CARIM ANNUAL REPORT 2020

SCHOOL FOR CARDIOVASCULAR DISEASES

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CONTENTS

PREFACE

THIS IS OURSELVES… UNDER PRESSURE…

With pride I present to you our CARIM Annual Report 2020. It is gratifying to see how a school holds up under harsh corona conditions, by being flexible and yet holding strong, with grateful reference to our clinicians that ran the extra mile for the much-needed COVID-19 treatment and care.

Notwithstanding 2020 also came with a toll. Let us remember the departed and bring courage to those that are still fighting the consequences of COVID-19. Also increased work pressure and lab closures in combination with social deprivation has made 2020 a challenging year. Many of us will recognise ourselves on the front cover, isolated from society in a distance learning and communication mode, requiring more energy and perseverance to keep up than during routine face-to-face interaction and learning.

It is therefore not a coincidence that workload and work pressure are hot topics in current academic discussions. I still would like to believe that we researchers have the most beautiful job in the world, with all the freedom to study biological mechanisms that keep us healthy, or consequently make us ill when impaired. Yes, we work hard, but if it is fun and gives you energy it should still be gratifying. The key success factor to healthy working is the intricate connection between work and private life, perhaps a “work-life blend” (see page 35), in which at least one of the biotopes at a time should function in a smooth and rewarding way. In a year with research delays and planning pressure in combination with challenging social and private situations due to societal shut down, an overall feeling of dismay and desperation might result, as both work and private lives are seriously affected. Therefore, currently, good mentorship becomes crucial for the well-being of our employees and functioning of our institute. That adequate care should be taken for early detection and prevention before succumbing to personal overload.

In this respect, great responsibilities lie with our principal investigators under their much-acclaimed mentorship qualifications, to guide their team members through these challenging times, and not only prepare them for their future, but also protect them from the present. To stay on the ball of dodging these personal challenges, CARIM has launched a senior coach programme for newly registered PhD candidates. With this, dedicated senior CARIM coaches will be appointed to all new PhD candidates.

PhD trajectories sometimes come with certain challenges on a personal and professional level, such as experimental setbacks and rejection of papers, which to some extent belong to the life of a scientist and in most cases should be absorbed. PhD candidates can contact their coach to discuss how these challenges are perceived by them in relation to the supervisory team and if these hurdles are taken in good stride. Always remember that “doing a PhD” is no walk in the park, and some hurdles and challenges need to be met as a person to prepare the candidate to become a mature and independent scientist. If hurdles seem to reach beyond regular challenges belonging to a PhD trajectory, or are unacceptable in any other way, the coach will intervene and seek for assistance.

CARIM continues to innovate in research management and talent programmes. Our successful HS-BAFTA programme has granted 9 pre-PhD, PhD, and postdoc fellowships in 2020 (see pages 92-94), and we have initiated an alternative funding programme with the CARIM Crijns’ Crowdfunding Doubler, allowing innovative and important research that is funded through crowdfunding to be doubled by CARIM when it reaches 25 k€ (see page 53). Our successful Strategic Board brought CARIM management to a higher level and provided crucial initiatives and support in implementing changes based on external review recommendations and

analyses, with new policies on well-being, diversity and inclusivity at CARIM (see page 11). Continuing with this positive trend, more is yet to come.

Policies on diversity and inclusivity are currently being implemented with a positive spin on science, management and organisation, and more changes are afoot on aspects of Recognition and Rewards. In short, these aim at valuing a broader spectrum of talents within research teams, achieving alternative possibilities for academics and support staff with expertise and talents other than pure scientific and teaching skills to team up and pursue an academic career. This will advance our current strategy of team science in which societal, economical and translational aspects in a multidisciplinary and collaborative team setting are gaining importance in performing and funding scientific research.

However, in an attempt to evaluate different expertise along similar rulers, as a consequence, evaluating purely scientific parameters such as individual h-indices and citations suddenly become off limits. This is eroding a sensible scoring system in which the importance of researchers' scientific output is valued by their scientific peers. Apart from the number of invited keynote lectures on international conferences there is no better indicator of scientific quality than personal citations of published papers. Yet, why does pursuing alternative strategies for academic careers mean personal citation scores have to be abandoned? Can't we add criteria instead of replacing? On an institutional level I am proud to inform you that in 2020 CARIM's group effort set a double record with 660 Scientific Citation Index papers with an average impact factor of 6.1.

