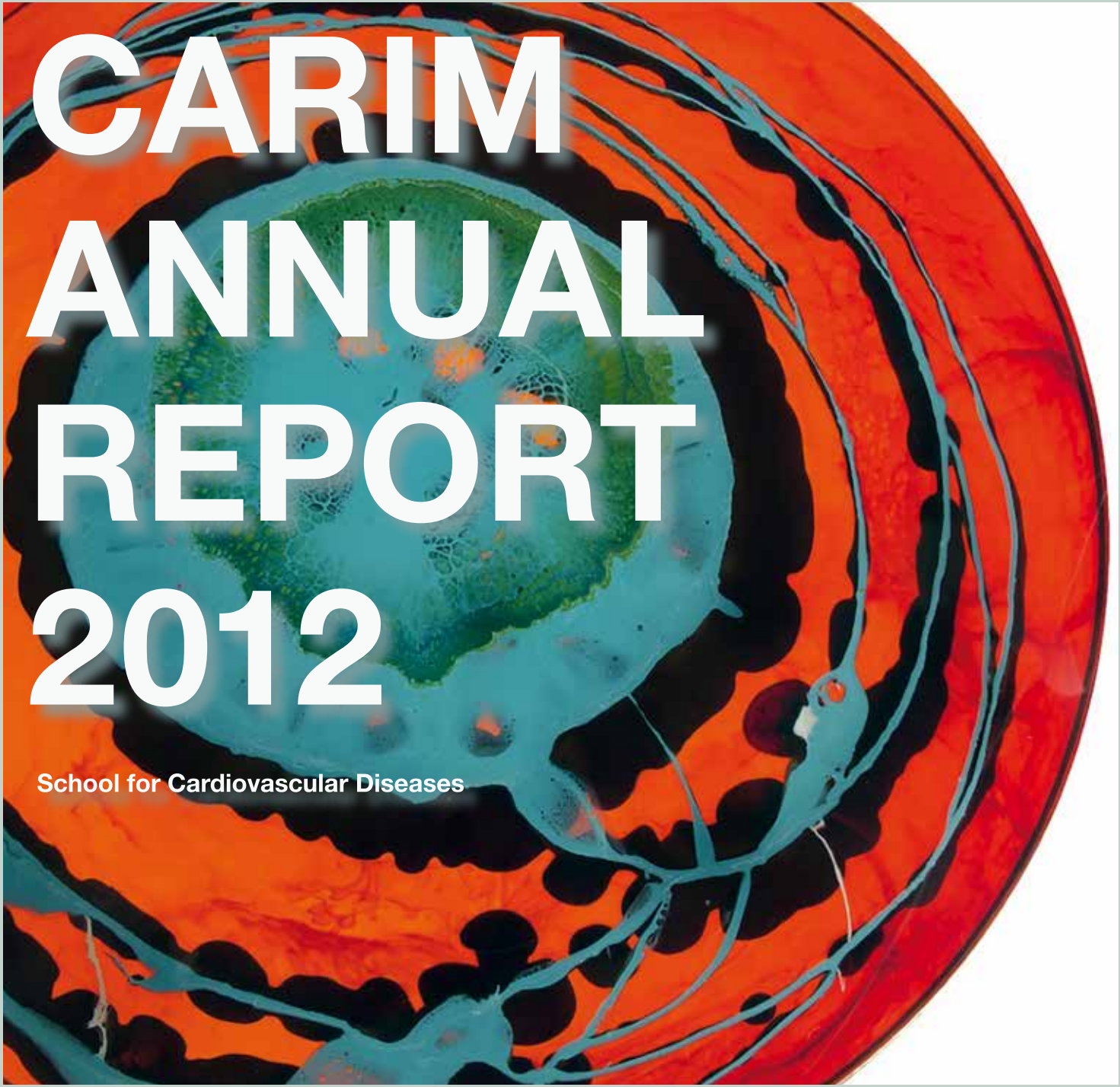

CARIM ANNUAL REPORT 2012

School for Cardiovascular Diseases

COVER
Painted Petri Dish by Klari Reis, 6 inch diameter.
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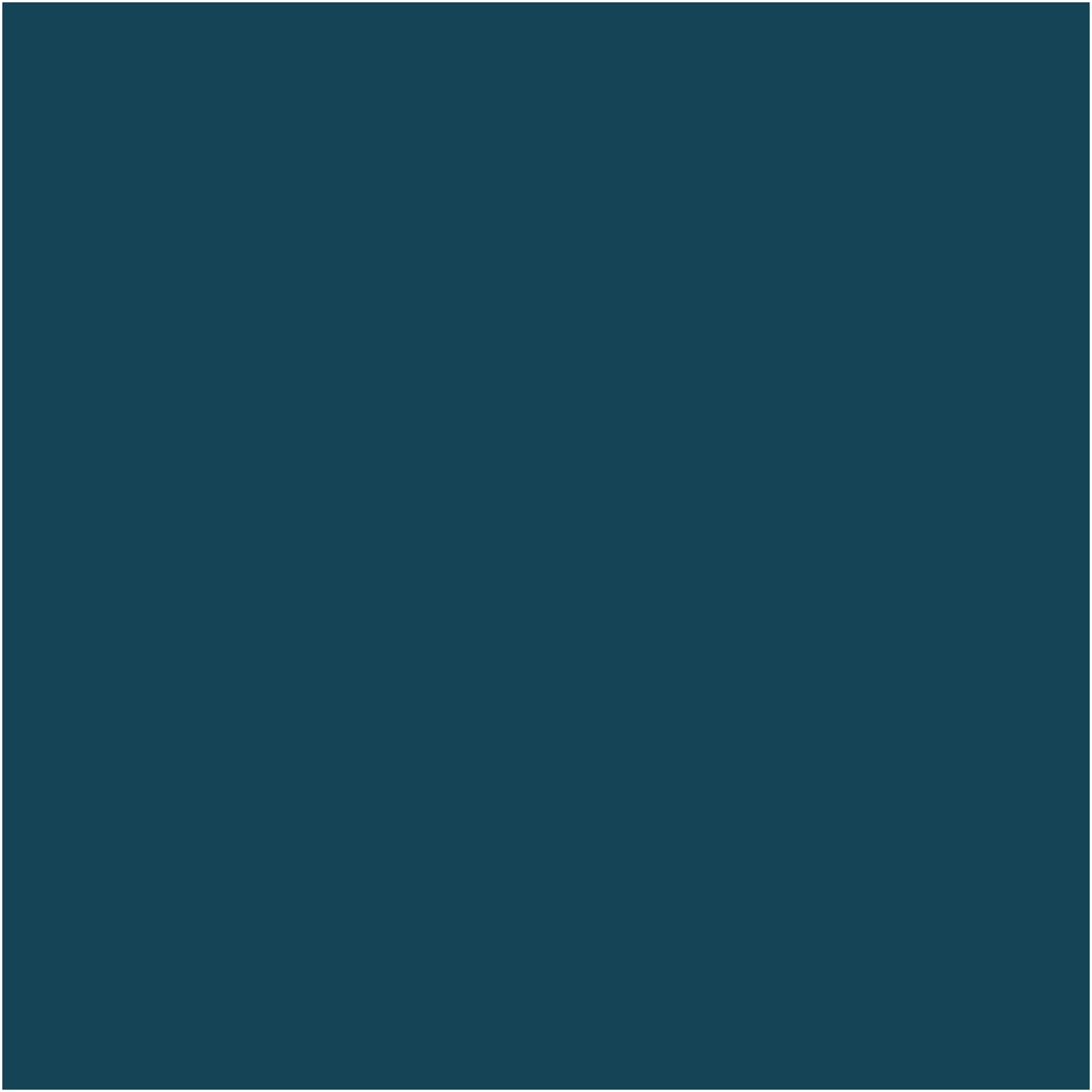
CARIM ANNUAL REPORT 2012

School for Cardiovascular Diseases



CONTENTS

PREFACE

Two thousand-and-twelve, this was the year when I came to Maastricht as the sixth Scientific Director of venerable CARIM which was founded in 1988. Trained in Germany, England and Canada, I was acquainted with various types of medical faculties but I had never been exposed to a system of "schools", i.e. scientific-administrative-educative units somewhere between the Dean of the faculty and the individual departments.

What is the task of such a school director? Well, first of all, he or she has to talk a lot. *Afspraken* and *overleggen*, *vergaderingen* and *besprekingen* are the daily bread and, different from the Anglo-American and German systems, these are usually not the end of a discussion crowned with a more or less unanimous decision but just the beginning of yet another round of reunions and talks. This can be tiring but, on the other hand, such a *poldering* system, as they call it in the Netherlands, has the advantage of broad participation of the involved in decision-making at usually flat hierarchies.

However, talking is not the only task of the director. Sometimes, he also has to think. That is, to ponder about the value of past achievements, present developments and, most importantly, about the future of the institution. Strategic thinking and decision making under the given circumstances are required following a thorough analysis of the present assets and shortcomings.

Thus, I started my new job with a visit to all the principle investigators, and after several of these visits, I became more and more enthusiastic about CARIM. Indeed, this school offers high quality on the main themes that form the core of cardiovascular research: the blood and its constituents, the blood vessels, and the heart. And, besides all efforts to defend a position in the rank and files of the global champions' league of research, CARIM also offers a large number of Master- and PhD students a unique opportunity to learn how biomedical science works, how to gain the first scientific merits and how to survive the inevitable frustrations.

Unique about CARIM is also the intimate relationship between basic and clinical research under one roof. Different from many other institutions around the world, there is practically no separation between the two within the school, so that translational research is not just a buzz-word but reality on a daily base. For instance, when the departments of Cardiology and Physiology both belong to the same school and reside in one building, basic-clinical co-operations on, let's say, atrial or ventriculat arrhythmias can be installed and maintained much more easily than if both departments belong to different academic units and reside several kilometers apart from each other. And when then the department of Biomedical Engineering joins the club, there is a solid basis for future-directed scientific achievements that may directly benefit the patient with cardiac arrhythmiya in a true translational way.

Since 2012, the CVC (Cardiovascular Centre) of the Maastricht University Medical Centre (MUMC) is gradually taking shape, i.e. a close, institutionalized collaboration between the "Heart and Vessel Centre" (HVC) as the clinical- and CARIM as the basic/clinical science partner. This is not an easy task since both sides are sometimes quite different in their visions and aspirations, but the energy by which this process of unification is performed deserves great respect.

Strategic thinking includes not only new ideas and "visions" but also a feeling for the realization of these under the current conditions and a consideration of the strengths and weaknesses of the players involved. It also requires a long breath and the ability to accept certain shortcomings of an institution and its members which cannot be amended on a short-term basis.

However, having said this, CARIM, as I found it, is a sound institution, a unique school with a great potential and, after certain corrections and strategic amendments that are now taking place, CARIM will certainly be able to defend its leading position in the cardiovascular field of research and in academic education.

Professor Thomas Unger
Scientific Director CARIM
School for Cardiovascular Diseases

01_
PROFILE

PROFILE

Founded in 1988, the Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, has established itself over the last two decades as a leading research institute in the field of cardiovascular disease. 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.

CARIM is built around three broader research themes, each led by a program leader: Thrombosis and Haemostasis, Cardiac Function and Failure, and Vascular Biology. These three themes comprise 26 basic and clinical programs. Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, high ambitions, good facilities and a critical learning. CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Centre+ (Maastricht UMC+). CARIM is recognised by the KNAW as a research school and as an international training site for Early Stage Researchers in the framework of the Marie Curie Program.

KEY FIGURES 2012

Annual budget: 25.138 K€
New contracts and grants: 12.248 K€
Researchers: 197 fte
Technical and supporting staff: 74 fte
Departments/disciplines: 13
Scientific articles: 635 (Wi-1: 556)
PhD theses: 50
Patents: 5

CARIM plays an important role in public-private research partnerships as main author and project manager of 6 out of 7 cardiovascular projects of the Centre for Translational Molecular Medicine (CTMM) in the Netherlands, CTMM is a public-private consortium that comprises universities, academic medical centres, medical technology enterprises and chemical and pharmaceutical companies. Other public-private research partnerships in which our researchers participate are: the BioMedical Material program (BMM) and Top Institute Pharma. In addition, CARIM is a member of several international networks, including the EU seventh Framework Program (FP7) and the Leducq Transatlantic Network.

‘It’s all about getting every detail right, that’s the CARIM culture’

Joost Lumens (Sittard, 1982), Researcher and Medical Engineer, Department of Biomedical Engineering

What are you researching?
“I’ve been given a junior post-doc grant by the Netherlands Heart Foundation to work on a computer model that can help doctors predict whether a patient with heart failure will benefit from pacemaker therapy. I try to reach a higher level of diagnostic integration by combining various routine measurements, like deformation patterns of the cardiac walls, in the CircAdapt model of the cardiovascular system. The idea is to obtain ‘hidden’ diagnostic information that better reflects the quality of the patient’s cardiac muscle than current measures. The effect of pacemaker therapy can then be tested in advance ‘in virtual reality’ so that the doctor can predict whether the therapy will have the intended effect. The model describes the physical and physiological principles underlying the way our heart and blood vessels work. Theo Arts, who was one of my PhD supervisors in 2010, developed the model, and my PhD project involved refining part of the model so that it could be applied to pulmonary hypertension and conduction disorders.”

What was a major event for you in 2012?
“Getting the junior post-doc grant, plus the publication of two important papers that laid the foundations for my current research. Frits Prinzen, one of my mentors, introduced me to two cardiologists from Utrecht at a party. They had a patient database on the movement patterns of the septum, the wall that separates the left and right parts of the heart, and they also had a number of questions that my model was later able to answer. A good combination, as Prinzen had already suspected.”

What does CARIM mean to you?
"In the clinic, engineers are often regarded as people who talk about very difficult things and who use many equations in their presentations, so doctors tend to quickly give up trying to follow them. We're the only engineering department in CARIM, so we're used to explaining things in clear and simple language to researchers from various disciplines. My other PhD supervisor, Tammo Delhaas, has shown me how to negotiate the interface between the clinic and fundamental research. That's helping me a lot, wherever I am. To me, that's CARIM.

