliances

The developed medical concept (Chapter 2), finally, also forms the policy framework on the basis of which CVC Maastricht will invest in (forms of) long-term collaboration with renowned national and international partners such as RWTH Aachen (Germany) and the Helmholtz-Institut für Biomedizinische Technik (Aachen, Germany), Gutenberg Research College (Mainz, Germany), Hospital Clinic (Barcelona, Spain), Imperial College London (UK), et cetera. In its policy, CVC Maastricht opts consistently for an approach in which the individual key focus areas and the cross-over areas form the points of departure from which collaboration materialises. The actual operational implementation and/or execution of such collaboration, however, will occur at the level of the stated fields of expertise (see examples in the text boxes). With regard to national and international collaboration, CVC Maastricht, within the context of Maastricht UMC+ and its policy in relation to such, will enter strategic alliances with a limited number of partners.

International collaboration in cardiovascular genetics: GIGA, LIFA and CVC Maastricht

Genetics has resulted in an explosion of knowledge in Life Sciences. Traditionally, the focus lies on mutations in DNA exons as the cause of monogenic disorders. Today however, many humane diseases are suspected to have a complex genetic basis with several gene variants contributing to the phenotype individually or by interacting with each other and/or environment factors.

CARIM researchers have successfully characterised the structural and functional basis of cardiovascular diseases. Current cardiovascular research at CARIM nevertheless lacks a strong genomic component. Conversely, this does exist at the Interdisciplinary Cluster for Applied Genoproteomics (GIGA), where genoproteomics is the core technology. GIGA, a center of excellence at the Université de Liège (UdL), is built up around eight thematic research units including ´cancer´, development, stem cells & regenerative medicine´, ´infection, immunity & inflammation´, ´neurosciences´ and ´cardiovascular conditions´. Besides these research units, GIGA has advanced technology platforms, its own ‘technology transfer office’, its own ‘incubator’ with corresponding facilities and a training center. GIGA has over 550 employees. GIGA has a strong relationship with the Center Hospitalier Universitaire de Liège (CHU) and is based in the buildings of the university hospital.

An international research alliance between CVC Maastricht and GIGA encourage and accelerate the development of the ´cardiovascular disorders´ unit within GIGA on the one hand and ´cardiovascular genetics´ as a research focus within CVC Maastricht on the other. In addition, this will synergistically increase the scientific output and fundraising of both centers.

In a genome-based research approach genome-wide association studies (GWAS) and gen-sequencing provide a stimulus for: (1) hypothesis-driven research, (2) pathophysiological insights, (3) risk¬assessment of disease-related complications, (4) system biological approach to complex disorders and (5) personalized medicine. Improved knowledge of molecular-genetic cascades could lead to improved therapy on a wide scale (regardless of the individual

genotype) or at an individual level (tailored to the specific genotype). Such an approach usually calls for large numbers of patients, an optimal technological environment with open access laboratories, shared equipment, multidisciplinary interaction and highly qualified academic personnel. The current situation regarding cardiovascular-genetic research within CARIM does not satisfactorily meet these requirements.

An essential condition for in-depth genetic research into multifactorial cardiovascular disorders is a laboratory environment with high-throughput genomic screening. This alone will not suffice, however. Besides the technological preconditions, the bioinformatics must also be very well organised. In addition, genomic analysis, bioinformatics and high-quality phenotyping should be optimally interlinked under the heading ‘functional genomics’.

Recent talks with Prof. Monika Stoll of Westfälischen Wilhelms-Universität in Münster, Germany, have resulted in a memorandum of understanding in which she offers her expertise to advise CVC Maastricht on complex genetic research.

Prof. Stoll leads a Genetic Epidemiogy department in Münster, which has highly-advanced techniques at its disposal for low and high-throughput genotyping. Her research group has developed new algorithms for the GWAS analysis and pathway analysis as well as for the targeted sequencing of associated genomic regions. In addition, she is Managing Director of Leibniz Institut für Arterioskleroseforschung (LIFA). LIFA has arrays for single-nucleotide polymorphisms, copy number variations, DNA-methylome and RNA¬transcriptome analysis including next-generation sequencing. Large datasets can also be analysed.

On the grounds of the above, a strategic alliance is currently being developed between CVC Maastricht, GIGA and LIFA to consolidate the cardiovascular genetic research in Maastricht. The fact that all three institutes are part of a University Medical Center (Maastricht, Liège and Münster) enables fast translational research initiatives (bench to bedside and vice versa) with improved diagnostics and therapy of the patient being one of the objectives.

CVC Maastricht as an international center for neuromonitoring during complex vascular procedures

One of the specialties of the Maastricht UMC+ is the surgical management of complex aneurysms of the aorta. In these complex procedures the dilated aorta must be replaced in order to prevent rupture and sudden death. One of the main complications that can occur after extensive aortic replacement is damage to the spinal cord, leading to paraplegia. The cause is interruption of the essential blood supply to the spinal cord, causing infarction of the spinal cord and subsequent paralysis. The risk of paralysis in the most extensive aortic replacement can reach 25%.

Together with the department of clinical neurophysiology, the CVC Maastricht has developed a technique to assess the function of the spinal cord online. If the function of the spinal cord is threatened, it can be restored by means of surgical and anesthesiological interventions. Using this neuromonitoring, the risk of spinal cord lesions has been significantly reduced (2% to 4%).

To transfer this expertise to other aortic centers, a 'telemedicine' technique has been developed: neuromonitoring takes place in real-time via the Internet. In 2006, the first connection was established with the department of vascular surgery in Aachen, Germany. A patient undergoing a major aortic procedure in Aachen is connected to the local neuromonitoring system but the data are transferred to the neurophysiologist in Maastricht via the Internet, on-line interpreted and immediately communicated to the surgeon in Aachen. Based on this data the surgeon decides whether specific interventions have to be carried out in order to safeguard the spinal cord function. Since then, the same connections have been set up with the university hospitals in Hamburg (Germany), Bern (Switzerland), and Regensburg (Germany). In total, more than 300 complex aortic procedures have now been performed with the aid of this centralized monitoring from Maastricht, and the incidence of paraplegia has fallen significantly in all centers. These experiences have recently been published in a prominent scientific journal. This is an example of the leading international role fulfilled by the CVC Maastricht.

Cardiovascular powerhouse

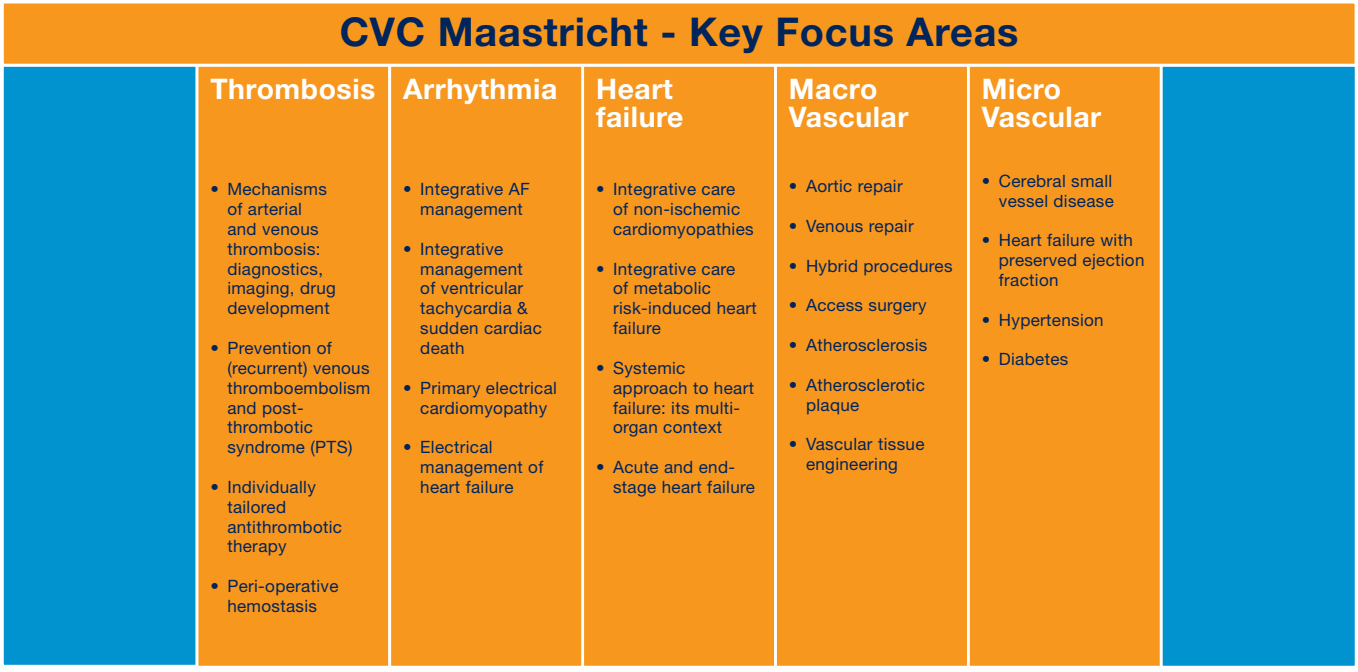
It is therefore justified to conclude that the combination of HVC and CARIM will create a ‘cardiovascular powerhouse’ which, in respect of the selected focus areas, could develop into one of the top 10 in Europe. Targeted investment in the further development of the focus areas, cross-over areas, and the corresponding infrastructures is essential, however.

2. Medical concept

The future development of cardiovascular knowledge and expertise within CARIM and HVC has been laid down in an integrated medical concept (see figure 1). From a competitive perspective and based on existing expertise and clinical, scientific and financial parameters, five key focus areas have been selected, namely:

- Thrombosis;
- Arrhythmia;
- Heart failure;
- Macro Vascular;
- Micro Vascular.

Figure 1 CVC Maastricht Key Focus Areas



Complementary to this are two so-called cross-over areas (see figure 2):

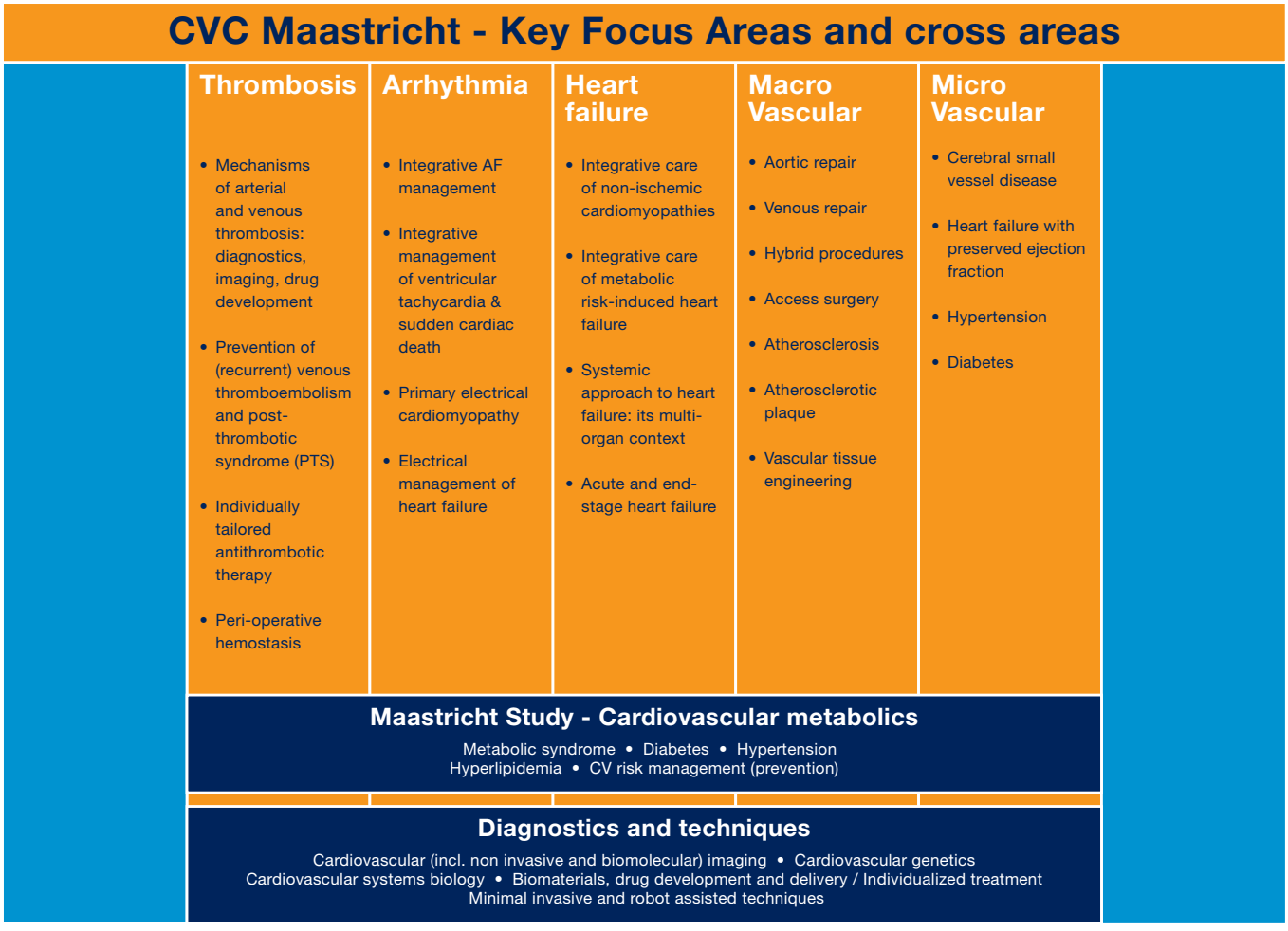
- Cardiovascular metabolics;
- Diagnostics and techniques.

Together, the key focus areas and cross-over areas form the medical concept.

As a whole, this guarantees a unique cardiovascular profile. A profile which distinguishes itself from other cardiovascular centers in the Netherlands and Europe, not only with regard to complex and highly specialized care but also in terms of scientific research. The medical concept is based on focus areas and cross-over areas which already have a proven reputation and contribute to the distinctive profile of CVC Maastricht mentioned above. The medical concept also forms the foundation in which such aspects as patient care, research, innovation, teaching, 'public outreach', and the correlation between them, are logically embedded.

These focus areas were further analysed[8] for the present master plan with the objective of determining a *strategic portfolio of cardiovascular*

Figure 2 Key focus areas and cross-over areas together form the medically based concept



areas of expertise, seen both independently and in coherence, nationally and internationally, as a benchmark and which in fact form the distinctive strength of CVC Maastricht. The fact that these areas of expertise comprise both (integrated) care and research components must not go unmentioned. As such, the defined areas of expertise are examples of complex and highly specialized care.

Thrombosis

Within the focus area Thrombosis, CVC Maastricht focuses on the following areas of expertise:

1. Mechanisms of arterial and venous thrombosis: diagnostics, imaging, drug development; Prevention of (recurrent) venous thromboembolism and post-thrombotic syndrome (PTS);
2. Individually tailored antithrombotic therapy;
3. Peri-operative hemostasis.

For the sake of clarity, a compact description is given of the specified areas of expertise for the focus area thrombosis (see page 23).

Arrhythmia

Within the focus area Arrhythmia, CVC Maastricht focuses on the following four areas of expertise:

1. Integrative AF management;
2. Integrative management of ventricular tachycardia and sudden death;
3. Primary electrical cardiomyopathy;
4. Electrical management of heart failure.

There are also clear interfaces between the last two areas of expertise above, in which experimental and clinical research into conduction disorders (3) and cardial resynchronization therapy (CRT (4)) play a key part, and the focus area of heart failure.

Heart Failure

Within the focus area heart failure CVC Maastricht focuses on the following four areas of expertise:

1. Integrative care of non-ischemic cardiomyopathies;
2. Integrative care of metabolic risk-induced heart failure;
3. Systemic approach to heart failure: its multiorgan context;
4. Acute and end-stage heart failure.

Macro-vasculair

Within the focus area Macro-Vascular CVC Maastricht focuses on the following seven areas of expertise:

1. Aortic repair;
2. Venous repair;
3. Hybrid procedures;
4. Access surgery;
5. Atherosclerosis;
6. Atherosclerotic plaque;
7. Vascular tissue engineering.

Micro-Vascular

Within the focus area Micro-Vascular CVC Maastricht focuses on the following four areas of expertise:

1. Cerebral small vessel disease;
2. Heart failure with preserved ejection fraction;
3. Hypertension;
4. Diabetes.

In part, CVC Maastricht is treading new ground with the focus area Micro-Vascular. The pathology of the great vessels is traditionally a key area of attention within Maastricht UMC+. However, an increasing number of patients develop syndromes without there being any problems with the great vessels and there is a growing theory that early vascular problems occur primarily in the smaller blood vessels (microcirculation). Maastricht UMC+ has a leading position, both nationally and internationally, in microcirculation and experimental models. The clinically practicable monitoring systems[9] that have recently become available make it possible for the vital role of microcirculation in the functioning of the heart, brain and kidneys to become a key focus area within CVC Maastricht[10]. This will enable CVC Maastricht to play a leading role in the early diagnosis and (specifically) the repair of microvascular vulnerability. The ultimate objective is to develop preventive strategies to prevent organ damage (see notes on p. 24).

With respect to the three cross-over areas specified, it may be noted that the cross area ‘Diagnostics and Techniques’ is divided into five functional areas of competency, namely:

1. Cardiovascular imaging[11];
2. Cardiovascular genetics;
3. Cardiovascular systems biology[12];
4. Biomaterials, drug development and delivery / individualized treatment;
5. Minimally invasive and robotic techniques.

A key characteristic of these five areas is that they greatly facilitate the stated focus areas and in part also the two other cross-over areas, yet concurrently go beyond focus areas and cross-over areas in terms of method and technique.

The other cross-over area, Maastricht Study - cardiovascular metabolics, also go beyond the focus area and provide CVC Maastricht with a necessary context and depth with regard to the aspect of integral cardiovascular health. This will be dealt with in more detail in Chapter 4.

Growth engines

An explicit aim within the five focus areas is the development of so-called 'growth engines'. This term refers to the substantive developments within a single focus area or between two or more focus areas. These growth engines are essential to the further qualitative and quantitative growth of both the individual focus areas and CVC Maastricht as a whole. To be able to anticipate these and other internal and external developments, CVC Maastricht will need to modify its strategic portfolio continuously.

Concise details of areas of expertise Thrombosis

Mechanisms of thrombosis (better diagnostics and intervention development; effect of clotting on such complex processes as AF and atherosclerosis):

1 Improvement of diagnostics to detect risk of haemorrhage and thrombosis. The basis for this lies in the CTMM- INCOAG program of which Maastricht is pioneer. The aim is to achieve increased sensitivity and improved applicability with regard to point of care tests. There is great potential in this respect as, in principle, all patients with hemostasis and thrombosis would be eligible.

2 Unravelling fundamental mechanisms which link hemostasis and clotting to thrombosis, but also to 'pleiotropic' complex disorders such as atherosclerosis, ischaemia¬reperfusion damage and cancer. This concerns much of the more fundamental and translational biochemical research related to structure- function coagulation proteins, drug design and imaging.

Prevention of recurrent VTE and Post thrombotic syndrome:

1) Deep venous thrombosis (DVT) care line: to promote the quality of care for the prevention of post-thrombotic syndrome (PTS) linked to clinical research, including effectiveness research (IDEAL study).
2) Catheter-directed thrombolysis and stenting in patients with (sub)acute DVT; development as reference center for the Netherlands and Euregio (European Venous Center).
3) Tailored treatment of VTE: in the near future through tailoring of anticoagulation medication, through tests developed in CTMM¬INCOAG, among others, also suitable for new oral anticoagulants. (in collaboration with regional and thrombosis service).

Antithrombotic therapy: individual, tailored: new care line and research to be set up in collaboration with Sint Antonius Hospital Nieuwegein and aimed at optimizing platelet lowering medication in individual patients. Concerns approx, 800 patients a year in own hospital with potential for regional growth.

Perioperative hemostasis (bleeding, transfusion): a number of studies are ongoing in collaboration with anaesthesiology and clinical chemistry into possible improvements of early detection of bleeding and transfusion policy. Thanks to the development and application of various diagnostic tests, Maastricht is the ideal place to raise such research to a higher level. This concerns hundreds of patients a year undergoing operations and is important to all surgery involving any risk of bleeding.
The PANE clinical study starting in 2013 is the first large-scale initiative (Annadal/azM/CARIM funded). Embedded in this research is the more basal research by Heemskerk et al, which concerns platelet function disorders in relation to hemostasis abnormalities (congenital but also acquired).

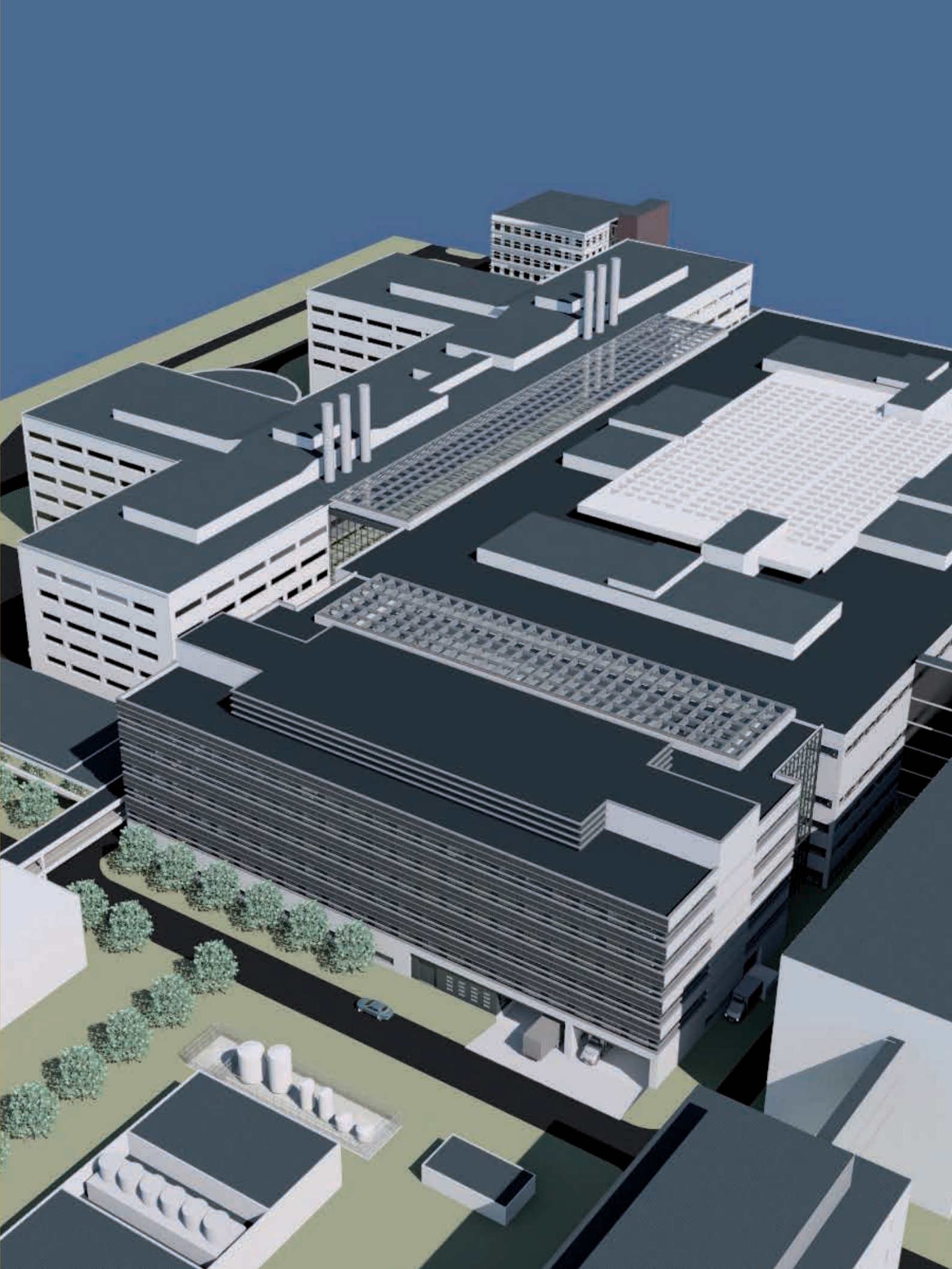
Microcirculation as focus area in CVC Maastricht

There are indications that vascular problems occur primarily in the smallest blood vessels; microcirculation. Depending on the organ concerned, there can be over 3,000 capillaries per mm^2 of tissue, and with the surface area of organ cells in our entire body totalling some 2000 m^2, the is a very close relationship between microcirculation and organ function.
Extensive expertise in the field of microcirculation is available within both CARIM and HVC. At CARIM there is broad knowledge of and facilities for research into the normal physiology of microcirculation on the one hand and pathophysiological mechanisms that take place in the vascular wall. At HVC there is clinical expertise relating to the consequences of microcirculation disorders in the heart and brain. Moreover, there is extensive knowledge of various system disorders associated with microcirculation, namely hypertension and diabetes mellitus.

Bundling this expertise under one overarching theme would produce a large critical mass in a domain in which CVC Maastricht holds a leading position, which it would also be able to further expand. This theme is called ‘microcirculation’ or ‘microvessels’. This includes research into the normal functions of these capillaries at vascular wall level on the one hand. On the other, research is also conducted into which pathophysiological mechnisms lead to dysfunctional microcirculation. Such dysfunctional microcirculation is known to impact the occurrence of system disorders such as hypertension and insulin insensitivity/diabetes mellitus. However, further research into this relationship is required in order to develop new therapeutic possibilities. The reverse interaction of microcirculation, namely the impact of diabetes or impaired glucose regulation and/or hypertension on the functioning of the vascular wall will also be researched in more depth.
The impact of dysfunctional microcirculation will be also be researched at organ level (heart and brain). The structure and function of the organ is therefore examined in these organs. This disorder at organ level reveals itself as a clinical manifestation such as pump failure, cerebral small vessel disease (cognitive decline and strokes), and such clinical manifestation of the disorder is therefore examined at microvessel level. The interaction between such cardiovascular risk factors as hypertension and diabetes mellitus combined with microvascular abnormalities is a phenomenon that amplifies

rapid structural changes in these organs with clinical consequences. These relations are also being researched.

This theme will ultimately lead to possibilities of applying the expertise at vascular level and utilizing the technical facilities available within the microcirculation lab, for example, for such higly specialized care problems as cognitive impairment and pump failure at organ level. But also for more systemic disorders such as diabetes melllitus and hypertension. A highly translational systems biology approach is thus guaranteed.



3 Research and Innovation

CVC Maastricht deliberately chooses to develop the stated focus areas on the basis of the entire research chain (see figure 3). That is to say that within each of the five chosen focus areas there are research activities for every research phase. The entire research chain consequently exists within each of the five stated focus areas. The translational phase, already strong and distinctive to Maastricht UMC+, will be used explicitly as a catalyst in strengthening the focus areas.

CVC intends to structure the organisation of the research for each focus area. The objective is to organise a permanent research chain for each focus area which will be led by a clinician and a researcher. On the basis of objective data with regard to current research achievements CVC Maastricht will become one of the most innovative cardiovascular centers in the given focus areas.

New, mostly state-of-the art developments in the field of diagnostics, therapeutics and interventions are regarded as ground-breaking in their field.
In terms of innovation driven research, CVC Maastricht will be positioned as 'product leader' for clinical solutions[13]. Several companies in the field of medical technology endorse this vision, as illustrated by their commitment to CVC Maastricht. One of the many examples of ground-breaking innovations is hybrid AF ablation.

Innovation themes

The chosen organisation of the focus areas and cross-over areas corresponds seamlessly with the selected strategic innovation themes of Maastricht UMC+. These strategic innovation themes are:

- *Lifestyle & prevention*
- *Smart technology*
- *Personalized health*
- *Operational excellence*

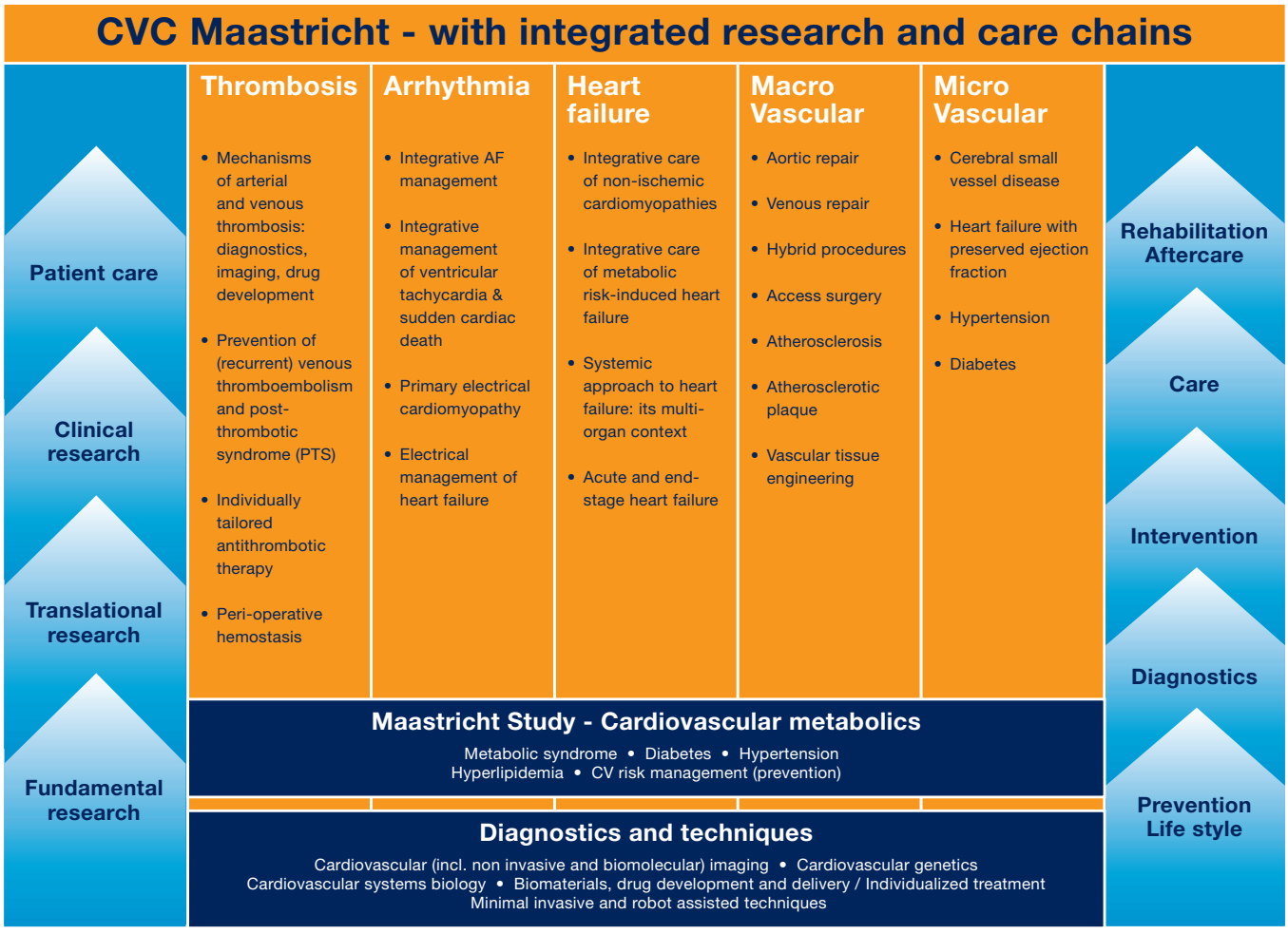
Systems biology based cardiovascular research

A major development is ongoing within CARIM to create a systems biology foundation for the fundamental cardiovascular research.

Multi-scale modelling is a central theme in various systems biology programs in Maastricht. To that end, a combination of experimental, theoretical and computational techniques is used to study interactions between a biological entity and its parts.

The aim is to develop technological platforms which make optimal use of the available infrastructure (genetics and genomics platforms, proteomics, cell culture facilities, imaging platforms, facilities for cellular and animal-experimental phenotyping). Efforts are also made to ensure optimum access for individual researchers. Within these platforms additional attention is also paid to a joint IT network for harmonized data presentation, documentation and storage.

Figure 3: Research and care chain (left and right respectively) in relation to the focus areas.



A key area of attention within the focus area heart failure and arrhythmia is the execution of screening assays based on hypothesis-free ‘high-content’ cell culture, linking phenotype to clinically relevant variants in protein coding genes and in non-coding DNA regions.
Another area of attention relates to the documentation of complex biological systems by combining data from the various ‘omics’ fields; a process to which bioinformatics, mathematical biology, systemic modelling and computational models enabling in-depth interpretation of imaging data and molecular analyses are key.

This cardiovascular systems biology approach enhances hypothesis driven research questions, guides the choice of the use of laboratory animals and will offer insight into the patient-specific course of a disease. In combination with an expansion of the biomarker research for the improved stratification of patient populations and the development of more effective therapies aimed at underlying biological mechanisms, this systematic approach will contribute to (the development of) individualized cardiovascular treatment as part of our complex and highly specialized care.

4 Patient care

Based on the five focus areas CVC Maastricht can provide a complete package of complex and highly specialized cardiovascular care[16]. Also in relation to its function in regional and Euregio networks. To meet the requirement for national and international promotion the focus within this package will be laid on the aforementioned focus areas in combination with cross links and functional areas of competency within the context of integrative care. An explanatory example: Heart failure is specified as one of the focus areas. As yet, the promotion of heart failure as a form of highly specialized care is not unique and distinctive enough. Other centers in the Netherlands also have good to excellent reputations and hence positions in this respect. Placing the emphasis on 'Integrative care of non-ischemic cardiomyopathies', for example, will provide in highly specialized care with a content-related competitive advantage compared with other leading centers. Among other things, the consequence of such an approach is reflected in improvement of our research position in this field (particularly the translational phase), an increase in the number of related clinical procedures (e.g. number of ICDs, including resynchronization therapy and the corresponding financial performances. Following on this line of thought, proactive efforts will be made to increase our complex and highly specialized cardiovascular care.

Clinical outcome

CVC Maastricht seeks to ensure maximum transparency about reports on the results achieved in relation to the quality of the care provided. To ensure the continuous and focused improvement of care quality and thus the added value for the patient CVC Maastricht will implement a management system of outcome indicators. Representative outcome indicators will be selected for each focus area and the corresponding patient groups.

The outcome indicators to be selected are explicitly not intended as a means of comparison between the focus areas. Rather, they pertain to the requirement of being able, on the one hand, to implement an objective method which clearly communicates what a patient can and may expect and, on the other, have clinically founded guiding information about how CVC Maastricht could become even better still. Patient support associations, health insurers, general practitioners and any other relevant stakeholders will be intensively involved in the selection and compilation of the outcome indicators.

Integrative health

CVC Maastricht chooses to adopt a proactive and leading role in the field of cardiovascular disorders within the continuum of integral health. To actually establish a health care chain for cardiovascular disorders, a long-term collaboration will be set up with CAPHRI, School for Public Health and Primary Care of Maastricht UMC+/Maastricht University. In particular, CAPHRI will contribute its high quality expertise in the field of prevention and early diagnostics.

As such, the knowledge and know-how of CAPHRI is highly complementary to that of CVC Maastricht. Besides contributing expertise, CAPHRI will also play a leading role in the collaboration process between CVC Maastricht and the extensive network of primary health care facilities to which CAPHRI has access in the south-east Netherlands.

The Maastricht Study

In the context of integral health care, besides the intended long-term collaboration with CAPHRI the in-depth collaboration with the Maastricht Study must also be explicitly mentioned. The Maastricht Study is a large-scale and long-term health study of 10,000 people. The Maastricht Study is symbolic of the nature of cardiovascular metabolics, going beyond the focus area, and as such also been listed as a cross area in the medical concept (see figure 3).

The goal is to generate more insight into the prevention, development, progression and treatment of such disorders as type 2 diabetes and cardiovascular diseases from a chronic perspective. Through the Maastricht Study CVC acquires important information regarding the state of health of the population (of Limburg), such as the prevalence and incidence figures for cardiovascular disorders and diabetes, but also for obesity, pulmonary diseases and mood disorders.

Foreign patients

CVC Maastricht expressly seeks to increase the number of foreign patients that visit CVC Maastricht. In contrast to several years ago, there are no more obstacles of principle to impede this aim. Of neither legal nor financial nature. Foreign patients and the related health care costs are not charged to the 'Budgetary Framework for Health' *[Budgettair Kader Zorg (BKZ))*] and are consequently not part of the maximum growth of 2.5% agreed in the 'Administrative Outline Agreement' [*Bestuurlijk Hoofdlijnenakkoord (BHA)]*. Clearly, this agreement relates only to production agreements to be made with Dutch health care insurers.

It is vitally important however, that the health care demand from patients insured with Dutch health insurers can be met without further reservations. In other words, as long as we can meet the health care demand of patients insured with Dutch health insurers quickly, flexibly and in a customer friendly manner (i.e. no waiting list and very short access time) they will not have any problem with the fact CVC Maastricht also uses its knowledge, expertise and capacity for the benefit of foreign patients. The situation would be different should CVC Maastricht use its capacity for 'lucrative' interventions for patient groups other than those of the health care insurers. Especially if any of the health care insurers' patients are still on a waiting list.

With regard to the chargeable fees, treatment-related pricing applies as of as per 1 January 2012. This implies that there is a free segment (nationally averaging 70%, in respect of which prices and volumes can be agreed) and a regulated segment (national average of 30%) which stipulates prices primarily for tertiary hospital treatments, for which the maximum prices determined by the Dutch health care authorities shall apply.

Cost effective and sustainable solutions

CVC Maastricht seeks continuously to develop new cost-effective and sustainable health-care concepts. The implementation of the outpatient clinic for Atrial Fibrillation is a clear example of this. Other examples include the use of minimally invasive techniques for both diagnostics and intervention.