Today it seems that changes must be implemented fast, if not yesterday. Sometimes you might feel left with the question, why so abrupt? If an academic evaluation system or procedure grows old, like trees do, it requires good governing to initiate new ideas as nuclei to blossom and develop into new concepts, like new sprouts, to replace those that were the pillars of what we once thought was good. The timing is crucial as not to wait until the prevailing trees have succumbed or thrown from their roots but to introduce renewal and change while the old are still appreciated and valued in their splendour.

The gains of change are in the perception of the beholder as opportunity awaits. On one hand current Recognition and Reward policies offer alternative ways to an academic career for the individual. On the other it offers great potential to create optimal conditions to establish a much-needed team science concept. One that is not governed by stringent academic criteria for appointing staff. The question remains if it is self-serving or for the benefit of our research community, I do believe and sincerely hope for the latter.

Our current annual report is again packed with division highlights, opinions, new personal grants and contracts, our new column Arts & Sciences, and all awards and prizes bestowed upon our fellow CARIM employees in this exceptional year.

This is CARIM 2020.

I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

01

PROFILE

Founded in 1988, the Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, has established itself over the last three 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 disease 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 partners, and the results of scientific research are published in high-ranking international journals. Masters students, PhD candidates and MD students are trained to become independent researchers, and postdocs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three research divisions, 'Blood', 'Vessels' and 'Heart', comprising six programmes: 1. Blood coagulation, venous thrombosis & bleeding; 2. Atherosclerosis, arterial thrombosis & stroke; 3. Vascular complications of diabetes & hypertension; 4. Regenerative & reconstructive cardiovascular medicine; 5. Structural heart failure and 6. Complex arrhythmias. These six programmes together host 21 Principal Investigator (PI) groups, which represent independent research, infrastructural and financial units within CARIM. CARIM addresses key scientific questions through optimal combinations of CARIM programmes, PIs, researchers, and infrastructure in an optimal team science setting combining track record, expertise, and innovative content and to disseminate results to scientific communities and to society as a whole.

All three divisions involve basic as well as clinical programmes, and are led according to a shared governance principle, executed by the division leader together with basic and clinical scientists from the division. This shared governance system enables shared responsibility for the scientific progress of programmes, for linking activities and seeking collaborations between PIs and divisions and for mentoring of PhD candidates, postdocs and tenure tracks. The individual PIs are responsible for the financial management of their groups. Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, stiff ambitions, good facilities and a critical learning environment. 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 appointed as research school by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Commission. CARIM researchers have been very active in EU networking activities and the establishment of (inter)national alliances. In total, CARIM is currently involved in more than 30 European projects; including ten ITN programmes with a total number of more than 30 Early Stage Researchers allocated to CARIM.

KEY FIGURES 2020

ANNUAL BUDGET: **21.5** M€

NEW CONTRACTS AND GRANTS: **9.4** M€

RESEARCHERS: **155.6** FTE (97 INTERNAL PHD CANDIDATES)