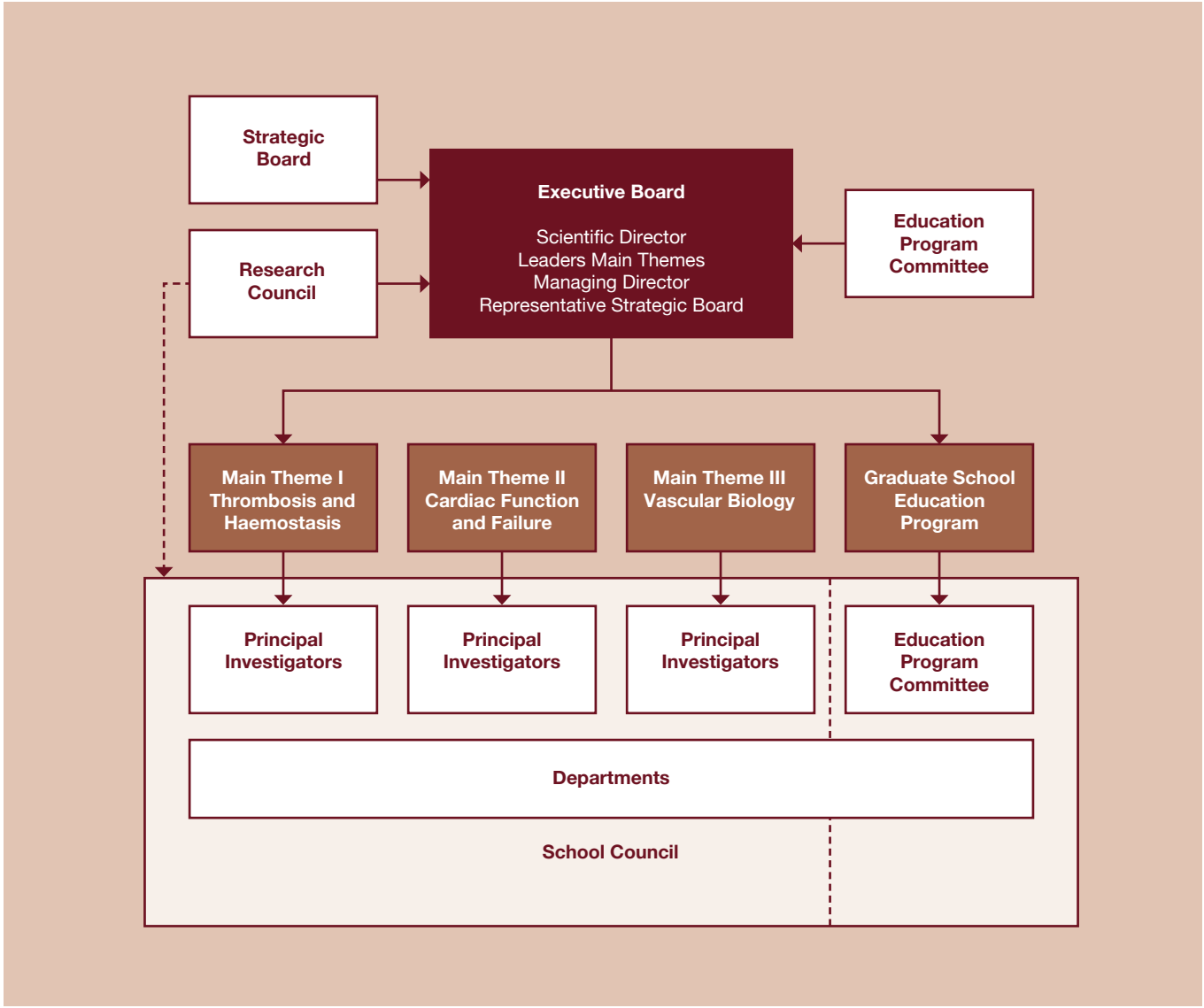
The level of the scientific debate here is very high. People are not easily satisfied, which means our research produces enduring results; we always try to identify the underlying mechanism. Significant results as such are not enough reason for us to publish a paper. This approach means that we can't write a lot of papers; you have to be thorough, and that's the main thing for me. My post-doc from Oxford deliberately opted for CARIM because of this high level of debate. I think this debating mentality is Rob Reneman's achievement: it's a matter of being precise. I find I'm also transferring this mentality to my own students. Sometimes we may talk for two days about something that will never be seen by reviewers. But it's all about getting every detail right; that's the CARIM culture."

What are you proud of?
"I'm really glad that we've been able to shape our model in such a way that it can be used by lay people and by teaching staff at university. Before, students had to learn about cardiovascular physiology and pathophysiology from textbooks; now they can get the necessary knowledge in a more interactive way by simulating their own 'virtual' patient; that's a good example of 'translation', putting research into practice."

How do you maintain a balance between work and private life?
"I'm at a difficult stage in my career, as I now have to switch from puzzling over our model and adjusting it all the time, which made me fall in love with research in the first place, to delegating tasks and supervising people. I have to admit that after a day at work, I often sit down at the computer to tinker with the code for a while. To be honest, I hope it will stay that way. To me, work is relaxing, however strange that may sound. Even during our honeymoon last year, I couldn't resist the temptation to test some new ideas with the help of simulations."

02_ ORGANISATION

ORGANISATION



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- Professor Tilman Hackeng, Leader Main Theme I
- Professor Harry Crijns, Leader Main Theme II
- Professor Coen Stehouwer, Leader Main Theme III
- Professor Mark Post, Leader Main Theme III (Scientific Director a.i. until April 2012)
- Professor Leon de Windt, representative Strategic Board
- Rob van der Zander, Managing Director
- Petra Uittenbogaard, advisor and project manager

Strategic Board

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- Professor Uli Schotten
- Professor Thomas Unger
- Professor Tilman Hackeng
- Professor Hugo ten Cate
- Professor Harald Schmidt
- Professor Leon de Windt

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- Dr Matthijs Blankesteijn, Dept. of Pharmacology
- Professor Hans Peter Brunner-La Rocca, Dept. of Cardiology
- Professor Harry Crijns, Dept. of Cardiology
- Professor Hugo ten Cate, Dept. of Biochemistry
- Professor Tammo Delhaas, Dept. of Biochemistry
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- Professor Tilman Hackeng, Dept. of Biochemistry
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- Professor Leon de Windt, Dept. of Cardiology

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- Dr Adriaan Duijvestijn, coordinator Research Master
- Dr Matthijs Blankesteijn, staff member
- Dr Vanessa van Empel, MD (until May 2012)
- Dr Eline Kooi, staff member
- Professor Hans Vink, staff member
- Yvonne Oligschläger, PhD student (from February 2012)
- Timo Rademakers, PhD student (until May 2012)
- Michael Rutjens, Master student (until September 2012)
- Siamack Sabrkhany, PhD student (from February 2012)
- Emiel van der Vorst, PhD student

CARIM Office

The CARIM office consists of Riet Daamen, Saskia Vocks (until October 2012), Tara de Koster (from October 2012) and Esther Willigers. The controllers are Martin Tossings (until July 2012) and Sietske Satijn (from December 2012).

HR-support

Patrick Janssen and Yves Engelen of the Human Resources Department of Maastricht University are related to CARIM.

Administrative support

The Finance Department of Maastricht University provides support on accounting the CARIM research projects on a part-time basis. At this moment the Finance employees are Henny Kerckhoffs, Esther van Heel, Joost von Weersch and Jan-Willem Janssen.

Participating departments and disciplines

The research in the three main themes involves the research activities of people working in several basic and clinical departments/disciplines of Maastricht Medical Centre+.

Basic Research Departments
Biochemistry
Biomedical Engineering
Genetics and Cell Biology
Pharmacology
Physiology

Clinical Departments
Cardiology
Cardio-thoracic Surgery
Clinical Chemistry
Internal Medicine
Neurology
Pathology
Radiology
Surgery

Executive Board CARIM
Tilman Hackeng, Rob van der Zander, Harry Crijns, Tara de Koster, Coen Stehouwer, Leon de Windt, Thomas Unger

Vascular calcification: from innocent bystander to culprit risk factor

Leon J Schurgers, Department of Biochemistry

Some 15 years ago, vascular calcification was regarded as an innocent bystander in cardiovascular disease. It was considered to be the passive chemical nucleation of calcium and phosphate ions on cellular debris and therefore the end-stage of atherosclerosis. Currently, vascular calcification is understood to be an actively regulated process involving cellular and humoral contributions that may offer targets for diagnosis and intervention. The discovery that vitamin K-dependent processes are involved in the inhibition of vascular calcification has boosted our mechanistic understanding of this process and has opened up novel avenues.

When starting my research on vascular calcification at the end of the last century, I went to the Department of Pathology to obtain human vessel specimens. The former head of Pathology and director of CARIM assured me that calcification was nothing special: “It is always present, especially in advanced atherosclerotic lesions.” The development of highly accurate CT imaging devices has shown that he could not have been more correct: today, vascular calcification is used as a measure of cardiovascular burden.[1] Vascular calcification can occur at distinct sites in the vasculature: the tunica media and tunica intima (Figure 1). Medial calcification is independent of lipid infiltration and inflammation, and starts with calcium crystal deposits at the site of the elastic lamellae. It commonly occurs in peripheral arteries of the lower limbs, where it is seen as “rail tracking” on plain radiographs. Medial calcification progresses with age and eventually leads to increased vessel stiffening and vessel rupture.[2]

▸▸

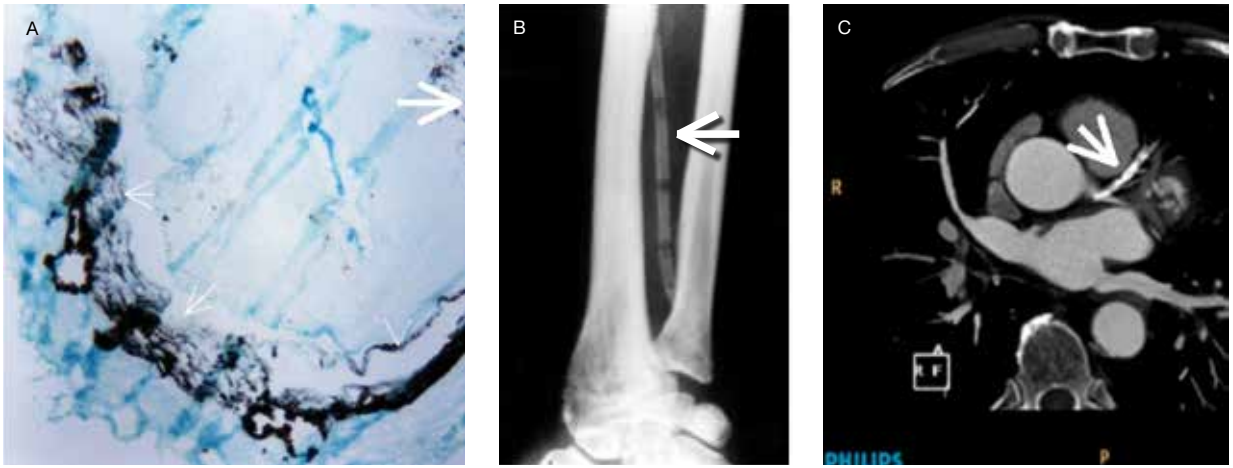

FIGURE 1

A: Histochemical von Kossa staining of a coronary specimen depicting calcification in black in both medial (arrow head) and intimal areas (arrow).
B: Medial calcification seen as “rail tracking” on plain X-ray.
C: Coronary computed tomographic angiography (CCTA) using a 64-slice multi detector scanner. Calcium scoring software (Philips Healthcare, Best, The Netherlands) with a threshold of 130 Hounsfield units (HU) was used to detect coronary calcification. Arrow depicts severe coronary calcification.

In atherosclerotic disease research, calcification was added to the growing list of biological events that play a role in driving vascular disease,[3] and is commonly used as a measure of atherosclerotic burden.[4] Vascular calcification is clearly associated with poor cardiovascular outcome, and may result in stiffened vessels and unstable lesions that can rupture and cause acute ischaemic events such as acute myocardial infarction and stroke.[5] What was not know at the time is that under certain conditions, the current thrombosis treatment using vitamin-K antagonists (VKAs) could paradoxically lead to a high risk of calcification, and this has become the focus of my research.

The human vasculature comprises several cell types, with a central role for vascular smooth muscle cells (VSMCs). VSMCs in the tunica media regulate vessel tone and diameter in order to maintain haemodynamic balance. Phenotypic flexibility of VSMCs is necessary to cope with the varying conditions of vascular tissue.[6] However, phenotypic switching of VSMCs plays a key role in vascular disease and is a precondition for vascular calcification. Vitamin K-dependent proteins such as the matrix Gla protein (MGP) produced by VSMCs are key factors in the inhibition of vascular calcification.[7]

VKAs are the most widely used anti-thrombotic drugs, with substantial efficacy in reducing the risk of arterial and venous thrombosis. We found that the inhibition was not restricted to vitamin-K dependent coagulation factors but also affected the synthesis of functional extra-hepatic vitamin-K dependent proteins (VKDPs), thereby eliciting adverse side effects (Figure 2).[8-10] Alterations in the activity of vitamin-K dependent proteins affect the progression of vascular remodelling, including the induction of calcification. It all started with a joint study by the universities of Maastricht and Tübingen, which showed that patients on VKA had significantly more vascular calcification than matched patients not on VKA. This was the starting point for a new research line that added to the coagulation-based research performed at our Department of Biochemistry. Joint research projects involving the Biochemistry Department and the Departments of Internal Medicine[11] and Cardiology,[12] and with other institutes such as

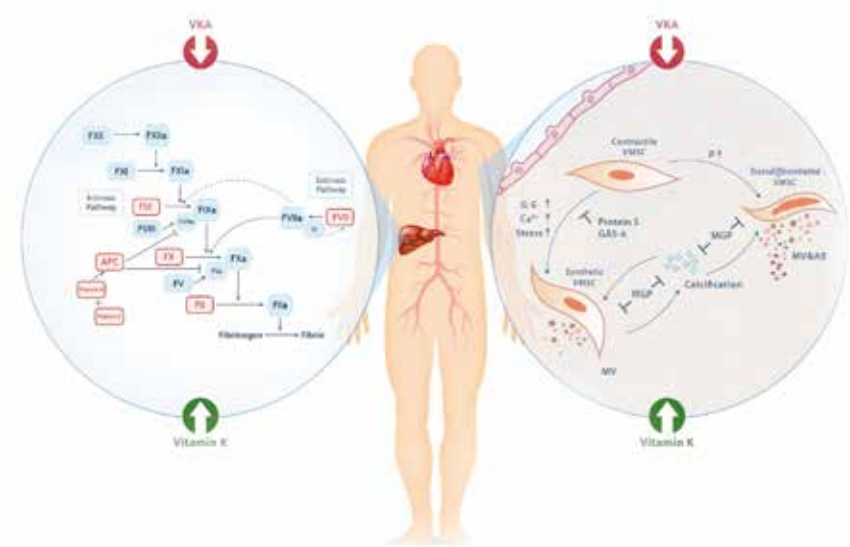

FIGURE 2

The interplay of systemically and locally expressed vitamin K-dependent proteins. Although discovered in relation to blood coagulation, most VKDP play a function in many other physiological processes, including vascular biology. In the liver, vitamin K assures the activation of vitamin K-dependent zymogens (factors depicted in red) involved in the coagulation cascade. These zymogenes circulate and are used when needed. VKDP are also involved in vascular biology. VSMCs are normally in the contractile phenotype, but become synthetic when being stressed. This phenotypic switch is influenced by protein S and Gas-6. Calcification of extracellular matrix is inhibited by MGP, thereby also inhibiting the transdifferentiation towards osteochondrogenic VSMCs. VKA does thus influence both systemic and local vitamin K-dependent processes.

Harvard,[13] further showed the detrimental effect of VKAs on the vasculature (Figure 3). A major part of our research is now devoted to investigating effects of VKA versus non-vitamin K antagonist oral anticoagulants (NOACs) on coagulation and vascular calcification.