EM-TRAC

5 Teaching and Training

CVC Maastricht researchers, clinicians and doctoral students are involved in the performance of teaching within the entire continuum of teaching and training programs. CVC Maastricht is involved, and in some cases leading, in block planning groups of practically all four Bachelor's programs at Maastricht UMC+. It is also closely involved in the Research Master's degree program Molecular Life Sciences (particularly in the track Cardiovascular Biology and Medicine) and Clinical Research Physician. The didactic framework of these programs is defined (on the basis of problem-based teaching) by educationalists of the Teaching Institute. Researchers and clinicians provide the content, Students of these two Research Master's programs follow specific cardiovascular blocks. Interaction with researchers and clinicians is extremely intensive during the internships, which are completed at CARIM. The European Union has recognized CARIM as an international training site for Early Stage Researchers.

A Research Master's is often followed by a PhD program.

CARIM has its own PhD training program and participates in the EuCAR PhD training program together with IMCAR (RWTH Aachen). PhD students receive very intensive supervision from a team of top researchers. They also have the option of taking supplementary courses; general biomedical and cardiovascular courses as well as courses that focus more on such general skills as statistics, writing skills, communication and teaching skills. The nature of the PhD program is decidedly international; 50% of the students are international and the EuCAR program awards a double degree (German Dr. rer.nat. and Dutch PhD). In addition, students have the opportunity of attending seminars, master classes and conferences enabling them to present their research abroad.

Within the clinic all the cardiovascular programs offered are accredited and recognised: cardiology, cardiothoracic surgery, vascular surgery, vascular medicine, vascular neurology and interventional radiology. CVC Maastricht will provide international cardiovascular fellowships enabling young specialists to develop further within the various focus areas.

An additional effect of this international profiling is the development of a dynamic reference and referral network. Indeed, fellows will refer to CVC Maastricht as the center of excellence that enjoys an excellent reputation in the given focus areas. It is therefore of vital importance that CVC Maastricht plays a significant role in postgraduate education and high-quality training.

One such example is the European Vascular Course. After 16 annual editions, this postgraduate event is renowned across Europe as a platform for learning and training in the vascular and endovascular field. It is associated with Maastricht and is recognised as one of the top congresses in Europe.

Furthermore, practically every sector of industry involved in the treatment of patients with venous problems is willing to provide facilities for a *European Venous Training Center* in Maastricht. The plan is for over 800 trainees will attend the Europe Venous Training Center every year. The European Venous Training Center is part of a larger development, namely the European Cardiovascular Training and Education Center.

European Cardiovascular Training and Education Center

A special development related to CVC Maastricht is the *European Cardiovascular Training and Education Center*. For the development and realisation of this initiative Maastricht UMC+ is collaborating closely with a large number of (industrial) partners. The objective of the planned center is to create an international medical education environment in which physicians and other health care professionals (e.g. lab technicians, managers and nursing staff) can widen and optimise their cardiovascular knowledge in accordance with the latest developments in science and technology. The ultimate goal is to ensure a healthier future for cardiovascular patients by investing in better trained and more professional physicians and health care professionals.

Maastricht UMC+ and its (potential) partners seeks to achieve this by providing national and international cardiovascular training programs and courses for cardiologists, fellows, technicians and nurses, taught by specialists from Maastricht UMC+. The aim is for these activities to contribute to the position of Maastricht UMC+ as European cardiovascular reference center within the specified focus areas. It also an provides excellent opportunity to disseminate Maastricht expertise internationally after the training/education and to stay in contact. This could be complementary to the further development of the referral of patients from clinics outside the traditional catchment area of Maastricht UMC+ and foreign attracting patients. The European Cardiovascular Training and Education Center will train over 3,000 trainees a year.

6 Organisational Development Heart and Vascular Center

To actually be able to position CVC Maastricht as an international center of excellence, it is essential that the operational processes and the corresponding logistics are top class, also referred to as operational excellence.

6.1 Operational Excellence Projects (application of Lean Six Sigma)

The application of the principles of Lean Six Sigma began in 2012 in the clinic and ultrasound rooms and with the start up of our new outpatient clinic. Despite these principles not being embedded in a broader program, the results of their application are encouraging. It has revealed what progress can be made by directly involving employees in the analyses and addressing operational obstacles. It also highlighted how labour intensive it is to conduct thorough process analyses and implement improvement measures.

Lean Six Sigma will be applied on a wider scale when organizing CVC Maastricht.

This is in keeping with the choice of the Executive Board of Maastricht UMC+ for Lean Six Sigma as organisational philosophy. A major point for consideration is the fact that HVC does not have sufficient expertise in this respect. In the context of the Competitive Dialogue to be started with potential business partners for CVC Maastricht, potential business partners will also be explicitly asked whether they are able and willing to provide Lean expertise for the purpose of the change program.

Integral Management

The introduction of integral management is considered as an important aspect of and prerequisite for the development of CVC Maastricht. Particularly in the context of operational excellence. Integral management focuses continuous attention on total quality and organization, resulting in a better quality product and service, a patient oriented organization and

manageable business processes and costs. Besides care quality there has, of late, been increasing focus on organisational quality, the process. Applying Lean Six Sigma will enable further process quality improvement within the CVC Maastricht, with the objective of improving efficiency and effectiveness. This approach results in a more manageable organizational structure in which outcome-based management is applied more than in the present organizational structure. The definition of outcome includes: customer satisfaction, care quality, accessibility (waiting times, lead times) and the medical outcome parameters. For the sake of clarity, customer satisfaction does not relate only to the patient but also to general practitioners, specialists from referring institutions and even internal customers (Maastricht UMC+ colleagues).

Integration an differentiation of activities associated with CVC Maastricht

The integration process necessary to realise the development of CVC Maastricht is complex and challenging. The integration includes actual activities (care lines and work processes) as well as personnel, capacity and financial resources. Should the Executive Board approve the proposal to place all cardiovascular activities under the management of one organizational unit, this would mean that jobs and and activities will be transferred from several profit centers to CVC Maastricht. An integration plan will be drawn up providing for the merger of activities in the course of 2013. The integration of activities is a prerequisite for the organizational differentiation and positioning of CVC Maastricht as an independent unit.

6.2 Volume policy and (Eu)-regional positioning

Sustained volume and (in some areas) volume growth are cornerstones of this plan. Without an effective policy on the reduction of state dependence it would be impossible to build up sufficient critical mass for a CVC Maastricht with international ambitions. In terms of patient volume, CVC Maastricht is largely dependent on the Limburg region in general and East and and South Limburg in particular. Collaboration with the hospitals in the region is consequently very important to securing sufficient numbers of patients. Good collaboration already exists in several areas, such as the collaboration with VieCuri Medical Center in the field of ICDs and PCIs.

The relationship to Orbis Medical Center and Atrium Medical Center is of strategic importance to the definition of the regional positioning of CVC Maastricht. It is therefore of importance that

agreements are made at Executive Board level to provide for long-term collaboration.

The collaboration with Atrium Medical Center in relation to interventional cardiology is key in this respect. The initiative to set up a joint PCI center and to invest in the (gradual) development of a regional department for (interventional) cardiology is not only important to cardiology but will also impact upon other areas (including referrals for cardiothoracic surgery and collaboration in relation to ICDs). A successful implementation of this collaboration is consequently a prerequisite for the development of CVC Maastricht.

The aim seeks to realize the organizational, operational and managerial integration of CARIM and HVC into a single entity within Maastricht UMC+. An entity which, with a large degree of independence (organizational differentiation) can respond to internal and external changes quickly, flexibly and therefore adequately.

From the perspective of an independent entity within Maastricht UMC+, CVC Maastricht expressly wishes to develop as a profit center. The foundation for this is financial robustness based on a high patient volume and successful research projects.

Masterplanning and Scheduling Project

The biggest challenge with regard to operational excellence concerns improving the planning. The current patient planning system is (extremely) fragmented and there is no alignment and coordination with the available resources (human and other resources) As HVC does not have professional planners, a quality strategy is also required in terms of staffing. While improved planning is part of the reorganisation of the care institution's management structure, the complexity of this project necessitates separate preparation.

Successful execution of the project will require external expertise. During the Competitive Dialogue Procedure potential business partners will therefore be asked explicitly how they could support us in this respect. The concrete question to be asked is whether the potential business partners are prepared and able to provide professional planners for a long-term period. We also expect the business partners to actively contribute to the project preparation, primarily with respect to data analyses and the definition and/or redefinition of care pathways and processes.

Catheterization Lab Management Project

A second project which, besides knowledge of Lean Six Sigma also requires external expertise, concerns the Catheterization Lab management. The key issue this project addresses is how the productivity of the cath labs can be consistently increased. This question will also be put to potential business partners during the Competitive Dialogue Procedure.

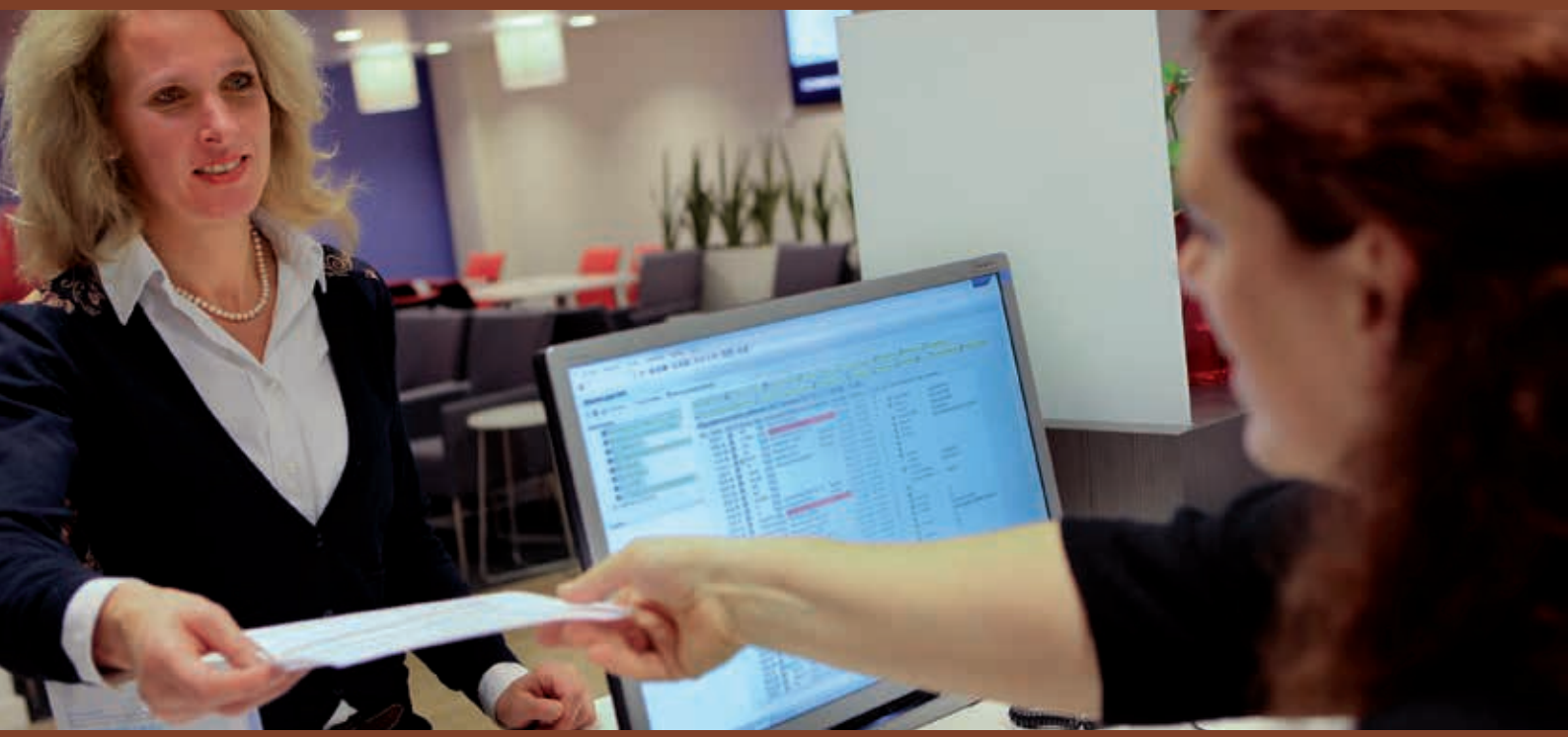
Maintaining lasting cooperative relationships with neighbouring hospitals is important not only to the quality of patient care, it is also a precondition for sustained patient volume and the realisation of volume growth in certain areas. Without strong regional partnerships it would be practically impossible to generate the numbers of patients an internationally oriented center of excellence need. The regional cooperation initiatives focus primarily on ICDs and PCIs.

With regard to the ICDs the aim is focused on realizing a high-volume ICD center (top 3 in the Netherlands) in collaboration with the hospitals in Limburg. Cardiologists from VieCuri Medical Center are to start a weekly ICD program in our cath labs as per June. A similar construction is currently under discussion with Atrium Medical Center and Orbis Medical Center. Concentration of the care in Maastricht is expected to lead to a growth in 2013 from 350 to 400 ICDs.

In respect of PCIs there has been intensive cooperation with Atrium Medical Center as per November 2012. The PCI program in Heerlen is currently carried out under the supervision of HVC and using HVC expertise and back-up. The objective of HVC focuses on having a successful bi-local PCI program at its disposal in 2013. A Professor of Interventional Cardiology is to be appointed to coordinate this program. The total volume of the bi-local PCI program in 2013 is estimated at 2600 PCIs.

With regard to EPS, the objective is firstly focused on expanding our capacity in the cath labs and thus reducing the referral to treatment time. Initial measures have been taken. The intention is subsequently to agree arrangements with referring hospitals in the region, which will lead to a growth in volume from 450 to 700 EPSs in 2013, thus providing CVC Maastricht with both a large ICD volume and a large scale and competitive EPS program.

With respect to vascular surgery, the European Vascular Center Aachen-Maastricht has been established as a joint venture between CVC Maastricht and the Universitätsklinikum Aachen (UKA), Germany.



7 Human resources: investment in excellent key players

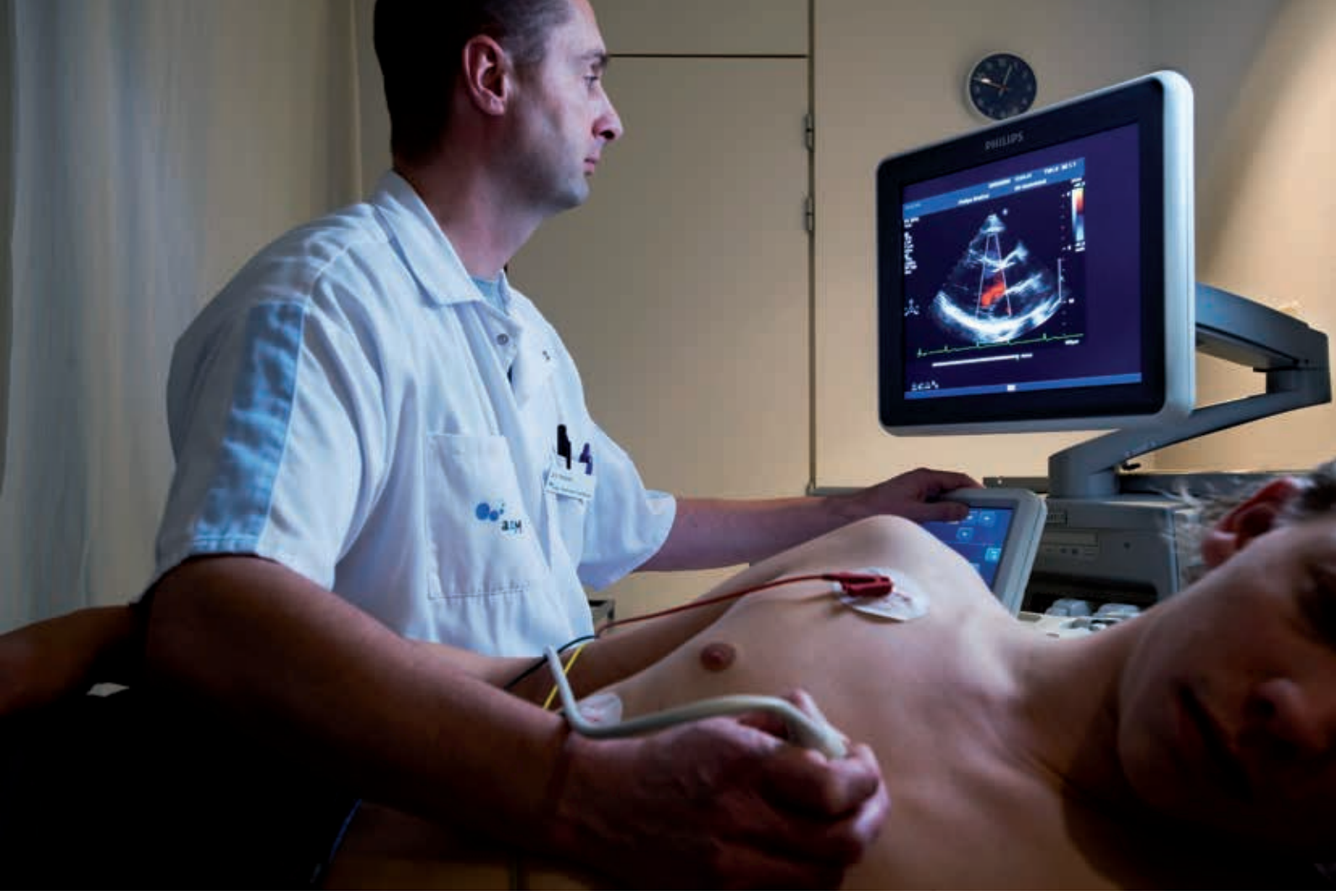
The development of CVC Maastricht stands or falls with *excellent key players*. The realisation of this requires the targeted and well considered investment in the recruitment of new excellent employees at various levels and in various fields.

The following posts will be introduced to strengthen the research activities:

- Senior Investigator in the field of electrophysiology, to strengthen the focus area of arrhythmia.
- Professor in the field of cardiogenetics to strengthen the focus areas of arrhythmia and heart failure.
- Postdoc in the field of cardiogenetics in relation to arrhythmia and heart failure.
- Professor to strengthen the focus area micro-vascular in a broader sense.
- Postdoc to strengthen the focus area micro-vascular in a broader sense.
- Postdoc to strengthen the focus area macro-vascular in a broader sense.
- Postdoc to strengthen imaging and drug-design related thrombosis research.
- Scientist-Clinician at associate professor level for the Maastricht Study.

The following posts will be created in respect of the clinic:

- Professor of clinical electrophysiology at the highest level to strengthen the focus area of arrhythmia.
- Professor of interventional cardiology for the planned regional collaboration in this field.
  The appointed professor will lead the planned regional interventional cardiology department and will also carry out research in this field.
- Cardiac surgeon.
- Vascular Surgeon in the field of thoracoabdominal aortic aneurysm (TAAA) interventions, to strengthen the focus area of macro-vascular.
- Internist to strengthen the focus area of thrombosis in the context of the Thrombosis Center of Expertise.



Appointments to the above posts will entail an expansion of the workforce and the consistent availability of additional staffing budget (for both CARIM and HVC).

There will be further investment in resources pertaining to management within HVC, particularly by recruiting a head of resource planning and introducing the post of patient case manager.

The development of targeted marketing/ branding/ communication of CVC Maastricht calls for dedicated resources in this area. This also lays the foundation for the organization of an 'International Office' which will focus explicitly on attracting foreign patients on the basis of complete packages.

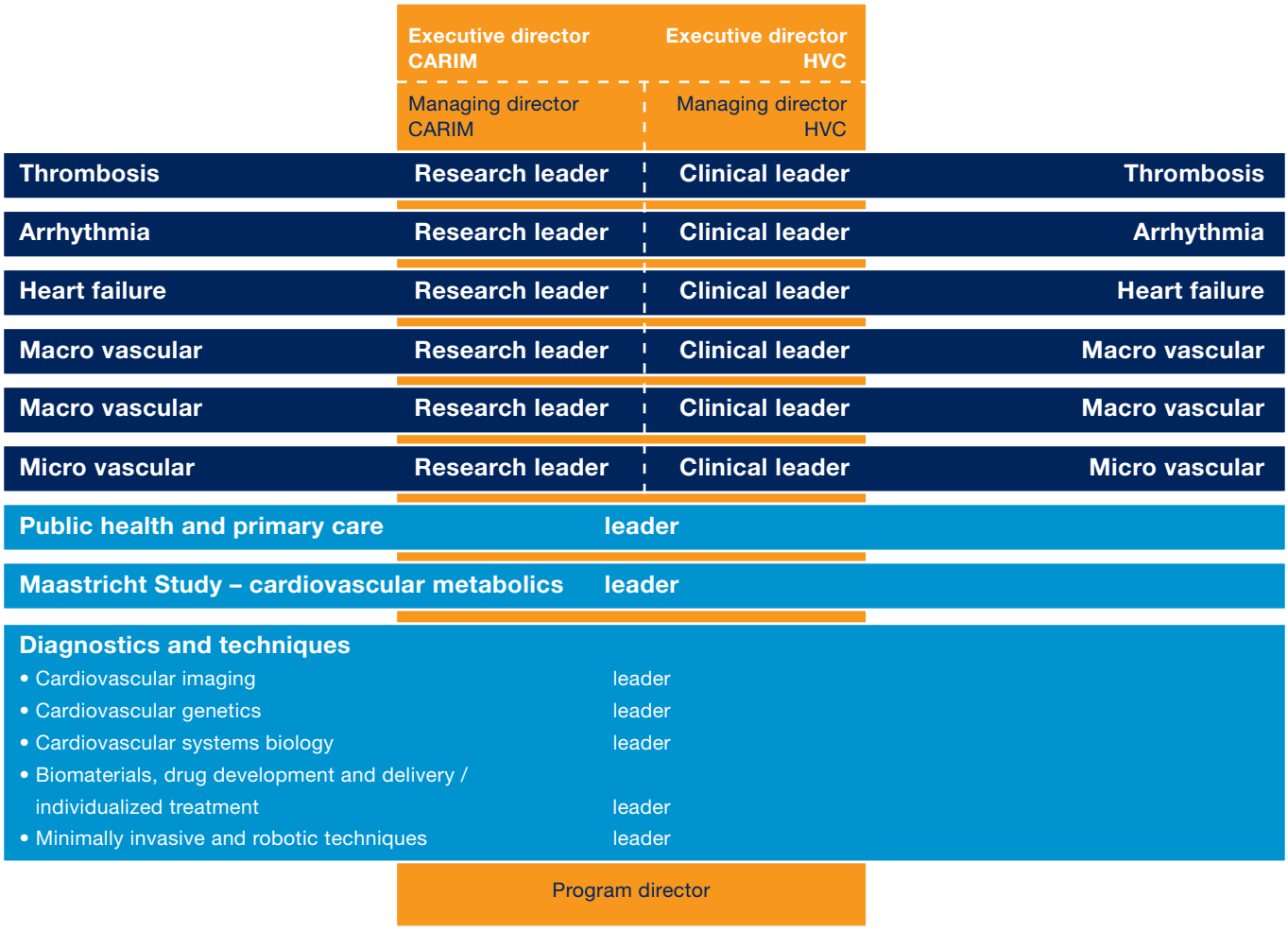
Finally, it will also be necessary to appoint professionals to staff the proposed European Cardiovascular Training and Education Center.

8 Management CVC Maastricht

CVC Maastricht has established a Management Board, which consists of the Executive Director of the clinical heart-vascular center (HVC), the Executive Director of CARIM, the Managing Directors of HVC and CARIM and the Director Strategy and Programs. Also participating are Focus Area Leaders and Cross Area Leaders, allowing cross fertilization at the highest level. The Management Board is contact partner for the Executive Board of Maastricht UMC+ and is responsible for the clinical, research-related and financial development of CVC Maastricht. The two managing directors are financially and operationally responsible for the clinical and research parts of CVC, respectively.

By implementing this management structure, a grow model is adopted, driving towards integral accountability for core activities.

Figure 4 Governance structure of CVC Maastricht




Reperfusion
damage
Cell lysis
2,500
2,000
1,500
1,000
500
0
Control
Hypoxia
3 x 5'
6 x 5'
Symp
+ 6 x 5'
CsA
*
*
†
Fig 3. CK released in control, hypoxia, 3 x 5'
streptomycin and CsA. * P < 0.0001 vs

9 Financial impact report

The revenue model is largely dependent on regional volumes. Safeguarding these volumes, insofar as possible, by means of cooperative agreements with regional hospitals is a crucial precondition for the financial feasibility of CVC Maastricht. To enable the preparation of realistic financial forecasts, the financial situation of HVC only has yet been adopted[18]. The total revenues and costs of the activities belonging to the HVC portfolio have been consolidated in a virtual profit and loss account. The financial year 2011 was taken as benchmark. Forecasts were prepared on the basis of this financial position and the existing expenses and income. For the sake of context, price pressure, lower subsidies and rising fixed expenses should be assumed to prevail. The following financial models provide insight into how CVC Maastricht anticipates these developments.

Explanatory notes on scenario 1 ‘Consolidation of current situation’

Volume component

Complex and highly specialized care: The attached forecast is based on successful regional collaboration and shows a sound indication of the production and profit development over the coming years. These partial forecasts correspond with the HVC activity plan for 2013 and existing assumptions for the longer term. These assumptions have been aligned with the physicians directly involved and provide a realistic reflection.

Basis and complex care: the growth is based on the ‘base case’ scenario defined by market research agency Gerbera as 2.5% per year.

Income component

Price component: Based on 'expert opinion'[19] a price erosion of 25% is expected for the next five years. It is expected that this price erosion will lead to lower purchase prices and hence be compensated (in part).

This impact on price development and purchase prices has been incorporated as a 12,5% drop in prices over the period between 2013 and 2017. It is assumed that the price erosion will level out during the subsequent period.

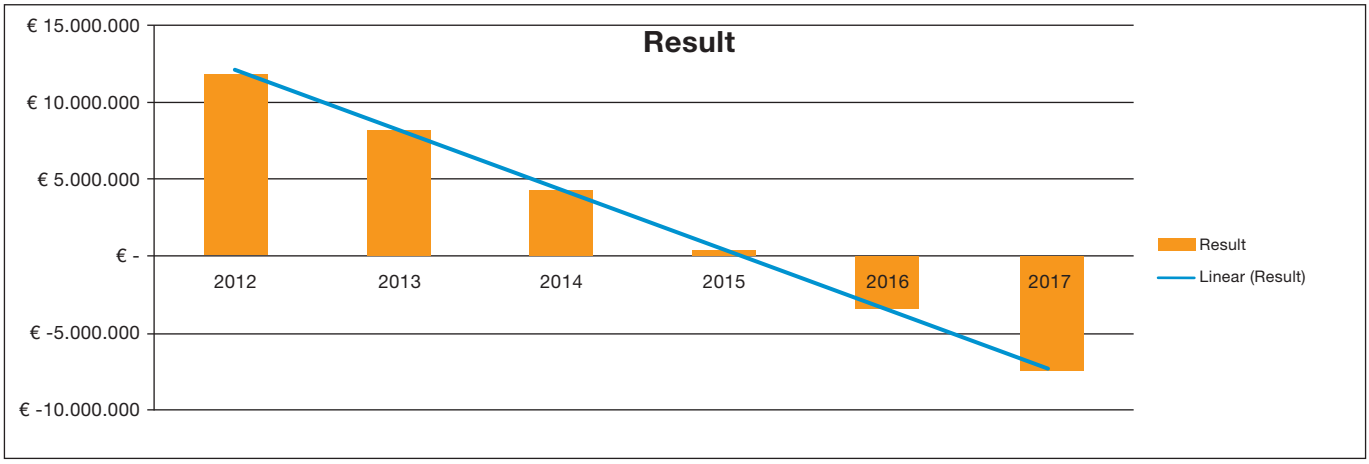
Subsidies: in the model it is assumed that the (standard) subsidies received up to now will fall by 6% in the period 2014 to 2017.

Cost component

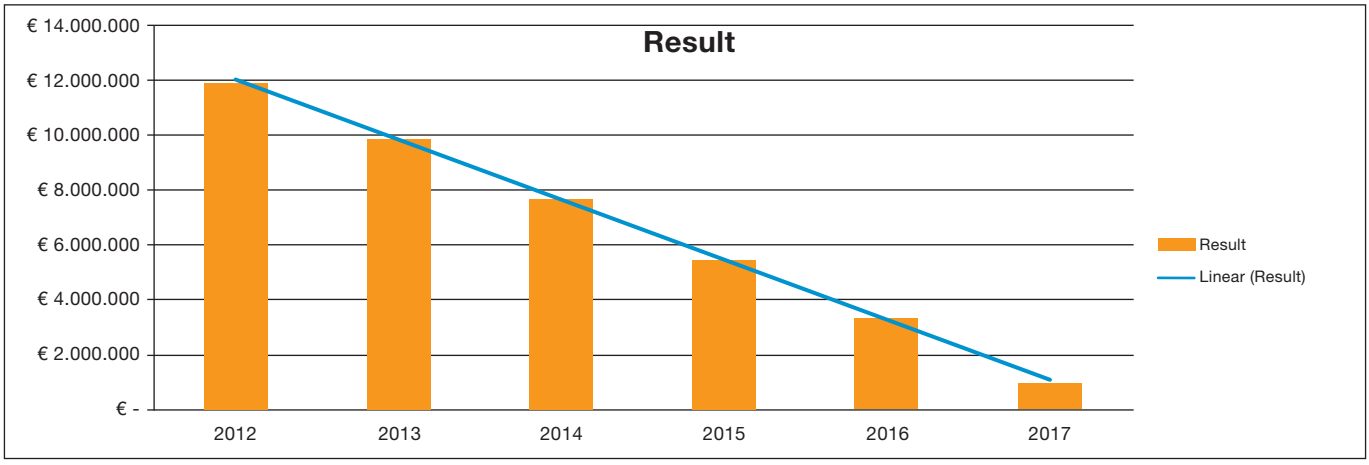
To ensure that CVC Maastricht continues to maintain a margin to enable investment, it is essential that during the initial years the investment emphasis of CVC Maastricht is on efficiency and productivity improvement. The need for such is described in detail in Chapter 6 and features prominently in the Competitive Tendering Procedure currently under preparation. The objective of this tendering procedure is to secure a partner to assist CVC Maastricht over the next five to seven years in its development to achieve operational excellence. The assumption was made that HVC will deliver 'more for less' from 2016 onwards. This assumption has been incorporated as such in the cost forecast. The financial model prepared for this forecast has been coordinated with and positively assessed by the corporate Finance department.

The following 4 graphs were produced on the basis of the above information:

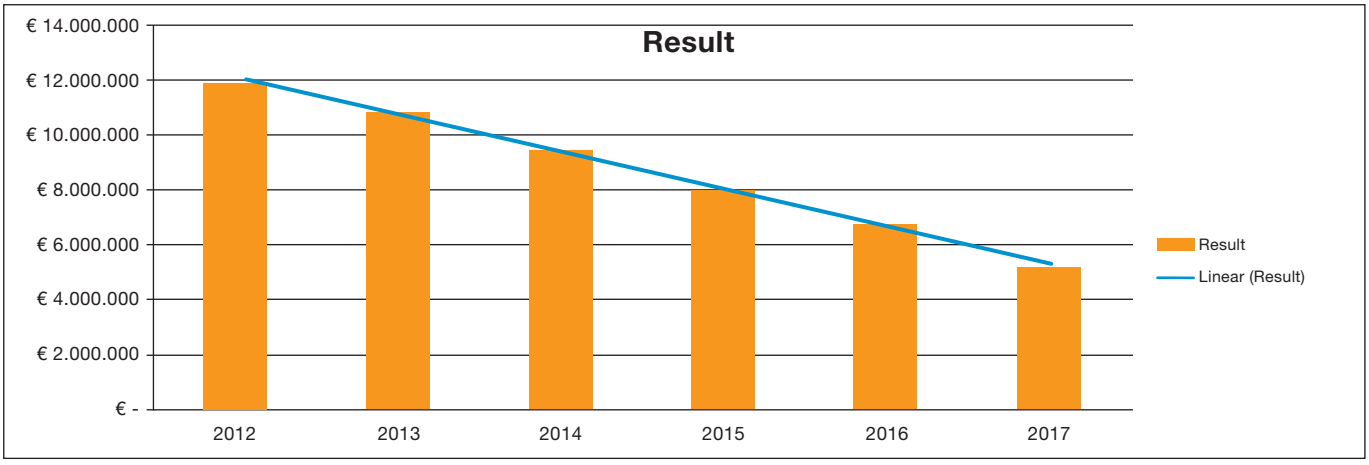
Graph 1 Worst case scenario (25% price erosion, 0% procurement advantage)



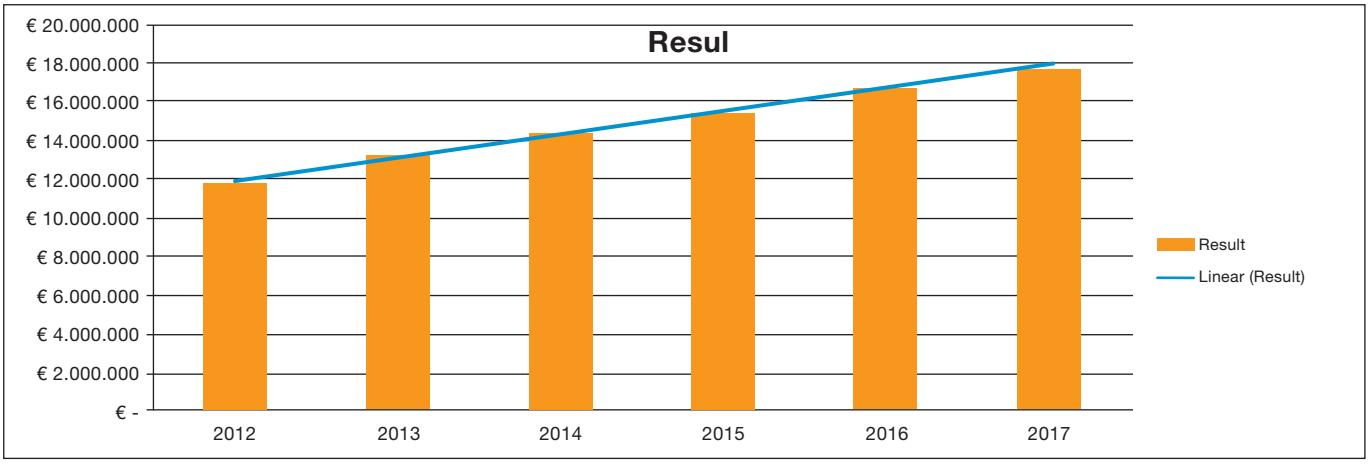
Graph 2 Most likely scenario (25% price erosion, 12.5 % procurement advantage)



Graph of 3, 50% scenario (12.5% price erosion, 6.25 % procurement advantage)



Graph 4 Best case scenario (0% price erosion, 12.5 % procurement advantage)

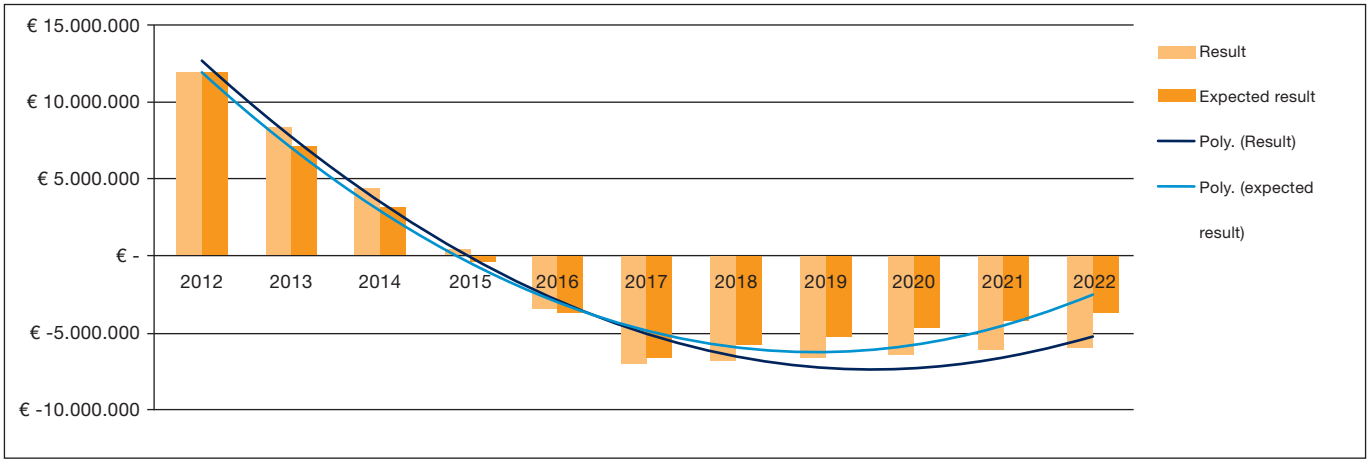


Explanatory notes on scenario 1 ‘Realisation of CVC (fully fledged)

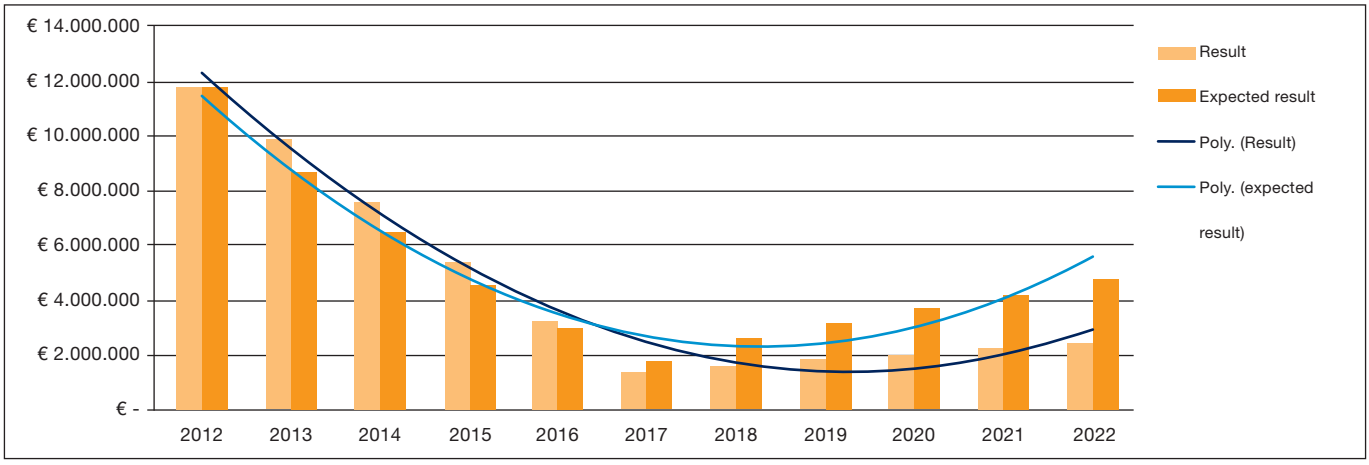
The graphs below are based on the conservative assumptions of scenario 1. The investments in new key players from 2013 have now been added. The return on these investments is reflected in the growth of tertiary referral patients from the Netherlands and abroad as from 2015. The calculations have been represented practically by adjusting the generic basic growth, after two years of investment, to 1% annual production growth a year until 2018 and then levelling it out to 0.5% annual growth. This development impacts the cost, income and subsidy components.