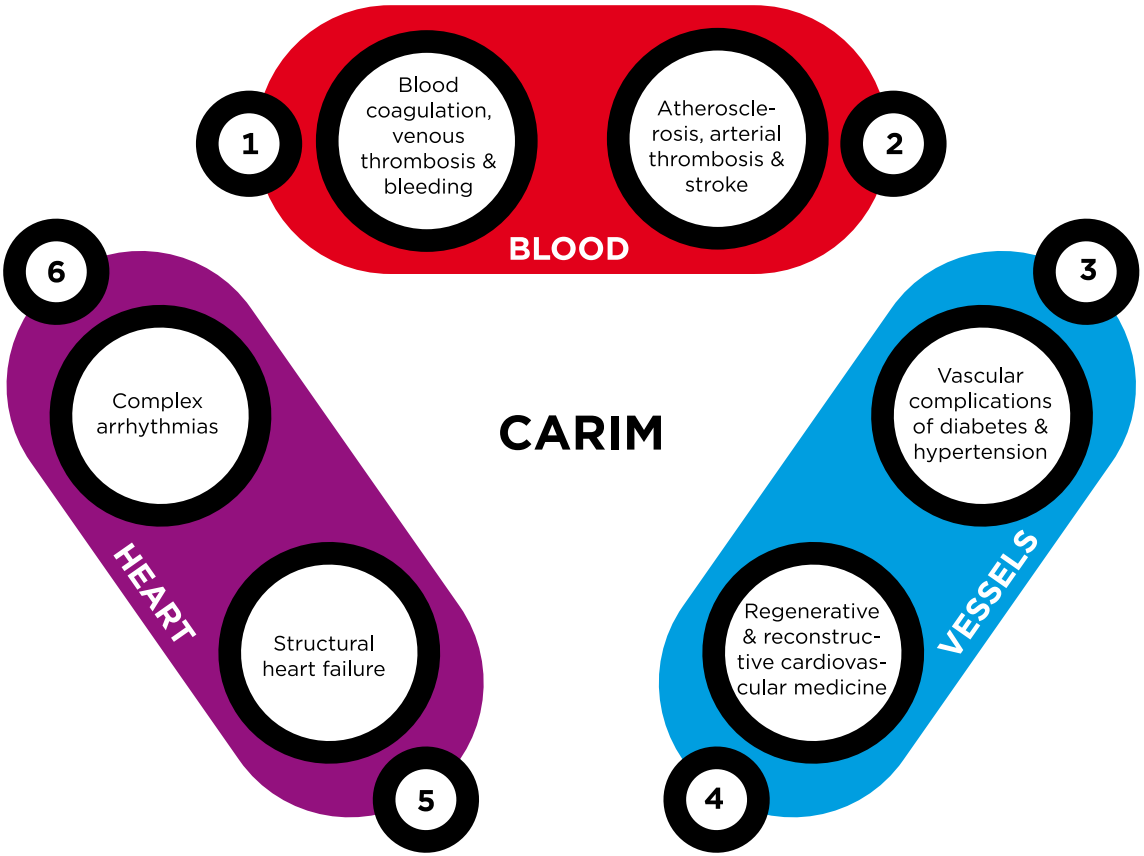
TECHNICAL AND SUPPORTING STAFF: **48.0** FTE

DEPARTMENTS/DISCIPLINES: **17**

SCIENTIFIC ARTICLES: **858** (SCI/SSCI: 660)

PHD THESES: **36**

CARIM has a long-lasting tradition of executing programmes in collaboration with industry, sharing its expertise but maintaining its independence as reflected by the right to publish. Ongoing collaborations with industry include, among others, Medtronic, Bayer, Roche, Abbot, Siemens and Philips. Furthermore, CARIM researchers are involved in other Public Private collaborations in (inter) national networks such as NHF CVON, Horizon 2020, ERA-CVD, Interreg and Leducq Transatlantic Network. To translate research into clinical practice, CARIM joined forces with the Heart+Vascular Center (HVC) of Maastricht UMC+, aiming to develop into a unique internationally recognised centre of excellence in cardiovascular medicine, including translational research and medical care.



WELL-BEING, DIVERSITY AND INCLUSIVITY AT CARIM

In recent years, interest in diversity and inclusivity has been growing in academia. For example, inclusivity is one of the main goals of our university's current strategic programme: 'Community at the Core'.[1] A transparent, hospitable and inclusive work environment is also important for creativity and productivity, and for the sustainability of long-term appointments of CARIM staff. Moreover, these elements are essential for creating a more equitable working atmosphere and for increasing diversity.

Greater diversity in leadership and management is not only a matter of equality and human rights, but also an important strategy towards more effective utilisation of everyone's qualifications and to improve organisational performance. One of the major components in the current diversity and inclusivity discussions is gender equality. While approximately half of the current medical students are women, significantly fewer women than men hold leadership and management positions within academic health centres.[2] Only 18% of full professors in Europe (23% in the Netherlands); 13% of heads of higher education institutions and 22% of board members involved in research decision-making are women.[3] The gender leadership gap has been slowly reduced over the years and tends to be narrower within hospitals than within the academic community.[3] Nonetheless, top hierarchical positions continue to be primarily occupied by men. CARIM is no exception, with 40% female employees overall and 40-50% female PhD candidates and postdocs, but with significantly fewer women in leadership positions.