Using experimental animal models, we have demonstrated that high supplemental vitamin-K intake halted progression of VKA-induced vascular calcification.[14,15] Our fundamental research has led to translational research: pilot studies demonstrated that vitamin-K deficiency in patients can be reversed by high supplemental vitamin-K intake, thereby improving vitamin-K dependent protein carboxylation.[16] Reducing vascular calcification is of great importance especially for people prone to develop vascular calcification,

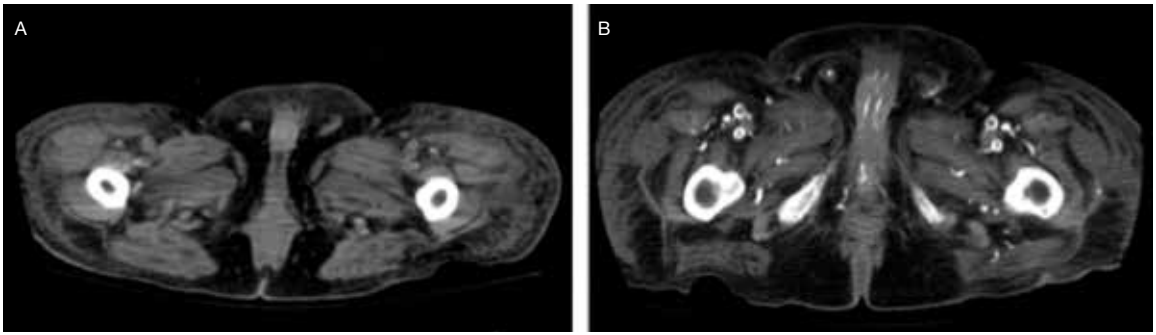

FIGURE 3

A 50-year-old patient developed kidney failure, requiring the initiation of hemodialysis therapy. In addition, he developed atrial fibrillation, and VKA therapy was initiated for systemic anticoagulation. Axial and coronal sections from computed tomographic scans of the abdomen and pelvis. Figure 3A shows minimal vessel calcification in the pelvis and abdomen. Nine month later, figure 3B shows extensive and widespread calcification involving the splenic artery, iliac and femoral vessels, and smaller vessels supplying the penis and superficial structures in the lower extremities.

such as the aging population and diabetes and chronic kidney disease patients. The work initiated at CARIM has resulted in joint research to evaluate the effects of supplemental vitamin K on vascular calcification progression in patients.[17]

Finally, an innovative Biohybrid platform, based on VSMCs used as a high-content-analysis (HCA) platform, is currently being developed at the Department of Biochemistry. This HCA platform aims to predict the efficacy of drug (i.e. VKA) and diet (i.e. vitamin K) interventions in patients and will constitute a fast surrogate readout for in-vitro pre-selection of candidate drugs or nutraceuticals for CVD.

References

1. Alexopoulos N, Raggi P. Calcification in atherosclerosis. Nature Reviews Cardiology. 2009;6:681–688.
2. Lehto S, Niskanen L, Suhonen M, Ronnemaa T, Laakso M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. Arterioscler Thromb Vasc Biol. 1996;16:978–983.
3. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114:1852–1866.
4. Nicholls SJ, Tuzcu EM, Wolski K, Sipahi I, Schoenhagen P, Crowe T, Kapadia SR, Hazen SL, Nissen SE. Coronary artery calcification and changes in atheroma burden in response to established medical therapies. J Am Coll Cardiol. 2007;49:263–270.
5. Patel J, Blaha MJ, McEvoy JW, Qadir S, Tota-Maharaj R, Shaw LJ, Rumberger JA, Callister TQ, Berman DS, Min JK, Raggi P, Agatston AA, Blumenthal RS, Budoff MJ, Nasir K. All-cause mortality in asymptomatic persons with extensive Agatston scores above 1000. J Cardiovasc Comput Tomogr. 2014;8:26–32.
6. Alexander MR, Owens GK. Epigenetic control of smooth muscle cell differentiation and phenotypic switching in vascular development and disease. Annu Rev Physiol. 2012;74:13–40.
7. Luo G, Ducy P, McKee M, Pinero G, Loyer E, Behringer R, Karsenty G. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997;385:78–81.
8. Chatrou MLL, Winckers K, Hackeng TM, Reutelingsperger CP, Schurgers LJ. Vascular calcification: The price to pay for anticoagulation therapy with vitamin K-antagonists. Blood Rev. 2012;
9. Willems BAG, Vermeer C, Reutelingsperger CPM, Schurgers LJ. The realm of vitamin K dependent proteins: Shifting from coagulation toward calcification. Mol Nutr Food Res. 2014;58:1620–1635.
10. Schurgers LJ, Joosen IA, Laufer EM, Chatrou MLL, Herfs M, Winkens MHM, Westenfeld R, Veulemans V, Krueger T, Shanahan CM, Jahnen-Dechent W, Biessen E, Narula J, Vermeer C, Hofstra L, Reutelingsperger CP. Vitamin k-antagonists accelerate atherosclerotic calcification and induce a vulnerable plaque phenotype. PLoS ONE. 2012;7:e43229.
11. Rennenberg RJMW, van Varik BJ, Schurgers LJ, Hamulyák K, Cate Ten H, Leiner T, Vermeer C, de Leeuw PW, Kroon AA. Chronic coumarin treatment is associated with increased extracoronary arterial calcification in humans. Blood. 2010;115:5121–5123.
12. Weijs B, Blaauw Y, Rennenberg RJMW, Schurgers LJ, Timmermans CCMM, Pison L, Nieuwlaat R, Hofstra L, Kroon AA, Wildberger J, Crijns HJGM. Patients using vitamin K antagonists show increased levels of coronary calcification: an observational study in low-risk atrial fibrillation patients. Eur Heart J. 2011;32:2555–2562.
13. Hristova M, van Beek C, Schurgers LJ, Lanske B, Danziger J. Rapidly progressive severe vascular calcification sparing the kidney allograft following warfarin initiation. Am J Kidney Dis. 2010;56:1158–1162.
14. Schurgers LJ, Spronk HM, Soute BA, Schiffers P, DeMey JGR, Vermeer C. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood [Internet]. 2007;109:2823–2831. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17158229&retmode=ref&cmd=prlinks
15. Krüger T, Oelenberg S, Kaesler N, Schurgers LJ, van de Sandt AM, Boor P, Schlieper G, Brandenburg VM, Fekete BC, Veulemans V, Ketteler M, Vermeer C, Jahnen-Dechent W, Floege J, Westenfeld R. Warfarin induces cardiovascular damage in mice. Arterioscler Thromb Vasc Biol. 2013;33:2618–2624.
16. Westenfeld R, Krueger T, Schlieper G, Cranenburg ECM, Magdeleyns EJ, Heidenreich S, Holzmann S, Vermeer C, Jahnen-Dechent W, Ketteler M, Floege J, Schurgers LJ. Effect of vitamin k(2) supplementation on functional vitamin k deficiency in hemodialysis patients: a randomized trial. Am J Kidney Dis. 2012;59:186–195.
17. Krueger T, Schlieper G, Schurgers L, Cornelis T, Cozzolino M, Jacobi J, Jadoul M, Ketteler M, Rump LC, Stenvinkel P, Westenfeld R, Wiecek A, Reinartz S, Hilgers R-D, Floege J. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. Nephrol Dial Transplant. 2013;

‘I’m in a flow here in Maastricht’

Judith Cosemans (Born, 1980), Assistant Professor, Department of Biochemistry

What are you researching?
“I’m studying the role of platelets in vascular remodeling. At present, vessel wall repair after a cardiac or cerebral infarction is less than optimal; which increases the risk of another infarction or atherosclerosis. I suspect that platelets are involved in this. So far I’ve been examining proteins of the matrix metalloproteinase family, but since I’ve now made the most of this class of proteins I’m going to switch to other candidate proteins in platelets, which I want to identify using a proteomics approach.”

What are you proud of?
“Of the flow chamber technique I’ve optimized, which reduces the use of test animals. It enables us to measure thrombotic tendencies in small volumes of blood, rather than inducing thrombosis in mice. It won me the Edmond Hunstinx prize. Eventually, we hope to develop this technique into a finger prick test with which you can estimate people’s risk of thrombosis or bleeding. I love solving puzzles, but I also like it when the results are relevant to patients. In the future, I’d like to make my research even more applied.”
When did you realize you wanted to go into research?
“I originally wanted to study medicine, but I failed to get a place in medical school due to the lottery system. Like so many people in my position I took up health science instead. During the graduation projects at the lab I got fascinated about research. If the programme for the degree of physician/clinical researcher had been available at the time, I would have loved to do that, as that gives you more insights into clinical issues. I now acquire those insights by contacting people at the hospital or elsewhere, but it continues to be a challenge to find the right people.”

What does CARIM mean to you?
"At first CARIM was an institute that was functioning in the background for me, but in the last few years I'm finding that the communication lines are becoming much shorter. Currently I'm on a steering committee to promote the centralization of research with Muroidea, which was initiated by CARIM. That's interesting and also beneficial for my network as I'm collaborating with researchers who are at the same stage in their careers. CARIM has also nominated me for a top-talent class offered by the Faculty, which is a programme to prepare you for a full professorship. Finally it's great that the Research Council gives me feedback on my research grant proposals. I'm currently in the process of applying for a senior post-doc Dekker grant. I'm very confident about the future. I don't expect every grant I apply for to be awarded, although when I apply for four of them, I trust I will get at least one."

How do you maintain a balance between work and private life?
"I maintain the balance by spending time outdoors; walking, cycling, gardening. I'm an outdoor kind of person. I've also found yoga exercises help me to unwind when dealing with tight deadlines. I enjoy lots of things, and I'd love to do them all. I'm now trying to develop a long-term vision: where do you want to be in five years' time? And how can you get there?"

Why Maastricht?
"I've had a great career here so far, and there are lots of options left. I did think about moving elsewhere at one stage, but I'm in a state of 'flow' here, so why should I? What I'm going to do is intensify my collaboration with Aachen. So far my trips abroad have been for a couple of weeks or months each and always related to experiments that generated a lot of publications. I always select those 'trips' for the research opportunities and for strategic reasons. In the end you have to do what is right for you; follow your own path and not be dictated by what other people think you should do. You have to try and satisfy your own needs and preferably also those of as many people around you as possible."

03_
FACTS AND FIGURES

Funding and expenditure at institutional level 2007-2012

	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

CARIM receives its basic funding from Maastricht University, through the Faculty of Health, Medicine and Life Sciences and the University Hospital Maastricht (azM). This basic funding is primarily intended to finance CARIM's tenured staff, post docs, PhD students, technicians, research infrastructure and PhD teaching program.
In addition to the funding by university and hospital, a significant part of our research program is supported by non-profit organisations and industry.

Research output in 2007-2012

	2007	2008	2009	2010	2011	2012
School level						
Scientific publications	498	466	514	544	571	635
Other publications	46	53	45	37	53	80
PhD theses	37	30	32	35	39	50
Total* (I)	**581**	**549**	**591**	**616**	**666**	**765**
Academic staff** (II)	**35,9**	**37,4**	**37,0**	**38,3**	**34,3**	**33,1**
Ratio I and II	**16,2**	**14,7**	**16,0**	**16,1**	**19,4**	**23,1**
Theme I						
Scientific publications	80	77	89	95	107	108
Other publications	7	6	9	6	12	12
PhD theses	9	9	9	5	8	8
Total	**96**	**92**	**107**	**106**	**127**	**128**
Theme II						
Scientific publications	147	141	153	190	214	246
Other publications	14	10	11	6	13	25
PhD theses	10	11	8	9	14	20
Total	**171**	**162**	**172**	**205**	**241**	**291**
Theme III						
Scientific publications	274	275	321	312	309	353
Other publications	25	35	26	25	28	45
PhD theses	18	15	15	21	17	22
Total	**317**	**325**	**362**	**358**	**354**	**420**

* Please note that the sum of the 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

PhD theses: including PhD theses externally prepared

Scientific publications: Wi-1 publications in refereed SCI-SSCI indexed journal, excluding abstracts, Wi-2 publications in refereed non SCI-SSCI indexed journals, and Letters to the Editor

Other publications: Wn (publications in national journals), Wb (book, or contribution to book, conference papers/proceedings), Vp (professional publications in national or international periodical)

New contracts and grants concluded in 2012

Funding	Theme I	Theme II	Theme III	Total Support K€
Type 2	978	1.570	300	2.848
Type 3	425	3.618	1.229	5.272
Type 4	1.090	874	1.414	3.378
Type 5	250	250	250	750
Total	**2.743**	**6.312**	**3.193**	**12.248**

Type 2 = Grants received in competition from national and international science foundations (NWO/ZonMw, STW, KNAW)

Type 3 = Grants received from third parties for specific research activities and from charities (NHS, EU Framework, CTMM, BMM, etc.)

Type 4 = Industry, excl. CTCM (turn over in 2012: 1.1601 K€)

Type 5 = Annual support (750 K€) Cardiovascular Center-CARIM “Pieken vanuit de Breedte”

Summary of scientific and technical staff CARIM 2012 (in fte)

Research Area	WP1			WP2			WP3			WP4			azM	TOTAL
	Faculty	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	PhD-stud	Post-doc	WP	fte
Thrombosis and haemostasis	7,5	6,1	1,1	0,3	-	-	-	16,1	7,1	1,7	3,4	4,5	0,6	48,3
Cardiac function and failure	12,4	10,0	2,5	1,0	5,5	2,1	1,0	17,5	11,0	-	1,0	1,7	1,1	66,7
Vascular biology	13,2	9,2	3,7	0,6	0,7	2,3	1,9	28,6	16,4	-	0,4	-	4,5	81,5
Total	**33,1**	**25,3**	**7,3**	**1,8**	**6,1**	**4,4**	**2,9**	**62,1**	**34,5**	**1,7**	**4,8**	**6,2**	**6,2**	**196,5**

	OBP 1	OBP 2	OBP 3	OBP 4	OBP azM	TOTAL
Thrombosis and haemostasis	5,5	-	4,5	2,4	1,3	13,7
Cardiac function and failure	16,1	1,0	6,0	-	0,3	23,4
Vacular biology	15,8	-	20,5	0,6	2,7	39,6
Total	**37,4**	**1,0**	**31,0**	**3,0**	**4,3**	**73,7**

WP: scientific staff
OBP: technical staff
1: University
2: NWO/KNAW
3: non-profit organisations
4: industry
azM: University Hospital Maastricht

Project: Hybrid Ablation of Atrial Fibrillation

Laurent Pison, Department of Cardiology

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an incidence that remains relatively low until around the seventh decade and from then on increases exponentially.[1] AF has been shown to be an independent predictor of cardiovascular and all-cause mortality.[2-6] It is a strong independent risk factor for stroke, and uncontrolled AF may contribute to the development of chronic heart failure.[2, 7, 8] As such, AF represents an increasing public health challenge.

The two goals of AF management are to reduce symptoms and to prevent complications associated with this arrhythmia. The latter relies on antithrombotic therapy, control of ventricular rate, and treating concomitant cardiac diseases. These therapeutic interventions may also suffice to achieve the former goal, but a substantial number of patients will need additional rhythm control therapy to relieve symptoms. This can be achieved by ablation therapy.

Although endocardial AF ablation techniques enable one to characterize the underlying substrate in order to tailor the ablation procedure, these ablation lesions are not always transmural nor long-lasting. Surgical AF ablation techniques, on the other hand, create reliable linear lesions, but the lesion set is based on empirical assumptions rather than specific patient characteristics. However, these two techniques seem to be complementary as, performed in combination (hence the name “hybrid” or “convergent” procedure), they offer the potential to overcome their respective shortcomings (Figure 1). Another important advantage of the hybrid

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FIGURE 1

In a specially designed hybrid operating room, cardiac surgeons and electrophysiologists are working side by side.

approach is the possibility to perform endocardial touch-up in case of an epicardial lesion that is not completely transmural.

We published our initial experience with hybrid AF ablation in a cohort of 26 consecutive patients in 2012.[9] The first steps of this procedure consisted of thoracoscopic isolation of the pulmonary veins (PV) as ipsilateral pairs using a bipolar radiofrequency (RF) clamp. If AF did not terminate or was still inducible, a roof line and an inferior line were created with a bipolar RF linear pen device. Making these linear lesions led to the posterior left atrium being isolated, which is also known as a box lesion (Figure 2). If bidirectional block was not reached within this box lesion, the conduction gaps were identified and ablated endocardially with a cooled tip RF catheter. The one-year success rate (i.e. no episode of atrial arrhythmia lasting more than 30 seconds off antiarrhythmic drugs after the 3-month blanking period) was 93% for patients with paroxysmal AF and 90% for patients with persistent AF.