In the light of the additions described above, the impact of the given assumptions have been visualised in the graph below. The assumptions in relation to price erosion and procurement advantage, in particular, can impact considerably impact on the result.

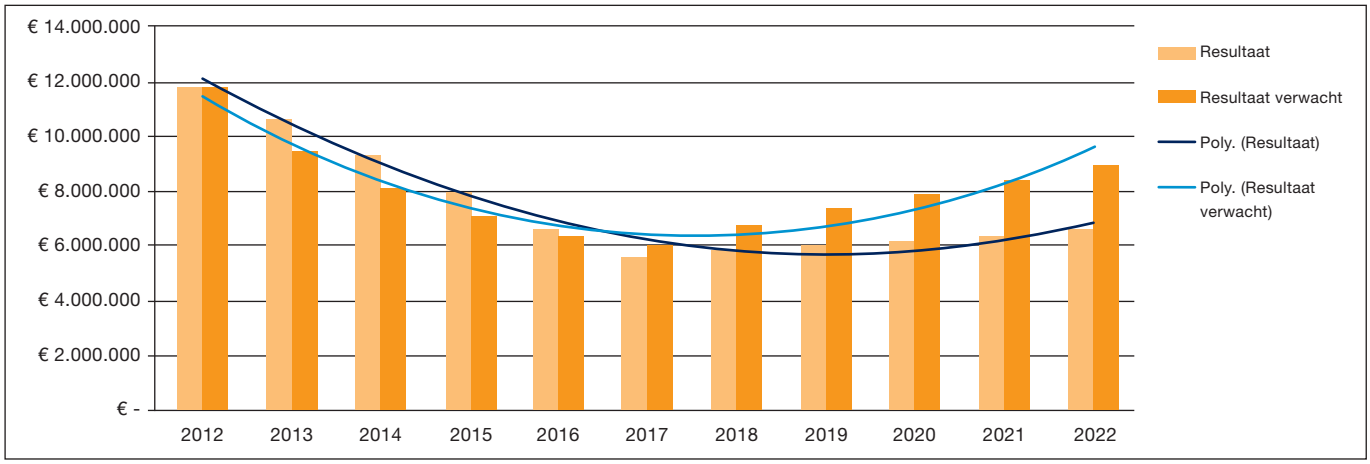
Graph 5 Worst case scenario (25% price erosion, 0% procurement advantage)



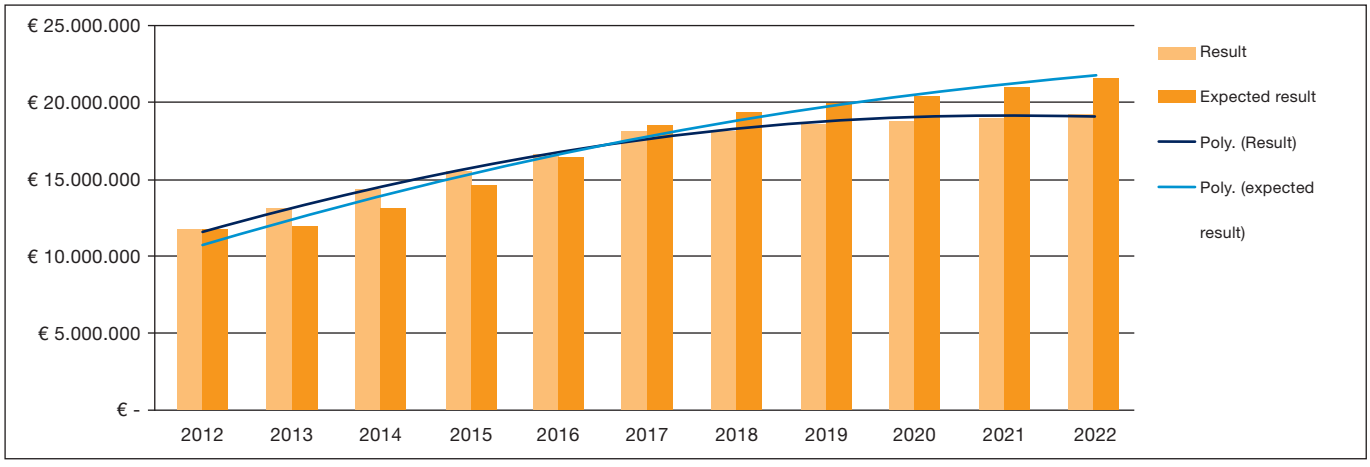
Graph 6 Most likely scenario (25% price erosion, 12.5 % procurement advantage)

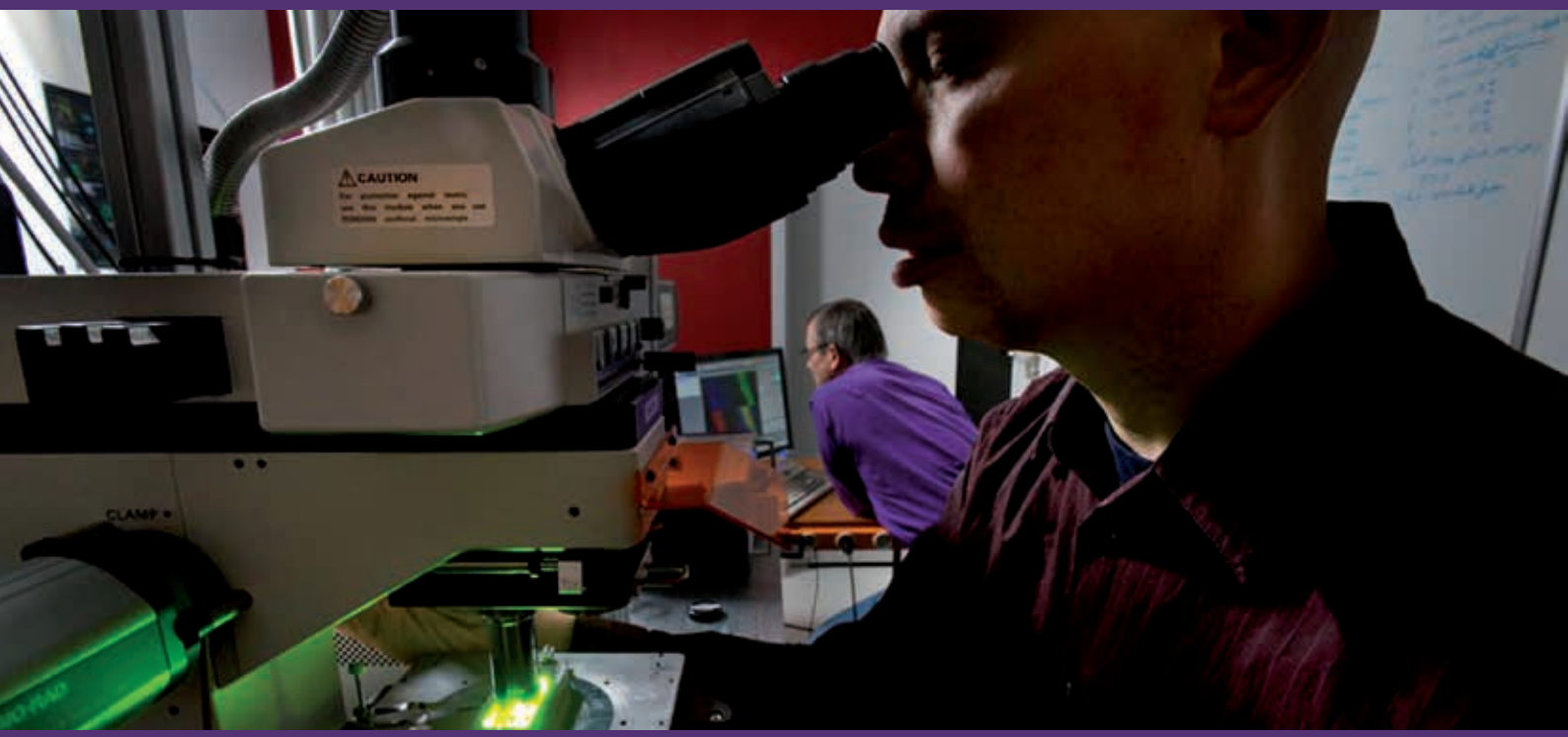


Graph 7 50% scenario (12.5% price erosion, 6.25 % procurement advantage)



Graph 8 Best case scenario (0% price erosion, 12.5 % procurement advantage)




CAUTION
CLAMP

10 Where to go from here

The Maastricht UMC Executive Board recently provided insight into their mindset in respect of the future strategic positioning of Maastricht UMC+. Based on the motto of 'Healthy Living' a strategic framework has been developed which, besides this motto, consists of four additional components. As well as a joint technology platform for patient care and research, a link to the region and societal mission, and several specialties, particularly significant here are four given disease-oriented centers of excellence and four innovation themes (for the latter see also Chapter 3). With these disease-oriented centers of excellence and innovation themes the Executive Board seeks to convey the distinctive strength of Maastricht UMC+.

Figure 5 The key opinion leaders of the focus areas and cross-over areas play an essential part in the realisation of CVC Maastricht

CVC Maastricht - Focus area and cross-over area key opinion leaders

Focus areas

- Thrombosis: Ten Cate / Hackeng
- Arrhythmia: Crijns – Volders – Maessen / Prinzen – Schotten
- Heart failure: Brunner la Rocca – Heymans / De Windt
- Macro vascular: Jacobs – Schurink / Post
- Micro vascular: Van Oostenbrugge / Vink

Cross-over areas

- Public health and primary care: Van Schayck
- Maastricht Study – Cardiovascular metabolics: Stehouwer
- Diagnostics and techniques
  - Cardiovascular imaging: Wildberger
  - Cardiovascular genetics: De Windt / Volders
  - Cardiovascular systems biology: Delhaas / Volders / Schotten
  - Biomaterials, drug development and delivery / Individualized treatment: Schmidt / Koole
  - Minimally invasive and robotic techniques: Maessen

Parallel to the above procedure and for the sake of swift and adequate progress with regard to the development and realisation of CVC Maastricht, the Executive Board of Maastricht UMC+ has expressly chosen to pursue a two-track policy. Such, also with a view to the requirement on the part of potential strategic partners for an effective and dynamic decision-making process.

This Master Plan is the final proposal for the development of CVC Maastricht. Following a positive decision by the Executive Board preparation of the detailed overall implementation plan will commence. Equally essential is the further elaboration as detailed roadmaps of the focus areas and cross-over areas by teams of professional experts under the leadership of the Management Board of CVC Maastricht (see figure 5). On the basis of this the first steps can then be taken towards the integration of CARIM and HVC.

To ensure that the development of CVC Maastricht remains flexible and above all manageable, in the light of the above, the project will be transformed into a modular program with corresponding management structure should the aforementioned explorations give rise to such. This will optimally safeguard the progress of the realisation process and the proposed operational status.

Following on from this, dialogue will be entered into with the Executive Board in respect of the wish to create a special status and position for CVC Maastricht, that is to say the establishment of CVC Maastricht as an indepedent organizational and financial entity within Maastricht UMC+.

Risk analysis

An initial rudimentary risk analysis reveals that the development and realization of CVC Maastricht would involve several risks.Examples include:

1. Difference between HVC and CARIM in terms of organizational culture;
2. Insufficient support for the demand for independent status;
3. Insufficient support for the demand for separate clinical production capacity;
4. Delay in attracting excellent key players;
5. Competitive dialogue does not produce the desired result;
6. Collaboration with regional hospitals failed.

Insofar as possible, these and future risks are to be made transparent in advance thereby indicating their impact on the development and realisation of CVC Maastricht. An adequate risk management system will be implemented to mitigate the risks where possible.

Conclusion

The realisation of CVC Maastricht as a center of excellence marks the following stage in the development of cardiovascular care and cardiovascular research in Maastricht UMC+. The proposed course is in every way both promising and challenging.

Endnotes

1 As profit center, the Cardiovascular Center consists of the following medical departments:
Cardiology and Cardiothoracic Surgery. It also includes the Venous Center. Furthermore, capacity is supplied by the medical departments Surgery, Neurology and Internal Medicine.

2 CARIM includes the research groups Internal Medicine, Clinical Chemistry, Cardiology, Cardiothoracic Surgery, Intensive Care, Pathology, Biochemistry, Biomedical Technology, Genetics & Cellular Biology, Physiology and Pharmacology.

3 The current lines of research by CARIM are:1) Thrombosis and Haemostasis; 2) Cardiac Function and Failure, and 3) Vascular Biology.

4 Defined as all new patients and all repeat consultations resulting in a DBC

5 Memorandum from the Dutch Ministry of Economic Affairs, Agriculture and Innovation (EL&I) on top sector policy and verbal communication with LSH top sector manager.

6 See strategy memorandum 'Heel de Mens' and the memoranda Focus & Chains 1 and Focus & Chains 2 with respect to research policy.

7 Cardiovascular knowledge and expertise together form a key growth engine for the regional economy. As such, it is one of the focus areas in the transition process in Limburg, moving towards a dynamic, enterprising and innovative knowledge economy. Through its valorisation activities CVC Maastricht has established a clear, identifiable relationship with the Maastricht Health Campus (MHC). With its project for the Cardiovascular Campus, CVC Maastricht has paved the way, both historically and substantively, for the development and realisation of the MHC.

8 See appendix 1. This shows, by way of example, the analysis and breakdown of the focus areas and cross-over areas into areas of expertise.

9 In part developed in Maastricht

10 The subject of cerebral small vessel disease supports both the research between schools in MUMC+ (CARIM – MheNS) and the research with the Faculty of Psychology Neurosciences. It is also a subject area in which the ultra high field imaging facility of Brains Unlimited BV can be used.

11 The competency areas Cardiovascular imaging and Cardiovascular systems biology are enhanced by the use of extensive expertise with computational models enabling more in-depth interpretation of imaging data and molecular analyses (computer-assisted diagnosis).

12 See endnote 11.

13 See appendix 3: 'Business cases in development', for an overview of new initiatives and products.

14 47% of the patient volume can be classified as tertiary clinical or tertiary referral patients.

15 CVC Maastricht meets all NFU criteria for tertiary referral care The specified focus areas are all de facto founded on tertiary referral functions or sub-category of such. An overview of Tertiary Referral Functions as per 1-9-2011.

16 Patient groups (conditions):
Heart diseases: Congenital cardiac abnormality; Chest pains+; Heart failure+; Heart infarct+; Cardiac valve disorder; Cardiac arrhythmia+; Myocardial disease+; Cardiac arrest+'; Inflammation of the heart.
Vascular diseases: Thrombosis+; Pulmonary embolism; Stroke+; Aneurysm+; Varicose veins+; Carotid artery stenosis+; Leg artery stenosis+; Cerebral vascular malformations+.
In respect of conditions marked with + knowledge excellence is either already available or utmost efforts will be made to acquire such.

17 Lean Six Sigma is a combination of two improvement methods. Lean reduces wastage of both time and materials, to which Six Sigma adds the aim to achieve good, consistent quality. This combination generates better, more efficient methods!

18 The relationship between the activities and the funding of the related costs to CARIM is such that the effect of consolidation with HVC is practically zero. CARIM's basic information (scientific staff and supporting technical personnel with permanent posts) and research infrastructure (e.g. scientific equipment) is financed from a fixed annual funding of 8 million euros from the Faculty of Health, Medicine & Life Science (FHML). In national and international competition CARIM also receives 14 million euros per year in the form of project-related subsidies and contracts, subject to tendering regulations, from the European Union, Netherlands Organization for Scientific Research [Nederlandse Organisatie voor Wetenschappelijk Onderzoek], medical-technological industry etc. CARIM uses this money directly to attract research staff (PhD students, temporary supporting project personnel). CARIM carries out research financed by third parties cost-effectively i.e. not for profit. As a rule CARIM renders account to the financiers of the effective expenditure of the research funds granted. The scale of the funds CARIM researchers are able to attract has relatively stable over the years and is expected to remain at the current level for the year ahead, provided the quality of the researchers and the scientific infrastructure is upheld to ensure success in national and international competition.

The prognoses were compiled using information (financial forecasts in the context of health trends) provided by an independent consultancy.

Appendices

Apendix 1: Subdivision of the focus area Arrythmia into areas of expertise on the basis of a structural analysis

Arrhythmia CVC Maastricht 2013 - 2020

Integrative AFib Management		Integrative Management of Ventricular Tachycardia & Sudden Cardiac Death		Primary Electrical Cardiomyopathy		Electrical Management of Heart Failure	
1. Early diagnosis and risk stratification of Afib progression and thromboembolism/ stroke	HC	1. Early diagnosis of VT substrate (including programd electrical stimulation, drug-provocation testing)	CT	1. Monogenetic basis of arrhythmias	PV	1. Diagnosis of electromechanical/ mechanoelectric aspects of heart disease	FP/KV
2. Classification of Afib to guide comprehensive and individualized rhythm control therapy	HC/US	2. VT substrate multimodality imaging	CT/BK/LP	2. Complex genetics	PV	2. Dyssynchronopathy ® cardiac resynchronization therapy	FP/KV/JM
3. Afib multimodality imaging	US/HC	3. Catheter ablation of VT substrate (including cryoablation, epicardial ablation)	CT/YB/JM			3. Irregulopathy ® ablation of ventricular extrasystoles/ tachycardia	FP/YB
4. Hybrid ablation	LP/JM	4. Intensive cardiac care management of severe arrhythmic heart disease	DD				
5. Cryoablation of paroxysmal Afib and long-term effects	CT/YB	5. ICD therapy	KV/YB				
6. Invasive stroke prevention, including left-atrial appendage occlusion	YB	6. Sudden cardiac arrest survivors; community programs; resuscitation education	TG				

Cardiogenetics

Systems biology, including autonomic nervous system

Appendix 2: Developments of variable and specific parameters

Parameter	2012	2017	2022	development absolute 2012-2017	development relative 2012-2017
PCI	2.297	1.000	1.054	-1297	-56%
Cath. Ablation	400	700	738	300	75%
Pacemakers	215	220	232	5	2%
ICD	318	400	422	82	26%
OHO	970	900	948	-70	-7%
Ablation OK	42	80	84	38	90%
Ablations	5.699	5.920	6.239	221	4%
Days hospitalization	38.249	39.331	41.450	1082	3%
Day care (normal)	4.892	4.609	4.857	-283	-6%
Day care (intensive)	235	258	272	23	10%
First Adm. Polyclinic Consultation	22.810	24.884	26.225	2074	9%
First polyclinic consultation	23.013	24.952	26.297	1939	8%
Following polyclinic consultation	31.133	34.895	36.775	3762	12%
Polyclinic consultation	5.908	6.054	6.380	146	2%
Telephone consultation	15.245	17.224	18.152	1979	13%

Specification of the expected specific and variable parameters. The following points of departure applied.

Growth:
The growth curve is based on the market research carried out by the market research agency in 2010. In this study the base case scenario was defined on the basis of an annual growth of 2.5% Based on ´expert opinion´ the growth was also adjusted fro growth on account of increased product excellence (product leader and operational excellence). This is presumed to take shape from 2015 onwards, when the collaboration with the business partner(s) becomes effective.

2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
	2,5%	2,5%	3,0%	4,0%	5,0%	6,0%	6,5%	7,0%	7,5%	8,0%

The basis 2012
The 2012 parameters were obtained as derivatives of the production actually delivered. The specific parameters relate to the cardiovascular article 2 production. The variable parameters relate to such regular parameters as admissions, outpatient treatments, days hospitalization et cetera. Prognosis to 2017
The specific parameters 2017 were determined on the basis of 'expert opinion'. Developments in the market and incidence were taken into account. The variable parameters 2017 were determined on the basis of the growth curve above. The years 2013 to 2016 inclusive were determined on the basis of interpolation.

Prognosis 2017 to 2022
The specific and variable parameters were determined on the basis of a conservative growth percentage as shown in the growth curve. The numbers in 2022 are of hypothetical value. Insomuch as that the numbers were obtained without allowing for the effect of the collaboration with one or more business partners as a result of which product growth could be realised within the existing infrastructure. Profits made influence the admission, day-care and days hospitalization parameters. The sum of admissions and day-care give a realistic idea of the scale of production in 2022. There is expected to be a shift from hospitalization to day-care. The extent to which the numbers will actually change is uncertain. The duration of nursing care will also decrease due to more minimally invasive surgery and telemonitoring. The days of hospitalization is consequently expected to stabilise from 2017 onwards.

Appendix 3: Business cases in development A continuous stream of new initiatives and products

The production growth reflected in the various scenarios will be achieved through expansion of the catchment area, particularly in respect of tertiary referral multidisciplinary products. Growth will also be achieved by consistently setting up new initiatives and/or products. Various business cases are currently being elaborated and assessed. Below is an outline overview of these initiatives:

Approved initiatives 2012

- BC Reveals: implanting a Reveal enables monitoring of the therapy's effectiveness.

Business cases prioritised in the 2013 budget

- BC AF-poli: AF patients are treated as outpatients by a specialised nurse in an ICT-guided care bay.
- BC Venous Surgery: in the last resort function deep-venous pathology is treated in the venous center.
- BC Thrombosis Expertise Center: this center is expanding its expertise and multidisciplinary treatments to include arterial thromboembolism patients, the objective being "tailored therapy".
- BC Cardiac rehabilitation: expansion of the Cardiac rehabilitation program at the Parkstad unit.
- BC Hypertension: expansion to include treatment of all new patients in the Hypertension care line.
- BC Shockwave: patients with asymptomatic 'chest pains' receive last-resort shockwave therapy at the polyclinic.

Business cases in development

- BC Cardio Vascular Risk Management (CVRM): cardiovascular patients receive coordinated multidisciplinary treatment with the aim of reducing cardiovascular morbidity and mortality.
- BC Suspected Deep Venous Thrombosis (DVT).
- BC Syncope.
- BC Shunt Surgery.
- BC Cardiomyopathy.