Insights into working conditions are crucial for the development of policies and other initiatives that contribute to the well-being of CARIM employees, the inclusivity and diversity of CARIM, and, in the long run, its competitiveness. To this end, CARIM's Strategic Board was asked to conduct a survey on the way CARIM employees experience their work, which was done in collaboration with the UM Diversity & Inclusivity Office. The Diversity & Inclusivity Office was responsible for the survey design, data collection and reporting of the results. The survey was conducted as an anonymous online questionnaire in October 2020. Raw data were only handled by researchers in the Diversity & Inclusivity Office and were not shared with CARIM, which only received aggregate figures. Initial findings were presented during the annual CARIM Symposium on 25 November 2020. Subsequently, the CARIM Strategic Board and the Diversity & Inclusivity Office discussed the findings of the survey.

The response rate was high, with 43% of all invited employees participating in the survey, suggesting that this is indeed a topic that people at CARIM care about. There was also a good gender balance among respondents, with 45% of all respondents being female, 49% male, and 6% who did not answer this question, closely corresponding to the

1 https://www.maastrichtuniversity.nl/about-um/diversity-inclusivity

2 Kuhlmann et all. Human Resources for Health (2017) 15:2: Closing the gender leadership gap: a multi-centre cross-country comparison of women in management and leadership in academic health centres in the European Union. DOI 10.1186/s12960-016-0175-y

3 https://www.rathenau.nl/en/science-figures/personnel/women-science/women-academia
https://www.catalyst.org/research/women-in-academia/

gender distribution of all CARIM employees. The response rate was 44% among support staff and 43% for scientific personnel. In the latter group, response rates were 35% among PhD candidates, 50% among post-docs, 52% among assistant professors, 84% among associate professors and 47% among full professors.

The survey revealed a number of positive aspects, as well as several characteristics that could be improved. Respondents were generally very positive about their relationships with colleagues and about the working atmosphere in their departments. A large majority were satisfied with the working climate and CARIM leadership. The majority of respondents (72.7%) also felt that CARIM is, overall, inclusive and that leadership roles are accessible to both men and women. However, slightly less than 20% of female respondents perceived CARIM as less inclusive for women than for men. Similarly, the feeling that leadership roles are more accessible to men was stronger among female employees. General findings among all respondents included a call for more transparency and better communication, as well as opportunities for improvements relating to recognition and rewards. For example, promotions are perceived as important steps of individual development, independent of gender and function. However, requirements for promotions are not frequently discussed between staff members (all ranks) and department heads/supervisors, and the requirements for promotion were perceived as non-transparent. Research was considered the most important task with regard to being promoted, followed by service work, clinical duties, education and administrative work. However, a majority of respondents from academic staff (56%) felt that the burden of service work is often shouldered by the same employees. Service work was also perceived to be more appreciated by colleagues than by supervisors or management. Finally, more than one third of respondents felt worn out after work and had difficulties focusing on or enjoying their private life after work, with three quarters of all respondents stating that their work requires extra hours beyond their contractual obligation.

The Strategic Board greatly appreciates the input provided by all CARIM employees. The results of this survey provide a starting point for further improving the already high level of appreciation and inclusivity at CARIM. To this end, the Strategic Board and the Diversity & Inclusivity Office have proposed a number of recommendations to the CARIM Board, which are summarised in **Table 1**.