Despite these encouraging results, it is clear that further technical improvements and a better understanding of the underlying arrhythmogenic mechanism are necessary. CARIM is actively engaged in both these areas.

The research on new ablation energy sources is important in the quest for technical improvements. CARIM plays a pivotal role in this field, especially by coordinating the collaboration between the Cardiology and Cardiac Surgery departments. One of the current 'hot topics' in this field is the development of electroporation ablation tools.[10] This energy source is capable of creating completely transmural lesions within a few milliseconds, apparently without thermal collateral damage.

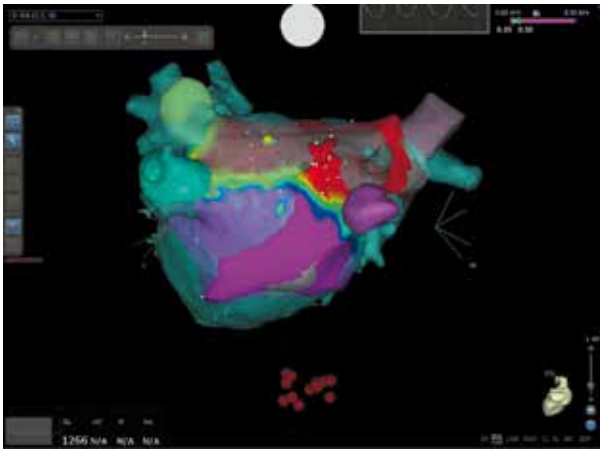

FIGURE 2

Posterior view of the left atrium (electroanatomical map merged with CT). The box lesion is clearly visible (zone in red represents voltages < 0.15mV).

A better understanding of the underlying arrhythmogenic mechanism holds substantial promise for improving the outcomes of hybrid AF ablation. Atrial sites demonstrating high-dominant frequency seem to be interesting ablation sites. In an animal model, these sites correspond to functional reentry and are called rotors.[11] Recently, localized rotors have been visualized in human AF by computational mapping.[12, 13] The PROTON trial (Panoramic Mapping of Atrial Fibrillation) is the result of a partnership between CARIM, the UM Physiology Department and the MUMC+ Cardiology Department. The primary objective of this study is to analyze the spatiotemporal activation pattern of the atria during AF using a 64-pole basket catheter and a new algorithm that has been developed by the UM Physiology Department (Figure 3). The findings of this study may generate new insights into the pathophysiology of AF, and hence hold the potential for taking an important step towards a tailored substrate ablation approach, especially in patients with persistent AF.

Finally, the Complex Arrhythmia Unit (CAU) is a remarkable example of the MUMC+ Cardiology and Cardiac Surgery Departments joining forces with the UM Physiology Department and CARIM. Besides being a platform for cutting-edge basic and clinical research, this unit will deliver state-of-the-art care to patients presenting with challenging ventricular or supraventricular arrhythmias.

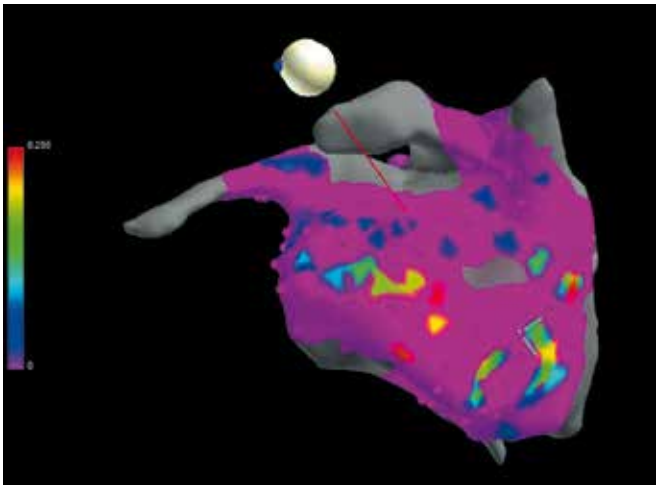

FIGURE 3
Phase singularity density map of the left atrium (left lateral view) displaying rotor occurence.

‘It was a good decision to stay in science’

Paula da Costa Martins (Maputo, 1976), Assistant Professor, Department of Cardiology

What are you researching?
“We focus on the genetic and molecular causes of heart failure, in the hope that we can help develop medication that addresses the disease, and not just relieves the symptoms. We look at molecular aspects that change at the onset or during the development of heart failure. More specifically, I’m looking into microRNAs that directly affect the genes and change the levels of different proteins in the body, leading to the development of the disease. Which microRNAs are changed in cardiac disease, why and how are they changed, and can we change them back to the normal levels? I found that microRNA 199b is very abundant in the heart during heart failure. In 2010 we published a paper in Nature Cell Biology on a medicine we developed that prevented or even cured heart failure in experimental models. We have patented it and are trying to get it further developed.”

Why Maastricht?
“I started to work as a post-doc at the Hubrecht Institute in Utrecht in 2006. In 2010 the group leader, Leon de Windt, got the opportunity to go to Maastricht and I was offered the chance to join the group. It would give me opportunities to move forward in my academic career, but I have a family and we’d just bought a house near Utrecht. It was a difficult choice, but two years ago we all settled in Eijsden.”

What does CARIM mean to you?
“It offers a healthy competitive atmosphere that is somewhat similar to what we had at the Hubrecht, which stimulates you to work hard and achieve something. I also like the interaction between basic science and the clinic, because as a basic researcher you can easily get lost in the ideal situation. CARIM provides a very international environment and is internationally recognized, which opens doors for you.

What are you most proud of?
"That Nature Cell Biology publication in 2010, because it's based on my own ideas and it was a great scientific breakthrough. I started my post-doc working on a different project and after a few months I became interested in microRNAs and their role in cardiac disease. The group was initially a bit sceptical about my ideas, but I was still given the opportunity to explore them. The moment we started to see the potential, we put all our efforts and work into it. The team and I worked really, really hard to get the paper in. It's very rewarding to publish in such a high impact journal and see the scientific community very well receives it. People have more faith in you and see you as an accomplished scientist when it comes to obtaining grants and getting invited to meetings. And you're invited to review grant applications and papers, which I also like to do. You get more involved in the other side of science and in other people's research."

How do you keep a balance between work and private life?
"After the article was accepted I had many mixed feelings and was seriously doubting about whether I wanted to stay in research as an academic. I have a family and I didn't want to put them in second place like that for the rest of my life. When you're so tired, you can't see things clearly anymore. It was Mat Daemen and Leon de Windt who convinced me in the end to give it a try. I was offered a tenure track position, and greater independence. I always had a lot of freedom, but this gave me the opportunity to move forward and develop my own ideas. I think I have now found a way to combine work and family. It was a good decision to stay in science."

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EVENTS AND HIGHLIGHTS

SCIENTIFIC HIGHLIGHTS 2012

In 2012 the hard work of our researchers paid off in **635 scientific publications** in peer refereed journals (556 WI-1 publications, excluding abstracts, and 38 Letters to the editor), **50 PhD theses, 5 patents,** 2.8 million Euros funding received in competition from national and international science foundations and 8.7 million Euros funding from third parties, charities, EU-framework programs, industry, etc. In 2012, the overall average Impact Factor is 5.0.

TOP PUBLICATIONS

with the highest Impact Factor in 2012 (CARIM researcher as first and/or last author)

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: 720-728 IF 14.739

Kappert K, Bohm 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: 934-41 IF 14.739

Lorusso R, Gelsomino S, Luca F, De Cicco G, Bille G, Carella R, Villa E, Troise G, Gagliardotto P, Vigano M, Banfi C, Gazzaruso C, Menicanti L, Formica F, Pastore M, Paolini G, Benussi S, Alfieri O, Ferrarese S, Mariscalco G, Cannata A, Di Credico G, Leva C, Russo C, Trevisan R, Livi U, Giustina A, Scrofani R, Antona C, Sala A, Gensini GF, **Maessen J –**
Type 2 Diabetes Mellitus Is Associated With Faster Degeneration of Bioprosthetic Valve Results From a Propensity Score-Matched Italian Multicenter Study.
Circulation 2012; 125: 604-614 IF 14.739

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TOP PUBLICATIONS

with the highest Impact Factor in 2012
(CARIM researcher as first and/or last author)

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: 2080-2088 IF 14.156

Eurlings LW, Sanders-van Wijk S, van Kimmenade R, Osinski A, van Helmond L, Vallinga M, **Crijns HJ, van Dieijen-Visser MP, Brunner-La Rocca HP, Pinto YM –**
Multimarker Strategy for Short-Term Risk Assessment in Patients With Dyspnea in the Emergency Department The MARKED (Multi mARKer Emergency Dyspnea)-Risk Score.
Journal of the American College of Cardiology 2012; 60: 1668-1677 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: 1719-1728 IF 14.156

Pison L, La Meir M, van Opstal J, Blaauw Y, **Maessen J, Crijns HJ –**
Hybrid Thoracoscopic Surgical and Transvenous Catheter Ablation of Atrial Fibrillation.
Journal of the American College of Cardiology 2012; 60: 54-61 IF 14.156

Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CHD, Ramos-Quiroga JA, Mick E, Grevet EH, Cormand B, Johans - son S, Haavik J, Lesch KP, **Reif A,** Int Multictr Persistent A –
The genetics of attention deficit/hyperactivity disorder in adults, a review.
Molecular Psychiatry 2012; 17: 960-987 IF 13.668

Bieghs V, **van Gorp PJ,** Walenbergh SMA, **Gijbels MJ, Verheyen F,** Buurman WA, Briles DE, **Hofker MH,** Binder CJ, **Shiri-Sverdlov R –**
Specific immunization strategies against oxidized low-density lipoprotein: A novel way to reduce nonalcoholic steatohepatitis in mice.
Hepatology 2012; 56: 894-903 IF 11.665

Grommes J, Alard JE, Drechsler M, Wantha S, Morgelin M, Kuebler WM, **Jacobs M,** von Hundelshausen P, Markart P, Wygrecka M, Preissner KT, **Hackeng TM, Koenen RR, Weber C, Soehnlein O –**
Disruption of Platelet-derived Chemokine Heteromers Prevents Neutrophil Extravasation in Acute Lung Injury.
American Journal of Respiratory and Critical Care Medicine 2012; 185: 628-636 IF 11.08

Brunner-La Rocca HP, Rickenbacher P, Muzzarelli S, Schindler R, Maeder MT, Jeker U, Kiowski W, Leventhal ME, Rickli H, Pfister O, Osswald S, Pfisterer ME, Investigators T-C –
End-of-life preferences of elderly patients with chronic heart failure.
European Heart Journal 2012; 33: 752-759 IF 10.478

Hendriks JML, de Wit R, **Crijns H,** Vrijhoef HJM, Prins MH, **Pisters R, Pison L,** Blaauw Y, **Tieleman RG –**
Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation.
European Heart Journal 2012; 33: 2692-2699 IF 10.478

Corsten MF, Schroen B, Heymans S –
Inflammation in viral myocarditis: friend or foe?
Trends in Molecular Medicine 2012; 18: 426-437 IF 10.355

TOP PUBLICATIONS

with the highest Impact Factor in 2012 (CARIM researcher as co-author)

Kaptoge S, Di Angelantonio E, Pennells L, **Stehouwer CDA,** Thompson SG, et.al. –
C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction.
New England Journal of Medicine 2012; 367: 1310-1320 IF 53.298

Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DRW, Baslund B, Brenchley P, Deloukas P, Bruchfeld A, Chaudhry AN, **Cohen Tervaert JW,** Feighery C, Gross WL, Hruskova Z, Guillevin L, Gunnarsson I, Harper L, Little MA, Martorana D, Pusey CD, Neumann T, Ohlsson S, Padmanabhan S, Salama AD, Sanders JSF, Smith KGC, Savage CO, Segelmark M, Stegeman CA, Tesar V, Vaglio A, Wieczorek S, **Wilde B,** Zwerina J, Rees AJ, Clayton DG –
Genetically Distinct Subsets within ANCA-Associated Vasculitis.
New England Journal of Medicine 2012; 367: 214-223 IF 53.298

Mees SMD, Algra A, Vandertop WP, van Kooten F, Kuijsten H, Boiten J, van **Oostenbrugge RJ**, Salman RA, Lavados PM, Rinkel GJE, van den Bergh WM –
Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial.
Lancet 2012; 380: 44-49 IF 38.278

Yang J, Loos RJF, Powell JE, **Staessen JAH**, Goddard ME, et.al. –
FTO genotype is associated with phenotypic variability of body mass index.
Nature 2012; 490: 267-72 IF 36.28

Roscioli T, Kamsteeg EJ, Buysse K, Maystadt I, van Reeuwijk J, van den Elzen C, van Beusekom E, Riemersma M, Altunoglu U, Pfundt R, Vissers L, Schraders M, Buckley MF, **Brunner-la Rocca HG,** Gilissen C, Grisart B, Zhou HQ, Veltman JA, Mancini GMS, Delree P, Bennett C, Willemsen MA, Ramadza DP, Chitayat D, Sheridan E, Peeters EAJ, van Bokhoven H, Tan-Sindhunata GMB, de Die-Smulders CE, Devriendt K, Kayserili H, El-Hashash OA, Stemple DL, Lefeber DJ, Lin YY –
Mutations in ISPD cause Walker-Warburg syndrome and defective glycosylation of alpha-dystroglycan.
Nature Genetics 2012; 44: 581-5 IF 35.532

Sansone SA, Rocca-Serra P, Field D, Maguire E, Taylor C, Hofmann O, Fang H, Neumann S, Booth T, Tong WD, Amaral-Zettler L, Begley K, Bougueleret L, Burns G, Copeland J, Chapman B, Clark T, Coleman LA, Das S, de Daruvar A, **Evelo CT**, de Matos P, Dix I, Edmunds S, Forster MJ, Gaudet P, Gilbert J, Goble C, Griffin JL, Jacob D, Hide W, Kleinjans J, Harland L, Haug K, Hermjakob H, Ho Sui SJ, Laederach A, Liang S, Marshall S, McGrath A, Merrill E, Reilly D, Roux M, Shamu CE, Shang CA, Steinbeck C, Trefethen A, Jones B, Wolstencroft K, Xenarios I –
Toward interoperable bioscience data.
Nature Genetics 2012; 44: 121-126 IF 35.532

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TOP PUBLICATIONS

with the highest Impact Factor in 2012 (CARIM researcher as co-author)

Den Ruijter HM, Peters SAE, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, Hofman A, de Graaf J, Grobbee DE, Hedblad B, Holewijn S, Ikeda A, Koffijberg H, Kavousi M, Kitagawa K, Kitamura A, Lonn EM, Lorenz MW, O'Leary DH, Polak JF, Price JF, Mathiesen EB, Nijpels G, Okazaki S, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Bots ML, **Stehouwer CDA,** Witteman JC, Moons KG –
Common Carotid Intima-Media Thickness Measurements in Cardiovascular Risk Prediction A Meta-analysis.
JAMA-Journal of the American Medical Association 2012; 308: 796-803 IF 30.026

Cheng C, Haasdijk R, Tempel D, van de Kamp EHM, Herpers R, Bos F, Den Dekker WK, Blonden LAJ, **Biessen EAL,** de Jong R, Burgisser PE, Chrifi I, Dimmeler S, Schulte-Merker S, Duckers HJ –
Endothelial Cell-Specific FGD5 Involvement in Vascular Pruning Defines Neovessel Fate in Mice.
Circulation 2012; 125: 3142-3158 IF 14.739