ANNEX 3
NATIONAL AND INTERNATIONAL COLLABORATIONS

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Arts I.	Collaboration in molecular epidemiology - Imperial College/ Prof. P. Vineis (London, UK)
Arts I.	Collaboration in molecular epidemiology - IRCCS San Raffaele Pisana/ Prof. S. Bonassi (Rome, Italy)
Arts I.	Collaboration in gut microbiota and cardiometabolic disease - Laboratory of Microbiology, Wageningen University/Prof. H. Smidt, Dr E. Zoetendal (Wageningen, the Netherlands)
Arts I.	Collaboration on purinergic signaling and inflammation - Department of Experimental and Diagnostic Medicine, University of Ferrara/Prof. F. Di Virgilio (Ferrara, Italy)
Biessen E.	Cytokine biomarkers in CVD - University Hospital Oslo/Prof. Aukrust/Halvorsen (Oslo, Norway)
Biessen E.	Chemotaxis in CVD – Ludwig Maximilian University/Prof. C Weber, Dr Soehnlein (Munich, Germany)
Biessen E.	Lymphangiogenesis - Biomedicum Helsinki/ Prof. K Alitalo (Helsinki, Finland)
Biessen E.	Immunology - Childrens Hospital Cincinatti/ Dr E. Janssen (Cincinatti, USA)
Biessen E.	Macrophage polarization - University of Bristol/Prof. A. Newby/Johnson (Bristol, UK)
Biessen E.	Vascular senescence - University of Cambridge/Prof. M. Bennett, (Cambridge, UK)
Blankesteijn M.	Effect of growth hormone/alginate on infarct healing - Univ. Of Ioannina/Theofilis Kolettis (Greece)
Brouwers, O.	Department of Internal Medicine, Raboud UMC (Nijmegen, the Netherlands)
Brouwers, O.	Department of Epidemiology, Erasmus MC (Rotterdam, the Netherlands)
Brouwers, O.	Lilly Research Laboratories, Eli Lilly and Company (Indiana, USA)
Brunner-La Rocca HP.	TIME-CHF – a.o. University Hospital Basel Switzerland (M. Pfisterer) and Hospital St.Gallen, Switzerland (H. Rickli)
Brunner-La Rocca HP.	Heart failure, HFpEF - Baker Medical Research Institute/D. Kaye, M. Esler (Melbourne, Australia)
Brunner-La Rocca HP.	Biomarkers in heart failure - University of Otago Christchurch/R. Troughton, AM Richards (Christchurch, New Zealand)
Brunner-La Rocca HP.	Biomarkers in heart failure - Massachusetts General Hospital/JL Januzzi (Boston, USA)
Brunner-La Rocca HP.	HOMAGE - Biomarkers early detection of heart failure (France, Austria, UK, Spain, Ireland, Germany, Belgium, Italy, USA)
Brunner-La Rocca HP.	RECAP - Telehealth, processmapping HF (Germany, Belgium, UK)
Bucerius J.	Atherosclerosis Imaging with PET / CT - James H. F. Rudd, MD, PhD; Division of Cardiovascular Medicine, Cambridge University (Cambridge, UK)
Bucerius J.	Atherosclerosis Imaging with PET / CT - Translational and Molecular Imaging Institute, Mount Sinai School of Medicine/Zahi A. Fayad, PhD (New York, USA)
Bucerius J.	Ahmed Tawakol - Massachusetts General Hospital, Harvard School of Medicine/Ahmed Tawakol, MD (Boston, USA)
Bucerius J.	Vascuar PET/CT Imaging of Nicotinic Acetylcholine Receptors - Department of Pharmacology at Hilo University/Daniela Gündisch, PhD (Hilo, Hawaii)
Bucerius J.	Vascuar PET/CT Imaging of Nicotinic Acetylcholine Receptors - Institute for Radiopharmacy-Helmholtz-Zentrum Dresden-Rossendorf, Research Site Leipzig/ Peter Brust, PhD, Winnie Deuther-Conrad, PhD (Leipzig, Germany)
Bucerius J.	Vascuar PET/CT Imaging of Nicotinic Acetylcholine Receptors - Research Institute, Heart Center Leipzig, University of Leipzig/ Stefan Dhein, MD, PhD, Sandy von Salisch (Leipzig, Germany)
Bucerius J.	Vascuar PET/CT Imaging of Nicotinic Acetylcholine Receptors - Department of Nuclear Medicine, University Hospital RWTH Aachen/Jörn Schmaljohann, PhD (Aachen, Germany)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Bucerius J.	Department of Nuclear Medicine, University of Bonn/Hojjat Ahmadzahdehfar, MD, PhD (Bonn, Germany)
Castoldi E.	Collaboration on various topics, ranging from bleeding disorders (factor V deficiency) to familial thrombophilia (APC resistance, protein S deficiency) - Department of Cardiologic, Thoracic and Vascular Sciences, University of Padua Medical School/Prof. Paolo Simioni (Padua, Italy)
Castoldi E.	Collaboration on the relationship between fibrinogen variants and venous thrombosis (the Netherlands, UK)
Castoldi E.	Collaboration on the development of molecular therapies for severe factor V deficiency - International Centre for Genetic Engineering and Biotechnology/ Prof. Francisco E. Baralle, Dr Marco Baralle (Trieste, Italy)
Castoldi E.	Collaboration on the identification of large gene rearrangements underlying factor V deficiency - Institute of Experimental Haematology and Transfusion Medicine/Dr Anna Pavlova (Bonn, Germany)
Castoldi E.	Collaboration on the identification of large gene rearrangements underlying factor V deficiency - Department of Biology and Genetics for Medical Sciences, University of Milan/Dr Stefano Duga (Milan, Italy)
Castoldi E.	Collaboration on genetically unexplained factor V deficiency - Department of Medicine, University of North Carolina at Chapel Hill/Prof. Nigel S. Key (NC, USA)
Crijns H.	UMC Groningen/Isabelle van Gelder (Groningen, the Netherlands)
Crijns H.	Consensus conferences, EAST/Paulus Kirchhof (Birmingham, UK)
Crijns H.	EAST, Record-AF, EHS-AF/John Camm (London, UK)
Crijns H.	EHS-AF/Alessandro Capucci (Piacenza, Italy)
Da Costa Martins P.	Identification of autophagic miRNAs in the failing human heart - University of Antwerp, Belgium (Dr D. Schrijvers) and Hannover Medical School, Germany (Dr T. Thum)
Da Costa Martins P.	MicroRNAs involved in angiogenesis and endothelial cell proliferation in the (failing) heart – Hubrecht Institute, Utrecht, the Netherlands (Dr S. Schulte-Merker)
Da Costa Martins P.	Role of microRNAs in cardiac reverse remodeling after LVAD support: Dr S. Lok (Meander Hospital Amersfoort, NL) and Dr R. de Weger (University Medical Center Utrecht, NL)
Da Costa Martins P.	Molecular players in right ventricular remodeling – MUMC Maastricht, the Netherlands (Dr V. van Empel) and Max Planck Institute for Heart and Lung Research, Germany (Dr T. Braun)
Da Costa Martins P.	Cardiac microRNAs regulating systemic energy homeostasis - UT Southwestern Medical Center, USA/Dr E. Olson and Dr.R. Bassel-Duby
Da Costa Martins P.	Underlying mechanisms of reverse remodeling and therapeutic implications - Oporto University/Dr. A. Leite Moreira (Porto, Portugal)
Dagnelie P., Henry, R.	NWO Investment grant, with Wageningen University, National Institute of Health and the Environment and TNO Quality of Life
Dagnelie P.	ATP infusions in rheumatoid arthritis -Atrium MC Heerlen, Orbis MC Sittard, Laurentius Hospital Roermond, St Jansgasthuis Weert (the Netherlands)
Dagnelie P.	ATP infusions in non-small-cell lung cancer: 10 centres in The Netherlands and Belgium
Dagnelie P.	ATP infusions in palliative home care -UMC Utrecht and Catharina Hospital Eindhoven (the Netherlands)
Dagnelie P.	Postoperative pain and ATP/adenosine infusion - Catharina Hospital Eindhoven (the Netherlands)
Dagnelie P., Henry R.	ZonMW Cost effectiveness study: Nutritional screening and intervention in elderly subjects after hip fracture - Atrium MC Heerlen, Orbis MC Sittard, and 16 rehabilitation centres and elderly homes in the region of South-Limburg (the Netherlands)
Dagnelie P.	University College London/Prof. G. Burnstock (London, UK)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Dagnelie P.	Medical School, New York University/ Prof. B. Cronstein (New York, USA)
Dagnelie P.	University of Ferrara/Prof. F. Di Virgilio (Ferrara, Italy)
Dagnelie P.	Copenhagen University Hospital Glostrup/ Dr N. Jorgensen (Copenhagen, Denmark)
Dagnelie P.	University College London/Prof. T. Arnett (London, UK)
Dagnelie P.	University of Liverpool/Prof. J Gallagher (London, UK)
Dagnelie P.	University of Sheffield/Dr A. Gartland (Sheffield, UK)
Dagnelie P.	St George's Hospital Medical School/ Prof. F. Capuccio (London, UK)
Dagnelie P.	Free University of Brussels/Prof. J.M. Boeynaems (Brussels, Belgium)
Dagnelie P.	Catholic University of Leuven/ Prof. J. Arnout (Leuven, Belgium)
Dagnelie P.	Catholic University of Leuven/Prof. F. Buntinx (Leuven, Belgium)
Dagnelie P.	Santa Maria Imbaro/Prof. L. Iacoviello (Italy)
Dagnelie P.	National Cancer Institute/Dr V. Krogh (Milan, Italy)
Dagnelie P.	National Research Council/Prof. A. Siani (Avellino, Italy)
Dagnelie P.	UFR de Médecine et Pharmacie/Prof. M. de Lorgeril (La Tronche, France)
Dagnelie P.	University Gießen /Max Rubner Institute/ Prof. I. Hoffmann (Karlsruhe, Germany)
Dagnelie P.	Unversity of Munich/Prof. B. Koletzko (Munich/Germany)
Dagnelie P.	Participatie in CTMM-TraIT
Delhaas T.	Acute and chronic effects of ventricular pacing in children - Leuven University Hospital/Prof. M. Gewillig, Prof. L. Mertens (Leuven, Belgium)
Delhaas T.	Acute and chronic effects of ventricular pacing in children - University Hospital Motol/Prof. J. Janousek (Prague, Czechia)
Delhaas T.	Multiscale patient-specific cardiovascular modeling in: heart failure, cardiac resynchronization therapy, and pulmonary arterial hypertension - CHU de Bordeaux/ Prof. M. Haissaguerre (Haut-Lévêque, France)
Delhaas T.	Multiscale patient-specific cardiovascular modeling in: heart failure, cardiac resynchronization therapy, and pulmonary arterial hypertension - University of Pittsburgh/Prof. J. Gorcsan (Pitssburgh, USA)
Donners, M	ADAMs - RWTH Aachen/Prof Dr A Ludwig (Aachen, Germany)
Engelen L., Schalkwijk C. Stehouwer C.	Removal-trial – a.o. Glasgow UK (Prof. J. Petrie) London UK (Prof. N. Chaturvedi and Prof. A. Hughes, Copenhagen Denmark (Prof. P. Rossing)
Engelen L., Schalkwijk C. Stehouwer C.	International Consortium on arterial stiffness (Grants Esaote and TIFN) – a.o. Paris France (Prof. S. Laurent, Prof. P. Boutouyrie) and Gent Belgium (Prof. L. Van Bortel)
Engelen L., Schalkwijk C. Stehouwer C.	Consortium financed by CVON, PSI, TIFN, CTMM, Vidi-Biessels, Vidi-Pouwers, industry – a.o. VUmc Amsterdam (Dr E. Eringa, Prof. Y. Smulders, Dr E. Serné, Prof. J. Dekker, Prof. V. van Hinsbergh, Prof. J. Niessen), UMC Utrecht (Prof. R. Grobbee, Prof. M. Bots, Prof. GJ. Biessels, Prof. Y. van der Schouw) Erasmus MC Rotterdam (Prof. D. Duncker)
Engelen L., Schalkwijk C. Stehouwer C.	Marie Curie – Paris, France (Prof. M. Safar) Athens, Greece (Dr A. Protogerou), Avignon, France (Prof. A. Vinet), Rio de Janerio, Brazil (Prof. E. Bouskela)
Engelen L., Schalkwijk C. Stehouwer C.	Steno Hospital; several consortia on diabetes, complications of diabetes and vascular function – Copenhagen, Denmark (Prof. P. Rossing, Prof. HH. Parving, Prof. AA. Vaag)
Engelen L., Schalkwijk C. Stehouwer C.	Prof. M Lorenz (Frankfurt), Prof. H Refsum en Prof. PM Ueland (Bergen), Prof. J Tuomilehto (Helsinki); J Danesh (Cambridge), Profs Brownlee (NY), Cooper (Australia), Forbes (Australia), Miyata (Japan), Stitt (Ireland), Nawroth (Germany)
Glatz J.	LUMC Leiden/Prof. K. Willems van Dijk (Leiden, the Netherlands)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Glatz J.	UMC Groningen/Prof. M. Hofker (Groningen, the Netherlands)
Glatz J.	Julius Center, Utrecht University/ Prof. A.W. Hoes (Utrecht, the Netherlands)
Glatz J.	Utrecht University, Utrecht/Prof. Y. van der Schouw, Prof. DJ van der Horst (Utrecht, the Netherlands)
Glatz J.	RUN-MC Nijmegen/Prof. A. Heerschap (Nijmegen, the Netherlands)
Glatz J.	VUMC Amsterdam/Prof. M. Diamant (Amsterdam, the Netherlands)
Glatz J.	AMC Amsterdam/Prof. R.J. Wanders (Amsterdam, the Netherlands)
Glatz J.	epartment of Human Health and Nutritional Sciences, Guelph University/Prof. A. Bonen (Guelph, Canada)
Glatz J.	De Duve Institute of Cellular Pathology, Université Catholique Louvain/Prof. L. Bertrand (Brussels, Belgium)
Glatz J.	Institute of Clinical Biochemistry and Pathobiochemistry, German Diabetes Center/ Prof. J. Eckel (Düsseldorf, Germany)
Glatz J.	Dept. of Physiology, University of Bialystok/ Prof. Górski, Dr A. Chabowski (Bialystok, Poland)
Glatz J.	Copenhagen Muscle Research Institute/ Dr B. Kiens (Copenhagen, Denmark)
Glatz J.	Dept. of Cardiology, University of Chieti/ Prof. R. de Caterina (Chieti, Italy)
Glatz J.	National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda/Prof. M. Sack (Maryland, USA)
Glatz J.	Dept. of Biophysics, Boston University Medical School/Prof. J.A. Hamilton (Boston, USA)
Glatz J.	Thrombosis and Vascular Biology Laboratory, Otsuka America Pharmaceutical Inc., Rockville MD/Dr NN. Tandon, (Rockville, USA)
Glatz J.	Dept. of Nutritional Physiology, University of Dijon/Prof. I. Niot, Prof. P. Besnard (Dijon, France)
Glatz J.	Dept of Medical Physiology, University of Tromsø/Prof. T. Larsen, Prof. E. Aasum (Tromsø, Norway)
Glatz J.	Dept. of Biosensors, Hong Kong University of Science and Technology/Prof. R. Renneberg (Hong Kong)
Glatz J.	Cardiac Metabolism Research Group, Dept. of Physiology, Anatomy and Genetics, University of Oxford/Prof. K. Clarke (Oxford, UK)
Glatz J.	Université Pierre et Marie Curie (UPMC)/ Dr B. Viollet (Paris, France)
Greevenbroek M. van	University of Oxford/Prof. Helga Refsum, Dr Amany Elshorbagy (Oxford, UK)
Greevenbroek M. van	LUMC Leiden/Dr Bas Heijmans (Leiden, the Netherlands)
Greevenbroek M. van	CODAM study - WUR Wageningen/ Prof. E. Feskens (Wageningen, the Netherlands)
Greevenbroek M. van	Erasmus MC Rotterdam/Dr A. Isaacs (Rotterdam, The Netherlands)
Greevenbroek M. van	RadboudMC Nijmegen/Prof. J. de Graaf (Nijmegen, the Netherlands)
Greevenbroek M. van	North Carolina Central University/ Dr Sujoy Ghosh (Durham, NC, USA)
Hackeng T.	Structure-function analysis and physiological implications of (impaired) anticoagulant pathways - Department of Molecular and Experimental Medicine, The Scripps Research Institute/Prof. John H. Griffin (La Jolla, CA, USA)
Hackeng T.	Covalent capture of polyvalent carbohydrate ligands of glycan-binding proteins form a dynamic library; a novel strategy in drug design - Department of Cell Biology, The Scripps Research Institute/Dr Philip E. Dawson (La Jolla, CA, USA)
Hackeng T.	Gamma carboxylation of (synthetic) hybrids of Gla domains from prothrombin and factor X - Department of Biology, The University of North Carolina at Chapel Hill/Prof. Darrel Stafford (Chapel Hill, NC, USA)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Hackeng T.	The role of PF4 and Rantes on endothelial monocyte arrest - Institute for Cardiovascular Prevention, Ludwig-Maximilians-Universität (LMU) München/Prof. Christian Weber (Munich, Germany)
Hackeng T.	Multivalent conjugation (contrast and homing tags) of (macromolecular) dendrimers - Biomedical Engineering, Eindhoven University of Technology/Prof. E.W. Meijer (Eindhoven, the Netherlands)
Hackeng T.	Tissue factor pathway inhibitor activity for prediction of recurrent thrombosis- Dept. Epidemiology, Leiden University Medical Center/Prof. Frits Rosendaal (Leiden, the Netherlands)
Heemskerk J.	Collaboration on platelets - University of Wurzburg/Prof. B. Nieswandt (Wurzburg, Germany)
Heemskerk J.	Collaboration on platelets/Prof. A. Poole (Bristol, UK)
Heemskerk J.	Collaboration on platelets/Prof. SP. Watson (Birmingham, UK)
Heemskerk J.	Collaboration on platelets/Prof. M. Gawaz (Tübingen, Germany)
Heemskerk J.	Collaboration on proteomics - CTH, Mainz University/Prof. U. Walter (Mainz, Germany)
Heemskerk J.	Collaboration on proteomics - ISAS, Dortmund/Prof. A. Sickmann (Dortmund. Germany)
Heemskerk J.	Collaboration on collagens - Cambrigde University/Prof. R. Farndale (Cambridge, UK)
Heemskerk J.	Collaboration on anoctamins - University of Regensburg/Prof. K. Kunzelmann (Regensburg, UK)
Heemskerk J.	Collaboration on calpains - Tufts Med School, Boston/Prof. A. Chishti (Boston, USA)
Heemskerk J.	Collaboration on inflammation - University of Munich/Prof.C. Weber (Munich, Germany)
Heemskerk J.	Collaboration on thrombosis models - Cath. University of Leuven/Prof. M. Hoylaerts (Leuven, Belgium)
Heemskerk J.	Collaboration on platelets - University of Liege/Dr C. Oury (Liege, Belgium)
Heemskerk J.	Collaboration on factor XII - Karolinska Stockholm/Prof. T. Renne (Stockholm, Sweden)
Heeneman S.	CARDIOrisk (EU-FP7) - Cardiovascular Risk after low radiation doses (Germany, France, UK, Poland, Germany, Finland)
Henry R.	Wageningen Universiteit, Vakgroep Humane Voeding en Epidemiologie, Nederland
Henry R.	Universiteit Kopenhagen, Denemarken
Henry R.	Department of Clinical Medicine, Prevention and Applied Biotechnologies, University of Milano-Bicocca and St Gerardo Hospital, Monza/Prof. Gianatassio (Milano, Italy)
Henry R.	BBMRI project BBMRI-FFQ) - Rijksinstituut voor Volksgezondheid en Milieuhygiene (RIVM) & WUR Wageningen (the Netherlands)
Henry R.	Interreg NL- Germany project FooDS - Hochschule Niederrhein, Mönchen-Gladbach, Germany and others
Heymans S.	Gene therapy, AAV technology - International Centre for Genetic Engineering and Biotechnology/Mauro Giacca (Trieste, Italy)
Heymans S.	Linc-RNAs and cardiovascular diseases - Uiversity of Lausanne Medical School, Department of Medicine, Experimental Cardiology Unit/Thierry Pedrazzini, (Lausanne, Switzerland)
Heymans S.	FP7-MEDIA network - Heart failure with preserved ejection fraction - Department of Physiology and Cardiothoracic Surgery, University of Porto/A. Leito-Morreira (Porto, Portugal)
Heymans S.	FP7-Fibrotargets network - Matrix biology - Department of Cardiovascular Pathophysiology, Pamplona/Javier Diez (Pamploma, Spain)
Heymans S.	FP7-Homage and FP7-Fibrotargets network - Biomarkers and Matrix Biology - Investigation Centre at the Institut National de la Santé et de la Recherche Médicale, Nancy/Faiez Zannad (Nancy, France)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Heymans S.	FP7-EU Mascara, Ingenious Hypercare network - Hypertension, biomarkers - Department of Hypertension, Cardiology, University of Leuven/Jan Staessen (Leuven, Belgium)
Heymans S.	WG of myocardial function network - Myocarditis, cardiac inflammation - Department of Biotechnology and Life Sciences, Molecular Biotechnology Center University of Torino/Valeria Poli, Guido Tarone, Emilio Hirsch, (Torino, Italy)
Heymans S.	FP7-MEDIA network - Myocarditis, cardiac fibrosis - Department of Cardiology, Charité, Berlin/Carsten Tschoeppe, D. Westermann, W. Poller (Berlin, Germany)
Heymans S.	MicroRNAs, biomarkers - Cardiovascular Research Department Luxemburg/D. Wagner, Y. Devaux (Luxemburg)
Heymans S.	Heart failure, matrix metalloproteinases - Department of Molecular Physiology and Biophysics, University of Iowa Carver College of Medicine, Iowa City/Mark Anderson (Iowa USA)
Heymans S.	FASEB meetings network - Diastolic heart failure, matrix proteins, SPARC - Division of Cardiology, Department of Medicine, University of Texas Health Science Center at San Antonio/Amy Bradshaw (San Antonio, USA)
Heymans S.	Angiogenesis, inflammation – Vesalius Institute, Leuven University/Peter Carmeliet (Leuven, Belgium)
Heymans S.	Heart Failure Association network - Oxidative stress, inflammation - Kings' college, London, Department of Cardioloy/A. Shah (London, UK)
Houben B.	The role of the microcirculation in the pathogenesis of insulin resistance and hypertension - Depts. of Physiology and Internal Medicine – VUMC Amsterdam/E. Eringa, E. Serne, Y. Smulders (Amsterdam, the Netherlands)
Houben B.	Muscle microcirculation studies: development of contrast enhanced ultrasonography - Dept. of Medicine, University of Virginia, USA (E. Barrett); Dept. of Physiology, VUMC Amsterdam, the Netherlands (E. Eringa) and Dept. of Biophysics, Maastricht University, the Netherlands (A. Hoeks)
Janssen, B.	Optimizing anesthesia and hemodynamic stability in mice - School of Engeneering, University of Cyprus/Christakis Constatinides (Cyprus)
Kallen, C. van der	CTMM/TRAIT/Philips/The Hyve
Kallen, C. van der	STW project/Brains Unlimited
Kooi E.	University of Washington/Prof. Chun Yuan (Seattle, USA)
Kooi E.	Erasmus MC Rotterdam/Prof. Aad van der Lugt/Dr Frank Gijssen (Rotterdam, the Netherlands)
Kooi E.	UMC Utrecht/Dr Jeroen Hendrikse (Utrecht, the Netherlands)
Kooi E.	AMC Amsterdam/Prof. Mat Daemen (Amsterdam, the Netherlands)
Kooi E.	Leiden UMC/Dr Rob van der Geest/ Dr Jos Westenberg (Leiden, the Netherlands)
Koole L.	Cardiovascular Biomaterials Science/New biomaterials for diagnistic applications - University of Malaya/Prof. Fatimah Ibrahim (Kuala Lumpur, Malaysia)
Koole L.	Biomaterials for Blood Contact - University of New South Wales/Prof. Laura Poole-Warren (Sydney, Australia)
Koole L.	Radiopaque Biomaterials, Iodinated Carboranes - Institute for Materials Science ICMAB/Prof. Clara Vinas (Barcelona, Spain)
Koole L.	Electron microscopy - Queen Mary University London/Prof. Alan Boyde (London, UK)
Koole L.	BioMiMedics - RWTH Aachen/Prof. D. Klee (Aachen, Germany)
Koole L.	BioMiMedic - University of Applied Technology/Prof. M. Schoening (Aachen, Germany)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Koole L.	BioMiMedics - University of Liege/ Prof. C. Jerome, Prof. C Grandfils (Liege, Belgium)
Koole L.	BioMiMedics - Universiteit Hasselt/ Prof. M. Ameloot, Prof. W. Gueudens (Hasselt, Belgium)
Koole L.	Radiopaque Biomaterials, physical-mechanical properties - ETH Zürich/ Prof. Th. Tervoort (Zürich, Switzerland)
Kroon A.	Device industry (CVRx, Minneapolis, MN, USA): phase II and III studies in patients with treatment resistant hypertension, using device-based baroreflex activation therapy ('baropacing')
Laat B. de	Montefiore Medical Center/Jacob Rand (New York, USA)
Laat B. de	The Scripps Research Institute/Zaverio Ruggeri (La Jolla, USA)
Laat B. de	University Medical Center Nancy/Denis Wahl (Nancy, France)
Laat B. de	Vittorio Pengo (Padua, Italy)
Leeuw P. de	Fibromuscular dysplasia - INSERM, HEGP (Paris, France)
Leeuw P. de	Baropacing - University of Rochester (USA)
Moulin D.	Biomaterial/Christian Grandfils (Liege, Belgium)
Neumann D.	AMPK regulation in pancreas - CSIC Valencia/Pascual Sanz (Valencia, Spain)
Neumann D.	Various aspects of creatine and creatne kinase/AMPK connection - Joseph Fourier University of Grenoble/Uwe Schlattner (Grenoble, France)
Neumann D.	Involvement of AMPK in kidney physiology and ion transport - Pittsburg University/ Kenneth Hallows, Nuria Pastor-Soler (Pittsburg, USA)
Neumann D.	AMPK structure-function relationship - Tsinghua University China/Jia-Wei Wu (China)
Neumann D.	AMPK-OGT relationship - Johns Hopkins University/Gerald Hart (Baltimore, USA)
Nicolaes G.	Several projects - Institut National de la Santé et de la Récherche Médicale (INSERM)/Dr BO. Villoutreix (Paris, France)
Nicolaes G.	Functional characterization of platelet factor V and its interaction with multimerin - Department of Pathology and Molecular Medicine, McMaster University, Hamilton/ Dr K. Hayward (Ontario, Canada)
Nicolaes G.	Several projects - Department of Pathology, Vanderbilt University School of Medicine, Nashville/Prof. P. Bock (Tennessee, USA)
Nicolaes G.	Crystal structure of small molecule inhibitors of membrane binding in complex with coagulation factors V and VIII - Prof. B. Furie and Dr M. Huang, Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts and the State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Fujian, China
Nicolaes G.	Unraveling the cytoprotective effects of activated protein C in ischemic injury -AMC Amsterdam/ Dr E. Lutgens (Amsterdam, the Netherlands)
Nicolaes G.	Unraveling the structure-function relationships of IRAK-M through structural bioinformatics guided approaches - Center for Experimental and Molecular Medicine, AMC Amsterdam/Dr C. van 't Veer (Amsterdam, the Netherlands
Nicolaes G.	Structure determination of the prothrombinase and intrinsic tenase complex by atomic force microscopy - CEA Marcoule/ Dr J-L Pellequer (Bagnols sur Cèze, France)
Nicolaes G.	Evolution of Protein S structure - Division of Haemostasis and Thrombosis, Department of Haematology, University Medical Centre Groningen/Dr R. Mulder (Groningen, The Netherlands)
Oostenbrugge R. van	University of Edinburgh/Prof. J. Wardlaw (Edinburgh, UK)
Oostenbrugge R. van	UCL London/Dr D. Werring (London, UK)
Post M.	Angiogenesis – Yale University/Mark Simons (Connecticut, USA)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Post M.	Angiongenesis/Yihai Cao (Stockholm, Sweden)
Post M.	Notch ADAM signaling/Rose John (Kiel Germany)
Post M.	Bioreactors/Marianne Ellis (Bath, UK)
Post M.	Consumer acceptance/Neil Stephens (Cardiff, UK)
Post M.	Hydrogels/Matthias Lutolf (Lausanne, Switzerland)
Post M.	Neovascularization/Johannes Waltenberger (Münster Germany)
Post M.	Life cycle analysis/Hanna Tuomisto (Oxford UK)
Post M.	Cost modeling/Jon Rowley (Walkersville, USA)
Prinzen F.	Narayana Hrudayalaya Cardiac Hospital (Bangalore, India)
Prinzen F.	COPHAR-CTMM project (UMCU, AMC, VUMC, UMCG)
Prinzen F.	Echocardiographic data in patients combined with mathematical model: now eight joint publications in four years – UMC Utrecht (the Netherlands)
Prinzen F.	Studies on the effect of LBBB during TAVI interventions and during conventional aortic valve surgery – Catharina Hospital Eindhoven (the Netherlands)
Prinzen F.	Collaboration with in the field of LBBB during TAVI – Erasmus MC Rotterdam/Prof. De Jaegere (Rotterdam, the Netherlands)
Prinzen F.	Cooperation in the field of measurement of collagen using MRI and the protein CNA35 (in the context of COHFAR study) – UMC Utrecht/Dr van Rijen (Utrecht, the Netherlands)
Prinzen F.	Project on short-term pacing in pigs with myocardial infarction – Erasmus MC Rotterdam/ Prof. D. Duncker (Rotterdam, the Netherlands)
Prinzen F.	Cardio Centro Ticino (CCT)/Prof. Auricchio (Lugano, Switzerland)
Prinzen F.	Cooperation in the context of the L2M2 group/a.o. Prof. Auricchio (CCT), Prof. Krause (USI)
Prinzen F.	LIRYC Institute at the University of Bordeaux/ a.o. Prof. Haissaguerre (Bordeaux, France)
Prinzen F.	University of Pittsburgh/Dr John Gorcsan III (Pittsburgh, USA)
Prinzen F.	Karolinska Institute Stockholm/Dr Liliane Wecke (Stockholm, Sweden)
Prinzen F.	Departments of Cardiology and Internal Medicine, Olso University/Prof. Smiseth, Prof. Christansen (Oslo, Norway)
Prinzen F.	Mayo Clinic/Prof. Andre Terzic (Minnesota, USA)
Reneman R.	Department of Bioengeneering, University of Washington in Seattle/Prof. Jim Bassingthwaighte (Seattle, USA)
Reneman R.	Department of Epidemiology, Erasmus MC Rotterdam/Dr FUS Mattace Russo, DrJCM Witteman (Rotterdam, the Netherlands)
Reutelingsperger C.	Collaboration on Annexin A1 and wound healing - University Emory University School of Medicine Atlanta/Prof. Asma Nusrat (Atlanta, USA)
Reutelingsperger C.	Collaboration on imaging cardiovascular diseases - Mount Sinai New York/Prof. Jagat Narula (New York, USA)
Reutelingsperger C.	Collaboration on Annexins - University of Cologne/Prof. Dr. Bent Brachvogel (Cologne, Germany)
Schaper N.	Diabetic foot disease - Tameside Hospital NHS Foundation Trust University of Manchester/E. Jude (Manchester, UK)
Schaper N.	Diabetic foot disease - The Research Unit for General Practice and Section of General Practice, Department of Public Health Copenhagen/V. Siersma (Copenhagen, Denmark)
Schaper N.	Diabetes and peripheral arterial disease - St George's Vascular Institute/R Hinchliffe (London, UK)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Schmidt H.	Diabetic nephropathy, atherosclerosis - Karin Kandeleit-Dahm, Baker IDI/Mark Cooper (Melbourne, Australia)
Schmidt H.	Diabetic retinopathy - Monash University/ Jennifer-Wilkinson-Berka (Melbourne, Australia)
Schmidt H.	COST Action EU-ROS - University Padova/ Fabio di Lisa (Padova, Italy)
Schmidt H.	Drugome - Harvard University/Albert-Laszlo Barabasi (Boston, USA)
Schmidt H.	NOX - Vanderbilt University/David Harrison (Nashville, USA)
Schmidt H.	NOX - University of Geneva/Karl-Heinz Krause (Geneva, Switzerland)
Schmidt H.	NOX, sGC - Harvard University/Joe Loscalzo (Boston, USA)
Schmidt H.	NOX, sGC in stroke and TBI - University of Würzburg/Christoph Kleinschnitz (Würzburg, Germany)
Schmidt H.	NOX, sGC, epidemiology - University of Leuven/Jan Staessen (Leuven, Belgium)
Schmidt H.	sGC activators, biomarkers, CAD - Baker IDI/ Karlheinz Peter (Melbourne, Australia)
Schotten U.	Leducq Foundation Network ENAFRA (European / North American Atrial Fibrillation Research Alliance) - Several partners on Ca2+ handling in atrial fibrillation
Schotten U.	EUTRAF (European Network for Translational Research in Atrial Fibrillation) - Several partners on Translational Research in atrial fibrillation
Schotten U.	RADOX (RADical reduction of OXidative stress in cardiovascular diseases) - Several partners on Role of reactive oxygen species in cardiovascular disease
Schotten U.	3D MRI and Atrial Anatomy Reconstruction – Oxford University/P. Kohl (UK)
Schroen B.	Proteomics - King's College London/Manuel Mayr (London, UK)
Schroen B.	AAV9 - International Centre for Genetic Engineering and Biotechnology (ICGEB)/ Mauro Giacca (Trieste, Italy)
Schroen B.	MicroRNA - Hannover Medical School/ Thomas Thum (Hannover, Germany)
Schroen B.	AAV9 sponges for microRNAs - University of Heidelberg/ Dirk Grimm (Heidelberg, Germany)
Schroen B.	Cardiac hypertrophy genetics - Imperial College London/Stuart Cook, Tim Aitman (London, UK)
Schurgers L.	Collaboration of vascular smooth muscle cells and vascular tissue as in vitro model for VC - Cardiovascular Division, Kings College London/Prof. C. Shanahan (London, UK)
Schurgers L.	Collaboration on the interplay between MGP and fetuin-A in vascular calcification – RWTH Aachen/Prof. J Floege/ Prof. W. Jahnen-Dechent (Aachen, Germany).
Schurgers L.	Collaboration on PXE induced elastin calcification - Jefferson Medical College, and Jefferson Institute of Molecular Medicine, Thomas Jefferson University/ Prof. J. Uitto (Philadelphia, USA)
Schurgers L.	Collaboration on vitamin K and vitamin K-dependent proteins analysis - Centre for Haemostasis and Thrombosis, St. Thomas hospital, London/Dr M. Shearer (London, UK)
Schurgers L.	Collaboration on intracellular calcium handling in vascular smooth muscle cells - The Babraham Institute, Babraham Research Campus, Cambridge/Dr D. Proudfoot (Cambridge, UK)
Sluimer J.	Autophagy - Columbia University New York/ Prof. A. Tall (New York, USA)
Sluimer J.	Angiogenesis - CVPath Institute, Inc., Gaithersburg/Prof. R. Virmani (Gaithersburg, USA)
Sluimer J.	Plaque angiogenesis - Inserm U833, Paris/ Prof. P. Corvol (Paris, France)
Sluimer J.	Macrophage and dendritic HIF1 in atherosclerosis - Wurzburg University/ Dr A. Zernecke (Wurzburg, Germany)
Sluimer J.	Hypoxia in murine model of vulnerable plaque - Antwerp University/Prof. G. Demyer, (Antwerp, Belgium)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Sluimer J.	Apoptosis in human atherosclerosis of USPIO-treated patients - Antwerp University/ Dr D. Schrijvers (Antwerp, Belgium)
Sluimer J.	Oxygen sensors in atherosclerosis - VIB, K.U. Leuven/Prof. P. Carmeliet (Leuven. Belgium)
Sluimer J.	Angiogenesis in murine atherosclerosis - University of Eastern Finland/ Prof. S. Yla-Herttuala (Finland)
Smeets B.	University of Newcastle upon Tyne/ Dr P.F. Chinnery, Prof. D. Turnbull, Dr R. Taylor (Newcastle, UK)
Smeets B.	Institute of Neurology "C. Besta"/Dr V. Tiranti, Prof. M. Zeviani (Milan, Italy)
Smeets B.	University Medical Centre Nijmegen/ Dr L. van den Heuvel, Prof. J. Smeitink (Nijmegen, the Netherlands)
Smeets B.	INSERM, Paris/Prof. A. Munnich (Paris, France)
Smeets B.	University of Liège/Prof. Wehenkel, Dr Mueller (Liége, Belgium)
Smeets B.	University of Hasselt/Prof. Noben (Hasselt, Belgium)
Smeets B.	RWTH Aachen/Dr Hofmann (Aachen, Germany)
Smeets B.	Brains Unlimited, Maastricht/Prof. Formisano (Maastricht, the Netherlands)
Smeets B.	Department of Neurology, Erasmus MC Rotterdam/Dr de Coo (Rotterdam, the Netherlands)
Smeets B.	The interdepartmental stem cell institute, KU Leuven/Dr Sampaolesi (Leuven, Belgium)
Smeets B.	IPSC technology – Erasmus MC Rotterdam/ Prof. Gribnau (Rotterdam, the Netherlansd)
Smeets B.	IPSC technology – Leiden University/ Prof. Mummery (Leiden, the Netherlands)
Struijker Boudier H.	Dept. of Pharmacology, Rotterdam/J. Danser (Rotterdam, the Netherlands)
Struijker Boudier H.	Dept. of Medical Biology, Groningen/ G. Molema (Groningen, the Netherlands)
Struijker Boudier H.	Dept. of cardiovascular epidemiology, Leuven/J. Staessen (Leuven, Belgium)
Struijker Boudier H.	Paris Cardiovascular Center, Hôpital Georges Pompidou/S. Laurent (Paris, France)
Struijker Boudier H.	Center for Cardiovascular Science, Edinburgh/J. Mullins (Edinburgh, UK)
Vink H.	LUMC/T. Rabelink (Leiden, the Netherlands)
Vink H.	Glycocalyx in Renal Physiology – RUNMC/ J. van der Vlag (Nijmegen, the Netherlands)
Vink H.	CTMM cohort study (HELIUS) on glycocalyx and ethnic background – AMC/S. Pinto (Amsterdam, the Netherlands)
Vink H.	Glycocalyx in cardiovascular patients – UPMC/J. Pacella (Pittburgh, USA)
Vink H.	Glycocalyx in Russian ethnic groups - Pharmapren LLC/O. Gorbacheva (Moscow, Russia)
Vink H.	Glycocalyx in pediatric cardiology patients – C. Nussbaum (Munich, Germany)
Volders P.	University of Manchester/David Eisner (Manchester, UK)
Volders P.	University of Milano-Bicocca/Antonio Zaza (Milano, Italy)
Volders P.	Université Paris-Sud/Rodolphe Fischmeister (Châtenay-Malabry, France)
Volders P.	Oslo University Hospital/Thor Edvardsen (Oslo, Norway)
Weber C.	Daniel J. Rader, University of Pennsylvania, Philadelphia USA (Leducq Transatlantic Network of Excellence)
Weber C.	Leducq Transatlantic Network of Excellence - Broad Institute, Harvard Medical School, Boston/Sekar Kathiresan (Boston, USA)
Weber C.	NMR spectroscopy of chemokine heteromers - University of Minnesota/Kevin Mayo (Minneapolis, USA)
Weber C.	MicroRNA functions - University of Texas, Southwestern Medical Center/Eric N. Olson (Dallas, USA)

National and international collaborations

NAME	NATIONAL AND INTERNATIONAL COLLABORATIONS
Wildberger J.	Epilepsie Centre Kempenhaege/ACE (Paul Hofman, Robert van Oostenbrugge, Bert Aldenkamp)
Wildberger J.	BOZ / HFL (Carla Boetes Fonds)
Wildberger J.	Plaque Imaging – Dept. of Pathology, AMC Amsterdam/Prof. M. Daemen (Amsterdam, the Netherlands)
Wildberger J.	Dept. of Radiology, UMC Utrecht/Tim Leiner, Riccardo Budde, Willem Mali (Utrecht, the Netherlands)
Wildberger J.	Dept. of Radiology, UMC Groningen/ Rozemarijn Vliegenthart, Peter van Ooijen, Mathijs Oudkerk (Groningen, the Netherlands)
Wildberger J.	Depts. of Radiology/Cardiology, Erasmus MC Rotterdam/Ad v.d. Lugt; Cardiale Beeldvorming: Koen Nieman, Gabriel Krestin (Rotterdam, the Netherlands)
Wildberger J.	Dept. of Radiology, Leiden UMC/Hildo Lamb, Albert de Roos (Leiden, the Netherlands)
Wildberger J.	Dept. of Radiology, St. Radboud Nijmegen/ Mathias Prokop (Nijmegen, the Netherlands)
Wildberger J.	CMIV/ Anders Persson (Linköpping, Sweden)
Wildberger J.	Universität Marburg/ Andreas Mahnken (Marburg, Germany)
Wildberger J.	MUSC, Charleston/Uwe Joseph Schoepf (Charleston, USA)
Wildberger J.	Duke University, Durham/Geoff Rubin (NC, USA)
Wildberger J.	Siemens Healthcare R&D, Philips Healthcare R&D, Bayer Healthcare R&D, GE Healthcare R&D, Agfa Healtcare R&D
Wouters K.	Inserm U1011/Prof. Bart Staels (Lille, France)
Wouters K.	Hasselt University/Dr Tim Vanmierlo, Dr Jerome Hendriks (Hasselt, Belgium)
Wouters K.	AMC Amsterdam/Prof. Menno de Winther (Amsterdam, the Netherlands)
Wouters K.	Dr Pieter Goossens (Marseille, France)
Zandvoort M. van	Cardiovascular Imagingusing multiphoton microscopy - Ludwig-Maximilians-University/ Christian Weber, Remco Megens, Andreas Schober (Munich, Germany)
Zandvoort M. van	Three photon microscopy - Ludwig-Maximilians-University, Steffen Dietzel (Munich, Germany)
Zandvoort M. van	Envision Network - Two photon microscopy development - University of Greifswald, Stephanie Koenemann (Greifswald, Germany)
Zandvoort M. van	DFG Network - Combined US and optical imaging of Tumors and cardiovascular – University Hospital Aachen/Fabian Kiessling, Twan Lammers, Rene Tolba (Aachen, (Germany)
Zandvoort M. van	Leukocyte microparticles (NHS proposal) - University of Sheffield/Victoria Ridger (Sheffield, UK)
Zandvoort M. van	Two photon microscopy development - University of Edinburgh/Carmen Heusa (Edinburgh, UK)
Zandvoort M. van	BMX imaging in carotids - University of Helsinki/Kari Alitalo (Helsinki, Finland)
Zandvoort M. van	Two-photon imaging of blood vessels in vivo - University of Geneva/Merlijn Meens, (Geneva, Switzerland)
Zandvoort M. van	Thrombus imaging in vivo - Baker IDI/ Erik Westein (Melbourne, Australia)
Zandvoort M. van	EuCAR- NO imaging in blood vessels – MIT/ Steve Lippard (Boston, USA)
Zandvoort M. van	EUCAR - Carbon Dots (EuCAR) - Ya Ping Sun Clemson University (USA)
Zandvoort M. van	Endothelial Progenitor cell imaging - Eberhard Karls University Tübingen/Meinrad Gawaz (Tubingen, Germany)

ANNEX 4
PARTICIPATION OF CARIM STAFF

Memberships of editorial boards of international journals

NAME	JOURNAL	POSITION
Arts I.	The Journal of Nutrition	Editor
Blankesteijn M.	Fibrogenesis and Tissue repair (since 2012)	Editor
Brunner-La Rocca HP.	Eur Heart J (since 2010)	Member
Brunner-La Rocca HP.	J Cardiovasc Pharmacol Therapeut (2004-2009)	Member
Bucerius J	Annals of Nuclear Medicine (2010)	Reviewer
Bucerius J.	Nuklearmedizin (2008, 2013)	Reviewer
Bucerius J.	Thrombosis and Haemostasis (2009-2010)	Reviewer
Bucerius J.	The Journal of Nuclear Cardiology (2010)	Reviewer
Bucerius J.	The International Journal of Clinical Practice (2010)	Reviewer
Bucerius J.	The Journal of Nuclear Medicine (2010)	Reviewer
Bucerius J.	JACC Cardiovascular Imaging (2011, 2012)	Reviewer
Cate H. ten	Journal of Thrombosis and Haemostasis	Editor
Cate H. ten	Dataset Papers in Medicine	Editor
Cate H. ten	World Science Journal	Editor
Cate, H. ten	Science Open	Editor
Cate, H. ten	PlosOne	Academic editor
Cate, H. ten	Thrombosis Journal	Editor in chief
Cate, H. ten	Thrombosis and Haemostasis	Section editor
Crijns H.	Editorial Board Netherlands Heart Journal	Member
Crijns H.	Editorial Board Journal Cardiovascular Drugs and Therapy	Member
Crijns H.	Editorial Board European Heart Journal	Member
Crijns H.	Editorial Board Journal of Cardiovascular Pharmacology and Therapeutics	Member
Crijns H.	Editorial Board Clinical Research in Cardiology	Member
Crijns H.	Editorial Board PACE	Member
Crijns H.	Editorial Board Journal of Atrial Fibrillation	Member
Crijns H.	Editorial Board of Hellenic Journal of Cardiology	Member
Da Costa Martin P.	PlosOne	Member

NAME	JOURNAL	POSITION
Da Costa Martin P.	American Journal of Physiology : Heart and Circulatory Physiology	Member
Delhaas T.	Pediatric Cardiology	Member
Dirkx E.	PlosOne	Reviewer
Glatz J.	Journal of Lipid Research (since 2011)	Member
Glatz J.	Molecular and Cellular Biochemistry (2002-2012)	Member
Glatz J.	Prostaglandines, Leukotrienes and Essential Fatty Acids (since 2009)	Member
Glatz J.	Frontiers in Fatty Acid and Lipid Physiology (since 2010)	Editor in chief
Glatz J.	American Journal of Physiology – Heart and Circulatory Physiology (2012)	Member
Hackeng T.	Thrombosis Journal	Associate editor
Hackeng T.	Blood	Reviewer
Hackeng T.	Blood Coagulation and Fibrinolysis	Reviewer
Hackeng T.	European Journal of Biochemistry	Reviewer
Hackeng T.	Journal of Thrombosis and Haemostasis	Reviewer
Hackeng T.	Thrombosis and Haemostasis	Reviewer
Hackeng T.	British Journal of Haematology	Reviewer
Hackeng T.	Arteriosclerosis Thrombosis and Vascular Biology	Reviewer
Hackeng T.	Journal of Polymer Science	Reviewer
Hackeng T.	Biochemistry	Reviewer
Hackeng T.	Biopolymers	Reviewer
Hackeng T.	Proceedings Of The National Academy Of Sciences U.S.A.	Reviewer
Heemskerk J.	Journal of Thrombosis and Haemostasis (since 2011)	Editor
Heemskerk J.	American Journal of Blood Research (since 2011)	Member
Heymans S.	Nature Medicine	Reviewer
Heymans S.	Circulation	Reviewer
Heymans S.	American Journal of Pathology	Reviewer
Heymans S.	Circulation Research	Reviewer
Heymans S.	Hypertension	Reviewer
Heymans S.	European Heart Journal	Reviewer

Memberships of editorial boards of international journals

NAME	JOURNAL	POSITION
Heymans S.	Cardiovascular Research	Reviewer
Kooi E.	Radiology section of the Editorial Board of Dataset Papers in Medicine	Member
Koole L.	European Cells and Materials (2010)	Guest editor
Kroon A.	Specialty editor Vascular Medicine & Cardiology of European Journal of Internal Medicine (2007-2010)	Editor
Kroon A.	Nieuwsbrief Vasculaire Geneeskunde (2003-2010)	Member
Kroon A.	Hartbulletin (2009-2012)	Member
Leeuw P. de	American Journal of Cardiovascular Disease (since 2011)	Member
Leeuw P. de	Blood pressure (since 2007)	Member
Leeuw P. de	Coronary Artery Disease (since 2007)	Member
Leeuw P. de	Current Hypertension Reports (since 2007)	Member
Leeuw P. de	Cardiovascular Drugs and Therapy (since 2007)	Editor
Leeuw P. de	Fundamental and Clinical Pharmacology (since 2007)	Member
Leeuw P. de	Hypertension (since 2007)	Member
Luiken J.	Archives of Physiology and Biochemistry (since 2004)	Member
Luiken J.	Frontiers in Lipidology (since 2010)	Member
Neumann D.	Frontiers in Fatty Acid and Lipid Physiology (since 2011)	Review editor
Neumann D.	Frontiers in Fatty Acid and Lipid Physiology (since 2011)	Member
Neumann D.	Life Sciences and Medicine Research (since 2009)	Member
Neumann D.	World Journal of Biological Chemistry (since 2009)	Member
Nicolaes G.	World Journal of Hematology (since 2011)	Member
Post M.	Cardiovascular Research (since 2004)	Editor
Prinzen F.	Europace	Editor
Prinzen F.	J. Cardiovasc. Tranmslation. Research	Editor
Reneman R.	Ultrasound in Medicine and Biology	
Reutelingsperger C.	JACC Cardiovascular Imaging (since 2008)	Member
Reutelingsperger C.	Journal of Immunological Methods (since 2009)	Member
Reutelingsperger C.	Nature Medicine	Reviewer
Reutelingsperger C.	Nature Biotechnology	Reviewer

Memberships of editorial boards of international journals

NAME	JOURNAL	POSITION
Reutelingsperger C.	Nature Protocols	Reviewer
Reutelingsperger C.	New England Journal of Medicine	Reviewer
Reutelingsperger C.	Cardiovascular Research	Reviewer
Reutelingsperger C.	Journal of Thrombosis and Haemostasis	Reviewer
Schalkwijk C.	Diabetologia (since 2012)	Associated editor
Schalkwijk C.	Clinical Science (since 2009)	Editorial advisory panel
Schaper N.	Diabetes Metabolsim Research Reviews (2007, 2011)	Guest editor
Schmidt H.	PLoS One	Editor
Schmidt H.	Antioxidants Redox Signalling	Guest editor
Schmidt H.	J. Molecular medicine (2008-2012)	Member
Schotten U.	Journal of Molecular and Cellular Cardiology (2004-2007)	Member
Schotten U.	Europace (since 2008)	Member
Schurgers L.	Circulation	Reviewer
Schurgers L.	Lancet Neurology	Reviewer
Schurgers L.	JASN	Reviewer
Schurgers L.	Blood	Reviewer
Schurgers L.	JTH	Reviewer
Smeets B.	Clinical and Translational Medicine	Member
Stehouwer C.	Metabolic Syndrome and Related Disorders (since 2003)	Editor
Stehouwer C.	Hypertension (since 2004)	Editor
Stehouwer C.	Netherlands Journal of Medicine (since 2005)	Editor
Stehouwer C.	International Diabetes Monitor (2007 - 2011)	Editor
Stehouwer C.	Journal of Diabetes and its Complications (since 2012)	Editor
Struijker-Boudier H.	Journal of Hypertension	Editor
Struijker-Boudier H.	Journal of Renin-Angiotensin-Aldosteron System	Editor
Struijker-Boudier H.	Journal of Cardiovasc. Med.	Editor
Struijker-Boudier H.	Acta Physiologica	Editor

Memberships of editorial boards of international journals

NAME	JOURNAL	POSITION
Unger T.	American Journal of Physiology	Member
Unger T.	Biochemical Pharmacology	Member
Unger T.	Blood Pressure	Member
Unger T.	Cardiovascular Drugs and Therapy	Member
Unger T.	Hypertension	Member
Unger T.	Hypertension Research (Associate Editor)	Member
Unger T.	International Journal of Hypertension (Associate Editor)	Member
Unger T.	Journal of Hypertension	Member
Unger T.	Journal of the Renin-Angiotensin-Aldosterone System	Member
Unger T.	Clinical and Experimental Hypertension	Member
Unger T.	Clinical Science (Field Editor until 1994)	Member
Unger T.	Fortschritte der Medizin- Münchner Med. Wochenschrift	Member
Unger T.	Fundamental and Clinical Pharmacology (Field Editor 1997-2002)	Member
Unger T.	Nature Reviews Cardiology	Member
Unger T.	Physiological Genomics	Member
Unger T.	Regulatory Peptides	Member
Unger T.	Renin Angiotensin System in Cardiovascular Medicine (Chief Editor 2004-2010)	Member
Weber,C.	Thrombosis Haemostasis (since 2010)	Editor
Weber C.	Arterioscler Thromb Vasc Biol (since 2012)	Editor
Weber C.	Molecular Metabolism (since 2012)	Editor
Weber C.	Circulation Research (since 2010)	Guest Editor
Weber C.	Eur Heart Journal (since 2009)	Member
Weber C.	Basic Res Cardiol (since 2009)	Member
Weber C.	EMBO Mol Med (since 2011)	Member
Weber C.	Cardiovasc Res (since 2012)	Member
Wildberger J.	Investigative Radiology (since 2008)	Member
Wildberger J.	Insights into Imaging (since 2012)	Member
Windt L. de	International Journal of Cardiology (since 2008)	Associate editor
Windt L. de	Plos One – Public Library of Sciences (since 2010)	Associate editor