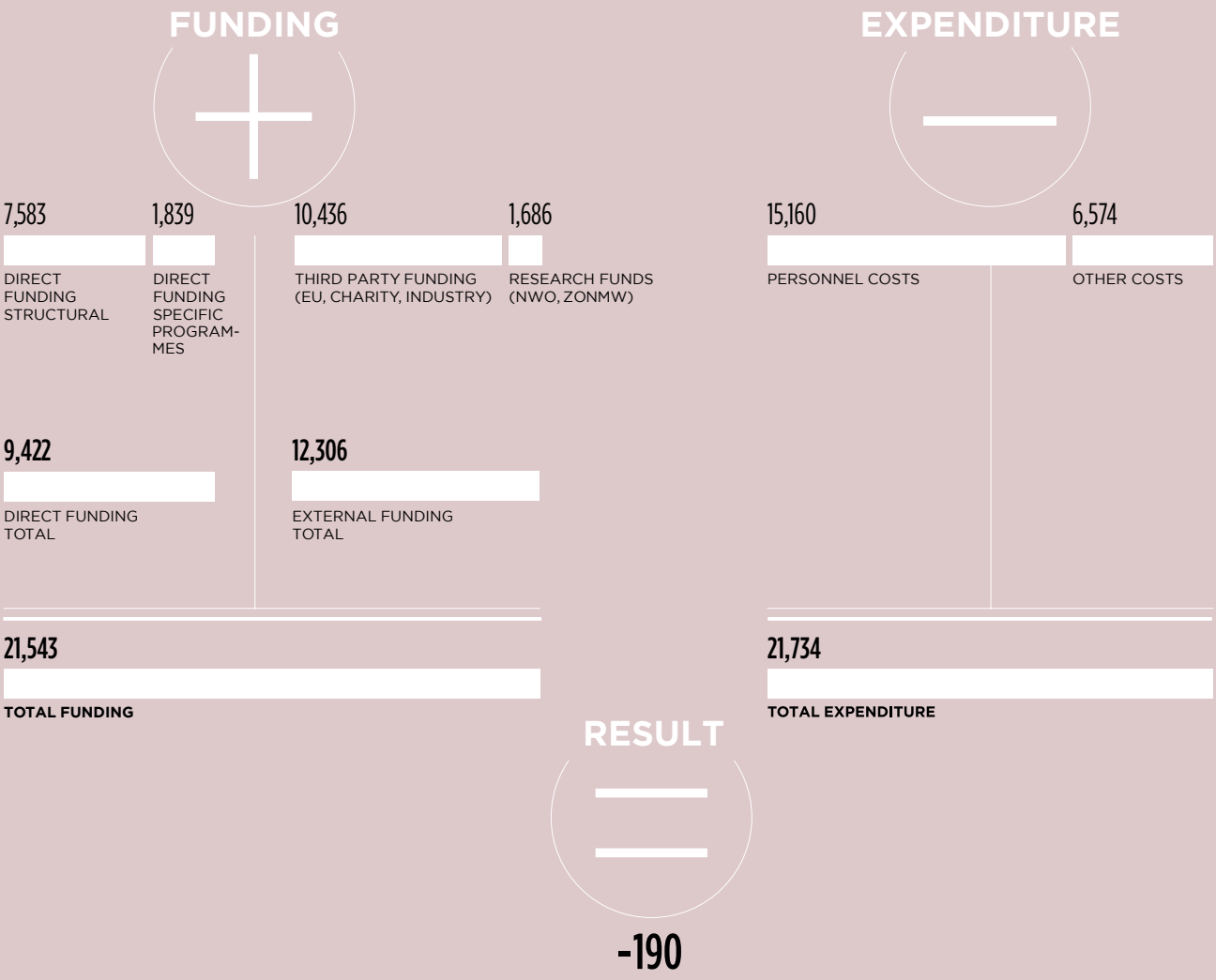
TRANSPARENCY AND COMMUNICATION	WELL-BEING AND RECOGNITION AND REWARDS
• Communicate opportunities and personalised criteria for promotion more transparently and on a permanent basis in annual talks with all employees, including support staff. • Communicate opportunities and criteria for becoming a PI or a member of decision-making bodies, to improve transparency. • Address ambitions explicitly. Also, explain limitations and end-points of career paths. • Publicly advertise available positions in decision-making bodies within CARIM, the university, or national or international scientific organisations.	• Include service tasks, educational and administrative tasks in the periodic evaluations of all employees and, if applicable, incorporate these in promotion criteria. • Streamline evaluation criteria with the spirit of 'Recognition and Rewards'. • Encourage managers to discuss workload and work–life balance during formal and informal meetings.
INCLUSIVITY IN CARIM DECISION-MAKING	**SOCIAL SAFETY**
• Publicly advertise available positions in decision-making bodies within CARIM, the university, or national or international scientific organisations. • Duration of membership of relevant bodies should be limited. • Actively encourage underrepresented groups to apply for leadership positions and try to promote women and minorities for promotion and membership of decision-making bodies, aiming for a balanced male/female ratio. • Selection committees need to be diverse and, preferably, trained in inclusive recruitment practices, and such inclusive recruitment practices should be adhered to when recruiting new CARIM members.	• Stimulate awareness and discussion about discrimination within CARIM and provide CARIM members with the tools necessary to engage in such conversations. • Define routes towards support. Ensure that complaint procedures are streamlined within the institution, that managers and employees are informed of them and that HR advisors and confidential advisors participate in them. • Promote a culture of addressing unwanted behaviour (regarding yourself or someone else).