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

Harada M, Luo XB, Qi XY, Tadevosyan A, Maguy A, Ordog B, Ledoux J, Kato T, Kamiya K, Naud P, Voigt N, Shi YF, Murohara T, Kodama I, Dobrev D, Tardif JC, **Schotten U,** Van Wagoner DR, Nattel S –
Transient Receptor Potential Canonical-3 Channel-Dependent Fibroblast Regulation in Atrial Fibrillation.
Circulation 2012; 126: 2051-64 IF 14.739

Kyriacou A, Whinnett ZI, Sen SY, Pabari PA, Wright I, **Cornelussen R,** Lefroy D, Davies DW, Hughes AD, Peters NS, Kanagaratnam P, Mayet J, Francis DP, Davies JE –
Improvement in Coronary Blood Flow Velocity With Acute Biventricular Pacing Is Predominantly Due to an Increase in a Diastolic Backward-Travelling Decompression (Suction) Wave.
Circulation 2012; 126: 1334-44 IF 14.739

Zellweger MJ, Kaiser C, Jeger R, **Brunner-La Rocca HP,** Buser P, Bader F, Mueller-Brand J, Pfisterer M –
Coronary Artery Disease Progression Late After Successful Stent Implantation.
Journal of the American College of Cardiology 2012; 59: 793-799 IF 14.156

Liao X, **Sluimer JC,** Wang Y , Subramanian M, Brown K, Pattison JS, Robbins J, Martinez J, Tabas I –
Macrophage autophagy plays a protective role in advanced atherosclerosis.
Cell Metab 2012; 15: 545-553 IF 13.668

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

Chen L, Wang J, Zhang YY, Yan SF, **Neumann D,** Schlattner U, Wang ZX, Wu JW –
AMP-activated protein kinase undergoes nucleotide-dependent conformational changes.
Nature Structural & Molecular Biology 2012; 19: 716-8 IF 12.712

TOP PUBLICATIONS

with the highest Impact Factor in 2012 (CARIM researcher as co-author)

Stergiakouli E, Hamshere M, Holmans P, Langley K, Zaharieva I, Hawi Z, Kent L, Williams N, **Reif A,** Owen MJ, O'Donovan M, Psychiat GWAS Consortium ADHD Subgrp, Thapar A –
Investigating the Contribution of Common Genetic Variants to the Risk and Pathogenesis of ADHD.
Am J Psychiatry 2012; 169: 186-194 IF 12.539

Williams NM, Franke B, Mick E, Anney RJL, Freitag CM, Gill M, Thapar A, O'Donovan MC, Middleton F, Owen MJ, Holmans P, Kent L, Zhang-James Y, Liu L , Romanos M, Meyer J, Nguyen TT, Romanos J, Seitz C, Renner TJ, Buitelaar J, Walitza S, Warnke A, Palmason H, Rommelse N, Vasquez AA, Faraone SV, Hawi Z, Langley K, Sergeant J, Steinhausen HC, Roeyers H, Biederman J, Zaharieva I, Hakonarson H, Elia J, Lionel AC, Crosbie J, Marshall CR, Schachar R, Scherer SW, Todorov A, Smalley SL, Loo S, Nelson S, Shtir C, Asherson P, **Reif A,** Lesch KP-

Genome-Wide Analysis of Copy Number Variants in Attention Deficit Hyperactivity Disorder: The Role of Rare Variants and Duplications at 15q13.3.
Am J Psychiatry 2012; 169: 195-204 IF 12.539

Faber CG, Hoeijmakers JGJ, Ahn HS, Cheng XY, Han CY, Choi JS, Estacion M, Lauria G, Drenth JPH, Vanhoutte EK, **Gerrits MM,** Dib-Hajj S, Waxman SG, Merkies ISJ –
Gain of function NaV1.7 mutations in idiopathic small fiber neuropathy.
Annals of Neurology 2012; 71: 26-39 IF 11.089

Camm AJ, Lip GY, De Caterina R, **Schotten U, Van Gelder IC,** ESC Committee for Practice Guidelines (CPG) –
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: 2719-47 IF 10.478

Reil JC, Hohl M, Selejan S, Lipp P, Drautz F, Kazakow A, Munz BM, Muller P, Bohm M, Steendijk P, Reil GH, **Allessie MA,** Neuberger HR –
Aldosterone promotes atrial fibrillation.
European Heart Journal 2012; 33: 2098-2108 IF 10.478

PATENTS

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

SCIENTIFIC GRANTS, AWARDS AND HONORS

In this part we present most of the CARIM researchers that were successful in obtaining projects and personal grants or awards and prizes.

ERC GRANTS

Prof. **Leon de Windt** is the recipient of a prestigious grant of the European Research Council (ERC). ERC Consolidator Grants are designed to support researchers at the stage at which they are consolidating their own independent research team or program. The scheme will strengthen independent and excellent new individual research teams that have been recently created. The next five years Leon de Windt will receive about 500 K€ to conduct his "CALMIRS" project: RNA-based regulation of signal transduction – Regulation of calcineurin/NFAT signaling by microRNA-based mechanisms.

NWO VIDI

In July 2012, the Netherlands Organisation for Scientific Research (NWO) granted a VIDI fellowship to Dr **Rory Koenen** (Dept. of Biochemistry). Rory received this 800 K€ grant to conduct his research on "Blood platelets as assassins". In the VIDI project granted to Dr Koenen, the mechanisms about how platelets can accelerate atherosclerosis will be investigated on a cellular and molecular level. This, by looking inside the platelet, but also at the interface between the platelet and the vessel wall in laboratory and animal models. Eventually, the findings will enable the generation of a model of the pro-atherogenic function of platelets, which enables the design of novel therapeutics against atherosclerosis. Platelets are vital for staunching bleeding, but can also contribute to the development of cardiovascular diseases by inflaming blood vessels. Possibilities to prevent this harmful role of blood platelets will be investigated.

NWO Meervoud

In April 2012, Dr **Paula da Costa Martins** (Dept. of Cardiology) received an NWO Meervoud grant to conduct her project "Post-transcriptional regulation of autophagy: MiR-216a as a cell death-regulating microRNA during myocardial repair". Paula will use her MEERVOUD grant on investigating the role of miR-216a in cell death during myocardial repair, and on identifying the miRNAs that are involved in regulating autophagy in cardiomyocytes. (Read a full interview with Paula on pages 32-33).

NWO Mosaic Scholarship

In 2012, two CARIM PhD students received a Mosaic Scholarship of 200 K€ from the NWO: **Eleana Zhang** (Dept. of Neurology) and **Chahinda Ghossein** (Dept. of Biomedical Engineering). In corporation with GROW, Chahinda will conduct research on the increased risk of developing cardiovascular diseases in women with severe pre-eclampsia. Using echocardiographic and hemodynamic data and a computer model of the cardiovascular system, Chahinda hopes to discover the underlying cardiovascular mechanisms associated with this increased susceptibility. Eleana will, in close collaboration with MH&NS, examine the function – or dysfunction – of the blood-brain barrier in patients with stroke and cognitive impairment by means of advanced MRI-techniques, hoping to provide more insight in the pathological mechanism of cerebral small vessel disease.

NHS E. Dekker Program

In the framework of the E. Dekker program of the Dutch Heart Foundation, Dr **Joost Lumens** (Dept. of Biomedical Engineering) obtained a Junior post doc grant for his project "Noninvasive patient-specific cardiovascular stimulation to optimize diagnosis and pacemaker treatment of heart failure". The general aim of this research project is to improve patient selection for and effectiveness of cardiac resynchronization therapy (CRT). (Read a full interview with Joost on pages 8-9).

Kootstra Fellowships

During the second round of the Kootstra Talent Fellowships

2012, **Karen Gabriels** (post doc Dept. of Pathology) was granted a fellowship. The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific career. The fellowship is meant to provide financial support for young researchers to bridge the time between graduation in Medicine, Health or Life Sciences and the start of a PhD, between the graduation of the PhD student and the start of an official contract as a post doc or enable them to combine their studies in Medicine, Health or Life Sciences with an active involvement in scientific research.

Outstanding Achievement Award and Galenus Research Prize

Professor **Leon de Windt** (Dept. of Cardiology) received the Galenus Research Prize on May 23 for his pioneering cardiovascular research, mainly on heart failure. According to the jury, Leon is the example of a young promising researcher, which is reflected by the grants he required, the awards he has won, his number of original publication and an h-index of 33 at the age of 42.

On August 26, the Outstanding Achievement Award 2012 was handed over to Leon de Windt by the ESC Council during the annual ESC congress in Munich. With this award the European Society of Cardiology honors two basic researchers with outstanding accomplishments in the early stage of their career.

Project Homage accepted

The European project proposal "Homage" (a FP7 cooperation coordinated from Paris), of which Dr **Blanche Schroen** and Prof. **Stephane Heymans** (Dept. of Cardiology) are part of, has been accepted. Their group has a major contribution in this project called "Heart 'omics' in AGEing' for the validation of –'omics-based biomarkers for disease affecting the elderly". They will participate as both clinical and preclinical partner.

NWO Meer Kennis met Minder Dieren

Prof. **Johan Heemskerk** (Dept. of Biochemistry) was granted an NWO subsidy within the program 'Meer Kennis met Minder Dieren' for his project "Whole blood assessment of thrombosis tendency: implementation of two in vitro tests as alternatives for in vivo thrombosis experiments".

NGI Pre-Seed Grant

Professor **Uli Schotten** (Dept. of Physiology) has been granted a Life Sciences Pre-Seed Grant (worth up to 250 K€), based on an excellent qualification by the Pre-Seed Grant commission of the Netherlands Genomics Initiative for his proposal "YOURRHYTMICS Non-invasively Classifying Atrial Fibrillation". Main goal of the YOURRHYTMICS project is to validate and commercialise a diagnostic method for the quantification and analyses of atrial fibrillation. During the Pre-Seed Grant period, the group of Uli Schotten will work on the development of a second prototype of the test.

EU COST grant

The group of Professor **Harald Schmidt** (Dept. of Pharmacology) received an EU COST-grant. The EU-ROS proposal has been approved by the European Cooperation in Science and Technology on June 7. COST is an intergovernmental framework, allowing the coordination of nationally-funded research on a European level.

Furthermore in 2012, **Ellen Dirkx** received a ESC research fellowship, **Vanessa van Empel** was granted an ICIN Fellowship, Dr **Judith Sluimer** received a CARIM PhD fellowship, Dr **Kim Radermacher** received a personal grant from the Netherlands Brain Foundation, the Willem Birkenhäger Award was presented to Prof. **Peter de Leeuw** by the Dutch Society for Hypertension (NHV), **Bart Corten** won the student competition of the FHML Honors Program, Dr Gerry Nicolaes received an NWO Middelgroot Investment Grant and Dr **Kristiaan Wouters** was awarded a Career Integration Grant within the EU FP 7 program (Marie Curie).

EVENTS AND HIGHLIGHTS

UM Award Martin Tossings
At the New Year's reception of Maastricht University on January 5, **Martin Tossings** received a UM Award of special merit for his work at Maastricht University. The UM Award is given to employees in recognition of their distinctive performance in administrative or academic matters, in the provision of services, or for commendable social work based at Maastricht University. Martin Tossings was praised for his expertise and unflagging dedication. For years, CARIM and the UM could rely on his 'high-level services' when it came to managing projects and his expertise and his friendly disposition that inspired a pleasant working atmosphere were highly appreciated.

New Scientific Director
As of April, Professor **Thomas Unger** has been appointed as the Scientific Director of CARIM for five years. Prof. Unger was Director of the Institute of Pharmacology at the Charité Universitatsmedizin Berlin, Germany, Director of the Center for Cardiovascular Research at the same university and is the Chairman of the German Institute for High Blood Pressure Research in Heidelberg.

Illumina HiSeq2000
The Department of Clinical Genetics has purchased the Illumina HiSeq2000, one of the most powerful next-generation DNA-sequencers currently available. The sequencer has a capacity of 600Gbase per run, equivalent to 100 human genomes. The sequencer will be used for diagnostic and research application.

Prof. Jan Glatz appointed as President of the SHVM
Prof. **Jan Glatz** (Dept. of Genetics and Cell Biology) has been appointed as President of the Society for Heart and Vascular Metabolism (SHVM) for a three year term. The SHVM was founded in 2000 with the aim to provide a forum for investigators interested in multiple roles of intermediary metabolism in the cardiovascular system, an area that receives growing recognition.

Prof. Hugo ten Cate appointed as fellow at Johannes Gutenberg University Mainz
Professor **Hugo ten Cate** (Dept. of Biochemistry) has been appointed as one of the Gutenberg Research College (GRC) fellows at Johannes Gutenberg University Mainz. Johannes Gutenberg University established its Gutenberg Research College in 2007 to highlight the university's academic strengths and to promote promising new research areas.

André Postema (left), Martin Tossings (middle), Erie van den Heuvel (right).

Glyoxalase 1 and methylglyoxal in Vascular AGE-ing

Casper G Schalkwijk, Department of Internal Medicine

Introduction

Traditionally, the formation of advanced glycation endproducts (AGEs) is viewed as a post-translational modification of proteins by reduced sugars that accumulate slowly on extracellular and long-lived proteins throughout life. Formation of AGEs can be regarded as a naturally occurring process resulting from normal metabolism, but increased under hyperglycaemic conditions as well as under conditions of increased oxidative stress and hyperlipidaemia. AGEs are not inert. Several mechanisms have been proposed by which AGEs contribute to the development of pathological conditions, including aberrant cross-linking of extracellular matrix proteins leading to arterial stiffness. Indeed, excellent experimental work by CARIM researchers in the late 1990s demonstrated that AGEs are involved in the diabetes-induced stiffening of large arteries. In addition, the ligation of AGEs to AGE receptors, including RAGE, leading to activation of different cells types through the transcription of specific genes, has been reported to contribute to the development of pathological conditions.

It was long believed that AGEs accumulate only on long-lived extracellular proteins. In recent years, however, the importance of very fast AGE formation has become increasingly clear, with the highly reactive methylglyoxal (MGO) as a key compound involved in the very fast generation of glycation adducts on cellular and short-lived extracellular proteins, lipids and DNA. In fact, MGO, mainly generated as a by-product of glycolysis, is believed to be the most potent glycation agent. To counteract the deleterious effects of MGO, organisms have an enzymatic glyoxalase defence system in which MGO is converted to D-lactate,

with glyoxalase 1 (GLO1) as the key enzyme in this system (Figure 1). Our research group has contributed significantly to the knowledge we have nowadays about the impact of the fast formation of AGEs, by providing data from basic science, using in vitro systems and animal models, and from cohort studies. We were among the first to show in several studies that there is a role of very fast formation of AGEs by MGO in diabetes and obesity and in age-related diseases such as atherosclerosis and myocardial infarction, and that this is, at least in part, a likely mechanism accounting for vascular senescence. To further highlight the potential importance of MGO and GLO-1, some lines of our current research are described below.