Memberships of editorial boards of international journals

NAME	JOURNAL	POSITION
Windt L. de	Cardiovascular Research (since 2006)	Member
Windt L. de	European Journal of Heart Failure (since 2008)	Member
Windt L. de	Circulation Research (since 2009)	Member
Windt L. de	Journal of Molecular and Cellular Cardiology (since 2009)	Member
Windt L. de	American Journal of Physiology – Heart and Circulatory Physiology (since 2010)	Associate editor
Windt L. de	International Journal of Cardiology – Heart & Vessels (since 2013)	Member
Zandvoort M. van	PlosOne	Editor
Zandvoort M. van	J of Vascular Research	Reviewer
Zandvoort M. van	Cytometry, Part A	Reviewer
Zandvoort M. van	Nature Communications	Reviewer
Zandvoort M. van	Integrative Biology	Reviewer
Zandvoort M. van	Molecular Imaging and Biology	Reviewer
Zandvoort M. van	Langmuir	Reviewer
Zandvoort M. van	Particle and Fiber Toxicology	Reviewer
Zandvoort M. van	Clinical Cancer Research	Reviewer
Zandvoort M. van	Journal of Biomedical Optics	Reviewer
Zandvoort M. van	Future Cardiology	Reviewer

MEMBERSHIPS EXTERNAL COMMITTEES

NAME	EXTERNAL COMITTEE	POSITION
Biessen E.	Dutch Atherosclerosis Society (since 2008)	Member
Biessen E.	TOP grant committee	Member Scientific Board
Biessen E.	CCVON (NHS) (since 2010)	Member Scientific Board
Biessen E.	CTMM Circulating Cell (since 2008)	Member Scientific Board
Biessen E.	IWT Doktoraalscollege Commissie (since 2010)	Member
Biessen E.	Scientific Advice Committee Dutch Heart Foundation (2003-2009)	Member
Biessen E.	Clinical Guideline Development Committee of the Dutch Institute for Healthcare Improvement CBO (2006-2009)	Member
Biessen E.	Advice Committee Dr. Dekker Fund Dutch Heart Foundation (2006-2012)	Member
Biessen E.	Advice Committee STW project 'Towards a technology to reduce fetal mortality' by Dr. R. Vullings (2006-2012)	Member
Blankesteijn M.	NHS PhD student course "cardiac function and adaptation", Papendal (since 2001)	Member Organisation Committee
Brunner-La Rocca HP.	Global Comparators; Global Outcome Accelerated Learing Heart Failure (since 2010)	Member
Brunner-La Rocca HP.	Committee on Surveys and Registries of Heart Failure Association of the European Society of Cardiology (since 2010)	Member
Brunner-La Rocca HP.	Wirking group of heart failure, Swiss Soceity of Cardiology (2006-2008)	Chair
Brunner-La Rocca HP.	European Society of Cardiology (fellow) (since 2008)	Member
Cate H. ten	Dutch Federation of Thrombosis and Haemostasis (2008-2012)	Member
Cate H. ten	Dutch Federation of Anticoagulation clinics (since 2011)	Chairman
Cate H. ten	Council on Thrombosis of the International Society for Thrombosis and Haemostasis (ISTH) (since 2008)	Member-elect
Cate H. ten	PR & Communications committee of the ISTH (since 2010)	Chairman
Cate H. ten	Animal Models committee of the ISTH- Scientific SubCommittee	Co-chairman
Crijns H.	Netherlands Society of cardiology (until 2009)	Chairman
Crijns H.	Concilium Cardiologicum (residence program) (until 2013)	Chairman
Crijns H.	Scientific board of the Interuniversity Cardiology Institute Netherlands (ICIN) (from 1997)	Member
Crijns H.	Board of the CV Educational Institute (CVOI) (from 2009)	Member
Crijns H.	Netherlands and European Heart Rhythm Association	Member

NAME	EXTERNAL COMITTEE	POSITION
Crijns H.	European Heart Rhythm Association, International Affairs cee (2011-2012)	Member
Crijns H.	Netherlands Health Council (2011-2012)	Member
Crijns H.	Clinical Fellows commite NWO (2011-2013)	Member
Crijns H.	Program committee Netherlands Heart Days (2012-2015)	Member
Crijns H.	European Society of Cardiology (fellow) (since 1997)	Fellow
Crijns H.	Evaluation committee German Centre for CV Research (BMBF) (2010-2011)	Member
Crijns H.	Steering Committee international EAST trial of AFNET/EHRA	Member
Crijns H.	Steering Committee EORP registry on AF, ESC, (from 2011)	Member
Crijns H.	Credentials Committee of the ESC (2009-2011)	Member
Crijns H.	Catheter Ablation of AF Consensus Statement Writing Group, HRS and EHRA, ESC (2011)	Member
Dagnelie P.	Dutch National Congress of Epidemiology (WEON)	Chairman
Dagnelie P.	Dutch Society of Epidemiology	Member
Dagnelie P.	Dutch Federation of Medical-Scientific Societies	Member
Dagnelie P.	International Society of Magnetic Resonance in Medicine	Member
Dagnelie P.	European Society for the Study of Diabetes	Member
Dirkx E.	Heart Failure Association (HFA) of the European Society of Cardiology (ESC) (since 2012)	Member
Glatz J.	Steering Committee of the International Conferences on the Biosciences of Lipids (ICBL) (2001-2011)	Member
Glatz J.	VENI Selection Committee of the Netherlands Organisation for Health Research and Development (ZonMW) (2008-2010)	Chairman
Glatz J.	VENI Selection Committee of the Netherlands Organisation for Health Research and Development (ZonMW) (2006-2007)	Vice chairman
Glatz J.	Board of Directors of the Society for Heart and Vascular Metabolism (SHVM) (2006-2012)	Member
Glatz J.	TOP/ECHO Selection Committee of the Netherlands Organisation for Scientific Research – Chemical Sciences (NWO – CW) (2008-2011)	Member
Glatz J.	TOP Grants Selection Committee of the Netherlands Organisation for Health Research and Development (ZonMW) (since 2012)	Chairman
Glatz J.	Society for Heart and Vascular Metabolism (SHVM) (since 2012)	President
Hackeng T.	Dutch Society of Thrombosis and Haemostasis (NVTH)	Chairman

Memberships external committees

NAME	EXTERNAL COMITTEE	POSITION
Hackeng T.	Scientific Stardardization Committee of Plasma Coagulation Inhibitors from the International Society on Trombosis & Haemostasis (2009-2013)	Co-chairman
Hackeng T.	Royal Netherlands Scientific Organisation (NWO) “Vereniging voor Vernieuwingsimpuls Onderzoekers” (VVViO) (2005-2008)	Founder and Chairman
Hackeng T.	Secretary to the Society of Academy Fellows of the Royal Netherlands Society of Arts and Sciences (KNAW) (2000-2008)	Board Member
Heemskerk J.	EUPLAN Network on Platelets (since 2011)	Chairman Scientific Board
Heemskerk J.	Science Foundation Ireland (2011)	Member Scientific Board
Heemskerk J.	Mainz Centre of Thrombosis and Haemostasis (since 2011)	Member Scientific Board
Heemskerk J.	Netherlands Thrombosis Foundation (since 2011)	Member Scientific Board
Heemskerk J.	Landsteiner Foundation for Blood Transfusion Research (since 2012)	Member Scientific Board
Heemskerk J.	Biorheology Subcommittee of Scientific Standardization Committee of ISTH (2006-2010)	Chairman Scientific Board
Heeneman S.	PARISk (since 2009)	Member Scientific Board
Heymans S.	Board member of the European Heart Failure Association of the ESC, Basic Science (since 2012)	Member
Heymans S.	Strategic Board Cardiovascular Research Institute Maastricht CARIM (2012-2014)	Chair
Heymans S.	Nucleus member Working Group of Myocardial Function of the European Society of Cardiology	Member
Heymans S.	Research department of Cardiology MUMC Maastricht (since 2011)	Chair
Heymans S.	Executive Committee member department of Cardiology MUMC Maastricht (since 2011)	Member
Heymans S.	Nucleus member Committee of Diastolic Heart Failure, European Heart Failure Association (since 2011)	Member
Heymans S.	Nucleus member Committee on Translational Research of the European Society of Heart Failure, European Heart Failure Association (since 2009)	Member
Heymans S.	American Heart Association (since 2009)	Member
Heymans S.	European Society of Cardiology	Member Scientific Board
Heymans S.	European Society of Heart Failure	Member Scientific Board
Heymans S.	European Council on Cardiovascular Research	Member Scientific Board
Heymans S.	Centre of Heart Failure Research MUMC Maastricht	Chair Scientific Board
Houben B.	Dutch Society for Microcirculation and Vascular Biology (MiVaB) (member since 1990, chairman since 2007)	Chairman

Memberships external committees

NAME	EXTERNAL COMITTEE	POSITION
Houben B.	European Society for Microcirculation (ESM) (member since 2005)	Communication officer
Koole L.	Consortium BioMiMedics (Interreg IV-A)	Chair Scientific Board
Koole L.	KNAW China Committee (2006-2011)	Member Scientific Board
Leeuw P. de	Working Group on Blood Pressure Monitoring, European Society of Hypertension (since 2007)	Member Scientific Board
Leeuw P. de	Working Group on Hypertension and the Kidney, European Society of Hypertension (since 2007)	Chair Scientific Board
Leeuw P. de	European Committee on the Study of Fibromuscular Dysplasia (2012)	Member
Luiken J.	TOP Grants Selection Committee of NWO-ALW (since 2011)	Member
Nicolaes G.	Vereniging voor Vernieuwingsimpuls Onderzoekers (VVViO)	Member
Nicolaes G.	Working group on Thrombosis and Haemostasis education of the Netherlands Organisation on Thrombosis and Haemostasis (NVTH)	Member
Nicolaes G.	Program committee “Cardiovascular PhD training courses” of the Netherlands Heart Foundation, representative for CARIM	Member
Nicolaes G.	Netherlands Society on Biomolecular Modelling (NSBM)	President
Nicolaes G.	Selection committee for national Veni grants, Netherlands Scientific Organisation (NWO)	Member
Post M.	WAC 3, NHS (2004-2009)	Member Scientific Board
Post M.	Nederlandse Vereniging voor Fysiologie (since 2011)	Chairman Scientific Board
Post M.	NFU cie Jaspers: Zorg en Techniek (2007-2010)	Member Scientific Board
Reesink, K.	Artery Society (since 2012)	Member
Reneman R.	Academia Europaea (The Academy of Europe)	Member
Reneman R.	Royal Netherlands Academy of Arts and Sciences	Member
Reneman R.	European Academy of Arts and Sciences	Member
Reneman R.	Foreign Correspondence Member Royal Academy for Medicine of Belgium	Member
Reneman R.	Hollandse Maatschappij der Wetenschappen	Member
Reneman R.	Fellow International Academy for Medical and Biological Engineering	Member
Reneman R.	Affiliate Professor of Bioengineering, University of Washington, Seattle, USA	Appointment
Reneman R.	Honorary Professor Institute for Microcirculation, Chinese Academy of Medical Sciences, Beijing, China	Appointment

Memberships external committees

NAME	EXTERNAL COMITTEE	POSITION
Reutelingsperger C.	Italian National Agency for the Evaluation of Universities and Research Institutes 2004 – 2010 (since 2012)	Reviewer
Reutelingsperger C.	Alessandro Liberati Programme for Young Investigators Italy	Reviewer
Reutelingsperger C.	BBSRC (Biotechnology and Biological Sciences Research Council UK)	Reviewer
Schalkwijk C.	Reviewer committee of the EFSD Research Programmes 2012 – 2014	Member
Schaper N.	European study group for diabetes and lower extremity disease (EURODIALE) (since 2001)	Chair Scientific Board
Schaper N.	Dutch study group for neurovascular compliocations of diabetes (since 2003)	Chair Scientific Board
Schaper N.	International Consensus Group on Diabetes and peripheral arterial disease (since 2003)	Chair
Schaper N.	International Working Group on the Diabetic Foot (since 1996)	Member
Schaper N.	International diabetes federation (IDF) tasc force for internal guidelines on Diabetes Mellitus (2012)	Member
Schmidt H.	European Society of Cardiology - Working Group 'Cardiovascular Therapeutics' Nucleus	Member
Schmidt H.	Galenusprize	Member Scientific Board
Schotten U.	Working Group for Cellular Electrophysiology of the German Society of Cardiology (since 2010)	Chair
Schotten U.	Steering Committee of the German Network of Competence for Atrial Fibrillation (AFNET) (since 2012)	Member
Schotten U.	Steering Committee of the European Network for Translational Research in Atrial Fibrillation (since 2010)	Member
Schotten U.	Scientific Document Committee of the European Heart Rhythm Association (EHRA) (2009-2012)	Member
Schotten U.	Task Force Guidelines for the Management of Atrial Fibrillation of ESC and EHRA (2009-2012)	Member
Schurgers L.	Scientific advisor of the Dutch NIGRAM consortium grant (FGF23 and vit D)	Advisory
Schurgers L.	Regular reviewer grant applications of NWO, the Dutch Heart Foundation, and Established Investigator Dekker program	Reviewer
Sluimer J.	European vascular biology Organisation (EVBO) (since 2012)	Member
Unger T.	European Council on Blood Pressure and Cardiovascular Research (ECCR) (since 2002)	Advisory Board
Unger T.	German Cardiological Society	Member
Unger T.	European Society of Cardiology (ESC), Fellow; Member of the WG for Cardiovascular Pharmacology and Drug Therapy	Member

Memberships external committees

NAME	EXTERNAL COMITTEE	POSITION
Unger T.	Berlin-Brandenburg Society of Cardiology	Vice-chair
Volders P.	ESC Working Group on Cardiac Cellular Electrophysiology (EWGCCE) (since 2012)	Chair Scientific Board
Volders P.	ESC Heart Rhythm Association (EHRA) (since 2011)	Member Executive Board
Volders P.	Biophysical Society (since 1997)	Member
Volders P.	Cardiac Electrophysiology Society (since 1998)	Member
Volders P.	Heart Rhythm Society (since 1999)	Member
Volders P.	Netherlands Society of Cardiology (since 2000)	Member
Volders P.	European Society of Cardiology (FESC) (since 2009)	Member
Volders P.	ESC Heart Rhythm Association (since 2012)	Member
Weber C.	ESC Working Group on Atherosclerosis and Vasculare Biology (since 2012)	Chair Scientific Board
Weber C.	PARCC Scientific Advisory Board (since 2010)	Member Scientific Board
Weber C.	University of Zürich, External Evaluation Committee, Dpt. Cardiology (since 2011)	Member Scientific Board
Wildberger J.	Deutsche Röngtengesellschaft (DRG) (since 1995)	Member
Wildberger J.	Cardiovascular Interventional Radiological Society of Europe (CIRSE) (since 1997)	Member
Wildberger J.	Akademie für Fort- und Weiterbildung in der Radiologie (AkRad) (since 1999)	Member
Wildberger J.	European Congress of Radiology (ECR) (since 2000)	Member
Wildberger J.	Arbeitsgemeinschaft Thoraxradiologie, DRG (since 2002)	Member
Wildberger J.	Arbeitsgemeinschaft Interventionelle Radiologie (2003-2008)	Member
Wildberger J.	Gesellschaft für Pädiatrische Radiologie (2005-2011)	Member
Wildberger J.	Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM) (2006-2013)	Member
Wildberger J.	Deutsche Gesellschaft für Interventionelle Radiologie, DRG (since 2008)	Member
Wildberger J.	Radiological Society of North America (RSNA) (since 2008)	Member
Wildberger J.	Nederlandse Vereniging voor Radiologie (NVvR) (since 2008)	Member
Wildberger J.	Industry Relations Committee, „European Society of Thoracic Imaging (ESTI) (since 2011)	Chair
Wildberger J.	European Society of Cardiac Radiology (ESCR) (since 2011)	Member
Wildberger J.	Industry Relations Committee, „European Society of Thoracic Imaging (ESTI)	Chair

Memberships external committees

NAME	EXTERNAL COMITTEE	POSITION
Zandvoort M. van	STW user committee “Non-linear Biopsy of Cancer” (STW 10322) (since 2010)	Member Scientific Board
Zandvoort M. van	STW user committee” Smart Microscopy of Biological tissues” (STW 10433) (since 2010)	Member
Zandvoort M. van	EnvisionInternational Advisory Board, DFG, University of Greifswald, Germany (since 2010)	Member
Zandvoort M. van	Representative Maastricht in NL-BioImaging_AM (since 2011)	Member

AWARDS AND PRICES

NAME	AWARD	REWARD	PERIOD
Arts I.	Selected for the Top Talent Programme 2010 of Maastricht University, Faculty of Health, Medicine, and Life sciences		2010
Blankesteijn M.	NHS acceleration grant	€ 58,000	2010
Borissoff J.	Young Investigator Award ISTH		2011
Brouwers O.	IMARS Travelship Grant (Conference Cairns)	€ 1,000	2009
Bucerius J.	German Academic International Network Reisestipendium, European Career Fair 2010; Boston, USA		2010
Cate H. ten	Runners-up price for the Third Sunstar Foundation World Perio Research Awards		2009
Cosemans J.	Travel grants from the Royal Dutch Academy of Science and the Netherlands Society for Thrombosis and Haemostasis to visit XXth (Sydney, Australia) Congress of the ISTH	€ 3,500	2007
Cosemans J.	Pier Mannucci Young Investigator Award for best article in the Journal of Thrombosis and Haemostasis	€ 1,000	2010
Cosemans J.	Willy van Heumen Prize of the 'Stimuleringsfonds Alternatieven voor Proefdieren' Foundation (Fund for the Promotion of Animal Testing Alternatives Foundation)	€ 25,000	2011
Cosemans J.	Netherlands Heart Foundation (Dekker program 2011/T6)	€ 332,000	2011
Cosemans J.	Research grants from Zon-MW to perform research at the Dept. of Medicine and Cardeza Foundation, Thomas Jefferson University, Philadelphia, USA (2009) and at the Australian Center for Blood Diseases, Monash University, Melbourne, Australia (2007)	€ 7,500	2007/2009
Cosemans J.	Young Investigator Award of the International Society on Thrombosis and Haemostasis (ISTH): XXIIIth Congress of the ISTH, Kyoto, Japan (2011) and XXIIth Congress of the ISTH, Boston, USA (2009)	€ 1,000	2009/2011
Cosemans J.	Landsteiner Foundation (LSBR 1006). Dynamic fibrin clot formation.	€ 245,000	2011-2015
Crijns H	Educational grant - Medapharma	€ 27,500	2009
Crijns H	Atricure Research grants	€ 57,000	2010
Crijns H	Electroechocardiography in atrial fibrillation, NHS	€ 198,000	2010
Crijns H	CTMM COHFAR	€ 208,200	2011
Crijns H	Integrated chronic care in atrial fibrillation, Health insurance companies research award	€ 1.225,000	2011

Awards and prices

NAME	AWARD	REWARD	PERIOD
Da Costa Martins P.	Heart Failure Association/European Society of Cardiology Fellowship ("MicroRNA function in Heart Failure)	€ 50,000	2007
Da Costa Martins P.	Young Investigator Award, Heart Failure Association/European Society of Cardiology (Les Diablerets, Switzerland)		2009
Da Costa Martins P.	Dutch Heart Foundation fellowship ("The embryonic transcription factor HAND2 regulates left and right ventricular remodeling and dilated cardiomyopathy")	€ 250,000	2010
Da Costa Martins P.	Fondation Leducq - Career Development Award ("MiR-216a: a cell-death regulating microRNA during myocardial repair")	€ 220,000	2011
Da Costa Martins P.	NWO-MEERVOUD ("Post-transcriptional regulation of autophagy: MiR-216a as a cell death-regulating microRNA during myocardial repair")	€ 230,000	2012
Delhaas T.	Maastricht University Supervisory Council Grant	€ 100,000	2007
Delhaas T.	Patient-specific modeling in pulmonary hypertension: towards non-invasive estimation of right ventricular pressure, Actelion Research Grant	€ 200,000	2005-2009
Delhaas T.	Facilitating therapy of congenital heart diseases by computer modeling of the heart and circulation, i.e., hypoplastic left heart syndrome (HLHS), NHF	€ 200,000	2008-2012
Delhaas T.	Best block/cluster prize Circulation & Lungs Medical School Maastricht University		2009 and 2010
Delhaas T.	Pre-eclampsia and the conducting properties of the great arteries, Maastricht University Supervisory Council Grant, Kootstra fellowship Ch. Ghossein	€ 20,000	2010-2011
Delhaas T.	Toward better pacing therapies in patients with congenital heart disease, NHF	€ 82,000	2010-2012
Delhaas T.	Reduction of ischemia/reperfusion injury by pre- and postconditioning, NHS	€ 220,000	2011-2014
Delhaas T.	Pre-eclampsia, arterial stiffnes and development of arterial hypertension, Mozaiek NWO	€ 200,000	2012-2016
Delhaas T., Lumens J.	Valorization of CircAdapt model, STITPRO	€ 41,650	2010-2012
Delhaas T., Reesink K.	Quantitative characterization of the interplay between smooth muscle cells and elastic matrix on arterial properties, Maastricht University Supervisory Council Grant, Kootstra fellowship B. Spronck	€ 20,000	2011-2012
Dipanjan C.	Marie Curie International Incoming Fellowship	€ 150,000	2011
Dirkx E.	Albert Renold Travel Fellowship, granted by the European Foundation for the Study of Diabetes (EFSD)	€ 4,750	2011
Dirkx E.	Early investigator award, granted by the Society for heart and vascular metabolism (SHVM) Brussels	€ 500	2011

Awards and prices

NAME	AWARD	REWARD	PERIOD
Dirkx E.	Graduate/Postdoctoral Travel Award, ASBMS Annual Meeting Washington DC	€ 1,000	2011
Dirkx E.	Research Fellowship of the Heart Failure Association of the European Society of Cardiology (ESC)	€ 30,000	2012
Dirkx E.	Co-applicant Dutch Diabetes foundation pilot grant	€ 50,000	2012
Donners M.	Dr. E. Dekker 'junior postdoc' grant	€ 250,000	2007
Donners M.	Support Grant 'From Targets to Novel Drugs', Bayer Schering Pharma	€ 5,000	2009
Donners M.	Bayer Grants4Targets	€ 5,000	2009
Donners, M.	CARIM PhD Award 2010 (grant for a 4 years PhD project for most talented student	€ 180,000	2010
Empel V. van	ICIN Fellowship (on HFpEF and PAH)		2012
Heemskerk J.	UM Investment program (CARIM). High-speed excitation laser-scanning microscopy	€ 573,000	2008
Heemskerk J.	CTMM program INCOAG, WP3 Thrombus formation	€ 1.812,000	2009
Heemskerk J.	Overseas training fellowship, Australian Heart Foundation. The multilayered thrombus (E. Westein). co-applicant	€ 300,000	2010
Heemskerk J.	BACH Investigator Recognition Award for contributions to hemostasis, ISTH		2011
Heemskerk J.	Willy van Heumen Award for Alternatives on Experimental Animal Use		2011
Heemskerk J.	Landsteiner Foundation. Dynamic fibrin clot formation	€ 250,000	2011
Heemskerk J.	Van Heumen award	€ 25,000	2011
Heemskerk J.	Aflac Children's Hospital Atlanta USA, vitisiting professorship		2012
Heemskerk J.	ZonWM 40-42600-98-011. Whole blood assessment of thrombosis	€ 300,000	2012
Heemskerk J.	Cardiovascular Centre. Thrombosis Expertise Centre. Co-applicant	€ 250,000 per year	since 2010
Heymans S.	Novartis, NOVEL trial, clinical study.	€ 105,000	2007
Heymans S.	Dutch Heart Foundation, 2007B036, Genetic susceptibility for viral heart disease.	€ 230,000	2007
Heymans S.	FWO (Belgian) MicroRNAs in cardiac rejection after transplantation.	€ 240,000	2008
Heymans S.	Sanguin Grant, Treatment of PVB19-related cardiomyopathy. PI.	€ 140,000	2008
Heymans S.	FWO (Belgian), matrix proteins.	€ 139,000	2008

Awards and prices

NAME	AWARD	REWARD	PERIOD
Heymans S.	Dutch Heart Foundation, 2008B011, SPARC and myocardial infarction.	€ 249,000	2008
Heymans S.	Dutch Heart Foundation, miRNA-155 in myocardial infarction. PI.	€ 250,000	2009
Heymans S.	NWO, Vidi Grant.	€ 600,000	2009
Heymans S.	FWO (Belgian) miRNA-221/222 in viral myocarditis. PI.	€ 250,000	2010
Heymans S.	Young investigator Award of the Heart Failure Association of the ESC.	€ 1,500	2010
Heymans S.	Young Investigator Award of the European Society of Cardiology.	€ 1,000	2010
Heymans S.	FP7 EU consortium MEDIA, diastolic heart failure. WP leader Systems biology.	€ 1.054,000	2011
Heymans S.	Marie-Curie IAPP programme, CardiomiR. Coordinator. Cenix-Liege, Maastricht exchange prgramma on miRNAs as therapeutic targets in cardiac diseases.	€ 1.040,000	2012
Heymans S.	Boehringer-Ingelheim (USA). Linagliptin and Dabigatran for viral myocarditis. Pre-clinical study.	€ 145,000	2012
Heymans S.	CVON, ARENA project NHS. Non-coding RNAs in heart failure. PI.	€ 550,000	2012
Janssen B.	NWO grant Medium Sized Investment Application 2009/2010	€ 400,000	2010
Knotnerus I.	Young Investigator Award. XXII Congress of the International Society on Thrombosis and Haemostasis, Boston MA		2009
Koenen R.	Oskar-Lapp-Preis	€ 12,000	2009
Kroon A.	Novartis Foundation for Cardiovascular Excellence (NFCVE). Cerebral Microbleeds: a new marker of cerebral target organ damage in hypertension. (A.A. Kroon & L. Henskens)		2007-2009
Kroon A.	European Hypertension Center of Excellence: awarded by the European Society of Hypertension for the scientific and outpatient activities of the “hypertension outpatient clinic” of the University Hospital of Maastricht (prof. P.W. de Leeuw & A.A. Kroon)		2010-2015
Laat, B de	Young investigator award, 56th annual Scientific Standardization Committee (SSC) meeting	€ 1,000	2010
Leeuw, P de	Center of Excellence in Hypertension		2010
Leeuw, P de	Björn Folkow Award and Lecture, European Society of Hypertension	$ 5,000	2011
Leeuw, P de	Willem Birkenhäger Award, Nederlandse Hypertensie Vereniging	€ 1,500	2012

Awards and prices

NAME	AWARD	REWARD	PERIOD
Loeffen R.	Young Investigator Award ISTH		2012
Neumann D.	VIDI Award (NWO-ALW)	€ 800,000	2010
Maessen J.	Award Innovative Minimal Invasive Surgery (Baltimore)	€ 10,000	2008
Maessen J.	STW Spacemaker project	€ 489,000	2010
Maessen J.	Research Grant Atricure	€ 25,000	2012
Maessen J.	Johnson & Johnson Research Grant	€ 15,000	2012
Nicolaes G.	Netherlands Organisation for Scientific Research, NWO (Middelgroot Investment Grant no. 91746330)	€ 425,000	2007
Nicolaes G.	Grant funded by the FHML and Netherlands province of Limburg	€ 196,000	2008
Nicolaes G.	Dutch Thrombosis Foundation (TSN), grant no. 125/2008/OPI	€ 40,000	2008
Nicolaes G.	Project funded by Bayer Haemophilia Foundation	$ 200,000	2009
Nicolaes G.	FES (fonds economische structuurversterking), LSH framework: FES0908	€ 350,000	2010
Nicolaes G.	Netherlands Organisation for Scientific Research, NWO (Middelgroot Investment Grant no. 91746330)	€ 239,000	2012
Prinzen F.	CTMM Valorization Grant		
Reesink K.	NWO-VI Veni grant, Non-invasive model-based assessment of individual cardiovascular interaction	€ 208,000	2008
Reesink K.	2nd Prize, Best Young Investigator Award, Artery 9 Conference, Cambridge, UK		2009
Reesink K.	Dutch Liver and Gastro-Intestines Foundation, Scientific Research Grant, Ultrasonic Perfluorohexane-loaded monocyte imaging	€ 120,000	2010
Reesink K.	Grant Imperial College Healthcare Charity, Special Purpose Fund, UK	€ 30,000	2011
Reesink K.	Travel Fellowship Award, Foundation for Innovative Applications of Ultrasound, NL	€ 50,000	2011
Reesink K.	British Heart Foundation Project Grant	€ 130,000	2012
Reesink K.	Honorary Research Fellow, Dept. of Disease Prevention, Imperial College London, UK		2012-2014
Reutelingsperger C.	Chairman of the Board of Euregional PACT		2007-2009
Reutelingsperger C.	Chairman of the Board of Euregional PACTII		2009-2013
Schaper N.	Dutch Award of the Diabetes Education Study Group (DESG)	€ 10,000	2009

Awards and prices

NAME	AWARD	REWARD	PERIOD
Schmidt H.	ProScientia		2010
Schmidt H.	ERC Advanced Investigator		2012
Schotten U.	Vernieuwingsimpuls VIDI grant: 3D conduction during atrial fibrillation	€ 600,000	2007-2012
Schroen B.	Keystone Symposia Scholarship	€ 1,500	2011
Sluimer J.	Young investigator award Master class “Plaque instability” colloquium		2007
Sluimer J.	Rubicon post-doc grant	€ 84,000	2008
Sluimer J.	International Atherosclerosis Society fellowship	€ 8,000	2008
Sluimer J.	Kootstra talent fellowship	€ 25,000	2008
Sluimer J.	ZonMW VENI Fellowship	€ 250,000	2010
Sluimer J.	CARIM PhD fellowship	€ 180,000	2012
Sluimer J.	Poster award (2011); Gordon conference on Atherosclerosis		
Stehouwer C.	Nederlandse Vereniging voor Vasculaire Geneeskunde – MSD Prize for excellence in the vascular medicine		2007
Stehouwer C.	Fellow, European Society of Cardiology		2010
Struijker-Boudier H.	Officer in the Order of Oranje-Nassau		2010
Unger T.	Honorary Member, British Hypertension Society		2009
Unger T.	Honorary Member, Italian Hypertension Society		2010
Vanagt W.	Incentive of Cardiovascular Research Institute Maastricht CARIM for publication in the New England Journal of Medicine (NEJM)	€ 100,000	2008
Vanagt W.	Cardiovascular Research Institute Maastricht CARIM award for best PhD thesis in 2007-2008	€ 1,000	2009
Vanagt W.	Stichting St.-Annadal” grant to perform 0.2 fte of research during specialization in Pediatrics	€ 16,000	2009-2010
Vanagt W.	Junior staff member, grant of the Duth Heart Foundation	€ 136,000	2011-2014
Vink H.	Grant Netherlands Heart Foundation: An intact endothelial glycocalyx is required for adequate shear stres	€ 233,000	2007
Vink H.	Grant Dutch Diabetes Foundation: ole of insulin-mediated glycocalyx modulation in insulin sensitivity	€ 210,000	2007
Vink H.	Program extension Grant CTMM-Predictt: Glycocalyx as early marker for vascular risk in diabetes	€ 660,000	2008

Awards and prices

NAME	AWARD	REWARD	PERIOD
Vink H.	Grant Netherlands Heart Foundation: recruitment capacity in the heart: indicator of coronary endothelial glycocalyx	€ 233,000	2009
Vink H.	Grant Dutch Kidney Foundation: Magnetic resonance imaging (MRI) of microvascular blood volume	€ 200,000	2009
Vink H.	Fellowship of the European Society of Cardiology (2010)		2010
Vink H.	Program extension Grant CTMM-Predictt: Glycocalyx as early marker for vascular risk in diabetes	€ 200,000	2010
Vink H.	Program Grant Dutch Kidney Foundation: 'GLYCOREN - Glycocalyx in renal physiology' (LUMC and RUNMC)	€ 1.225,000	2010
Volders P.	VIDI	€ 720,000	2009
Weber C.	W.H. Hauss-Award, German Society of Atherosclerosis Research		2008
Weber C.	Paul-Martini-Award, Paul-Martini-Stiftung		2008
Weber C.	Outstanding Achievement Award, European Society of Cardiology (ESC)		2008
Weber C.	Galenus-von-Pergamon-Award, Prix Galien Foundation		2009
Weber C.	ATVB Special Recognition Award, American Heart Association (AHA)		2009
Weber C.	ERC Advanced Investigator Grant		2010
Weber C.	VICI, Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO)		2010
Wildberger J.	Eugenie-und-Felix-Wachsmann Preis		2008
Windt L. de	Netherlands Foundation of Health Research and Development - Innovational Research Incentives Scheme, VIDI laureate		2007
Windt L. de	Invited seminar "Best of 2008" session at Heart Failure Congress 2008 (European Society of Cardiology, Milan, Italy)		2008
Windt L. de	Coordinator of "CardioVasculair Onderzoek Nederland" 5 M€ consortium		2012
Windt L. de	Galenus Research Prize Award (www.galenusprijs.nl)		2012
Windt L. de	Outstanding Achievement Award, European Society of Cardiology		2012
Wouters K.	Kootstra Fellowship, Maastricht University, The Netherlands	€ 28,000	2007
Wouters K.	NWO Veni	€ 250,000	2011
Wouters K.	FP7 Career Integration Grant	€ 100,000	2012

ANNEX 5
SOCIETAL RELEVANCE

Invited lectures (selection)

NAME	LECTURE
Biessen E	"Impact of leukocytes and their associated chemokines in atherosclerosis" - British Cardiovascular Society meeting, Manchester, UK (2008)
Biessen E	"Perivascular Inflammation By Mast Cells in CVD and hypertension?" - ISH/ESH Meeting Berlin, Germany (2008)
Biessen E	"Unstable Plaque and Inflammation" and "Perivascular Inflammation By Mast Cells - Epiphenomenon or Active Contributor?" - Scientific sessions AHA, New Orleans (USA), Columbia University, New York, USA (2009)
Biessen E	"Bioactive lysolipids in atherosclerosis: bystanders or actors" - EVGN meeting, Bad Hofgastein, Austria (2009)
Biessen E	"Sphingosine-1-phosphate in atherosclerosis: a tale of two cities" - Dutch German Molecular Cardiology meeting Rotterdam, the Netherlands (2010)
Biessen E	"Macrophage inhibitory cytokine-1 deficiency protects against atherosclerosis by attenuating TGF signaling and MCP-1 chemotaxis" - ESC frontiers meeting Berlin, Germany (2010)
Biessen E	"Macrophage inhibitory cytokine-1 deficiency protects against atherosclerosis by attenuating TGF signaling and MCP-1 chemotaxis" - 14th International Immunology Congress, Kobe, Japan (2010)
Biessen E	"MCI-1: a key regulator of multinucleated giant cell formation" - British Atherosclerosis Society meeting, Oxford, UK (2010)
Biessen E	"Plaque Adventitia: Service Hatch or Battleground?" - EAS conference Goteborg, Sweden (2011)
Blankesteijn M.	"Blocking frizzled-1 and -2 receptors with a high affinity antagonist has a beneficial effect on wound healing after myocardial infarction" - Lund Univ, Sweden (2009)
Blankesteijn M.	"Targeting the Infarct Area as a Novel Approach to Prevent Heart Failure post-MI" - Univ. Texas San Antonio, USA (2012)
Brouwers O.	"The methylglyoxal-induced impairment of nitric oxide-dependent vasodilatation in rat mesenteric arteries is not due to inhibition of nitric oxide synthase (eNOS) by methylglyoxal-arginine adducts" - IMARS, Munich, Germany (2007)
Brouwers O.	"Methylglyoxal leads to impairment of endothelium dependent vasodilatation in rat mesenteric arteries via indirect quenching of nitric oxide" - NVDO, Doorwerth, the Netherlands (2007)
Brouwers O.	"Intracellular methylglyoxal levels explain hyperglycaemia-induced impaired endothelium dependent vasorelaxation in an oxidative stress-dependent pathway"- EASD, Vienna, Austria (2009)
Brouwers O.	"Glyoxalase-I overexpression reduces glyoxal, methylglyoxal, advanced glycation endproducts and markers of oxidative stress in diabetic rats" - NVDO, Palm Cove, Australia (2009)
Brouwers O.	"Glyoxalase-I overexpression reduces glyoxal, methylglyoxal, advanced glycation endproducts and markers of oxidative stress in diabetic rats"- NVDO, Oosterbeek, the Netherlands (2009)
Brouwers O.	"Glyoxalase-1 overexpression attenuates early renal impairment in diabetic rats" - EDNSG, Ljubljana, Slovenia (2011)