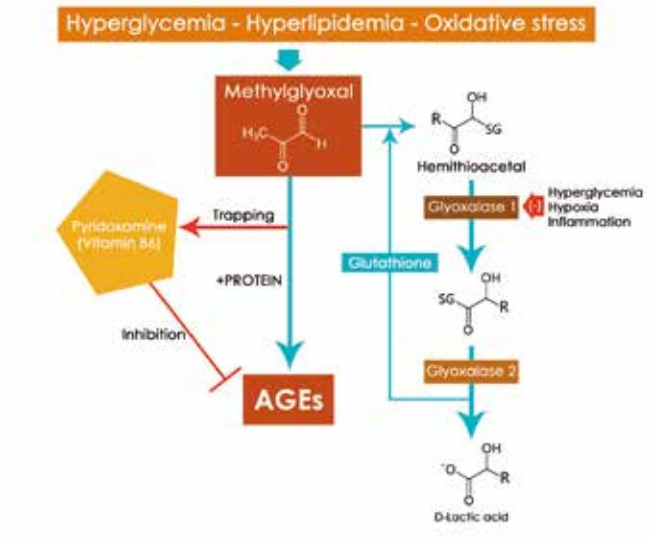

FIGURE 1

Formation of methylglyoxal, glyoxalase1 activity and the mechanism of the AGE-lowering effect of pyridoxamine.

Diabetes

As GLO1 is the main detoxification enzyme for MGO, and MGO is the main precursor in the formation of AGEs, it is plausible to hypothesize that alterations in the expression of GLO1 influence AGE production and hence the development of vascular complications. Indeed, we recently demonstrated in preclinical studies that overexpression of GLO1 reduced the MGO concentration and AGE levels. Overexpression of GLO1 in a diabetic rat model diminished levels of oxidative stress and improved hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries (Figure 2). Most importantly, we demonstrated in several studies that overexpression of GLO1 along with a

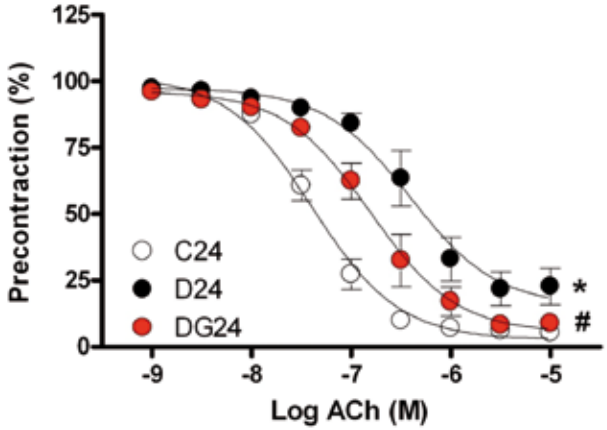

FIGURE 2

Diabetes-induced impairment of vasorelaxation in rat mesenteric arteries is reduced by Glo1 overexpression.

Twenty-four weeks of diabetes (D24) resulted in a decrease in total acetylcholine-induced, endothelium-dependent, nitric oxide mediated vasorelaxation of the mesenteric arteries compared with control (C24; *$p<0.05$). Overexpression of Glo1 (DG24) partially prevented this impairment (# $p<0.05$, DG24 vs D24).

decrease in MGO-dependent protein glycation prevents the development of several microvascular complications i.e. diabetic retinopathy and nephropathy.
In addition to microvascular complications, diabetes is also associated with an increased risk of heart failure. Recent studies using our diabetic animal models showed that early signs of mild cardiac alterations, as indicated by an increase in oxidative stress, inflammation and fibrosis, are at least partially mediated by glycation.
Taken together, these studies were the first to demonstrate a significant role of the glyoxalase pathway in the development of complications in diabetes.

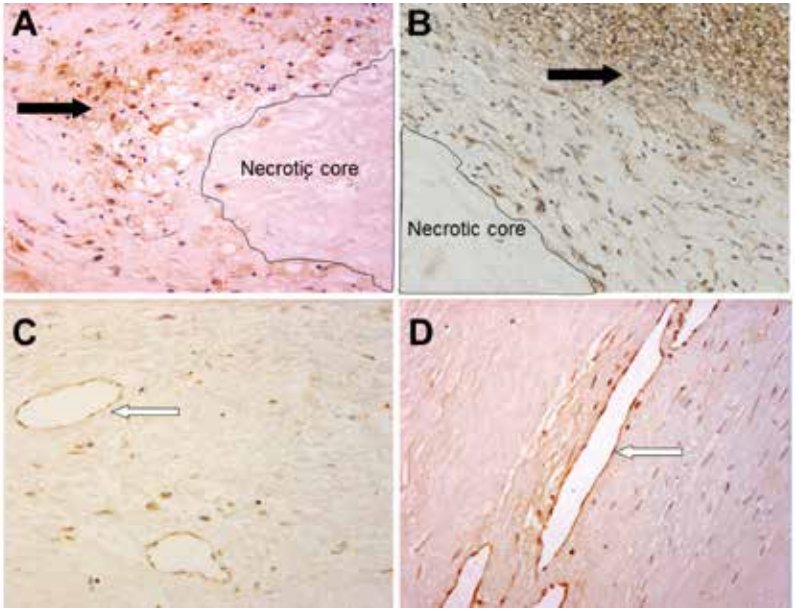

FIGURE 3
Immunohistochemical staining of AGEs in atherosclerotic lesions.
Advanced carotid atherosclerotic lesions, showing staining of de AGEs CML (A) and MG-H1(B) in the cytoplasm of macrophages (A,B indicated by black arrows) surrounding the necrotic core (indicated by black line). In addition, CML (C) and MG-H1 (D) accumulate in plaque vessels (indicated by white arrows). Magnification is 200x.

Obesity
As described above, the increased formation of AGEs occurs under hyperglycaemic conditions and under conditions of increased oxidative stress and hyperlipidaemia. This metabolic profile is generally considered to be characteristic of obesity.
And indeed, we detected, with state-of-the art UPLC/MSMS analysis, increased levels of MGO and specific AGEs such as Ne-(carboxymethyl)lysine (CML) in adipose tissue.
The development of obesity is accompanied by a wide array of health problems, including a high risk of developing type 2 diabetes and cardiovascular disease. In particular, a dysregulated production of adipokines is involved in the development of complications associated with obesity. We have shown that the accumulation of AGEs in adipose tissue is involved in obesity-induced dysregulation of adipokine expression and insulin resistance. The effects were, at least partly, mediated by RAGE. Thus, reducing AGE accumulation in obesity is potentially of medical importance. This is why we have started, in collaboration with Prof. T Miyata from the Tohoku University in Japan, to study the effect of pyridoxamine (PM), a vitamin B6 analogue with anti-glycating activity, on metabolic and vascular function in high-fat diet induced obesity in mice (Figure 1). We found that a delayed intervention with PM is associated with improvement of several aspects of obesity including body weight gain, insulin resistance, adipose tissue inflammation and vascular function in HFD-induced obese mice. Thus, PM may be a novel intervention strategy in obesity, and we soon intend to start a clinical trial with PM in overweight people, with insulin sensitivity and vascular function parameters as primary outcomes.

Atherosclerosis
AGEs and their major precursor MGO are formed during high metabolic activity; they can have detrimental effects

on cellular function and may induce cell death. Since rupture-prone atherosclerotic plaques are characterized by inflammation and high metabolic activity, we recently investigated whether plaque AGEs are increased in human carotid rupture-prone plaques and are associated with plaque inflammation and necrotic core formation (Figure 3). In collaboration with Prof. Pasterkamp of UMC Utrecht, we showed for the first time that AGEs are associated with rupture-prone plaques. Immunohistochemistry showed that AGEs accumulated predominantly in macrophages surrounding the necrotic core and co-localized with cleaved caspase-3. Intra-plaque comparison of plaques stored in the CARIM biobank revealed that the expression of GLO-1 was decreased in ruptured compared with stable plaque segments. Our study suggests a cascade linking inflammation, reduced GLO-1 and MGO and AGE accumulation, and subsequent apoptosis.
In large cohort studies we also investigated whether circulating markers of the AGE pathway were associated with prevalent cardiovascular disease (CVD). A prospective study involving case-cohort analysis, including a subset of Dutch diabetic individuals from the European Prospective Investigation into Cancer and Nutrition (EPIC-NL), revealed that the protein-bound AGEs CML and CEL were associated with incident CVD after adjustment for confounders.
We conclude that AGEs may act as mediators of the progression of stable to rupture-prone plaques, opening a window towards novel treatments and biomarkers in cardiovascular diseases.

Arteriogenesis

Arterial occlusive lesions caused by atherosclerosis lead to cardiovascular and peripheral arterial diseases. In the presence of arterial occlusions, the fate of the affected organ is not only related to the severity of the occlusion, but also to the ability of the developing collateral vessel system to compensate for blood perfusion loss. This development of new vessels is significantly reduced in patients with diabetes, who therefore suffer from both more arterial occlusion and less compensatory collateral capacity, leading to more foot ulcerations and lower extremity amputations than in non-diabetic patients. One of the possible mechanisms mediating these effects is the production of AGEs or their reactive precursors. Recently we performed experiments in GLO-I transgenic rats with or without diabetes which were subjected to ligation of the right femoral artery. Laser Doppler perfusion imaging showed a significantly decreased blood perfusion recovery after 6 days in the diabetic animals compared with control animals, without any effect of Glo1 overexpression. In collaboration with the Departments of Physiology and Radiology, we used in vivo time-of-flight magnetic resonance angiography at 7 Tesla to show a significant decrease in the number and volume of collaterals in the wild-type diabetic animals compared with the control animals (Figure 4). Glo1 overexpression partially prevented this decrease in the diabetic animals. Thus, diabetes-induced impairment of arteriogenic adaptation can be partially rescued by overexpression of GLO-I, indicating a role of AGEs in diabetes-induced impaired collateral formation.

In summary

It is obvious from our findings that MGO and the accumulation of AGEs have deleterious effects on the vascular system. The glyoxalase pathway has a clear protective action. Increased formation of MGO and downregulation of GLO1 by inflammatory signalling in vascular cells leads to a markedly increased modification of proteins by MGO at the sites of vascular complications, including atherosclerosis. MGO and the glyoxalase system will be an ongoing focus of our research on biomarkers, pathophysiological pathways and prevention of vascular complications in people with and without diabetes.

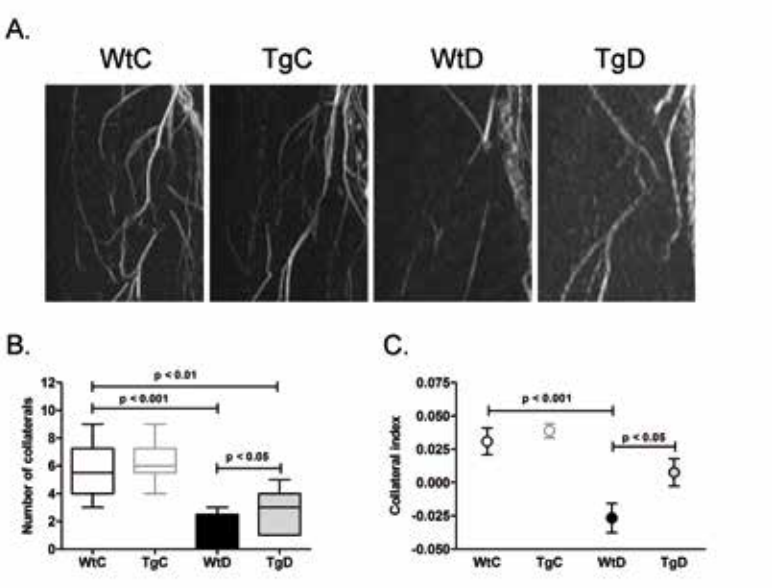

FIGURE 4

Glyoxalase 1 overexpression partially prevents diabetes-induced impairment of collateral growth after hind-limb ligation.

Collateral growth was imaged with MRA (A) in wild-type control (WtC), transgenic control (TgC), wild-type diabetic (WtD) and transgenic diabetic (TgD) rats after ligation of the right femoral artery on day 6 after ligation. The number (B) and intensity (C) of the collaterals were quantified with the OsiriX software.

‘The more complex it is, the more I like it’

Marjo Donners (Sittard, 1978), Assistant Professor, Department of Pathology

What are you researching?
“The overarching research theme in our group is atherosclerosis. I’m examining proteases called A-Disintegrin And Metalloproteases (ADAMs), enzymes that are able to remove various proteins from the cell membranes and thereby regulate a number of processes, like inhibiting inflammatory cells that have an adverse effect on plaque growth and stability.”

Why are you doing research?
“I like solving puzzles. Collecting data and consulting the literature to find out how something works. The more complex, the more I like it. It’s when the results of an experiment turn out to be the opposite of what you expected them to be that it becomes interesting. Sometimes I read papers presenting very obvious results: they’re not less important, but not as exciting.”

Why Maastricht?
“I studied medical biology at Utrecht University, and while I was doing my graduation research project, my supervisor asked me if I’d like to do a PhD under his supervision. But I didn’t want to accept the first offer I got. The researcher in me wanted to look further afield. My second graduation project was here at Maastricht University, and Mat Daemen also offered me a PhD position. So I decided to do my PhD in Maastricht. Since then I’ve worked in various labs, both in Maastricht and during a short stay at a lab in the US, and recently I’ve returned to the Pathology Department. I’ve learned a lot from all these different experiences.”

What was a major event for you in 2012?
"The highlight for me was being awarded the Dr Dekker senior post-doc grant by the Netherlands Heart Foundation. It followed on from junior Dekker grant that I'd been given earlier. The idea with this new grant is that you set up your own research team, so that's what I'm doing now. I'm currently supervising two PhD students."

What are you proud of?
"I don't like to boast, but when I look at the grants I've been able to secure, that makes me rather proud. In applying for these grants you sometimes have to compete with people with a huge list of publications to their name. But then when I look at the collaborative network I've built up and the publications I've produced, I think: these are my own achievements. I tend to be rather autonomous in my work, which means that I've accumulated rather a lot of expertise, and that I know what I'm talking about. When you're being interviewed by a grant committee, you have to come across as enthusiastic, and that's what I do. Although I'm not a great talker by nature, people often say: ' I only have to ask about your research project to get you going.' That passion can be a decisive factor."

What does CARIM mean to you?
"CARIM supplies me with an infrastructure that facilitates a lot of interaction with other researchers and in which I've developed a large network of valuable people to cooperate with. The senior researchers here work from a vision of how to do research as an institute and they help you with that. I also like the fact that the research council helps researchers apply for grants."

When do you consider a working day successful?
"My best days are the ones with a full diary; I like to work efficiently, as indeed I have to, with two young kids at home. And I also like being able to help people on their way. My first supervisor always took enough time to explain things to me, and that taught me a lot. So I want to give the students I supervise a good start too, provided they are sufficiently motivated and prepared to work hard. I've always wondered what my supervisors saw in me when they offered me a PhD position, but now I know. It's the people who think things through just that little bit more, and who keep asking questions, those are the real researchers."

‘There’s still so much I’d like to find out’

Peter de Leeuw,
Professor of Internal Medicine

“If you know how scientific research works, you know that you’ll never find definitive proof for anything. You can never prove hypotheses; the most you can hope for is to find evidence that fits a particular model. That will work until you find something that doesn’t fit, and then you have to develop a new model. This is the kind of attitude I miss in today’s health care practitioners. That’s why I always want to teach young doctors how research works and how knowledge is accumulated.”

Peter de Leeuw, Professor of Internal Medicine, with special focus on hypertension and nephrology, will retire in 2013. In his case, retirement certainly does not imply he has stopped working. “We all have to die sooner or later, and there are a few things I want to figure out before that time.”