NAME	LECTURE
Brouwers O.	"Glyoxalase-I overexpression partially prevents diabetes-induced impaired arteriogenesis in rats" - Nederlands Vereniging voor Diabetes Onderzoek (NVDO), Oosterbeek, the Netherlands (2011)
Brunner-La Rocca HP.	"Update on BASKET - Are drug eluting stents good for all patients" - Snowmass. International meeting Interventional Cardiology, USA (2008)
Brunner-La Rocca HP.	"TIME-CHF main results" - Hotline session European Society of Cardiology, Munich, Germany (2008)
Brunner-La Rocca HP.	"End of Life preferences in elderly heart failure patients" - American Heart Association, New Orleans, USA (2008)
Brunner-La Rocca HP.	"Heart failure in the elderly" - St. Petersburg, Russia (2009)
Brunner-La Rocca HP.	"Biomarker-guided therapy is useful in daily practice" - Controversy at ESC 2010, Stockholm, Sweden (2010)
Brunner-La Rocca HP.	"Biomarker guided therapy in heart failure - is the concept proven?" - CVCT Paris, France (2010)
Brunner-La Rocca HP.	"NT-proBNP and systolic heart failure" Dr. Fuster meeting New York, USA (2010)
Brunner-La Rocca HP.	"Elderly patients with heart failure" - HFA meeting, Gothenburg, Sweden (2011)
Brunner-La Rocca HP.	"Use of biomarkers to guide therapy" - Gothenburg Sweden (2011)
Brunner-La Rocca HP.	"Conceptual overview of therapy guidance" - ProCardio meeting, Paris, France (2011)
Brunner-La Rocca HP.	"HFpEF biomarkers - Age and renal function" - International biomarker meeting Graz, Austria (2012)
Brunner-La Rocca HP.	Participation yearly with presentations at international biomarker meeting in Cannes, France (since 2010)
Bucerius J.	"Combined PET / MRT for the diagnosis of vessel wall changes - a new gold standard?" - PET/CT Symposium, Oldenburg, the Netherlands (2010)
Bucerius J.	"PET / CT imaging of vessel wall changes - a new approach to identify patients at risk?" - CARIM Symposium, Maastricht, the Netherlands (2011)
Bucerius J.	"SPECT / CT for cardiac indications" - Symposium "SPECT/CT" RWTH Aachen, Germany (2012)
Bucerius J.	"Non-invasive Imaging of Vascular Nicotinic Receptors with PET/CT" - Radiology Grand Rounds (2012)
Bucerius J.	"Vascular PET – From Non-Invasive Imaging of Inflammation to Receptor Imaging" - Grand Rounds, Translational and Molecular Imaging Institute, Mount Sinai School of Medicine, New York City, USA (2012)
Bucerius J.	"Pathophysiologie und Zusammenfassung der Bedeutung der Myokardszintigraphie" - Echokardiographie Symposium Köln, Germany (2012)
Bucerius J.	"Vascular PET - From non-invasive imaging of inflammation to receptor imaging" - Radiology Grand Rounds (2012)
Bucerius J.	"PET / CT imaging of vascular disease" - Cardiovascular Grand Rounds, Maastricht, the Netherlands (2012)
Castoldi E.	"Molecular mechanisms of thrombosis risk in protein S deficiency" - 55th Scientific and Standardization Committee Meeting of the ISTH, Boston, USA (2009)
Castoldi E.	"Thrombin generation tests" - 4th International Symposium on Women's Health Issues in Thrombosis and Haemostasis. Berlin, Germany (2011)
Castoldi E.	"APC resistance: Biological basis and acquired influences" - 57th Annual Scientific and Standardization Committee Meeting of the ISTH, Kyoto, Japan (2011)

Invited lectures (selection)

NAME	LECTURE
Castoldi E.	"Thrombin generation as an intermediate phenotype for genetic studies on venous thrombosis" - 58th Annual Scientific and Standardization Committee Meeting of the ISTH, Liverpool, UK (2012)
Castoldi, E.	"Thrombin generation and thrombophilia" - 2nd Maastricht Meeting on Thrombin Generation. Maastricht, the Netherlands (2012)
Cate H. ten	EHA Amsterdam, Educational lecture on coagulation and atherosclerosis (2012)
Cate H. ten	SSC Birmingham 2012 Plenary lecture on Coagulation and inflammation crosstalk
Cate H. ten	Plenary lecture on coagulation and atherosclerosis, Fibrinogen workshop Brighton (2012)
Cosemans J.	"Targeting FXII inhibits the pathological process of thrombus formation on ruptured plaques in vivo and in vitro" - The 58th Annual Scientific and Standardization Committee Meeting (SSC), Liverpool, UK (2012)
Cosemans J.	"Role of platelets in vascular remodeling" - CARIM Annual Scientific Symposium, Maastricht, the Netherlands (2011)
Cosemans J.	"Distinct functions of extrinsic and intrinsic coagulation pathways in thrombus formation on ruptured plaques in vivo" - The XXIIIth Congress of the ISTH, Kyoto, Japan (2011)
Cosemans J.	"Standardization of the use of flow devices to measure thrombus formation" - The 55th Annual SSC Meeting, Kyoto, Japan (2011)
Cosemans J.	"Use of flow devices in detecting hemostatic insufficiencies" - International Symposium on Bleeding, Maastricht, the Netherlands (2011)
Cosemans J.	"Towards diagnostic use of flow chamber technology for measuring thrombus formation" - 54th Annual Meeting German Society of Thrombosis and Haemostasis Research, Nürnberg, Germany (2010)
Cosemans J.	"Human Gas6 contributes to late integrin aIIbb3 activation and thrombus stabilization: involvement of Akt" - The XXIIth Congress of the ISTH, Boston, USA (2009)
Cosemans J.	"Processing of plaque and model collagens and thrombogenicity" - The 53rd Annual SSC Meeting, Genova, Switzerland (2007)
Crijns H.	"Ablation: what do the guidelines say?" - International Crossing borders AF Course, Maastricht (2008)
Crijns H.	"Atrial Fibrillation, Treatment in daily clinical practice" - Refereeravond Cardiology Maastricht (2008)
Crijns H.	Syncope, new developments" - Tour d'Horizon, Wijk aan Zee (2008)
Crijns H.	"Palpitations - How adverse are they?" - Cri de Coeur, Heerlen (2008)
Crijns H.	"Rhythm control is preferred to rate control in patients less than 65 years" - C-Care, Berlin (2008)
Crijns H.	"Most patients can be managed with rate control" - ESC Congres - Munich (2008)
Crijns H.	"How to achieve proper rate control" - ESC Congres - Munich (2008)
Crijns H.	"Reverse remodeling post AF cure - ESC Congres - Munich (2008)
Crijns H.	"Focus CP, practical approach to AF, chairman - ESC Congres - Munich (2008)
Crijns H.	Ïmpact of heart failure and ischemia on antiarrhythmic drug therapy - EHRA course on pharmacological therapy for arrhythmias - Nice (2008)

Invited lectures (selection)

NAME	LECTURE
Crijns H.	"Current AF treatment in registries: In line with guidelines?" - AFNET/EHRA consensus conference at ESC - Nice (2008)
Crijns H.	"Rhythm control for whom?" - SJM Congres - Utrecht (2008)
Crijns H.	"Rhythm control: when and how ablation" - International Crossing borders AF Course, Maastricht (2009)
Crijns H.	"Effect of Dronedarone on clinical endpoints in patients with AF and coronary heart disease" - ESC Congres - Barcelona (2009)
Crijns H.	"The clinical impact of AF on vascular events" - ESC Congres - Barcelona (2009)
Crijns H.	Discussant "Clinical Trial Update I, GISSI-AF" - ESC Congres - Barcelona (2009)
Crijns H.	"EQ-5D Utility Index in AF: Insights from Record AF - AHA Scientific Session - Orlando (2009)
Crijns H.	"Chronic vagal nerve stimulation, Cardiofit"- AHA Scientific Session - Orlando (2009)
Crijns H.	"Farmacologic treatment of AF" - CVOI, Netherlands Society of Cardiology - Utrecht (2009)
Crijns H.	"Antiarrhythmic drugs" - Cochrane Library meeting - London (2009)
Crijns H.	"New Clinical data in AF management - Belgian Society of Cardiology meeting - Brussels (2010)
Crijns H.	"Treatment of AF: Insights from the Athena trial - Finnish Society of Cardiology - Helsinki (2010)
Crijns H.	"Redefining therapeutic goals in AF"- Netherlands Society of Cardiology - Arnhem (2010)
Crijns H.	"New developemnts in prevention of arterial embolism" - Netherlands Internists Days - Maastricht (2010)
Crijns H.	"What is the optimal heart rate in AF" - Heart Rhythm Society - Denver (2010)
Crijns H.	"How are AF patients managed?" - Heart Rhythm Society - Denver (2010)
Crijns H.	"Progression of AF, can we prevent it?" - ESC Congress - Stockholm (2010)
Crijns H.	"Dronedarone, hype or hope?" - ESC Congress - Stockholm (2010)
Crijns H.	"Treatment of AF in Heart Failure, Rate control, which drugs?" - ESC Congress - Stockholm (2010)
Crijns H.	"Ventricular function in advanced heart failure - Extended follow-up CardioFit - ESC Congres - Stockholm (2010)
Crijns H.	"Treatment of acute AF - Vernakalant" - Netherlands Society of Cardiology - Egmond aan zee (2010)
Crijns H.	"Pharmacological Rhythm control" - Netherlands Society of Cardiology - Arnhem (2011)
Crijns H.	"Lone AF, are antiarrhythmic drugs enough?" - Netherlands Society of Cardiology - Arnhem (2011)
Crijns H.	"Determine how the timing of catheter ablation influences the natural progression of AF - Heart Rhythm Society - San Francisco (2011)
Crijns H.	"AF progression, Risk factors and early intervention - Heart Rhythm Society - San Francisco (2011)
Crijns H.	"Rate control" - Europace congress, ESC - Madrid (2011)
Crijns H.	"Management of AF patients in 2011: what have we achieved, where are the evidence gaps?" - Europace congress, ESC - Madrid (2011)
Crijns H.	"Breakthroughs: antithrombotics in atrial fibrillation" - Lancet and JACC meeting - Hong Kong (2011)
Crijns H.	"RHYTHM-AF: A real-world look at treatment for recent onset AF" - ESC Congres - Paris (2011)

Invited lectures (selection)

NAME	LECTURE
Crijns H.	"Recent and ongoing clinical trials in AF management" - International forum of arrhythmias - Antalya (2012)
Crijns H.	"Antiarryhtmic drugs for AF - New insights in basics of arrhythmias" - Cardiostim meeting - Nice (2012)
Crijns H.	"Rhythm control, what is new?" - ESC Congress - Munich (2012)
Da Costa Martins P.	"MicroRNA-199b: a new therapeutic target in pathological cardiac remodeling?" - Heart Failure Congress (Session: Best of 2008) (2008)
Da Costa Martins P.	"MicroRNA-199b: a new therapeutic target in pathological cardiac remodeling?" - Heart Failure Association Winter Research Meeting; Les Diablerets, Switzerland (2009)
Da Costa Martins P.	"MicroRNAs as therapeutic targets in heart failure" - LeDucq meeting "MicroRNAs as therapeutic targets in heart failure"; Capri, Italy (2009)
Da Costa Martins P.	"MicroRNAs as new therapeutic targets in pathological cardiac remodeling" - Seminar at the Department of Physiology, Faculty of Medicine, University of Porto, Portugal (2009)
Da Costa Martins P.	"MicroRNA-199b: a new therapeutic target in pathological cardiac remodeling?" - MicroRNAs Europe 2009; Cambridge, UK (2009)
Da Costa Martins P.	"MicroRNA control of cardiac hypertrophy" - Heart Failure Association Winter Research Meeting; Les Diablerets, Switzerland (2011)
Da Costa Martins P.	"Regulation of pathologic cardiac hypertrophy by miR-199 family members" - Annual meeting of the working group on myocardial function and the working group on cellular biology – Translating cellular mechanisms to therapeutic targets, Varenna, Italy (2011)
Da Costa Martins P.	"Role of Hand2 and miR-25 in Heart Failure" - EMBO Workshop on MicroRNA Biology; Ascona, Switzerland (2012)
Da Costa Martins P.	"Functional high-content screens to identify autophagy-regulating microRNA" - LeDucq meeting; Amsterdam, the Netherlands (2012)
Delhaas T.	"Belangrijkste recente vernieuwingen in de kindercardiologie" - 2nd Pediatric Conference, Maarssen, the Netherlands (2007)
Delhaas T.	"Pathofysiologische overwegingen bij het Ventrikel Septum Defect" - Dutch Pediatric and Adult Congenital Heart Defect Meeting, Utrecht, the Netherlands (2007)
Delhaas T.	"Pathobiology of left ventricular dyssynchrony and resynchronization" - Venice Arrhythmias, Venice, Italy (2007)
Delhaas T.	"Where to put the ventricular pacing lead in pediatric patients" - Leipzig Heart Center, Leipzig, Germany (2008)
Delhaas T.	"Fysiologische Overwegingen aangaande het Rechter Ventrikel" - 2nd Flemish Interuniversity Symposium Congenital Cardiology, Leuven, Belgium (2008)
Delhaas T.	"Resynchronisation in the pediatric age group" - Europace 2009, Berlin, Germany (2009)
Delhaas T.	"Epicardial ventricular pacing in pediatric patients: right, left, or biventricular" - Tips and Tricks in Congenital and Structural Interventions, Rome, Italy (2010)
Delhaas T.	"Relation between Fiber Orientation Pattern and Deformation in the Situs Inversus Totalis Left Ventricle" - 19th Cardiovascular System Dynamics Society Conference, Fukuoka, Japan (2010)
Delhaas T.	"Modeling Right Ventricular Function in Pulmonary Arterial Hypertension" - 3rd ABEPH (Advisory Board of Experts in Pulmonary Hypertension) Meeting, Paris, France (2011)
Delhaas T.	"Optimal pacing sites in congenital heart disease: right, left, or biventricular?" - European Society of Cardiology, Paris, France (2011)

Invited lectures (selection)

NAME	LECTURE
Delhaas T.	"Venous Pressure and Flow Regulation" - Masterclass Hemodynamics in Extracorporeal Life Support, Maastricht, the Netherlands (2012)
Dirkx E.	"(Post)-transcriptional reactivation of the bHLH transcription factor Hand2 in the postnatal myocardium causes heart failure" - MicroRNAs & Single Molecule Biology Europe-2012, Univ of Cambridge, UK (2012)
Dirkx E.	"microRNA-216a: a novel target for obesity and its associated cardiovascular diseases?" - 4th meeting of the Transatlantic Network of Excellence on MicroRNAs (Foundation Leducq), Amsterdam, the Netherlands (2012)
Dirkx E.	"Protein kinase-D1 overexpression in mice prevents lipid-induced insulin resistance and cardiomyopathy by upregulation of glucose uptake" - 9th Annual Conference of the Society for heart and vascular metabolism (SHVM), Brussels, Belgium (2011)
Dirkx E.	"Protein kinase-D1 overexpression in mice prevents lipid-induced insulin resistance and cardiomyopathy by upregulation of glucose uptake" - Experimental Biology, ASBMB annual meeting, Washington, DC, USA (2011)
Dirkx E.	"Protein kinase-D1 overexpression in mice prevents lipid-induced insulin resistance and cardiomyopathy by upregulation of glucose uptake" - Cardiovascular PhD-training course of the Dutch Heart Foundation, Arnhem, the Netherlands (2010)
Dirkx E.	"Regulation of myocardial substrate uptake by protein kinase D" - Consortium meeting EU FP6 Integrated Project "Exgenesis", Paris, France (2009)
Dirkx E.	"A role for protein kinase D in the contraction signaling pathway, independent of AMPK" - 6th Annual Conference of the Society for heart and vascular metabolism, Boston, USA (2008)
Dirkx E.	"Identification of a downstream substrate of protein kinase D in contraction signaling" - Consortium meeting EU FP6 Integrated Project "Exgenesis", Padova, Italy (2008)
Donners M.	"A Disintegrin and Metalloprotease 10 (ADAM10) is a novel mediator of VEGF-induced endothelial cell function in angiogenesis and atherosclerosis"- Dutch Endothelial Biology Society fall meeting, Amsterdam, the Netherlands (2010)
Donners M.	"A Disintegrin and Metalloproteases (ADAMs): Cell surface scissors regulating vascular cell functions and atherosclerosis" - University Medical Centre Aachen, Germany (2012)
Glatz J.	"Transport proteins governing cellular fatty acid metabolism" - 15th European Congress on Obesity, Budapest, Hungary (2007)
Glatz J.	"CD36 – The policeman of fatty acid traffic" - 67th Scientific Sessions of the American Diabates Association, Chicago, USA (2007)
Glatz J.	"The diabetic heart: New insights in fatty acid metabolism" - International Conference of the European Society of Cardiology, Vienna, Austria (2007)
Glatz J.	"Cardiac metabolism and fatty acids" - Maastricht Metabolic and Vascular Congress, Maastricht, the Netherlands (2008)
Glatz J.	"Fatty acids, type-2 diabetes, and cardiovascular disease"- 3rd Euregional Biomedica Conference – The Life Sciences Summit, Liège, Belgium (2009)
Glatz J.	"Fatty acid transport across the cell membrane" - 9th International Conference on Fatty Acids in Cell Signalling, Oxford, UK (2009)
Glatz J.	"CD36 and the fate of fatty acids in the heart" - 7th Conference of the International Society for Heart and Vascular Metabolism, Padua, Italy (2009)

Invited lectures (selection)

NAME	LECTURE
Glatz J.	"Fatty acid chaperones and transporters" - 9th Conference of the International Society for the Study of Fatty Acids and Lipids (ISSFAL), Maastricht, the Netherlands (2010)
Glatz J.	"CD36 and the fate of fatty acids in the heart" - 8th Conference of the International Society for Heart and Vascular Metabolism (SHVM), Kananaskis, Canada (2010)
Glatz J.	"Substrate transporters GLUT4 and CD36 as regulators of myocardial glucose and fatty acid utilization" - 35th European Symposium on Hormones and Cell Regulation, Mont Sainte-Odile, Alsace, France (2010)
Glatz J.	"Membrane fatty acid transporters regulate cellular lipid metabolism: Implications for metabolic disease" - 79th Congress of the European Atherosclerosis Society (EAS), Gothenburg, Sweden (2011)
Glatz J.	"Integrating molecular biosciences within the medical curriculum: the Maastricht approach" - 36th Congress of the Fedration of European Biochemical Societies (FEBS), Torino, Italy (2011)
Glatz J.	"CD36 as target to prevent cardiac lipotoxicity and insulin resistance" - 10th Fatty Acids in Cell Signaling Meeting (FACS), New Orleans, USA (2011)
Glatz J.	"Genetics and fatty acid-binding proteins" - 10th Congress of the International Society for the Study of Fatty Acids and Lipids, Vancouver, Canada (2012)
Hackeng T.	"Global Haemostasis Assays"- Advanced Course in Haemostasis & Thrombosis. Belgrade, Serbia (2012)
Hackeng T.	"Current Concepts of the Coagulation System"- Advanced Course in Haemostasis & Thrombosis. Belgrade, Serbia (2012)
Hackeng T.	"Novel Insights in Anticoagulant Mechanisms"- Netherlands Society for Hematology, Klinisch Hematologische Dag, Utrecht, The Netherlands (2012)
Hackeng T.	"Targeted cardiovascular imaging"- Cardiovascular Network Retreat, Deutsche Forschungsgemeinschaft, Rauischholzhausen Castle, Germany (2012)
Hackeng T.	"Targeted biomolecular imaging of cardiovascular disease with chemically synthesized peptide/protein-based imaging agents"- Centennial Symposium of the Department of Farmacy, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil (2011)
Hackeng T.	"Protein S and the regulation of thrombin formation"- Centennial Symposium of the Department of Farmacy, Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil (2011)
Hackeng T.	"Targeted biomolecular imaging of atherosclerosis using chemically synthesized natural ligand Rantes for instable plaque biomarker CCR5" - 22nd American Peptide Symposium, San Diego, USA (2011)
Hackeng T.	"Tissue factor pathway inhibitor" - 16th Congress of European Hematology Association, London, UK (2011)
Hackeng T.	"Protein S and the regulation of thrombin formation"- University of North Carolina at Chapel Hill, USA (2011)
Hackeng T.	"Biomolecular Imaging of Cardiovascular Disease" - 2nd Joint Symposium SFB612/SFB688 Bad Brueckenau, Germany (2010)
Hackeng T.	"The central role of protein S in regulation of coagulation" - Symposium. The International Society on Trombosis & Haemostasis 51st Annual SSC Meeting. Cairo, Egypt (2010)

Invited lectures (selection)

NAME	LECTURE
Hackeng T.	"Mechanisms of anticoagulant activities of protein S" - 1st Joint Meeting GTH & NVTH, 54. Jahrestagung der Gesellschaft für Thrombose und Hämostaseforschung (GTH) & Symposium of the Nederlandse Vereniging voor Trombose en Hemostase (NVTH), Nuremberg, Germany (2010)
Hackeng T.	"Regulation of tissue factor pathway inhibitor by protein S" - Symposium of the Belgian Society of Biochemistry and Molecular Biology, University of Antwerp, Belgium (2010)
Hackeng T.	"Regulation of TFPI function by protein S" - State of the Art Lecture.The International Society on Trombosis & Haemostasis XXIIth Congress. Boston, USA (2009)
Hackeng T.	"Novel functions of protein S" - The International Society on Trombosis & Haemostasis XXIth Congress and 51st Annual SSC Meeting. Geneva, Switzerland (2007)
Heymans S.	"Matricellular proteins protect against heart failure" - British Society of Cardiovascular Research, Belfast, UK (2012)
Heymans S.	"MicroRNAs as biomarkers for ischemic heart disease" - European Society of Cardiology, Munchen, Germany (2012)
Heymans S.	"Treatment of myocarditis" - European Society of Cardiology, Munchen, Germany (2012)
Heymans S.	"SPARC and extracellular matrix remodelling" - Frontiers of Cardiovascular Biology, ESC, London, UK (2012)
Heymans S.	"Inflammatory cardiomyopathies" - Infectious Diseases, Grindelwald, Switzerland (2012)
Heymans S.	"Matrix remodelling in heart failure" - International Society of Heart Research, Haifa, Israel (2011)
Heymans S.	"Myocarditis and dilated cardiomyopathy. Diagnosis and management" - Cardiology and Vascular Medicine, an ESC UPDATE programme in Cardiology, Rotterdam , the Netherlands (2011)
Heymans S.	" Implication of inflammation microRNAs in heart failure" - European Myocardial Function Meeting, Varenna, Italy (2011)
Heymans S.	"Implication of inflammatory microRNAs in cardiac failure" - Keystone Meeting on non-coding RNAs in human health and disease, Banff, Canada (2011)
Heymans S.	"Use of CMR for viral myocarditis" - CMR symposium Den Haag, the Netherlands (2010)
Heymans S.	"A protective role of matricellular proteins against heart failure" - FASEB summer meeting, Colorado, USA (2010)
Heymans S.	"Matricellular proteins in inflammation and fibrosis" - European Heart Failure Association Meeting, Berlin, Germany (2010)
Heymans S.	"Matrix remodelling as a target for cardiomyopathies" - International symposium. New Molecular Pathomechanisms and Novel Therapeutic Approaches in Heart Failure, Berlin, Germany (2010)
Heymans S.	"Matrix as a target for diastolic heart failure" - International diastolic heart failure meeting, Graz, Austria (2009)
Heymans S.	"Inflammation as a Therapeutic Target in Heart Failure" - 7th Annual Symposium of CHFR, Oslo, Norway (2009)
Heymans S.	"Matricellular proteins" - European Association of Heart Failure, Nice, France (2009)

Invited lectures (selection)

NAME	LECTURE
Heymans S.	"Inflammation as a Theurapeutic Target in Heart Failure? A Scientific Statement of the European Heart Failure Association" - European Meeting on Diabetes and Heart Failure, Vrsac, Serbie (2009)
Heymans S.	"The extracellular matrix and inflammation" - Heart Failure Winter Meeting (2008)
Heymans S.	"Interstitial Matrix Remodeling" - Scientific symposium. DFG Clinical Research Unit 136. Adaptation and Regeneration in the Cardiovascular System, Hannover Germany (2008)
Heymans S.	"Cardiac inflammation and extracellular matrix" - Annual meeting of the Working Group on Myocardial Function, Anacapri, Italy (2008)
Heymans S.	"Matricellular proteins and heart failure" - Heart failure association congress, Milan, Italy (2008).
Heymans S.	"Basic mechanisms for heart failure" - European association of Cardiothoracic Surgery, Lisbon, Portugal (2008)
Heymans S.	"Matrix proteins: novel diagnostic and therapeutic targets for heart failure" - Cardiovascular biomarkers. FNRS, Luxembourg (2008)
Heymans S.	"Role of metalloproteinases and matricellular proteins in cardiac inflammation" - Heart Failure Winter Meeting (2007)
Heymans S.	"Viral cardiomyopathies: detailed diagnosis and refined therapy" - Tour d'Horizon, NVVC, Noordwijk, the Netherlands (2007)
Heymans S.	"Matrix metalloproteinases and matricellular proteins do interact during heart failure" - Gordon Meeting, Matrix metalloproteinases, Il Ciocco, Italy (2007)
Heymans S.	"Metalloproteinases and myocardial infarction" - European Heart Failure Association (2007)
Heymans S.	"Matricellular proteins as novel targets" - Meeting on autoimmunity in heart failure, Gôteborg, Sweden (2007)
Kooi E.	"Quantification of inflammation with 18F FDG PET and neovascularization with DCE MRI in carotid plaques" - Munich Vascular Conference, Munich, Germany (2012)
Kooi E.	"Multimodal imaging assessment of extra-cranial vessels and vascular risk factors" - 11th Belgium Stroke Council International Symposium. Leuven, Belgium (2012)
Kooi E.	"The Plaque At RISK (ParisK): Prospective clinical study: diagnostic efficacy for high risk plaque and stroke" - Academisch Medisch Centrum, Amsterdam, the Netherlands (2011)
Kooi E.	"Vessel wall imaging of atherosclerotic disease: changes to come" - Cardiovasculaire Conferentie, Noordwijkerhout, the Netherlands (2011)
Kooi E.	"MR imaging of atherosclerotic plaque" - Klinikum rechts der Isar, der Technischen Universität München, Germany (2011)
Kooi E.	"MR Imaging of Atherosclerosis-Symposium: Imaging and pathophysiology of atherosclerosis and vascular disease, Universitätsklinikum Würzburg, Germany (2010)
Kooi E.	"Molecular MRI of early thrombus formation using a bimodal alpha2-antiplasmin-based contrast agent" (Satelite symposium, "International Factor XIII Symposium/Workshop" of the joint meeting of the Gesellschaft für Thrombose und Hämostaseforschung (GTH) and Nederlandse Vereniging voor Trombose en Hemostase (NVTH), Nürnberg, Germany (2010)
Kooi E.	"Assessment of atherosclerotic lesions with MR Imaging" - Eindhoven University of Technology, the Netherlands (2009)

Invited lectures (selection)

NAME	LECTURE
Kooi E.	"Novel molecular magnetic resonance imaging contrast agents validated at the macroscopic and microscopic level" - Symposium Advanced Microscopy and Vital Imaging, Maastricht, the Netherlands (2009)
Kroon, A.	2007-2012: yearly congress of the European Society of Hypertension (ESH), several invited lectures on home blood pressure measurements (2007), renal blood flow in renal artery stenosis (2008), target organ damage of the brain in hypertension (2009), baroreflex activation therapy in resistant hypertension (2010, 2011), renal handling of ADMA in hypertensive target organ damage (2012).
Leeuw P. de	"Management of masked hypertension" - ESH (2007)
Leeuw P. de	"Renal artery stenosis" - ESC (2007)
Leeuw P. de	"Medical treatment and revascularization in renal artery stenosis" - ISH/ESH-meeting (2008)
Leeuw P. de	"Potential for device therapy in hypertension" - ESC (2008)
Leeuw P. de	"Device-based reduction in blood pressure" - AHA (2008)
Leeuw P. de	"Correction of renal artery stenosis" - ESH (2009)
Leeuw P. de	"Carotis-Sinus-Stimulation und Radiofrequenz-Ablation der renal Nerven" - Zürcher Herz-Kurs (2009)
Leeuw P. de	"Ambulatory blood pressure monitoring in renal patients" - ESH (2010)
Leeuw P. de	"The CVRx implantable carotid sinus modulation system" - CSI Course (2011)
Leeuw P. de	"Bjorn Folkow lecture" - ESH (2011)
Leeuw P. de	"Results of baroreflex activation therapy in hypertension" - ESC (2011)
Leeuw P. de	"Barostim neo" - ACC (2012)
Leeuw P. de	"Renal aspects of prehypertension" - ERA-EDTA (2012)
Leeuw P. de	"Renal function in FMD" - ESH (2012)
Maessen J.	Surgical treatment of stand-alone longlasting persistent atrial fibrillation using a monolateral thoracoscopic approach." 57th ESCVS Int. Congress Barcelona – Spain. (2008)
Maessen J.	Thoracoscopic epicardiale pulmonary vein isolation is a realistic alternative for endocardial radiofrequency ablation: lower risk of arterial embolism." 57th ESCVS Int.Congress Barcelona – Spain (2008)
Maessen J.	Post Graduate Course EACTS Hybrid approach in the Treatment of AF, TECHNO college video-presentation - EACTS, Lisbon, Portugal (2008)
Maessen J.	Discussant: PREVENTION OF ATRIAL FIBRILLATION AFTER CORONARY ARTERY BYPASS GRAFTING VIA ATRIAL ELECTROMECHANICAL INTERVAL AND USE OF AMIODARONE PROPHYLAXIS by Dr. Roshanal - EACTS, Lisbon, Portugal (2008)
Maessen J.	ESCTS Cardiac Course Level C, Bergamo, Italy, 10-15 November 2008:Atrial Fibrillation
Maessen J.	Get Rhythm, symposium over atrium fibrilleren, Utrecht the Netherland (2008)
Maessen J.	Moderator: European Vascular Course / European Cardiac Course- Maastricht The Netherlands (2009)
Maessen J.	Post graduate Course EACTS: "The Emblocker" Vienna, Austria(2009)
Maessen J.	"Minimal invasive placement of the LV lead." Europace Berlin, Germany (2009)
Maessen J.	"Surgical approach for CRT" Venice Arrhythmia Venice. Italy (2009)
Maessen J.	5000 ablations, 500 Isolations pour FA, 100 thoracoscopies pour FA, 10 ans de resynchronisation", Brussels Belgium (2009)

Invited lectures (selection)

NAME	LECTURE
Maessen J.	European Postgraduate Gastro-Surgical School - Back to Business: De Robot chirurgie: noodzaak of alleen dure PR? “De visie van de Thorax chirurg” Amsterdam the Netherlands (2009)
Maessen J.	Moderator: European Vascular Course / European Cardiac Course, Maastricht, the Netherlands (2010)
Maessen J.	“Single Port Heart-Lung Machine Support as an Alternative for Mechanical Ventilation” - Euronotes, Rome, Italy (2010)
Maessen J.	“Thoracoscopic radical thymectomy for myasthenia gravis by a robotic assisted approach”, 18e ESTS, Valladolid, Spain (2010)
Maessen J.	“Enkele thema’s en stages in het nieuwe format van de opleiding” 17e Landelijke Cursorische Onderwijsdagen voor AIOS, AMC Amsterdam, the Netherlands (2011)
Maessen J.	SURGICAL APPROACH TO CARDIAC RESYNCHRONIZATION THERAPY - Venice Arrhythmias -Venice, Italy (2011)
Maessen J.	Epicardial left ventricular lead placement for CRT: how to select optimal pace site? - Venice Arrhythmias - Venice, Italy (2011)
Maessen J.	“Robotics in de borstkas”, Nederlandse Vereniging voor Endoscopische Chirurgie, Leiden the Netherlands (2011)
Maessen J.	Moderne Versorgung von Patienten mit kardialen Erkrankungen, Universitätsklinikum Aachen: „Rhythmuschirurgie“, Aachen, Germany (2012)
Maessen J.	“De Novo” Innovaties binnen het Hartlongcentrum van de Isala Kliniekn: “Thoracale toepassingen robotchirurgie/Robot enhanced Midcab in Hybride setting, Zwolle, the Netherlands (2012)
Maessen J.	Focus Session Teach the Teacher: “The supervision of training in the Netherlands”. EACTS Barcelona, Spain (2012)
Maessen J.	Robotic resections - 6e Amsterdam Longchirurgie Symposium, Amsterdam the Netherlands (2012)
Maessen J.	High-flow resin absorption on extracorporeal life support for the treatment of endotoxemia- 1st European ELSO Meeting Rome, Italy (2012)
Neumann D.	“Revealing downstream targets of AMPK by proteomic approaches” - UPMC Renal Grand Rounds, University of Pittsburgh School of Medicine, USA (2012)
Neumann D.	“Revealing downstream targets of AMP-activated protein kinase by proteomic approaches” - Pittsburgh University, USA (2012)
Nicolaes G.	“Structure-function studies of FV implications for the etiology, diagnosis and therapy of thromboemolic disease” - Centre for Molecular and Biomolecular Informatics (CMBI), Radboud University Nijmegen-Medical Centre, the Netherlands (2008)
Nicolaes G.	“A generic platform for the cost-effective identification and development of small molecules that affect protein-membrane interactions” - 15th annual conference of the Society for Biomolecular Sciences (SBS), Lille, France (2009)
Nicolaes G.	“Application of in silico methods in blood coagulation research: from virtual proteins to wet protein chemistry” - XXIIth congress of the International Society on Thrombosis and Haemostasis (ISTH), In silico Drug Design session, Boston, USA (2009)
Nicolaes G.	“Structural bioinformatics as guidance for protein structure-function studies and as a tool for rational drug design” - Annual symposium of the Center for Experimental and Molecular Medicine of the Amsterdam Medical Center, the Netherlands (2009)

Invited lectures (selection)

NAME	LECTURE
Nicolaes G.	"Structure-driven approaches for the rational design of the next-generation pro- or antithrombotic therapies" - Joint meeting of the GTH (German Society on Thrombosis and Haemostasis) and the NVTH (Netherlands Society on Thrombosis and Haemostasis), Nürnberg, Germany (2010)
Nicolaes G.	"Structure-function studies on the C-domains of Factor V and VIII: Opportunities for diagnosis and therapy" - Novo Nordisk research facility at Måløv, Denmark (2012)
Nicolaes G.	"Towards a new generation of anticoagulants" - 19th Amstol Symposium Amsterdam, the Netherlands (2012)
Oostenbrugge R. van	Lecture during European Stroke Conference 2012
Post M.	Invited Lecture, 15th international LDDR, Geneva (2008)
Post M.	Invited Lecture, PhD course Coeur, Rotterdam (2008)
Post M.	Invited Lecture, Symposium vasc GNK Groningen (2009)
Post M.	Invited Lecture, PhD course Coeur, Rotterdam (2009)
Post M.	Invited Lecture, TEDx Brainport 2020 Eindhoven (2011)
Post M.	Invited Lecture, Cardiovascular Grand Rounds (MUMC) (2011)
Post M.	Invited Lecture, Molecular Cardiology meeting, Ulm (2011)
Post M.	"Advances in small diameter vascular tissue engineering" - Aegean Int Conf Tissue Engineering, Crete, Greece (2011)
Post M.	Invited Lecture, If2q conference London (2011)
Post M.	Session chair, Sci Foo, Mountain View, CA (2011)
Post M.	Invited Lecture, Science Café, Twente (2011)
Post M.	Invited Lecture, Next Nature, Amsterdam (2011)
Post M.	Invited Lecture, European Manufacturing and Safety Summit, Noordwijk (2012)
Post M.	Invited Lecture, Het Eten van de Toekomst, Groen Links, Europarlementariër Bas Eijckhout (2012)
Post M.	"Advances, challenges and prospects for cultivation of tissue engineered meat" - American Association for the Advancement of Science, Vancouver, Canada (2012)
Post M.	Invited Lecture, PhD course, Coeur, Rotterdam (2012)
Post M.	Invited Lecture, Bright Night, Amsterdam (2012)
Post M.	Invited Lecture, IRTG, Giessen (2012)
Post M.	Invited Lecture, Future tense, Washington DC (2012)
Post M.	"Sharing the emerging possibilities of growing meat from stem cells and its potential for reducing future stress on our food system" - Innovation Forum SHELL, Rotterdam (2012)
Post M.	Invited Lecture, MMSRC, CISS, Maastricht (2012)
Post M.	Keynote Lecture, ICoMST, Montreal (2012)
Post M.	"Notch signalling in vascular patterning" - Grand Rounds, Cardiovascular Research Institute, Yale, USA (2012)
Post M.	Grand Rounds, Cardiology Department, Dartmouth-Hitchcock (2012)
Post M.	Session Chair, European Society of Cardiology, Munich (2012)
Post M.	Invited Lecture, TERMIS, Vienna (2012)

Invited lectures (selection)

NAME	LECTURE
Post M.	Invited Lecture, Bioinnovation International Summit, Gdansk (2012)
Prinzen F.	“Molecular biology and imaging in CRT” - Heart Rhythm, Boston, USA (2012)
Prinzen F.	“The physiological basis of CRT” - European Society of Cardiology, Munich, Germany (2012)
Reesink K.	“Radiofrequency data: state-of-the-art and new developments”- Seminar ‘Whatt’s the role of ultrasound in cardiovascular prevention?’ Artery 12, Vienna, AU (2012)
Reesink K.	“Pressure dependence of arterial stiffness: physical basis and potential clinical implications” - ESH London, UK (2012)
Reesink K.	“Echogenic perfluorohexane-loaded blood cells to identify inflammation in vascular territories” - ICarVU Colloquium, VUMC, Amsterdam, the Netherlands (2012)
Reneman R.	“Wall shear stress distribution in the arterial system. Reconsiderations based upon in vivo measurements” - Biannual meeting European Society for Microcirculation. Budapest, Hungary (2008)
Reneman R.	“Wall shear stress distribution in the arterial system. (Re)considerations based upon in vivo measurements” - London, UK (2008)
Reneman R.	“Wall shear stress revisited” - Mc Donald lecture, biannual meeting Artery Europe. Ghent, Belgium (2008)
Reutelingsperger C.	“Cell surface expressed phosphatidylserine as target for diagnosis and treatment of cardiovascular disease” - New York Academy of Sciences, USA (2012)
Reutelingsperger C.	“Annexin A5 in chronic inflammation” - 6th conference on Annexins, Barcelona, Spain (2011)
Reutelingsperger C.	“Molecular Imaging of apoptosis for diagnosis of cardiovascular diseases” - Symposium Arterial calcification and vitamin K, Pyongyang, North Korea (2010)
Reutelingsperger C.	“Apoptosis in cardiovascular diseases: a potential target for diagnosis and therapy” - William Harvey Lecture, London, UK (2010)
Reutelingsperger C.	“Annexin A5 – diagnostic and therapeutic applications” - Symposium Annexins: Bordeaux, France (2009)
Reutelingsperger C.	“Molecular Imaging of Cardiovascular Disease – Potential for Clinical application” - American Physiological Society at Experimental Biology New Orleans, USA (2009)
Reutelingsperger C.	“Imaging the biomarker Phosphatidylserine” - Keystone Cell Death Pathways: Imaging the biomarker Phosphatidylserine (2009)
Reutelingsperger C.	“Annexin A5, shifting from a diagnostic towards a therapeutic realm” - European Calcium Society: “Annexin A5, shifting from a diagnostic towards a terapeutic realm”, Leuven, Belgium (2008)
Reutelingsperger C.	“Annexin A5, a tale of mice and men” - Annexin Conference San Diego, USA (2007)
Reutelingsperger C.	“Molecular Imaging of Apoptosis” - ISMRM Berlin Meeting, Berlin, Germany (2007)
Reutelingsperger C.	“Shifting from a diagnostic towards a therapeutic realm” - Seminar University Basel, Switzerland (2007)
Reutelingsperger C.	“Molecular Imaging and Drug Targeting” - Biomedica Aachen, Germany (2007)
Schalkwijk C.	“Ne-(Carboxymethyl)lysine - RAGE axis: a novel link between obesity, inflammation and insulin resistance” - EASD Berlin, Germany (2012)
Schalkwijk C.	“Advanced glycation endproducts in food and medicine” - 5th meeting of D&CVD, Paris, France (2012)