Peter de Leeuw was already thinking of doing a PhD when he was still in secondary school, “without knowing what that involved. I was always a bit of a researcher. While I was studying medicine in Rotterdam I was given the opportunity to do research for six months, and that’s when I became hooked.” As a student he was considering becoming a general practitioner. “I liked the wide spectrum of tasks and the fact that you’re close to patients.” For his clinical internship in internal medicine he was originally assigned a place at the Dijkzigtziekenhuis hospital. “I didn’t think that was a good idea, as such a large university hospital treats the more complex cases. And since internal medicine is such a major part of general practice medicine, I thought it would be better to do that internship at an affiliated hospital.” He managed to change places with another intern and ended up at the Zuiderziekenhuis (now Maasstadziekenhuis)

hospital in Rotterdam. “It’s there that I got fascinated by internal medicine, stimulated by my very inspiring mentor Willem Birkenhäger. Birkenhäger was doing research into hypertension, and talked about it with great enthusiasm, so after that all I wanted to do was to practice internal medicine, at that particular hospital, and join in that particular research.” He managed to get his way. He did a PhD during his training, after which he was able to continue the research as a staff member.

Great opportunity

“Opportunities for research are of course much more limited at a non-university hospital than at a university hospital. I had a team of lab workers, but no research group consisting of specialists.” It was therefore a great opportunity when a position became vacant at Maastricht in 1991, for which they were keen to appoint someone interested in doing circulation and hypertension research. “It was time for me to move to a university environment. Although I have to admit that I’d had a rather rosy idea of what that environment was like,” he comments drily. “I had imagined the university as a temple of civilisation and culture, but that proved an illusion. I’m exaggerating of course, but there was more jealousy and animosity than I had expected. And the university hospital didn’t prove to be a place filled with people who knew everything. Nevertheless, I’ve never regretted the move.” In time, he also got to know people at CARIM, and managed to fathom its structure. “Although it did take me a couple of years,” he admits. “This matrix structure, and the distribution of the support staff; I didn’t have a background in academia, so it took me a while to work out all the power mechanisms. We did enter into some partnerships with other departments, but we also partly went our own way. I’m slightly sceptical about the added value of such an institution, even though at times it may come in handy, especially when it comes to procuring expensive equipment that several groups can work with.”

Baropacer

At Maastricht, Peter de Leeuw got to work setting up a programme for vascular medicine within the Department of Internal Medicine. This deals with disease entities like hypertension, thrombosis and dyslipidaemia. “A purely cardiological view of things like hypertension is too limited, even though there are cardiologists who disagree with me in that respect,” says Peter de Leeuw. “But they’re regrouping, as I noticed recently at the European Society of Cardiology conference, where I always present a session on hypertension. Cardiologists are of course very enthusiastic about the baropacer, a kind of mini-pacemaker in the carotid artery. That’s the kind of device they’d also like to work with. Oh well, I suppose it’s just the swing of the pendulum,” he shrugs. When the European Society of Hypertension granted the Maastricht Hypertension Centre the right to call itself a Centre of Excellence in 2010, that was a milestone, of course. But when asked what makes him proud, Peter de Leeuw also mentions the many PhD students he got to know as students and who then decided that they would like to come and work in his group. “It gives you a sense of satisfaction when you’re able to help someone along in their career.”

He certainly does not think everybody should go into research; only those who feel so inclined. “Doing research makes you think a bit more about what you’re doing as a physician. I have my doubts about the current trend of evidence-based medicine, with all these protocols that turn a doctor’s work into something like a cookery book. First do this, then that, and if you don’t do it the healthcare inspectorate will come down on you. Inventiveness is being squeezed out to some extent. It’s becoming almost impossible to just try out something new. Even though many of these protocols are not based on hard evidence. In fact, you can never really prove anything definitively in science.”

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Editor in Chief

Apart from his work as a clinician and researcher, Peter de Leeuw also had many additional functions. He was a member of the executive committee of the Netherlands Association of Internal Medicine and editor of the Netherlands Journal of Medicine and the European Journal of Internal Medicine, and since 2008 he has been Editor in Chief of the Nederlands Tijdschrift voor Geneeskunde (NTvG). “My term there will end in 2015, and until that time I will still work at the outpatient clinic once a week. I think that as an Editor in Chief you have to keep in touch with practice. I’m glad I am allowed to continue doing that even though I turn 65 next year.” He spends two days a week in Amsterdam to work for the NTvG. “What makes it interesting is that you come into contact with so many different disciplines, so you learn a lot. It’s that same broad range of interests that originally made me lean towards general practice medicine as a student. And it means you have a voice in deciding what will be published.” Peter de Leeuw also spent eight years as chair of the Board of Examiners of the Maastricht medical studies programme, which was hard work. When asked how he managed to juggle so many different tasks, he shrugs. “Good planning enables you to get a lot of things done. And of course a working day doesn’t end at five. Even on holidays I always take some work along.”

Full of energy

He has “mixed feelings” about his approaching retirement age. “There’s still so much I’d like to find out. Although I still feel energetic, I do get the sense that I have to hurry to figure out some things.” One example is that the baropacer produces certain effects that seem to contradict current physiological views. “I’d really like to find out what’s actually going on there and so, as it were, rewrite classical physiology.” But he would also like to write a book on the history, people and significance of Vals-les-Bains, the French village in the Ardèche region where he owns a second home. “I would regularly go there for a week or so with two PhD students and Bram Kroon, who is now leading the research group. I would get the groceries and do the dishes, and they had time to write. In the evenings I would check what they had written, and by the time we returned home we had completed several publications. We would work without being disturbed, in a pleasant climate, at nine hundred kilometres from Maastricht. It really creates a bond. We’ll be going there again soon.”

05_ TRAINING AND EDUCATION

INTRODUCTION

CARIM offers a flexible and integrated education and training program that suits individual ambitions of our students. The education program consists of a specialisation within the FHML Master of Biomedical Sciences, a Physician-Clinical Investigator Program (MSc/MD) and a contiguous PhD (doctoral) training program. The content of the education program has been developed by CARIM's top researchers. Its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactic system that is based on problem-based learning. For more details on our education program please visit www.carimmaastricht.nl.

RESEARCH MASTER

Last year the Faculty of Health, Medicine and Life Science (FHML) decided to integrate the individual school research Master's programs into a newly designed FHML Master's of Biomedical Sciences (BMS). This new Master's degree still allows specialisation in the research disciplines of the individual FHML Schools. As a consequence, from September 2011 first year students were able to enrol in the Biomedical Sciences Master program. The students then entering the second year of the CARIM research Master's program all successfully finished their Master.

In the 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.

Graduate students CARIM Research Master's CBM in 2012

Anandan Sampath-Kumar
Geert Hendrikx
Marcel Hoven
Kevin Hughes
Mike Jeurisse
Arina Nugraheni
Michael Rutjens

PhD PROGRAM

Our PhD program is accessible for students of the UM Research Master Biomedical Sciences, and for excellent students from other national or international medical or biomedical Masters. At the end of 2012, 136 PhD students attended our PhD program.

Number of PhD students at 31.12.2012

Funding source	PhD students 2009	PhD students 2010	PhD students 2011	PhD students 2012
University	28	31	48	42
NWO	6	8	14	13
Non-profit + Industry	62	78	79	81
TOTAL	**96**	**117**	**141**	**136**

Besides our regular PhD program, we offer the EuCAR program, which is a joint initiative of CARIM and our German partner institute IMCAR in Aachen. This EuCAR-group involves 14 PhD students who are labeled as EuCAR PhD. Each PhD project is supervised by at least one investigator from IMCAR, Aachen and one from CARIM, Maastricht. EuCAR students will obtain a PhD in Aachen as well as in Maastricht.

PhD DELIVERABLES

PhD student careers from 2007 till 2012 (date set 01-01-13)

Year intake	2007	2008	2009	2010	2011	2012
Cohort volume (annual intake)	28	26	41	38	31	21
Male	16	14	23	15	14	9
Female	12	12	18	23	13	12
PhD from abroad	7	9	19	16	10	8
Thesis completed	14	3	2	-	1	-
Drop out	1	4	5	2	-	-
Drop out > 1 year	0	2	2	1	-	-
Average duration (in months)	56,6	52	36,5	-	-	-
Ongoing	13	19	34	35	26	21

Dr Julian Ilcheff Borissoff (left) and Professor Hugo ten Cate (right)

Dr Karen Gilio (left) and Professor Johan Heemskerk (right)

CARIM THESES IN 2012

Eckstein J -
The three-dimensional substrate of Atrial Fibrillation in the goat
Promotores: Prof. M Allessie, Prof. U Schotten
Maastricht University, January 18, 2012

Costanzo S -
Alcohol Consumption in Relation to Cardiovascular Risk and Mortality
Promotores: Prof. C Hemker, Prof. G de Gaetano (Campobasso, Italy), Prof. H ten Cate
Maastricht University, January 26, 2012

Dirkx E -
Protein kinase D: At the crossroad of cardiac function and metabolism
Promotor: Prof. J Glatz
Co-promotores: Dr J Luiken, Dr G van Eys
Maastricht University, February 3, 2012

Mingels A -
High-sensitivity cardiac troponin assays; Laboratory and clinical aspects
Promotor: Prof. M van Dieijen-Visser
Co-promotor: Dr W Wodzig
Maastricht University, February 3, 2012

Jacobs L -
The release of cardiac troponin: when, where and how
Promotor: Prof. M van Dieijen-Visser
Co-promotor: Dr W Wodzig
Maastricht University, February 3, 2012

Goossens P -
A fatal attraction: Macrophage recruitment to the atherosclerotic plaque
Promotor: Prof. J Glatz
Co-promotor: Dr M De Winther
Maastricht University, February 15, 2012

Borissoff J -
The coagulation-inflammation Axis in Atherosclerosis (CUM LAUDE)
Promotor: Prof. H ten Cate
Co-promotor: Dr H Spronk
Maastricht University, February 29, 2012

Huberts W -
Personalized computational modeling of vascular access creation
Promotores: Prof. F van den Vosse, Prof. T Delhaas
Co-promotores: Dr E Bosboom, Dr J Tordoir
Maastricht University, March 1, 2012

Huberts W -
Personalized computational modeling of vascular access creation
Promotores: Prof. F van den Vosse, Prof. T Delhaas
Co-promotores: Dr E Bosboom, Dr J Tordoir
Maastricht University, March 1, 2012

Knottnerus I -
Vascular endothelial function and genetic epidemiology in lacunar stroke subtypes
Promotores: Prof. R van Oostenbrugge, Prof. H ten Cate, Prof. J Lodder
Maastricht University, March 2, 2012

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CARIM THESES IN 2012

Rouhl R -
Celebral Small Vessel Disease: Endothelial Progenitor Cells and Markers of Vascular Inflammation
Promotores: Prof. J Lodder, Prof. J Cohen Tervaert, Prof. R van Oostenbrugge
Maastricht University, March 2, 2012

Manusama R -
The value of catheter-based cryoablation for the management of cardiac arrhytmias
Promotor: Prof. H Crijns
Co-promotor: Dr C Timmermans
Maastricht University, March 16, 2012

Bouman H –
Towards personalized antiplatelet therapy
Promotor: Prof. H ten Cate
Co-promotores: Dr C Hackeng, Dr J van Werkum
Maastricht University, March 22, 2012

Pisters R -
Antithrombotic management of patients with atrial fibrillation
Promotor: Prof. H Crijns
Maastricht University, March 23, 2012

Cnossen T -
New Developments in Peritoneal Dialysis
Promotor: Prof. K Leunissen
Co-promotores: Dr J Kooman, Dr C Konings
Maastricht University, March 29, 2012

Daissormont I -
Peri- and extravascular inflammation: impact on Atherosclerosis
Promotor: Prof. E Biessen
Maastricht University, April 13, 2012

Bolderman R -
Epicardial amiodarone therapy for atrial fibrillation
Promotor: Prof. J Maessen
Co-promotor: Dr J Hermans
Maastricht University, April 20, 2012

Heijman J -
Computational analysis of β-adrenergic stimulation and its effects on cardiac ventricular electrophysiology
Promotores: Prof. H Crijns, Prof. R Peeters
Co-promotores: Dr P Volders, Dr R Westra
Maastricht University, April 27, 2012

Croes S -
Staphylococcus aureus biofilm
Promotores: Prof. C Bruggeman, Prof. C Neef
Co-promotor: Dr E Stobberingh
Maastricht University, April 27, 2012

Van Almen G -
Pleiotropic effects of non-structural matrix proteins in the stressed heart. ECM remodeling in cardiotoxicity, aging and cardiac allograft rejection
Promotor: Prof. S Heymans
Co-promotor: Dr B Schroen
Maastricht University, May 16, 2012

Voets A -
New pathophysiological concepts and potential therapeutic targets for oxidative phosforylation disorders
Promotor: Prof. H Smeets
Co-promotor: Dr I de Coo
Maastricht University, May 24, 2012

CARIM THESES IN 2012

Pijpers E -
Morbidity and mortality risk of aging diabetic and psychogeriatric patients
Promotores: Prof. A Nieuwenhuijzen Kruseman, Prof. C Stehouwer
Co-promotor: Dr I Ferreira
Maastricht University, May 25, 2012

Bode A -
Tailoring Hemodialysis Vascular Acces. Preoperative imaging techniques and computational modeling
Promotor: Prof. P Kitslaar
Co-promotores: Dr J Tordoir, Dr T Leiner
Maastricht University, June 1, 2012

Nin J -
Advanced glycation and type 1 diabetes
Promotores: Prof. C Stehouwer, Prof. C Schalkwijk
Co-promotor: Dr I Ferreira
Maastricht University, June 7, 2012

Reitsma S -
The endothelial glycocalyx in early atherogenesis. Role in platelet adhesion?
Promotores: Prof. D Slaaf, Prof. M van Zandvoort, Prof. M oude Egbrink
Maastricht University, June 7, 2012

Van Onzenoort H -
Treatment adherence in hypertension. Methodological aspects and new strategies
Promotores: Prof. P de Leeuw, Prof. C Neef
Co-promotores: Dr P van der Kuy, Dr W Verberk
Maastricht University, June 27, 2012

Ruiter M -
Reactivity, recruitment and remodeling of collateral arteries in diabetes
Promotores: Prof. N Schaper, Prof. C Stehouwer
Co-promotores: Dr M Huijberts, Dr J van Golde
Maastricht University, September 6, 2012

Rooijens P -
Primary vascular access for hemodialysis treatment
Promotor: Prof. P Kitslaar
Co-promotores: Dr J Tordoir, Dr T Yo (Rotterdam)
Maastricht University, September 13, 2012

Corsten M -
MicroRNAs in the heart: micromanagers and sentinels of cardiac disease
Promotor: Prof. S Heymans
Co-promotor: Dr B Schroen
Maastricht University, September 14, 2012

Weijs B -
Clinical implications of idiopathic atrial fibrillation
Promotor: Prof. H Crijns
Co-promotor: Dr R Pisters
Maastricht University, September 21, 2012

Vermeulen Windsant I -
Connecting hemosysis and visceral injury during cardiovascular surgery; studies on the causes, effects, and treatment of hemolysis-induced organ injury
Promotores: Prof. W Buurman, Prof. M Jacobs
Maastricht University, September 28, 2012

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CARIM THESES IN 2012

Pulinx B -
Protein biomarkers in chronic disease. Proteomics-driven discovery
Promotores: Prof. M van Dieijen-Visser, Prof. G Schurink
Co-promotor: Dr W Wodzig
Maastricht University, October 3, 2012

Engel D -
Caveolin-1 and CD40L-CD40-TRAF interactions in vascular and metabolic disease
Promotores: Prof. E Lutgens, Prof. E Biessen
Maastricht University, October 12, 2012

Engelen L -
The glycation pathway in type 2 diabetes and cardiovascular disease
Promotores: Prof. C Stehouwer, Prof. C Schalkwijk
Co-promotor: Dr I Ferreira
Maastricht University, October 12, 2012