Invited lectures (selection)

NAME	LECTURE
Schalkwijk C.	"N2(carboxymethyl)lysine trapping in adipose tissue: implications for obesity-associated changes in adipokine expression" - AHA, Orlando, USA (2009)
Schalkwijk C.	"Plasma CML levels are inversely associated with markers of inflammation in obese patients and explain the association between obesity and inflammation" - 10th International Symposium on the Maillard Reaction, Australia (2009)
Schalkwijk C.	"Glyoxalase-1 overexpression reduces methylglyoxal, AGEs and oxidative stress in diabetic rats" - 10th International Symposium on the Maillard Reaction, Australia (2009)
Schalkwijk C.	"The axis chronic inflammation-endothelial activation-vascular complications: a focus on advanced glycation endproducts (AGEs)" - CTMM Utrecht, the Netherlands (2008)
Schalkwijk C.	"Diet and early changes in endothelial function" - project 1004 TIFN, Wageningen, the Netherlands (2008)
Schalkwijk C.	"AGEs in health and disease" - International Life Sciences Institute (ILSI) Europe; metabolic syndrome task force, Brussels, Belgium (2008)
Schalkwijk C.	"High-fat diet causes liver steatosis accompanied by accumulation of AGEs.ALEs in the liver" - 9th International Symposium on the Maillard reaction Munich, Germany (2007)
Schaper N.	Cardiovascular and Interventional Radiological Society of Europe, Lissabon (2009)
Schaper N.	European Association for the Study of Diabetes (EASD), Stockholm, Sweden (2010)
Schaper N.	British Vascular Society, Londen, UK (2011)
Schaper N.	International Symposium on the Diabetic Foot, Noordwijkerhout, the Netherlands (2011)
Schaper N.	Cardiovascular and Interventional Radiological Society of Europe, Lissabon, Portugal (2011)
Schaper N.	Chinese Diabetes Association, Shanghai, 2011
Schaper N.	World congress of the International union of Angiology. Prague (2012)
Schaper N.	Cardiovascular and interventional radiological society of Europe, Lissabon, Portugal (2012)
Schaper N.	IDF-WPR Congress, Kyoto, Japan (2012)
Schotten U.	"3D Wavefront Propagation during atrial fibrillation" - Annual sessions of the Dutch-German Working Group for Molecular Cardiology (2007)
Schotten U.	"How pathophysiology can help us to tailor AF therapy" - 2nd consensus conference on atrial fibrillation of the European Heart Rhythm Assocoation of the German Competence Network Atrial Fibrillation, Nice, France (2008)
Schotten U.	"Alterations in Atrial Ca Handling as Cause and Consequence of Atrial Fibrillation" - Mammalian Myocardium meeting Manchester, UK (2010)
Schotten U.	"Role of Altered Spatio-Tremporal Pattern of Ca2+ Release in the Pathophysiology of Atrial Fibrillation" - Europace congress Madrid, Spain (2011)
Schotten U.	"Mechanisms and Implications of the 3D Substrate for Atrial Fibrillation" - Ann Arbor Michigan University, USA (2012)
Schotten U.	"Atrial Fibrillation Mechanisms – New Insights from Mapping Studies" - ECAS Congress Munich, Germany (2012)
Schroen B.	"Targeting microRNA-155 protects against adverse cardiac inflammation, hypertrophy and failure" - weekly Training Seminar organized by Prof Jörg Heineke from the department of Cardiology and Angiology of the Hannover School of Medicine

Invited lectures (selection)

NAME	LECTURE
Schroen B.	"Role of microRNAs in aging" - 7th international conference, Oxford, UK (2012)
Schroen B.	"MicroRNAs and beyond: the heart reveils its treasures" - Summer School on Inflammatory Cardiomyopathy Berlin, Germany (2011)
Schroen B.	"Macrophage-derived microRNAs are implicated in heart failure" - European Society of Cardiology Congres, Paris, France (2012)
Schroen B.	"Targeting microRNA-155 protects against adverse cardiac inflammation, hypertrophy and failure"- 9th Dutch-German Joint Meeting of the Molecular Cardiology Working Groups (2011)
Schurgers L.	"Strategies for prevention and regression of vascular calcification: new treatment options?" - ECS 2012 Munich, Germany (2012)
Schurgers L.	"Vascular calcification: new treatment options?" ECS 2012 Munich, Germany (2012)
Schurgers L.	"Vascular calcification: the price to pay for anticoagulation with vitamin K-antagonists" - Cardiovascular Grand Rounds CARIM, Maastricht, the Netherlands (2012)
Schurgers L.	"Vascular calcification: the price to pay for anticoagulation with vitamin K-antagonists"- NIGRAM (2012)
Schurgers L.	"The role of vitamin K and vitamin K-dependent proteins in the arterial vessel wall" - NVTH 2011, The Netherlands (2011)
Schurgers L.	"The role of vitamin K in arterial calcification" - FASEB 2011 Arizona, USA (2011)
Schurgers L.	"Vascular Calcification"- Abbott 2011 Barcelona, Spain (2011)
Schurgers L.	"Role of vitamin K in vascular calcification" - GTH 2011 Wiesbaden, Germany (2011)
Schurgers L.	"Vascular calcifications as a risk factor for cardiovascular mortality" - ERA-EDTA Munich, Germany (2010)
Schurgers L.	"Vascular calcification in Dialysis: modulated by vitamin K-status?"- Belgium Nephrology Symposium (2010)
Schurgers L.	"Vascular calcification in Chronic Kidney Disease: importance of vitamin K-status"- Dutch Nephrology symposium (2010)
Schurgers L.	"Vitamin K: a modifiable risk factor" - American Society of Nephrology (2008)
Schurgers L.	"MGP: the calcification inhibitor in need of vitamin K" - Angers, France (2008)
Schurgers L.	"MGP and Vitamin K: importance for vascular health" - Sendai, Japan (2008)
Schurgers L.	"Function of vitamin K and MGP in pseudoxanthoma elastica" - EuroPXE, Budapest, Hungaria (2007)
Sluimer J.	"Angiogenesis and hypoxia: novel links to plaque progression?" - European microvascular biology meeting, Krakow, Poland (2011)
Sluimer J.	"Intraplaque microvessels: not fit for the job?" - European Cardiology Society congress, Stockholm, Sweden (2010)
Sluimer J.	"Research in atherosclerosis: on mice and man" - Bsc laboratory technician, Maastricht, the Netherlands (2010)
Sluimer J.	"Research in atherosclerosis theme III: the postdoc experience" - I'm CARIM PhD/Msc weekend, Maastricht, the Netherlands (2010)
Smeets B.	"Teaching Programs on Molecular Biology in Modern Medicine" - University of Medicine Medicine and Pharmacology (UMP), Ho Chi Minh City, Vietnam, (2010)
Smeets B.	"Molecular Diagnostics in Clinical Genetics" - University of Medicine Medicine and Pharmacology (UMP), Ho Chi Minh City, Vietnam (2010)

Invited lectures (selection)

NAME	LECTURE
Smeets B.	"Preimplantation Genetic Diagnosis offers a fair chance of having unaffected offspring for mtDNA disorders" - HFEA advisory board, London, UK (2011)
Smeets B.	"Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review" - Advisor Nuffield Council on Bioethics London, UK (2012)
Smeets B.	"Preventing the Transmission of mitochondrial DNA Disorders: Selecting the good Guys or kicking out the bad Guys" - Meeting in honour of Noble price winner Bob Edwards, Cambridge, UK (2012)
Spronk H.	"Inflammatory Stimulation in Vivo" - Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference, Chicago, USA (2007)
Spronk H.	"Feedback Activation of Factor XI by Thrombin is Essential for In Vivo Haemostasis" - XXII Congress of the International Society of Thrombosis and Haemostasis (2009)
Spronk H.	"Feedback activation of factor XI by thrombin is essential for haemostasis in vivo" - 51st ASH Annual Meeting and Exposition, New Orleans, USA (2009)
Spronk H.	"Feedback Activation of Factor XI by Thrombin" - 56th Annual Meeting of the Scientific and Standardization Committee of the ISTH, Cairo, Egypt (2010)
Spronk H.	"Feedback Activation of Factor XI by Thrombin: Facts and Fictions" - 54 Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung, Nürnberg, Germany (2010)
Spronk H.	"Platelet Microparticles Generate Thrombin in a Factor XII Dependent Manner" - 55 Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung, Wiesbaden, Germany (2011)
Spronk H.	"Administration of oral dabigatran etexilate substantially counteracts inflammation and enhances plaque stability in a hypercoagulable model of aggressive atherosclerosis"- XXIII Congress of the International Society of Thrombosis and Haemostasis, Kyoto, Japan (2011)
Spronk H.	"Plasma Thrombin Generation and Thromboelastometry to Monitor Correction of Coagulopathy with PCC: Application in a Pig Model of Blunt Liver Injury" - CEMD The 4th Annual Congress, Beijng, China (2011)
Spronk H.	"Thrombin Inhibition Prevents Against Severe Atherosclerosis Progression in Prothrombotic Mice" - 56 Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung, Sankt Gallen, Switzerland (2012)
Spronk H.	"Contact System Activation by Microparticles" - 58th Annual Meeting of the Scientific and Standardization Committee of the ISTH, Liverpool, UK (2012)
Spronk H.	"Pro-haemostatic Agents in a Pig Model of Coagulopathy"- 58th Annual Meeting of the Scientific and Standardization Committee of the ISTH, Liverpool, UK (2012)
Spronk H.	"Thrombin Inhibition Prevents against Severe Atherosclerosis Progression in Prothrombotic Mice" - 54th ASH Annual Meeting and Exposition, Atlanta, USA (2012)
Stehouwer C.	"Obesity, Hypertension, and Insulin Resistance: Does Microcirculatory Function Provide a Link?" - Swiss Cardiovascular Research Training Network Symposium on the Blood, the Vasculature, and the Perivasculature, Fribourg, Germany (2007)
Stehouwer C.	"Obesity, Hypertension, and Insulin Resistance: Does Microcirculatory Function Provide a Link?" - 6th International Workshop on Structure and function of the vascular system, Paris, France (2007)

Invited lectures (selection)

NAME	LECTURE
Stehouwer C.	"Endothelial dysfunction: a target for preventing cardiovascular disease"- 3rd Mantua Workshop on Diabetes Mellitus and Related Conditions Novel Therapies: Scientific Backgrounds and Clinical Perspectives (2007)
Stehouwer C.	"Insulin sensitivity and endothelial function" - International Meeting: The Endothelium: Regulation and Regeneration, Padova, Italy (2007)
Stehouwer C.	"Hyperhomocysteinemia and diabetes" - World Congress on Hyperhomocysteinemia, Saarbrücken, Germany (2007)
Stehouwer C.	"Large artery stiffness as a pathway of cardiovascular disease in (pre)diabetes and the metabolic syndrome" - 2nd International Congress on 'Prediabetes' and the Metabolic Syndrome, Barcelona, Spain (2007)
Stehouwer C.	"Dysfunction of the microcirculation as a key to understanding the metabolic syndrome" - 2nd International Congress on 'Prediabetes' and the Metabolic Syndrome, Barcelona, Spain (2007)
Stehouwer C.	"Peripheral arterial disease: within the scope of the internist" - 7th Congress of the European Federation of Internal Medicine, Rome, Italy (2008)
Stehouwer C.	"Microcirculatory dysfunction as a link between obesity, hypertension and insulin resistance" - 44th European Association for the Study of Diabetes, Rome, Italy (2008)
Stehouwer C.	"Fat Cell-Derived Modulators of Vascular Cell Pathophysiology in Diabetes" - The G.B. Morgagni Prizes Symposium 2008, Padua, Italy (2008)
Stehouwer C.	"Microcirculatory Dysfunction Links Obesity to Hypertension and Insulin Resistance" - Steno Symposium on Novel insights in Diabetes Mellitus and its Complications, Copenhagen, Denmark (2009)
Stehouwer C.	"Body Fat and Vascular Health" - European Society of Cardiology, Barcelona, Spain (2009)
Stehouwer C.	"Microcirculatory dysfunction as a link between obesity, hypertension and insulin resistance" - 24th International Meeting on Clinical Cardiology, Athens, Greece (2009)
Stehouwer C.	"Arterial ageing in diabetes" - 20th European Meeting on Hypertension, Oslo, Norway (2010)
Stehouwer C.	"Vasculature as a central factor in obesity, diabetes and hypertension" - 3rd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy), Prague, Czechia (2010)
Stehouwer C.	"Microcirculatory Dysfunction: Key to Understanding the Metabolic Syndrome" - Ruysch Lecture, Academic Medical Centre & University of Amsterdam, the Netherlands (2010)
Stehouwer C.	"Microvascular dysfunction as as a link between obesity and hypertension" - 9th World Congress for Microcirculation, Paris, France (2010)
Stehouwer C.	"The metabolic syndrome" - 8th International Conference on Homocysteine Metabolism, Lisbon, Portugal (2011)
Stehouwer C.	"Microcirculatory function as a novel target in the prevention of diabetes" - 4th International Congress on Prediabetes and the Metabolic Syndrome, Madrid, Spain (2011)
Stehouwer C.	"Microcirculatory function as a novel target in the prevention of diabetes" - 19th European Congress on Obesity, Lyon, France (2012)
Unger T.	"Wann und Warum stoppt man klinische Studien?" - Key note lecture DHL Hypertonie Kongress Berlin, Germany (2012)
Vink H.	Invited lecture ISHR International Society of Heart Research, Athens, Greece (2008)
Vink H.	Invted Lecture Penn State Univ. Biomechanics symposium - Plenary Lecture, Pennsylvania, USA (2008)

Invited lectures (selection)

NAME	LECTURE
Vink H.	Invited lecture Japanese BioPhysics Society, Tokyo, Japan (2008)
Vink H.	Invited Lecture Virginia Commonwealth University, Richmond, USA (2008)
Vink H.	Papendal lectures 2008 - 2013
Vink H.	Invited Lecture Genzyme - Cardiovascular Division, Boston, USA (2009)
Vink H.	Invited Lecture Dutch Atherosclerosis Society, Ede, the Netherlands (2009)
Vink H.	Invited Lecture University of Bristol, Bristol, UK (2010)
Vink H.	Invited Lecture State University of Rio de Janeiro, Rio de Janeiro, Brazil (2010)
Vink H.	Invited Lecture University of Oxford - Cardiology department, Oxford, UK (2010)
Vink H.	Invited Lecture University of Münster, Münster, Germany (2010)
Vink H.	Invted Lecture - International Cardiology Conference, Athens, Greece (2011)
Vink H.	Invited Lecture TNO, the Netherlands (2011)
Vink, H.	Invited Lecture University of Pittsburgh Medical center, Pittsburgh, USA (2011)
Vink H.	Invited Lecture Great Ormond Street Hospital - Dept. Vascular Physiology, London, UK (2011)
Vink H.	Invited Lecture Virginia Tech University, Virginia, USA (2012)
Volders P.	"An In-Vivo Canine Model of Drug-Induced Long-QT1 Syndrome" - Cardiac Bioelectricity and Arrhythmia Center, Washington University St. Louis, USA (2007)
Volders P.	"Torsades de Pointes and Novel Biomarkers" - Organon Cardiovascular Safety Symposium, Oss, the Netherlands (2007)
Volders P.	"Cardiac Ventricular Repolarization and Arrhythmogenesis: Lessons from a Novel Model of Drug-Induced Long-QT1 Syndrome" - Spring Meeting of the Belgian Society of Fundamental and Clinical Physiology and Pharmacology, Antwerp, Belgium (2007)
Volders P.	"Repolarization of the Heart: Importance of Iks" - Department of Physiology, Masaryk University, Brno, Czech Republic (2007)
Volders P.	"Electro-Mechanical Remodeling In Hypertrophy and Dilatation" - 29th Annual Scientific Sessions of the Heart Rhythm Society, San Francisco, USA (2008)
Volders P.	"Novel Insights from In-Vivo Animal Models of Arrhythmias" - meeting EUROPACE of the European Society of Cardiology, Berlin, Germany (2009)
Volders P.	"Dominant-Negative Suppression of cAMP-Dependent IKs Upregulation by the Long-QT1 Mutation A341V" - Department of Cardiology, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy (2010)
Volders P.	"Mechanical Heterogeneity and Torsades de Pointes" - International Workshop on Cardiac Mechano-Electric Coupling and Arrhythmias, University of Oxford, UK (2010)
Volders P.	"Tiny Currents, Grave Arrhythmias" - Cardiovascular Grand Rounds Maastricht, Maastricht, the Netherlands (2011)
Volders P.	"Treatment of Common Rhythm Disorders in the ICU" - 2nd Annual International Euregion Intensive Care Symposium – Maastricht-Aachen CardioVascular Update for Intensivists, Maastricht, the Netherlands (2011)
Volders P.	"Does Exercise Result in RV Dilatation/ Disease Progression?" - 6th Annual International Symposium on Ventricular Arrhythmias: Pathophysiology and Therapy, Philadelphia, USA (2011)

Invited lectures (selection)

NAME	LECTURE
Volders P.	"How Much Practice/Knowledge in Basic Science Should Be Included in a Clinical EP Training Program?" - Spring Summit of the ESC Heart Rhythm Association, Sophia Antipolis, France (2012)
Volders P.	"Cardiac Repolarization and Arrhythmogenesis during Sympathetic Nervous Stimulation" - Scientific Meeting 75th Anniversary of Albert Szent-Györgyi's Nobel Prize Award, Szeged, Hungary (2012)
Volders P.	"Cardiogenetics: Role of the General Practitioner" (in Dutch) - meeting Cardio 2013, Hasselt, Belgium (2012)
Weber C.	"Platelet & inflammatory cell interactions"- British Atherosclerosis Society, Glasgow, UK (2007)
Weber C.	"Chemokine-like functions of MIF in leukocyte recruitment" - Joint Lecture. Keystone Symposia Leukocyte Trafficking / Chemokines and Chemokine Receptors, Keystone, USA (2008)
Weber C.	"Chemokines and chemokine-like ligands in vascular inflammation" - Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference, Atlanta, USA (2008)
Weber C.	"Structural basis and in vivo relevance of chemokine heteromerization"- Gordon Research Conference on Chemotactic Cytokines, Aussois, France (2008)
Weber C.	"Progenitor cell trafficking in the vascular wall"- International Society of Thrombosis and Haemostasis (ISTH) Meeting 2009, Boston, USA (2009)
Weber C.	"A miRNA-mediated mechanism for functional chemokine induction" - Gordon Research Conference on Chemotactic Cytokines, Il Ciocco, Italy (2010)
Weber C.	"Chemokines in the vascular inflammatory response" European Society of Cardiology (ESC), Stockholm, Sweden (2010)
Weber C.	"Chemokine-induced cell recruitment"- European Society of Cardiology (ESC), Paris, France (2011)
Weber C.	"The inflammatory pathogenesis of atherosclerosis" - Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain (2011)
Weber C.	"Chemokines and their receptors as therapeutic targets in atherosclerosis"- EMBO Molecular Medicine Conference, Heidelberg, Germany (2011)
Weber C.	"Chemokines as Therapeutic Targets"- International Atherosclerosis Symposium 2012, Sydney, Australia (2012)
Weber C.	"Role of chemokines in cardiovascular disease" - Gordon Research Conference on Chemotactic Cytokines, Il Ciocco, Italy (2012)
Weber C.	"Therapeutic targeting of microRNAs in atherosclerosis"- European Society of Cardiology (ESC), Munich, Germany (2012)
Weber C.	"CXCL12 – is it important?" - American Heart Association, Scientific Session 2012, Los Angeles, USA (2012)
Wildberger J.	"Teaching and education - help yourself: Requirements for the future of radiology" - 22. European Congress of Radiology, Wien, Austria (2010)
Wildberger J.	"DRG meets ESTI II: Pulmonary tumors and vessels" - 91. Deutscher Röntgenkongreß, Berlin, Germany (2010)
Wildberger J.	"Acute chest pain: The imaging perspective" - 16th Nederlandse Radiologendagen, Maastricht, the Netherlands (2011)
Wildberger J.	"How I report: CT angiography" - 24. European Congress of Radiology, Wien, Austria (2012)
Wildberger J.	"CT Angio und Perfusion. What you need to know…" - 24. European Congress of Radiology, Wien, Austria (2012)

Invited lectures (selection)

NAME	LECTURE
Wildberger J.	"From morphological to functional radiology" - 13th European Vascular Course (EVC) (2009)
Wildberger J.	"Live case: New possibilities with venous MRA" - 13th European Venous Course (EVC) (2009)
Wildberger J.	"The iodine delivery rate (IDR): A prerequisite for optimization of a CTA protocol" - 11th Annual International Symposium on Multidetector-Row CT, Stanford University San Francisco, USA (2009)
Wildberger J.	"Optimized use of indirect CT-phlebography in suspected pulmonary embolism" - 11th Annual International Symposium on Multidetector-Row CT, Stanford University San Francisco, USA (2009)
Wildberger J.	"New cardiac techniques: CT" - 5th Netherlands Heart Days, Curacao (2010)
Wildberger J.	"CT-guided interventions"- 4th Annual Meeting of the Russian Radiological Society (2010)
Wildberger J.	"CT voor longembolie en triple rule-out: mogelijkheden, zin en onzin" - Sandwichcursus Cardiovasculaire Radiologie, Ede, the Netherlands (2010)
Wildberger J.	"ESCR meets the Netherlands: Cardiac CT applications in Southern Netherlands" - Annual Meeting of the European Society of Cardiac Radiology (ESCR), Prague, Czechia (2010)
Wildberger J.	"CT in acute coronary syndrome" - 6th Netherlands Heart Days, Curacao (2011)
Wildberger J.	"CT-diagnostics for pulmonary embolism: State of the Art " - 6th Netherlands Heart Days, Curacao (2011)
Wildberger J.	"CT in acute coronary syndrome" - British Society of Cardiovascular Imaging, Manchester, UK (2011)
Wildberger J.	"Cardio CT: state of the art and future perspectives" - 5e Sectiemiddag Cardiovasculaire Radiologie Nederland, Amsterdam, the Netherlands (2011)
Wildberger J.	"Cardio CT: State of the art and future perspectives" - Cardiac Grand Round Lectures (2011)
Wildberger J.	"Contrast media delivery: The basics" - 14th Annual International Symposium on Multidetector-Row CT, Stanford University San Francisco, USA (2012)
Wildberger J.	"Contrast Induced Nephropathy: Practical Implications" - 14th Annual International Symposium on Multidetector-Row CT, Stanford University San Francisco, USA (2012)
Wildberger J.	"Acute chest pain: Current status" - 14th Annual International Symposium on Multidetector-Row CT, Stanford University, San Francisco, USA (2012)
Wildberger J.	"Triple rule-out strategy" - 1st Summer Course, European Society of Emergency Radiology (ESER), München, Germany (2012)
Wildberger J.	"CT of coronary artery disease" - 10th Anniversary of CMIV, Linköping, Sweden (2012)
Windt L. de	"Cardiac hypertrophy" - 5th Dutch-German Molecular Cardiology Meeting, Wurzburg, Germany (2007)
Windt L. de	"Calcineurin signaling in hypertrophy and heart failure" - European Society of Cardiology (ESC) Congress 2007, Vienna, Austria (2007)
Windt L. de	"Calcineurin/NFAT target genes in heart failure" - 5th Annual CHFR Symposium, Oslo, Norway (2007)
Windt L. de	"microRNA biogenesis and stress-activated microRNAs in heart failure" - 3rd HFA Winter Meeting on Basic Sciences in Heart Failure, European Society of Cardiology (ESC), Garmisch-Partenkirchen, Germany (2008)

Invited lectures (selection)

NAME	LECTURE
Windt L. de	"mitochondrially targeted therapeutic agents" - European Society of Cardiology (ESC) Congress 2008, Munchen, Germany (2008)
Windt L. de	"microRNA-199b targets Dyrk1a in heart failure" - 4th Winter Research, Heart Failure Association, European Society of Cardiology, Les Diablerets, Switzerland (2009)
Windt L. de	"CalmiRs: microRNAs Controlling Calcineurin/NFAT Signaling in Heart Failure" - The 6th Oulu Symposium: Advances in Molecular Mechanisms of Heart Failure, Atherosclerosis and Vasoactive Factors", Vuokatti, Finland (2009)
Windt L. de	"microRNA control of ventricular remodeling" - Annual meeting of the Working Group on Myocardial Function and the Working Group on Cell Biology, Villa Monastero, Italy (2009)
Windt L. de	"Role of DICER in cardiac hypertrophy" - ESC Heart Failure Congress 2009, Nice, France (2009)
Windt L. de	"Transcriptional pathways regulating hypertrophy" - Heart Failure meeting of the European Society of Cardiology, Berlin, Germany (2010)
Windt L. de	"Biomarkers in Heart Failure" - 2nd Annual Meeting of the Centre of Translational and Molecular Medicine, Utrecht, The Netherlands (2010)
Windt L. de	"Gene Regulatory Mechanisms in Heart Failure" - Annual Meeting of the 'Northern Cardiac Research Group' (NCRG) at the University of Hull, UK (2011)
Windt L. de	"Signaling in Cardiomyocyte Hypertrophy" - 2011 Summer School in Cardiovascular Sciences "From Basic Mechanisms to Clinical Application", the European Society of Cardiology Council on Basic Cardiovascular Science, Nice-Côte d'Azur, France (2011)
Windt L. de	"MicroRNAs" - 2011 Summer School in Cardiovascular Sciences "From Basic Mechanisms to Clinical Application" - the European Society of Cardiology Council on Basic Cardiovascular Science, Nice-Côte d'Azur, France (2011)
Windt L. de	"MicroRNAs that regulate cardiac growth"- European Society of Cardiology (ESC) Congress 2011, Paris, France. (2011)
Windt L. de	"Embryonic signals in foetal gene reactivation" - 10th HFA Winter Meeting on Basic Sciences in Heart Failure, European Society of Cardiology (ESC), Les Diablerets, Switzerland (2012)
Windt L. de	"MicroRNAs controlling myocardial function" - Frontiers in CardioVascular Biology 2012 Congress, European Society of Cardiology (ESC), London, UK (2012)
Windt L. de	"MicroRNA based Therapeutic strategies" - MiRNA and Cardiovascular Diseases", Satellite Meeting of the 80th EAS Congress, Milan, Italy (2012)
Windt L. de	"Calcineurin signalling: beyond hypertrophy" - European Society of Cardiology (ESC) Congress 2012, Munchen, Germany (2012)
Windt L. de	"MicroRNAs regulation in Cardiac hypertrophy and Heart Failure" - MicroRNAs Europe-2012 meeting, Cambridge, UK (2012)
Windt L. de	"Intracellular miRNA-Based Mechanisms of Cardiac Hypertrophy" - American Heart Association (AHA) Scientific Sessions 2012, Los Angeles,USA (2012)
Windt L. de	"MicroRNA Regulation of Transcriptional Networks" - American Heart Association (AHA) Scientific Sessions 2012, Los Angeles, USA (2012)
Wouters K.	"White Blood cells in disguise" - 36th Dies Natalis of Maastricht University, the Netherlands (2012)

Invited lectures (selection)

NAME	LECTURE
Wouters K.	"The tumour suppressor p16INK4a: a novel modulator of macrophage polarization" - Frontiers in Cardiovascular Biology meeting, London, UK (2012)
Zandvoort M. van	Univ. of Magdeburg, Dep. Neurology, Magdeburg, Germany, Prof. Reymann (2011)
Zandvoort M. van	World Molecular Imaging Congress, San Diego, USA, Prof. Kiessling (2011)
Zandvoort M. van	Univ. of Munich, Workshop small vessel imaging, Munich, Germany, Prof Dietzel (2011)
Zandvoort M. van	Univ. of Munich, GfMVB congress, Munich, Germany, Prof. U. Pohl (2011)
Zandvoort M. van	Univ. of Giessen, EuCar retreat, Giessen, Germany, Prof. K. Preissner (2011)
Zandvoort M. van	Univ. of Singapore, FOM2012, Singapore, Singapore, Prof. F. Brakenhof (2012)
Zandvoort M. van	Univ. of Maastricht, Dep. Gen & Cell Biol., Maastricht, the Netherlands, Prof. Glatz (2012)
Zandvoort M. van	Univ. of Edinburg, Roslyn Institute, Edinburg, Schotland, Prof. M. McGrew (2012)
Zandvoort M. van	Univ. of Heidelberg, SFB/TR23 lecture series, Mannheim, Germany, Prof. J. Kroll (2012)
Zandvoort M. van	Univ. of Maastricht, Cardiovascular Grand Rounds, Maastricht, Dr B. Schroen (2012)

MEDIA COVERAGE

NAME	TOPIC, TITLE AND DESCRIPTION
Brunner-La Rocca HP.	"Interview on heart failure care/ ICD" – L1 (2010)
Brunner-La Rocca HP.	"End of Life preferences in elderly heart failure patients" - American Heart Association; press conference (2008)
Brunner-La Rocca HP.	"TIME-CHF main results" - Hotline session European Society of Cardiology, Munich; press conference (2008)
Cosemans J.	"Article on Willy van Heumen Award" - http://www.proefdierenalt.nl/prijsuitreiking2011.html (2011)
Cosemans J.	"Article on Willy van Heumen Award" - http://www.alttox.org/spotlight/057.html
Cosemans J.	"Article on Willy van Heumen Award" - Mediator, jaargang 22, nr 5, okt 2011
Cosemans J.	"Article on Dekker grant/Pier Mannucci grant" - http://www.hartstichting.nl/wetenschappelijk_onderzoek/welk_onderzoek_krijgt_geld/genezen/vaatwand_genezen_na_infarct/
Cosemans J.	"Article on Dekker grant/Pier Mannucci grant" -http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)15387836/homepage/best_papers_by_young_authors.htm
Crijns H.	Interview on Radio 1 as Chair Netherlands Society of Cardiology - Future of cardiology after its 75th anniversary - Dit is de dag (2009)
Crijns H.	Interview on TV as Chair Netherlands Society of Cardiology - Ontbijtshow, Goedemorgen Nederland (2009)
Hackeng T.	"Voorkom ziekten met slimme eiwitten" by Tilman M. Hackeng - invited column on artsennet. nl Dutch: http://www.artsennet.nl/Kennisbank/Columns/Column/Voorkom-ziekten-met-slimme-eiwitten.htm
Hackeng T.	"Smart proteins with bells and whistles (Slimme eiwitten met vlaggen, toeters en bellen)" - Interview with Prof. Tilman Hackeng by Annelotte Huiskes 17-11-2009 University Maastricht. Dutch: http://www.unimaas.nl/researchmagazine/default.asp?id=208&thema=4&template=thema.html&taal=nl English:http://www.unimaas.nl/researchmagazine/default.asp?id=208&thema=4&template=thema.html&taal=en
Janssen B.	"Tool for optimizing pharmacotherapy" - www.pscribe.eu
Koole L.	http://nieuws.zuidlimburg.nl/blog/bijdrage-provincie-voor-biomimedics.html
Koole L.	www.youtube.com/watch?v=rReo0COImQk
Koole L.	http://nieuws.zuidlimburg.nl/blog/biomimedics-euregionale-samenwerking-op-gebied-van-nieuwe-materialen.html
Laat B. de	Several interviews and articles based on the "Red meets White" project (Volkskrant, Telegraaf, several Swiss and French newspapers)
Laat B. de	National Swiss and Dutch TV coverage of the "Red meets White" project
Leeuw P. de	Interviews on radio and TV (premature death in popstars) (2011, 2012)
Post M.	> 20 TV appearance and < 10 documentaries: CNN, ABC, NBC, CBC, Ned2, TVE, L1, BBC, ZDF, WRD a.o. (since 2009)

NAME	TOPIC, TITLE AND DESCRIPTION
Post M.	> 1000 newspaper articles: Sunday Times, New York Times, NRC, Volkskrant, Trouw, AD, Le Monde, Figaro, de Tijd, Guardian, among many others (since 2009)
Post M.	> 20 radio interviews: BBC Hardtalk; BBC4, RTL, ARTE, NPR stations and many others
Post M.	Other press conferences
Schaper N.	Head editor of the Dutch diabetes website DIEP (www.diep.info ,> 100.000 unique visitors/year)
Schurgers L.	"Vitamins in the prevention of human diseases" (De Gruyter, 2011): chapter 12: Vitamin K (2011)
Schurgers L.	"Het vitamine K Kookboek. Cooking book with information on vitamin K content in regular food items, meant for thrombosis service patients and coworkers" (2012)
Schurgers L.	Cary Nosler show (USA, California) - one hour radio show with "Health benefits of vitamin K" (2007)
Schurgers L.	The Heart show, De. F Vagnini (USA, New York) - one hour radio show with "Health benefits of vitamin K" (2007)
Smeets B.	Radio-interview L1 Nieuws, 17-12-2010 and attention in the newspapers as a result of the inaugural lecture
Smeets B.	Studio Guest, Hilversum, Hoezo Radio, Radio 5, 20-21u, 25 minutes interview
Windt L. de	http://drimble.nl/weblogs/gezondheid/10376840/onderscheiding-voor-leon-de-windt.html (2012)
Windt L. de	http://www.gezondheidsnet.nl/hart-en-vaatziekten/gen-ontdekt-dat-hartfalen-veroorzaakt (2010)
Windt L. de	http://www.rtlnieuws.nl/nieuws/binnenland/hartfalen-mogelijk-snel-te-genezen (2010)
Windt L. de	http://www.nu.nl/gezondheid/2396305/hartfalen-mogelijk-snel-genezen.html (2010)
Windt L. de	http://www.hbvl.be/nieuws/wetenschap/aid997640/maastrichtse-onderzoekers-schakelen-gen-uit-dat-hartfalen-veroorzaakt.aspx (2010)
Windt L. de	http://zakelijkcuracao.com/index.asp?page=http://zakelijkcuracao.com/news/4157/Cura%C3%A7ao se+wetenschapper+werkt+aan+doorbraak+bij+hartkwalen.htm (2011)
Windt L. de	http://www.dichtbij.nl/geleen/regionaal-nieuws/artikel/2493970/hartstichting-geeft-geld-voor-maastrichts-onderzoek-naar-hartfalen.aspx (2011)
Windt L. de	TV: http://www.mumc.nl/actueel/mumctv/specialismen/hart_en_vaat_centrum/703737011001-hartfalen-geneesmiddel
Windt L. de	TV: AVRO, TROS, 14 apr 2011

ORGANISATION OF SYMPOSIA

NAME	TOPIC, TITLE AND DESCRIPTION
Arts I.	Co-director of the International Course on Molecular Epidemiology of Chronic Diseases (www.M2E2.nl). First edition held in Maastricht, The Netherlands from 23-27 April 2012. Third edition planned for 16-20 June 2014
Biessen E.	Organiser KNAW Colloquium on the Vulnerable Plaque (2007)
Biessen E.	Organiser of a workshop at the Scientific Sessions of the American Heart Association (2007)
Brunner-La Rocca HP.	3-Ländertreffen Working groups of heart failure of D, A, CH; president of scientific committee; member of scientific committee in following 3 years (2008)
Crijns H.	Co-organiser Hybrid AF ablation Course: Crossing Borders – Maastricht, the Netherlands (yearly, starting 2008)
Crijns H.	Co-organiser EHRA course on pharmacological therapy for arrhythmias - ESC, Nice (2008 and 2009)
Crijns H.	Co-organiser AFNET/EHRA consensus conference - Nice (2008 and 2009)
Crijns H.	Organiser International Create EP Mini Course - Maastricht (2009)
Crijns H.	Co-organiser Netherlands Heart Days - Willemstad - Curacao (yearly from 2012)
Cosemans J.	Member abstract reviewing committee The 1st EUPLAN Platelet Conference, Maastricht, The Netherlands (September 2012)
Cosemans J.	Organiser of The 1st EUPLAN Platelet Conference, September 19th – 21th 2012, Maastricht, The Netherlands
Cosemans J.	Member abstract reviewing committee 54th Annual Meeting German Society of Thrombosis and Haemostasis Research, February 24th – 27th 2010, Nürnberg, Germany
Da Costa Martins P.	Co-organiser of the Cardiovascular Grand Rounds Maastricht, the Netherlands (since 2011)
Donners M.	Coordinator Lecture series of the CARIM Atherothrombosis cluster, Maastricht, the Netherlands (since 2012)
Glatz J.	5th Annual Conference of the Society for Heart and Vascular Metabolism (SHVM) “New developments in cardiac lipid metabolism: from substrate to signaling”, Maastricht, the Netherlands (2007)
Glatz J.	Chair organizating committee 49th International Conference on the Biosciences of Lipids (ICBL), Maastricht, the Netherlands (2008)
Glatz J.	9th Conference of the International Society for the Study of Fatty Acids and Lipids (ISSFAL), Maastricht (2010)
Hackeng T.	Member of the Scientific Program Committee for The International Society on Trombosis & Haemostasis XXIIth Congress and 55st Annual SSC Meeting, Boston, USA, July 11-17, 2009
Hackeng T.	Organisation and Chairman of the International Symposium on Chemical Protein Synthesis, Maastricht, the Netherlands (2009)
Hackeng T.	Organisation of the Symposium: “Blij met het Nieuwe Wetenschapsbeleid?”. Vereniging van Vernieuwingsimpuls Onderzoekers, Sociëteit “de Witte” Den Haag, the Netherlands (2007)