Grottke O -
Effects of haemostatic agents on trauma induced bleeding
Promotores: Prof. H ten Cate, Prof. R Rossaint (Aachen), Dr H Spronk
Maastricht University, November 1, 2012

Gilio K -
All roads to thrombus formation; demystifying platelet signaling pathways (CUM LAUDE)
Promotor Prof. J Heemskerk
Co-promotor: Dr J Cosemans
Maastricht University, November 12, 2012

Van Geldorp I -
Improving ventricular pacing in adults and children; to treat or to avoid dyssynchrony-induced cardiac failure
Promotores: Prof. T Delhaas, Prof. F Prinzen, Prof. J Janousek
Maastricht University, November 16, 2012

Salic K -
MicroRNAs: small directors with crucial powers in heart failure
Promotor: Prof. L de Windt
Co-promotor: Dr P da Costa Martins
Maastricht University, November 21, 2012

Hellenthal F -
Prediction of Abdominal Aortic Aneurysm progression
Promotor: Prof. G Schurink
Co-promotores: Dr W Wodzig, Dr S Heeneman
Maastricht University, November 28, 2012

Panova-Noeva M -
Platelet-associated hypercoagulability in patients with Essential Thrombocythemia and Polycythemia Vera
Promotor: Prof. H ten Cate
Co-promotores: Dr A Falanga, Dr M Marchetti
Maastricht University, November 29, 2012

Gaajetaan G -
Limiting viral infections with immunomodulating agents
Promotor: Prof. C Bruggeman
Co-promotor: Dr F Stassen
Maastricht University, November 29, 2012

CARIM THESES IN 2012

La Meir M -
Hybrid thoracoscopic epicardial and transvenous endocardial catheter ablation of atrial fibrillation
Promotor: Prof. J Maessen
Co-promotores: Prof. F Wellens, Dr S Gelsomino
Maastricht University, November 30, 2012

Hazewindus M -
Tomatoes as functional food
Promotores: Prof. A Bast, Prof. G Haenen
Maastricht University, December 6, 2012

Sigala F -
The role of neovascularization and oxidative stress in human carotid atherosclerotic lesions
Promotor: Prof. M Jacobs
Co-promotores: Dr V Gorgoulis, Dr A Kotsinas (Athens, Greece)
Maastricht University, December 10, 2012

Gerards M -
Unraveling genetic defects and pathophysiological mechanisms in OXPHOS disease
Promotor: Prof. B Smeets
Co-promotor: Dr I de Coo (Rotterdam)
Maastricht University, December 12, 2012

Hermsen I -
Adrenocortical carcinoma
Promotores: Prof. C Stehouwer, Prof. J Romijn (Amsterdam)
Co-promotor: Dr H Haak (Eindhoven)
Maastricht University, December 13, 2012

Zhu F -
Application of Bioimpedance to study body composition in dialysis patients
Promotores: Prof. K Leunissen, Prof. N Levin, Prof. P Kotanko (New York, USA)
Maastricht University, December 13, 2012

PhD AWARD 2012

On March 7, 2012, four students of the CARIM Research Master Cardiovascular Biology and Medicine defended their project ideas to compete for a CARIM funded PhD position. Thomas Theelen, Mike Jeurissen, Michael Rutjens and Geert Hendrikx all defended their project proposal. The jury ranked the presentation of Thomas Theelen “Small vessels with huge impact – leaky microvessels exacerbate atherosclerosis” as the winning project. (Supervisors: Dr Judith Sluimer, Prof. Erik Biessen). In April, Thomas was granted a Scholarship by the Netherlands Heart Foundation which enabled him to return to the place of his junior internship, the laboratory of Prof. Seppo Ylä-Herttuala at the University of Eastern Finland. The funded project is supervised by Prof. Erik Biessen and Dr Judith Sluimer.

KNOWLEDGE TRANSFER

CARIM Course week

In 2012, the second CARIM Course Week took place from June 18 until June 22. The course week consisted of three parallel courses, covering several aspects of CARIM’s research, alternated with a combined scientific program and a social program organised by I’M CARIM, the organisation of CARIM’s PhD students. The courses organised in 2012 were: Advanced Microscopy and Vital Imaging, Human Heart Failure: From Bench to Bedside, and Modern Biochemistry of Cardiovascular Disease. More than 50 PhDs and Research Master students participated in the Course Week.

CARIM Lecture Series, Cardiovascular Grand Rounds and symposia

The CARIM Lecture Series, the Cardiovascular Grand Rounds Maastricht and the yearly CARIM Symposium are means to update the knowledge of our graduate students, our researchers and other external people with interest in the field of cardiovascular research. In 2012, ten lectures were organised in the CARIM Lecture Series.

CARIM Lecture Series 2012

DATE: 17-01-2012
LECTURER: Prof. P Schrauwen, Maastricht University, the Netherlands
LECTURE TITLE: Metabolic health of muscle

DATE: 28-02-2012
LECTURER: Dr M Zenke, University Hospital Aachen, Germany
TITLE: Deciphering Dendritic Cell Development

DATE: 01-03-2012
LECTURER: Prof. J Wardlaw, University of Edinburgh, UK
TITLE: Small vessels in de brain cause big problems for society, but why?

DATE: 13-04-2012
LECTURER: Dr E Janssen, Cincinnati Children's Hospital, USA
TITLE: Immune responses to dead and dying cells; the good, the bad and the ugly

DATE: 20-04-2012
LECTURER: Prof. A Ludwig, RWTH Aachen University, Germany
TITLE: The importance of proteolic shedding for acute lung inflammation

DATE: 14-05-2012
LECTURER: Prof. T Dahl, Oslo University Hospital, Norway
TITLE: The role of nampt in lipid accumulation in atherosclerosis

DATE: 11-06-2012
LECTURER: Dr J Bakkers, Hubrecht Institute Utrecht, the Netherlands
TITLE: Studying cardiovascular development and disease using the zebrafish model

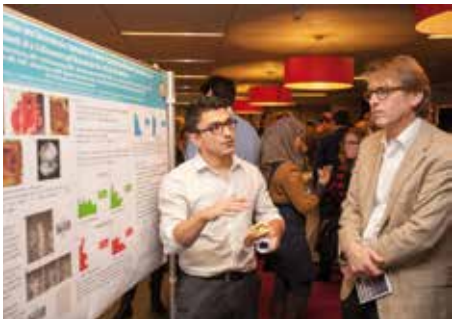
DATE: 10-07-2012
LECTURER: Prof. F Limbourg, Hannover Medical School, Germany
TITLE: How do arteries grow and regenerate?

DATE: 17-09-2012
LECTURER: Prof. N Marx, University Hospital Aachen, Germany
TITLE: Novel aspects on pathophysiology and treatment of vascular disease in diabetes

DATE: 24-09-2012
LECTURER: Dr I Bot
TITLE: Stress-induces Mast Cell Activation: A Final Trigger in Atherothrombosis

Cardiovascular Grand Rounds Maastricht

Another successful lecture series, the Cardiovascular Grand Rounds Maastricht, was organised again in 2012. Three lecture series were organised, with cardiovascular lectures given by national and international experts, on a weekly basis. For the full programs please visit www.carimmaastricht.nl, 'CARIM lectures' in the 'Education' section.

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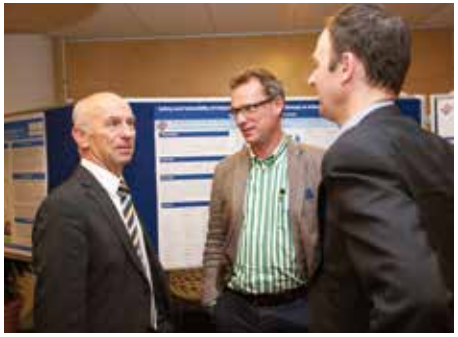


CARIM
SYMPOSIUM
2012

CARIM Symposium 2012

CARIM's annual scientific symposium was held in Maastricht on November 14. As in previous years, the heart of the program was the poster session, in which scientists of the institute presented their recent research findings. The lecture program included a number of highlights of CARIM's present activities and future developments. CARIM PhD award winner Thomas Theelen presented a lecture on leaky microvessels and VIDI laureate Rory Koenen held a lecture titled "Propellants of atherosclerosis – Molecular aspects of RANTES- and PF4-release by activated platelets". Other lectures were given by Prof. Axel Pries, Prof. Kevin Mayo and Prof. Leon de Windt. This year's CARIM day was concluded with the Robert Reneman lecture given by Prof. David Kass: "Reverse remodeling the failing heart: Mechanisms and therapeutic opportunities". Professor Kass is the Abraham and Virginia Weiss Professor of Cardiology and professor of biomedical engineering at John Hopkins University. Prof. Kass is a world leader in integrative cardiovascular physiology, and has focused his research career on defining the mechanisms of cardiac failure and hypertrophy, and developing novel treatment of these diseases, on the aging heart and vasculature, and on ventricular-arterial interaction.

Other lectures, seminars and symposia

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2012. Some of them are presented below.

The **10th Dutch German joint meeting of Molecular Cardiology** was organised from February 2 until 4 by Prof. **Leon de Windt,** Prof. **Stephane Heymans** and Dr **Paul Volders**.

On February 17, Prof. **Jos Maessen,** Prof. **Harry Crijns,** Prof. **Uli Schotten,** Drs **Mark La Meir** and Drs **Laurent Pison** organised the **Third Crossing Borders Meeting "Hybrid AF Ablation".** The one-day course focused entirely on recent advances made in the complex world of atrial fibrillation through an open environment where electrophysiologists and cardiac surgeons were equally represented.

Prof. **Johan Heemskerk,** Prof. **Hugo ten Cate** and Dr **Judith Cosemans** (Dept. of Biochemistry) organised the **1st EUPLAN Platelet Conference Maastricht** on September 20 and 21. The European Platelet Network (EUPLAN) aims to provide an international excellence platform for information exchange and promotion of basal and clinical research on blood platelets and megakaryocytes. The network therefore supports the organisation of a biannual conference in Europe. Prior to the conference on September 19, practical and methodological workshops were given with support of several companies and a special clinical seminar on the implementation of newly developed antiplatelet medications was organised by sponsors.

From October 2 until 5, Dr **Raed Al Dieri** and Dr **Bas de Laat** organised the **2nd Maastricht Meeting on Thrombin Generation**. The 4-day program comprised lectures by experienced faculty, hands on experience with different available techniques and master classes in which attendees had the opportunity to present their research in front of a panel from the faculty.

On November 30, the Biannual International Forum **"Frontiers in Drug Discovery"** was organised by Prof. **Harald Schmidt,** who gave his inaugural lecture afterwards. The symposium was held under the auspices of the 8th Global Cardiovascular Clinical Trialists Forum, CVCT, and jointly with the European Society of Cardiology Working Group Cardiovascular Pharmacology and Drug Therapy. This year's focus of the meeting was the future of academic and industrial synergies in meeting the massive challenge to find new validated drug targets and disease mechanisms in order to move further towards a more personalized and precision medicine.

‘Research is all about people’

Dietbert Neumann (Düsseldorf 1968), Associate Professor, Department of Molecular Genetics

What are you researching?
“In general I’m interested in the balance of energy metabolism. All my research is centred around a molecule, called AMP-activated protein kinase, which is an energy sensor that regulates the metabolic balance. We look at ways to activate this system artificially, using synthetic drugs or endogenous substances that we all have in our bodies and that can also switch on this pathway. The ultimate aim is to treat diseases that we die from through cardiovascular complications, such as diabetes or obesity. That’s where CARIM comes in.”

Why Maastricht?
“I got the NWO VIDI grant in 2010 and came here. I had met Professor Jan Glatz at a European consortium, EXGENESIS, and he supported my application. I had been in Switzerland, at ETH Zürich, for ten years, with a brief interruption, and it was time to make a move. So with my wife and our five-year-old twins I moved to Eijsden. I’m happier now than I was in Switzerland, because of the lifestyle. Here it’s more relaxed; people are more open and friendly. The Dutch culture fits me better than the Swiss. I was born in Düsseldorf and raised in Cologne, so South-Limburg is like coming home.”

What does CARIM mean to you?
“CARIM is a platform with an international standing. When I go to a conference abroad, people know about CARIM. That also helps with grant applications. It gives you a sort of home. I get to know more and more people from the institute, but I’m not there yet. It takes time.”

Have the past years been successful for you?
"Yes, there have been several developments. The work in Zürich was very fundamental. Here I'm building a line of research which is developing into the translational area. It's partly what is demanded by society and partly what I wanted. Funding in the Netherlands is very much dependent on grant applications nowadays. Fundamental research also benefits society, but it's less obvious. Previously, when I was asked by family and friends what I was doing, they always wanted to know: 'Yeah, but how can we benefit from it?' I had a hard time explaining that. Now it's actually much easier."

What makes a good working day?
"I think it's about people. If I see the people in my group are happy, then everything's fine. Not every day has to produce a lot of results. For a scientist, it's clear that most of the days are probably more or less frustrating, because most of the time is spent preparing experiments, such as creating the required toolbox of research materials, and then you do this experiment, and sometimes it doesn't work. Actually most of the time it doesn't. Until you reach the point where it works: those are the days to celebrate. But if you only depend on those few days, you shouldn't be a scientist. I think it's mostly about social contacts. A good atmosphere in your group is the basis for success."
Was there a specific event in 2012 that was important to you?
"We were successful in applying for a Marie Curie grant for our postdoctoral researcher Dipanjan Chanda, an Indian scientist who was moving here from Harvard. My group of five PhD students is very international, because I think that's what a university should be about: international cooperation. It creates a completely different setting, and that's what encourages and inspires me."

LIST OF ABBREVIATIONS

BMM	BioMedical Materials program
CARIM	Cardiovascular Research Institute Maastricht
CBM	Research Master's Cardiovascular Biology & Medicine
CGRM	Cardiovascular Grand Rounds Maastricht
CTMM	Center for Translational Molecular Medicine
CVON	CardioVasculair Onderzoek Nederland
EPC	Education Program Committee
ERC	European Research Council
EuCAR	Euregio Cardiovascular International Research Training Group
FHML	Faculty of Health Medicine and Life Sciences (Maastricht University)
FP7	Seventh European Framework Programme
IMCAR	Institute for Molecular Cardiovascular Research, Aachen, Germany
KNAW	Royal Netherlands Academy of Arts and Sciences
Maastricht UMC+	Maastricht University Medical Centre+
MD	Doctor of Medicine
NHF	Netherlands Heart Foundation (see also NHS)
NHS	Dutch Heart Foundation
NWO	Netherlands Organisation for Scientific Research
OBP	Technical staff
PI	Principal Investigator
SCI-SSCI	Science Citation Index-Social Science Citation Index
UM	Maastricht University
WP	Scientific staff
ZonMw	Netherlands Organisation for Health Research and Development

COLOPHON

EDITOR
Tara de Koster, CARIM

In cooperation with
CARIM School Office
CARIM staff members

INTERVIEWS
Femke Kools, FemKools

PHOTOGRAPHY
Joey Roberts, Maastricht

COVER
Painted Petri Dish by Klari Reis, 6 inch diameter.
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GRAPHIC REALIZATION
Muis Mücher, Maastricht

PRINT
Drukkerij Hendrix

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CARIM School for Cardiovascular Diseases
Maastricht University Medical Centre +
Universiteitssingel 50, 6229 ER Maastricht
P.O. Box 616 6200 MD Maastricht, the Netherlands

Telephone	+31 (0)43 3881766
E-mail	carim-office@maastrichtuniversity.nl
Website	www.carimmaastricht.nl

School for Cardiovascular Diseases

Maastricht UMC+

university hospital Maastricht

azM

Maastricht University