NAME	TOPIC, TITLE AND DESCRIPTION
Heemskerk J.	Co-organiser scientific meeting Lütherstadt Wittenberg, Germnay (2007)
Heemskerk J.	Co-organiser GTH/NVTH congress Nürnberg, Germany (2010)
Heemskerk J.	Co-organiser European Platelet Conference Maastricht (2012)
Heymans S.	CVOI course Viral myocarditis and cardiomyopathies, Utrecht (2010)
Heymans S.	First workshop of the Committee on Translational Research of the European Heart Failure Association, Brussels. Inflammation and Heart Failure (2008)
Houben B.	Emerging role for the microcirculation in cardiovascular disease. Joint meeting of German and Dutch Societies for Microcirculation and Vascular Biology, 2012 Mannheim (D). (co-organiser: DEBS – www.debsociety.nl)
Leeuw P. de	Organisation of the Annual Meeting of the Working Group on Hypertension and the Kidney (ESH) (2007-2012)
Luiken J.	Member organizating committee 49th International Conference on the Biosciences of Lipids (ICBL), Maastricht (2008)
Maessen J.	First “Crossing-Borders” AF meeting Maastricht – Hybrid approaches in AF treatment - Maastricht the Netherlands (2008)
Maessen J.	European Vascular Course – Maastricht the Netherlands (2009)
Maessen J.	European Cardiac Course – Maastricht the Netherlands (2010)
Maessen J.	Hybrid AF ablation Course: Crossing Borders – Maastricht, the Netherlands (2012)
Maessen J.	Minimally Invasive Thoracic Surgery: exploring the frontiers Roermond, the Netherlands (2012)
Nicolaes G.	Organisation and lectures at the 2nd symposium of the Netherlands Society on Biomolecular Modeling (NSBM), Centre for Molecular and Biomolecular Informatics (CMBI), Nijmegen, Netherlands (2010)
Nicolaes G.	Organisation and lectures at the 3nd symposium of the Netherlands Society on Biomolecular Modeling (NSBM) during the Netherlands Bioinformatics Centre (NBIC) Conference, Lunteren (2011)
Nicolaes G.	Organisation and lectures at the 5th symposium of the Netherlands Society on Biomolecular Modeling (NSBM) during the Netherlands Bioinformatics Centre (NBIC) Conference, Lunteren (2012)
Nicolaes G.	Organisation and lectures at the 6th symposium of the Netherlands Society on Biomolecular Modeling (NSBM), Academiegebouw Utrecht University, Utrecht (2012)
Oostenbrugge R. van	Chairman teaching session during European Stroke Conference (2012)
Post M.	NVF symposium (2012)
Reutelingsperger C.	Biomedica “Molecular Imaging and Drug Targeting” – Aachen (2007)
Schaper N.	Organising committee 5th International Symposium on the Diabetic Foot (2007)

Organisation of symposia

NAME	TOPIC, TITLE AND DESCRIPTION
Schaper N.	Organising committee 6th International Symposium on the Diabetic Foot (2011)
Schmidt H.	cGMP (2009)
Schmidt H.	cGMP (2011)
Schmidt H.	Frontiers in Drug Discovery
Schotten U.	As chairman of the Working Group of Cellular Electrophysiology of the German Society of Cardiology: 2 symposia (2012)
Schroen B.	Co-organiser of the Cardiovascular Grand Rounds Maastricht, the Netherlands (since 2011)
Smeets B.	MitoCricle meeting Naarden (2008)
Smeets B.	Workshop Resequencing CHIPs, Maastricht (2008)
Smeets B.	Organiser annual one and two day meetings Dutch Society of human Genetics (2007, 2008)
Smeets B.	Organiser scientific/educational/training meetings within the Alma In Silico project (2010, 2012)
Unger T.	Vice President and Chairman of the Scientific Programme Committee International Society of Hypertension (ISH) / European Society of Hypertension (ESH)/ German Hypertension Society (DHL), Berlin - Vice President and Chairman of the Scientific Programme Committee (2008)
Unger T.	The Drug Development Continuum – Academia, Start-ups, Big Pharma, Berlin (with. Funke-Kaiser, F. Zollmann, U. Kintscher) (2008)
Unger T.	Spotlight on the Renin-Angiotensin System, Berlin (with A. Pries, U. Kintscher) (2010)
Volders P.	Organiser of the Scientific Meeting 'Frontiers in Computational Electrocardiology1'. Maastricht, Netherlands (2008)
Volders P.	Organiser of the Scientific Meeting 'Frontiers in Computational Electrocardiology2'. Maastricht, Netherlands (2009)
Volders P.	Organiser of the Scientific Meeting 'Frontiers in Computational Electrocardiology3'. Maastricht, Netherlands (2010)
Weber C.	Abcam Meeting Inflammation and Atherosclerosis 2012, Munich (2012)
Weber C.	International Vascular Biology Meeting (IVBM) 2012, Wiesbaden (2012)
Weber C.	Annual Meeting of the Society for Microzirculation & Vascular Biology (GfMVB 2008) and 2nd Euregio-Symposium (2008)
Wildberger J.	Wissenschaftlicher Kongreßbeirat Dt. Röntgenkongreß 2008, 2009, 2010, 2011 and 2012
Wildberger J.	Scientific Programme Committee 6th Netherlands Heart Days Curacao (2011)
Wildberger J.	Scientific Program Committee Radiologendagen Maastricht (2011)
Windt L. de	Co-organiser 6th Dutch-German Molecular Cardiology Meeting, Amsterdam, The Netherlands (2008)

Organisation of symposia

NAME	TOPIC, TITLE AND DESCRIPTION
Windt L. de	Co-organiser 7th Dutch-German Molecular Cardiology Meeting, Hamburg, Germany (2008)
Windt L. de	Co-organiser 8th Dutch-German Molecular Cardiology Meeting, Rotterdam, the Netherlands (2009)
Windt L. de	Program committee member 5th HFA Translational Winter Research Meeting, Les Diablerets, Switzerland (2009)
Windt L. de	Program committee member American Heart Association's Basic Cardiovascular Sciences Conference 2010, "Technological and Conceptual Advances in Cardiovascular Disease", Rancho Mirage, CA, USA (2010)
Windt L. de	Program committee member 6th HFA Translational Winter Research Meeting, Les Diablerets, Switzerland (2011)
Windt L. de	Co-organiser 9th Dutch-German Molecular Cardiology Meeting, Ulm, Germany (2011)
Windt L. de	Organiser Mini-symposium on "microRNA in Cardiovascular Disease" 2011, Maastricht, the Netherlands (2011)
Windt L. de	Coordinator and co-organiser 10th Dutch-German Molecular Cardiology Meeting, Kerkrade, The Netherlands (2011)
Windt L. de	Coordinator and co-organiser 4th meeting of the Fondation Leducq Transatlantic Network for Excellence on MicroRNAs, Amsterdam, The Netherlands (2012)
Zandvoort M. van	Co-organiser yearly Maastricht Microscopy Meeting (MMM), Maastricht University, the Netherlands (since 2011)
Zandvoort M. van	Maastricht Microscopy Meeting (since 2010)

OTHER

NAAM	TOPIC, TITLE AND DESCRIPTION	PERIOD
Brunner-La Rocca HP.	Guidelines on heart failure in Switzerland, first author (pocket cards 2009; update 2013)	2007-2013
Crijns H.	AFNET-EHRA AF consensus conference 2009: Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, John Camm A, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. Eur Heart J 2009; 30:2969-77c	2009
Crijns H.	Catheter Ablation of AF Consensus Statement Writing Group, HRS and EHRA, ESC (2011)	2011
Koole L.	BioMiMedics. Development of the new device X-SpheresTM for targeted embolization of uterine fibroids.	
Leeuw P. de	Uniform format for disclosure of competing interests in ICMJE journals. Published in a.o.: New Engl J Med 2009;361:1896-1897	2009
Leeuw P. de	European Society of Hypertension practice guidelines for home blood pressure monitoring. Published in: J Hyperten 2010;24:779-785	2010
Schaper N.	Dutch guidelines on teh Diabetic Foot	2006
Schaper N.	Dutch KNGF committee on Standard of Care Physical Exercise and Diabetes	2012
Schaper N.	IDF guidelines on diabetes mellitus	2006, 2012
Schaper N.	Dutch guideline commission multi-agency care for diabetes mellitus	2011-2012
Schaper N.	International guidelines on the Diabetic Foot	Since 1996
Schaper N.	Dutch NAD committee Standard of Care Pharmacotherapy Diabetes Mellitus	Since 2012
Schotten U.	AFNET-EHRA AF consensus conference 2009: Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, John Camm A, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. Eur Heart J 2009; 30:2969-77c	2009

NAAM	TOPIC, TITLE AND DESCRIPTION	PERIOD
Schotten U.	European Guidelines AF Management: Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-429	2010
Schotten U.	AFNET-EHRA Consensus Conference on AF 2011: Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kääb S, Schotten U, Wegscheider K, Boriani G, Ezekowitz M, Diener H, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Vardas P, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. Thromb Haemost. 2011;106:1012-9	2011
Schotten U.	Focussed Update Guidelines AF Management: Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blömstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbüchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33(21):2719-47	2012
Schotten U.	Position paper on standardisation of experimental data reporting: Quinn TA, Granite S, Allessie MA, Antzelevitch C, Bollensdorff C, Bub G, Burton RA, Cerbai E, Chen PS, Delmar M, Difrancesco D, Earm YE, Efimov IR, Egger M, Entcheva E, Fink M, Fischmeister R, Franz MR, Garny A, Giles WR, Hannes T, Harding SE, Hunter PJ, Iribe G, Jalife J, Johnson CR, Kass RS, Kodama I, Koren G, Lord P, Markhasin VS, Matsuoka S, McCulloch AD, Mirams GR, Morley GE, Nattel S, Noble D, Olesen SP, Panfilov AV, Trayanova NA, Ravens U, Richard S, Rosenbaum DS, Rudy Y, Sachs F, Sachse FB, Saint DA, Schotten U, Solovyova O, Taggart P, Tung L, Varro A, Volders PG, Wang K, Weiss JN, Wettwer E, White E, Wilders R, Winslow RL, Kohl P. Minimum Information about a Cardiac Electrophysiology Experiment (MICEE): Standardised reporting for model reproducibility, interoperability, and data sharing. Prog Biophys Mol Biol. 2011;107:4-10	2012
Schotten U.	Hardware and software solution for non-invasive classification of AF based on a transesophageal ECG, Patent filed in 2012.	2012

ANNEX 6 DOCUMENT DUTCH HEART FOUNDATION: CARIM'S SOCIETAL RELEVANCE

CARIM is one of the largest cardiovascular research institutes in Europe. At the national level the Dutch Heart Foundation (DHF) uses that strong scientific position by inviting CARIM's principal investigators and senior researchers to review grant applications and to be member of its selection and advisory committees. The chairman of the Scientific Advisory Committee of the DHF is a well known principal investigator of CARIM.
The central concept underlying Maastricht UMC+ is the chain concept, which means that the Cardiovascular Patient Center is directly associated with CARIM. This connection enables the Center to provide specialized treatment and offer the very highest standards of care. Besides the delivery of high quality healthcare can have beneficial effects on the research process: the challenge is to accelerate the translational process. This approach to health care and research fits very well with the mission statement of the Heart Foundation to significantly reduce the impact of cardiovascular disease. The DHF finds it encouraging that CARIM seeks the growing involvement and participation of patient Organisations in their research efforts.
Another chance to provide patients with the most effective treatment available lies in the public – private research cooperation combining the innovative capabilities of the industrial and academic sectors. Such partnerships are firmly focused on the translational aspects of research.
CARIM is the main author of the Center for Translational Molecular Medicine, a national example, also supported by the DHF. In this way CARIM's ideas are brought to the national science policy level.
The DHF also appreciates CARIM's role in the formulation of the report of the CardioVascular Profiling Commission (March 2010). CARIM chaired and contributed to this Commission formulating innovative recommendations about how scientific cardiovascular research in the Netherlands can take up a competitive position in the European front line. Scaling up to the national level, synergy and impact are essential in comparison with the current situation of the orientation to the local (UMC) level. The DHF encourages CARIM to initiate the Organisation and coordination of the cardiovascular research in the Netherlands in the way as recommended by the Profiling Commission.
CARIM has initiated training courses for young researchers. Together with the DHF these courses were raised to a national level, with input from all cardiovascular institutes: the DHF – Papendal courses. This national training program is highly appreciated by the participants (over 100 young researchers per annum).
With the growing need for transparency in science the DHF looks forward to combine efforts with CARIM to both (1) communicate more intensely with patients and the general public about the societal impact of research , as well as (2) enhance the visibility of the national scientific cardiovascular field in order to survive in an increasingly competitive European scientific environment.

ANNEX 7
PATENTS AND SPIN-OFF COMPANIES

PATENTS

2007

Dias AA, Koole LH, Pijls RT
Coiled wire for the controlled release of drugs to the eye (published)
WO07006427

2008

Vander Borght A, Ummelen M, Ramaekers F, van den Eijnde S, Broers J, Falkenberg F, Hahnel C
Cancer Vaccine (published)
US 8133682 B2

Vermeer C, Schurgers LJ, Klaveness J, Vik H, Vik AB, Westbye S
Pharmaceutical and nutraceutical products comprising vitamin k2 (published)
CA2657748 A1

Koole LH, Hanssen JHL
Wire, tube of catheter with hydrophilic coating (published)
US2008033373

Van Hooy-Corstjesn CSJ, Koole LH
Homogeneous intrinsic radiopaque embolic particles (published)
AU20077314726

Hemker HC, Wagenvoord RJ, de Smedt E
Novel thrombin substrates (filed)
EU patent 081668956

2009

Cleutjes CBJM
Peptides for use in diagnosing the presence of ruptured atherosclerotic lesions in an individual (published)
EP2016093

Weber C, Koenen RR
Glycosaminoglycan-antagonising mcp-1 mutants and methods of using same (published)
WO 2009/015884.A1

Waltenberger JL, Czepluch FS, Eggerman J
Cellular stress testing in the cardiovascular system (published)
WO2009061191 A1

Roumen L, Peeters JW, Hermans JJRM
N-benzyl imidazole derivatives (published)
EP08152079.3; US Provisional Application 61/032282

Moens AL
Protective effect of high dose folate on myocardial ischemia (published)
WO2009098279.A1

Nicolaes GAF, Rosing J, ten Cate H, Dahlbäck B
A method for the prevention or treatment of ischemia reperfusion injury (published)
WO200911548.A3/ EP2103310 A8

Koole LH, van Hooy-Corstjens CSJ
Two-component cement for vertebroplasty (published)
US2010275671

2010

Da Costa Martins P, de Windt LJ
MicroRNA-199b function in heart failure (published)
P83990PC00

Hemker HC, Apitz-Castro RJ
A method and assembly for measuring thrombin generation in plasma (published)
WO2010016762 A1/EP2313785A1/US20110195441

Ramaekers FCS, Broers JLV, Houben F, van Oostveldt PMV, de Vos WH
Method for the prediction of the severity of nuclear envelope related diseases (published)
EP2264455 A1

Blankesteijn WM, Laeremans H, Hackeng TM
Antagonistic peptides for frizzled-1 and frizzled-2 (published)
WO2010100035 A1

Pisters R, Hermans M
Medicijn Manager (published)

2011

Weber C, Zernecke A, Bidzhekov K
mIR-126 and tissue repair (published)
WO 2009/073921

Seigneric RG, Evelo C, et al
Gene Signature of Early Hypoxia to Predict Patient Survival (published)
US7960114 B2

Vermeer C
Diagnostic assay for human Matrix Gla-Protein and its use as a biomarker (published)
US8.003.075 B2

El Azzouzi H, de Windt LJ
Means and methods for counteracting, delaying and/or preventing adverse energy metabolism switches in heart disease: PPARdelta (published)
PCT/NL2009/050484

2012

Hemker HC, Hemker PW
Time-course corrected measurement of enzymatic activity (published)
EU patent 081511818/US8551722 B2

Schotten U, Zeemering S, Maesen B
Non-invasive classification of atrial fibrillation by probabilistic interval analysis of a transesophageal electrocardiogram (published)
WO2012160066 A1/ EP2526861A1

Vermeer C
Use of vitamin K for weight maintenance and weight control (published)
WO 2012/080519

Voets A, Nalbantov G, Smeets H, Lambin P
Methods mtDNA-dyspnea prediction (published)
EP12160154.6

Brunner la Rocca HP
NTproBNT and cardiac tropenin based therapy guidance in heart failure (filed)
US Patent Application Serial No 61/724,316

SPIN-OFFS

NAME OF THE COMPANY	COMPANY PROFILE	YEAR OF ESTABLISHMENT
VitaK BV	VitaK is a research company specialized in discovering new functions for vitamin K, developing food supplements and health food containing new formulations of vitamin K in combination with other vitamins, minerals and trace elements. VitaK develops new assays to specifically assess the vitamin K status in liver, bone, cartilage and vascular tissue. One aspect of the latter line is diagnostics based on circulating MGP, which is a patented system to monitor cardiovascular disease via biochemical markers in blood.	2000
Pharma Target BV	Pharma Target BV aims to accelerate the drug development process by offering its products and services with regard to molecular imaging and the Annexin A5 technology.	2002
ACS Biomarker BV	ACS Biomarker BV is an emerging biomarker development company aiming to discover and develop biomarkers that improve prognosis and management of cardiac disease.	2007-2011
FABPulous BV	FABPulous develops ultra-rapid point-of-care diagnostic tests which can be used in the first line medical care for the determination of acute tissue injury. These tests provide rapid and accurate diagnosis and benefit both the patient (live-saving) as well as the healthcare sector, the insurance industry, governments and society in general (cost-saving).	2008
Synapse BV	Synapse BV carries out developmental research in the field of the (patho-)physiology of haemostasis and thrombosis, operating in the niche between biochemistry and molecular biology on the one side, and pharmaceutical- and clinical sciences on the other. It more specifically explores the overall function of the thrombin generating system in platelet poor- and platelet rich plasma and blood as a diagnostic tool and a pharmaceutical target.	2009 member of the STAGO Diagnostica Group
Glycocheck BV	Glycocheck BV has developed a unique software platform to detect, measure and monitor online the Glycocalyx layer under the tongue. GlycoCheck BV develops market worldwide clinical relevant imaging solutions based on a 'on line' measurement of the Glycocalyx layer. Products of GlycoCheck BV are unique and designed to be used by healthcare professionals for the accurate, reliable and non-invasive selection, detection & monitoring of cardiovascular patients. Solutions will be based on specific applications of our technology in hospital departments like internal medicine and cardiology.	2010
Mirabilis BV	Mirabilis Therapeutics BV i.o. will be incorporated as a spin-off company from MUMC+, with scientific input from CARIM. The company's mission statement is: Improving and changing the treatment of cardiovascular disease by the discovery of micrRNA-based therapy and reaching proof of concept for microRNA-based Therapy.	2012
YourRhythmics BV	YourRhythmics uses scientific knowledge within CARIM's research school to develop a clinically relevant and IP-protected solution for the detection and quantification of Atrium Fibrillation (AF).	2012
MirNext BV	MirNext is a spin-off company of ACS Biomarker. It develops prognostic microRNA biomarkers for heart failure.	2012

ANNEX 8 DESCRIPTION IMAGING UNITS

The EuroBioImaging unit in Maastricht consists of an Electron Microscopic (EM), an Advanced Optical microcopy, and a non-invasive imaging unit.
The EM unit has, next to standard EM (SEMXL30, TEM-CM12, TEM-CM100), also available a home-built Vitrobot (vitrification of solutions on EM grids for CryoTEM), a Tecnai cryo-iCORR-120kV Correlative Light EM, and a Cryo-microtome. So far, the EM part has mostly been a Euregional facility, although significant cooperations with other Dutch academia and companies do exist. The reason for this position is the fact that EM in Maastricht has been used for biomedical applications, not so much for developmental purposes. Extreme resolutions for imaging at anatomical level are not needed. With the presence of iCORR within the context of Enabling Technologies, that will change. The use of this equipment will ask for dedicated probe and technology development. The needed expertise for this will be ensured by the arrival of the group of Prof. P. Peters, a renowned EM specialist, to Maastricht, also making available new EM equipment.

The optical unit offers, next to standard microscopy (trans-illumination, fluorescence, and confocal microscopes), highly specialized equipment, such as super-resolution white light confocal and gated STED, Nuance FX Multi-color Pathology, intravital Live fluorescence microscope, High Content Analyzer, low-speed Multiphoton microscope, and Resonant Scanning intravital Multiphoton (lifetime) microscope. The Maastricht optical site is 1 of the 18 national imaging nodes within NL-BioImaging-AM focusing on the use of light microscopic techniques for cardiovascular, oncological imaging, and metabolic purposes. Within NL-BioImaging-AM we have a unique position in that we do not develop new microscopic techniques, but apply the newest available microscopy to biomedical and material science. With the Organisation of the world conference Focus on Microscopy 2013 in Maastricht, and the biomedical topic therein, this role was firmly established.

The non-invasive imaging site has available an Explore Optix MX2 Whole body fluorescence mouse and rat imaging system, a 7T Bruker Biospec 70/30 for mouse, rat, and rabbit MRI and MRS, a Micro-SPECT-II MiLabs for murines, a Micro-PET FOCUS 120 for murine and rabbit legs, a Micro-CT, a Micro-SPECT-MRI translational bed for murine animals, a VisualSonics Vevo2100 small animal Ultrasound scanner, and various medical scanners (MRI, PET, CT) also available for research purposes. The non-invasive site is member of the Benelux Chapter of the International Society of Magnetic Resonance in Medicine, actively involved in the Netherlands Society for Radiology, as well as the Netherlands Society for Nuclear Medicine and the Radiology Chapter of the Netherlands Society for Medical Physics. Furthermore, collaborations with most of the other University Medical Centers in the Netherlands are numerous.
Via Enabling Technologies (ET) the “Excellence in Imaging” unit furthermore has 10% free access to imaging infrastructure at DSM Resolve, while also Mass Spectroscopic Imaging is now available at UM. Strong interactions are in place and further being developed with SME’s and start-ups within the framework of ET, further broadening the field of expertise outside biomedical applications. This creates a facility with several unique European features, such as the combination of research within life sciences and material sciences, the strong interaction between academia and industry, the unique combination of studies on biomedical, polymeric and catalytic materials (e.g. biocompatibility). This generates a unique leverage for future developments into valorization. Strong cooperations on many aspects of imaging (microscopic, nuclear) furthermore exist with the Universitätsklinikum Aachen.

ANNEX 9
NMR PROJECTS IN CARIM

Currently, several projects in the Biochemistry use the capabilities of the new NMR equipment in Maastricht to give new insights in the structural biochemistry of cardiovascular important proteins.

1. Galectin-3
2. RANTES (CCL5)
3. Annexin A1
4. TFPI Kunitz domains

Galectin-3

Galectins play crucial roles in diverse physiological events (e.g. cell adhesion and migration, wound healing, immunity, and inflammation) and pathological disorders (e.g. tumor growth, progression, cardiovascular disease, atherosclerosis, diabetes). Galectin-3 (Gal-3) is unique among galectins, because as the only chimera-type galectin, it has an extended N-terminal domain (ND 116 residues for human Gal-3) composed of repeats of short segments (collagen-like rich in Pro, Gly and Tyr residues) connected to a C-terminal Carbohydrate Recognition Domain (CRD 134 residues) that binds galactose containing glycans. However, while X-ray and NMR structures of Gal-3 CRD are known, none are reported for ND and CRD together in full length Gal-3, and the relationship between structure and dynamics of CRD and ND, which are crucial to Gal-3 function, remains unknown. In our group high-resolution NMR spectroscopy has been used to assign resonances of full-length Gal-3 (Biomol Assign 2014 accepted for publication). A comparison between the spectra of Gal-3 CRD, isolated ND domain segments and full-length Gal-3 show that the ND-domain binds on the backside of the CRD domain, opposite to the sugar front binding surface. Based on these NMR data the backside of Gal-3 is involved in intermolecular recognition of Gal-3, but seems also crucial to bind inhibitors such as the calixarene-based O118 compound that counter act tumor growth. Structural knowledge of Gal-3 will be used to design functional inhibitors and synthetic peptidomimetics for the development of inhibitors of cardiac disease and atherosclerosis.

RANTES (CCL5)

Atherosclerosis is characterized by chronic inflammation of the arterial wall due to chemokine-driven mononuclear cell recruitment. Activated platelets can synergize with chemokines to exacerbate atherogenesis; for example, by deposition of the chemokines platelet factor-4 (PF4, also known as CXCL4) and RANTES (CCL5), triggering monocyte arrest on inflamed endothelium. Homo-oligomerization is required for the recruitment functions of CCL5, and chemokine heteromerization has more recently emerged as an additional regulatory mechanism, by enhanced monocyte arrest resulting from CCL5-CXCL4 interactions. NMR spectroscopy have been applied to study the direct interaction in solution between native RANTES (and its dimeric E66S mutant) and PF4 as a function of concentration and pH. Moreover, heterodimer constructs between RANTES and PF4, were made using either synthetic peptide chemistry or by means of E.Coli expression methods . NMR data on glycine–linked RANTES-PF4 and PF4-RANTES hetero complexes show that the individual chemokine domains fold independently, although it remains unclear at this moment how strong the hetero-oligomerization process competes with homo-oligomerization of the chemokines. More NMR data are required to draw definite conclusions.

Annexin A1

Annexin A1 (anxA1) (38.5 kDa) binds negatively charged phospholipids and formyl peptide receptors (FPR1,-2), both resulting in anti-inflammatory responses. To investigate therapeutic potential of anxA1 in atherosclerosis recombinant human anxA1 was expressed in minimal growth media containing uniformly isotope labeled [13C]-glucose and [15N]-ammonium chloride. Expression in 4 liter media yield some 80 mg pure of doubly labeled AnxA1 protein, enough to study the protein in detail by NMR spectroscopy. No crystal structure of full-length human AnxA1 is yet available, with only the crystal structure of the porcine analog protein as best homologous candidate around. We attempt to solve the solution structure of human AnxA1 triple resonance NMR spectroscopy, both in the calcium bound form as well as in the apo form. Preliminary NMR results show that, despite the considerably large size of the protein, good NMR spectra are obtained up to 0.5 mM protein concentration. Large spectral differences are observed in the protein spectra upon addition of calcium, demonstrating the existence of multiple conformations of the N-terminal domain in the calcium-free states, and that all gradually move into a single preferred open state after stabilization by calcium binding. Because AnxA1 binds phospholipids in a calcium-dependent manner, we also recorded NMR

spectra in the presence of Small Unilamellar Vesicles (SUV) containing 80%:20% DOPC:DOPS. Efficient removal of calcium ions by EDTA permit high quality spectra of AnxA1 in phospholipid vesicles that are virtually identical to the spectrum of free protein, demonstrating minor interference of protein and phospholipids. In contrast, addition of only small amounts of calcium to the apo protein in SUV vesicles result in immediate loss of protein signal, This loss of signal is interpretated as dynamic exchange broadening of ordered protein regions that exists in a non-bound and a calcium induced state that transiently binds DOPS patches on the vesicle wall.

TFPI Kunitz domains

NMR spectroscopy is successfully applied to study the isolated Kunitz domains 2 and 3 of Tissue Factor Pathway Inhibitor (TFPI), made synthetically by peptide synthesis. Despite lack of isotope labeling, NMR resonances of both domains were completely assigned and structurally characterized. In full-length TFPI, Kunitz-2 domain binds factor X, while the Kunitz-3 domain is responsible for protein S binding. In structural terms both Kunitz domains have similar topology and binding modes. However, the Kunitz-2 domain intrinsically contains a more dynamic recognition loop, which fact indicates that the flexibility of specific amino acids are important for specific interaction towards its enzyme target. In addition, slow irreversible molecular changes, not seen before, take place the Kunitz-2 protein, and which may have biological significance to the complete native TFPI protein.

Our final goal is to first solve the structure of Kunitz domain 1 of TFPI, which is still not known. The next step is to combine the NMR data recorded on the separate domains of TFPI as a reference to look for differences of the active, full-length TFPI protein. The separate TFPI domains can also be used to monitor the tight complex between inhibitor and enzyme in real-time by NMR spectra, e.g. by mixing [13C,15N] labelled factor X and unlabelled TFPI. This method allows us to selectively observe only one of the two protein partners in the final complex.

ANNEX 10
OVERVIEW CARIM PHD COURSES 2007-2012

2007

May 7-9
Clinical Aspects of Cardiovascular and Peripheral Vascular Diseases
Organiser: Dr Jean Bronzwaer

May 21-25
Introduction into Cardiovascular Pharmacology
Organiser: Prof. Jo De Mey

June 18-22
Advanced Microscopy and Vital Imaging
Organiser: Prof. Frans Ramaekers

2008

February 25-March 7
Molecular Biology and Genetics of Heart and Blood Vessels
Organiser: Dr Guillaume van Eys

April 21-25
Biophysics of Heart and Circulation
Organisers: Prof. Robert Heethaar

May 27-29
Physiology of Heart and Circulation
Organisers: Dr Jurgen van Teeffelen and Prof. Hans Vink

June 9-13
Introduction to Cardiovascular Pharmacology
Organiser: Prof. Jo De Mey

June 16-20
Advanced Microscopy and Vital Imaging
Organiser: Prof. Frans Ramaekers

2009

May 11-15
Clinical Aspects of Cardiovascular and Peripheral Vascular Diseases
Organiser: Dr Jean Bronzwaer
June 9-12
Advanced Microscopy and Vital Imaging
Organiser: Prof. Frans Ramaekers

2010

May 17-21
Pharmacology of the Heart and Circulation
Organiser: Prof. Jo De Mey

June 28-July 2
Molecular Biology of the Heart and Circulation
Organiser: Dr Guillaume van Eys

October 4-6
Physiological and Clinical Aspects of Heart and Circulation
Organiser: Dr Jurgen van Teeffelen

November 8-12
Non-invasive Biomedical Imaging
Organisers: Prof. Joachim Wildberger and Dr Eline Kooi

2011

July 4-8
Advanced Microscopy and Vital Imaging
Organiser: Prof. Frans Ramaekers

Atherosclerosis Phenotyping
Organisers: Prof. Esther Lutgens and Dr Menno de Winther

Human Heart Failure: From Bench To Bedside
Organisers: Prof. Leon de Windt and Prof. Stephane Heymans

Modern Biochemistry of Cardiovascular Disease
Organisers: Prof. Hugo ten Cate and Dr Henry Spronk

Non-invasive Biomedical Imaging
Organisers: Prof. Joachim Wildberger and Dr Eline Kooi

2012

June 18-22
Advanced Microscopy and Vital Imaging
Organiser: Prof. Frans Ramaekers

Human Heart Failure: From Bench To Bedside
Organisers: Prof. Hans Peter Brunner-La Rocca and Prof. Stephane Heymans

Modern Biochemistry of Cardiovascular Disease
Organisers: Prof. Hugo ten Cate and Dr Henry Spronk

ANNEX 11
OVERVIEW
TENURE TRACKS

	Name	Starting date	(Expected) ending date
Ongoing	Judith Cosemans	April 1, 2010	April 1, 2013
	Marjo Donners	October 1, 2009	July 1, 2013
	Judith Sluimer	November 1, 2009	November 1, 2013
	Paula da Costa Martins	January 1, 2011	January 1, 2014
	Leon Schurgers	January 1, 2011	January 1, 2014
	Jan Bucerius	June 1, 2011	June 1, 2014
	Dietbert Neumann	March 1, 2011	April 1, 2016
	Ward Vanagt	December 1, 2011	December 1, 2016
	Kristiaan Wouters	April 1, 2012	April 1, 2017
Finished	Blanche Schroen	January 9, 2008	January 9, 2012

ANNEX 12
PROGRAM SWOT WORKSHOP DAY

FOCUS DAYS

Participants: 40 senior staff of CARIM
When: 8-9th of January 2013
Location: Abdij Rolduc, Kerkrade

Objective: Develop together SMART (Specific, Measurable, Achievable, Relevant, and Timed) goals and implementation steps, setting priorities and making choices on what to do and what not, in order to make the CARIM mission work. The results of this SWOT workshop will be used as an input for the External Review in 2014.

Our Mission within CARIM: "CARIM belongs to the top 5 of the best CV research institutes in the EU. CARIM takes the lead in building bridges towards other EU and Dutch CV centres." Approach: Based on a fully open SWOT questionnaire all answers were grouped into 12 topics. Of these, four topics (1-4) that received either the most comments or had the highest ratio of negative comments were chosen for further analysis and finding solutions in subsequent workshops:

1. Infrastructure, e.g. shared infrastructure in CARIM
2. Culture (communication and internal collaboration incl. Research Schools)
3. Scientific excellence (talent and funding),
4. Funding (external, e.g. EU, and internal support)

For the two FOCUS DAYS, four groups (A-D) of 11 members have been pre-assigned with a good mix of senior and junior staff and from different CARIM lines/departments. A chair (*italic*) will lead the discussions, take notes, and also report to the plenary.

A. *Heymans S*, Arts I, Biessen E, Bilsen M van, Ferreira I, Glatz J F, Kooi E, Nicolaes G, Stehouwer C, Verheule S, Vink H
B. *Windt de L*, Blankesteijn M, Cate ten H, Cosemans J, da Costa Martins P, Gijbels M, Heemskerk J, Kroon A, Neumann D, Oostenbrugge R van, Zander R van der
C. *Schmidt H*, Brunner-La Rocca HP, Crijns H, Heeneman S, Houben B, Prinzen F, Reesink K, Reutelingsperger C, Schotten U, Schroen B, Zandvoort van M
D. *Hackeng T*, Dagnelie P, Delhaas T, Kallen C van der, Koole L, Reneman R S, Schalkwijk C, Schurgers L, Smeets B, Unger T, Volders P

Each group will work for half a day on every topic in parallel and develop short-, mid- and long- term action points. Afterwards results are shared, discussed and summarised in a plenary session. Then the next topic is dealt with. At the end of the two days, we will ideally end up with about 12 agreed action points (3 per topic) with high positive impact to CARIM.

Preparation: Everyone should re-read all comments made. Think about concrete measures (Specific, Measurable, Achievable, Relevant, and Timed) how opportunities could be utilised, how threats be prevented, weaknesses could be improved, and strengths kept. Try to be as specific as possible. Bring your own laptop and note pads.

Programme day 1: 8th January

Time	Activity	Chair(s)
09.30-10.00	Arrival with coffee and cake & fruits	
10.00-10.15	Welcome : - *Objectives of the 2 days* - *Setting expectations* - *Explaining the programme*	Thomas Unger, Stephane Heymans
10.15-10.30	Mission and vision of CARIM - *How do we translate the mission and vision into realistic goals?* - *What are the driving forces that help us realise these goals?* - *What are the restraining forces?*	Thomas Unger
10.30-10.45	The way forward - *Speak with a signature* - *Open minded and with clear proposals* - *Friendly & (self)-critical environment* - *What can **we** improve easily tomorrow (low hanging fruit) without the help of people outside CARIM?* - *What can **we** improve < 2 year without the help of people outside CARIM?* - *What can we solve with the help of the UM and the EU and how can we influence them?* - *What do we have to accept as a fact of live ?*	Stephane Heymans
10.45-11.00	Analysis of the SWOT - What does work? - What can wait? - What needs work?	Harald Schmidt, Leon de Windt
11.00-11.30	Coffee/Tea break	
11.30-12.30	Group A Topic 1 Group B Topic 1 Group C Topic 2 Group D Topic 2	Stephane Heymans Leon de Windt Harald Schmidt Tilman Hackeng
12.30-13.30	Lunch	
13.30-14.30	Group A Topic 2 Group B Topic 2 Group C Topic 1 Group D Topic 1	Stephane Heymans Leon de Windt Harald Schmidt Tilman Hackeng
14.30-15.30	Topic 1 group presentations, 5 min each, discussion and ranking	Different Group members
16.00-17.00	Topic 2 group presentations, 5 min each, discussion and ranking	
17.00-17.05	Closure for the day	Thomas Unger
17.05-…	Mixer with drinks and *bitterballen*	

Programme day 2: 9th January

Time	Activity	Chair(s)
9.30-10.00	Arrival with coffee and cake & fruits	
10.00-10.15	Short feedback on day 1, possible adaptations	Different Group members
10.15-11.15	Group A Topic 3	Stephane Heymans
	Group B Topic 3	Leon de Windt
	Group C Topic 4	Harald Schmidt
	Group D Topic 4	Tilman Hackeng
11.15-11.30	Short coffee/tea break	
11.30-12.30	Topic 3 group presentations, 5 min each, discussion and ranking (Take coffee/tea inside plenary room)	Different Group members
12.30-13.30	Lunch	
13.30-14.30	Group A Topic 4	Stephane Heymans
	Group B Topic 4	Leon de Windt
	Group C Topic 3	Harald Schmidt
	Group D Topic 3	Tilman Hackeng
14.30-15.30	Topic 4 group presentations, 5 min each, discussion and ranking	Different Group members
15.30-16.00	Coffee/Tea break	
16.00-17.00	Final review of the proposals	All
17.00-17.15	Evaluation and farewell	Thomas Unger

Original comments:
For your convenience, on the following pages, please find the original answers grouped into possible subtopics ranked according to frequency and negativity. First those areas that were felt to 'work', then those which 'need work', and then areas which 'could wait.' Of course this is just a suggestion to trigger your thought process to find solutions. Feel free to introduce any other sub- grouping or ranking.