TABLE 1

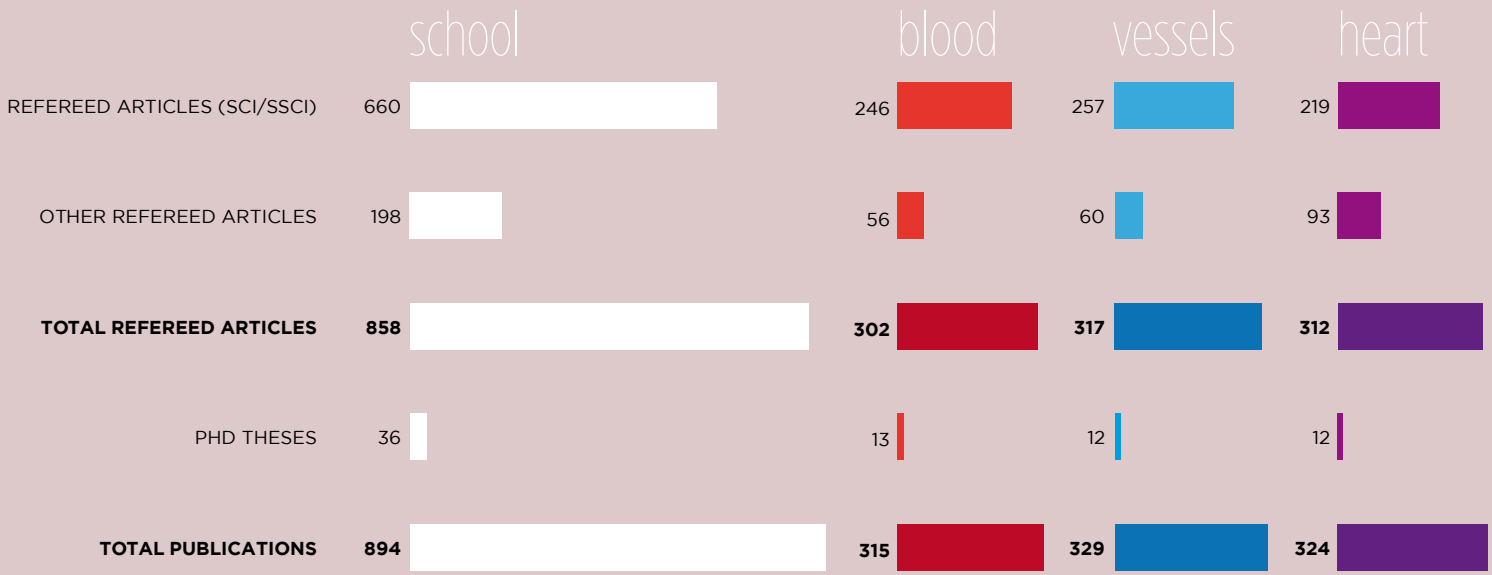
FACTS AND FIGURES

02

FUNDING AND EXPENDITURE (K€) AT INSTITUTIONAL LEVEL 2020



RESEARCH OUTPUT IN 2020

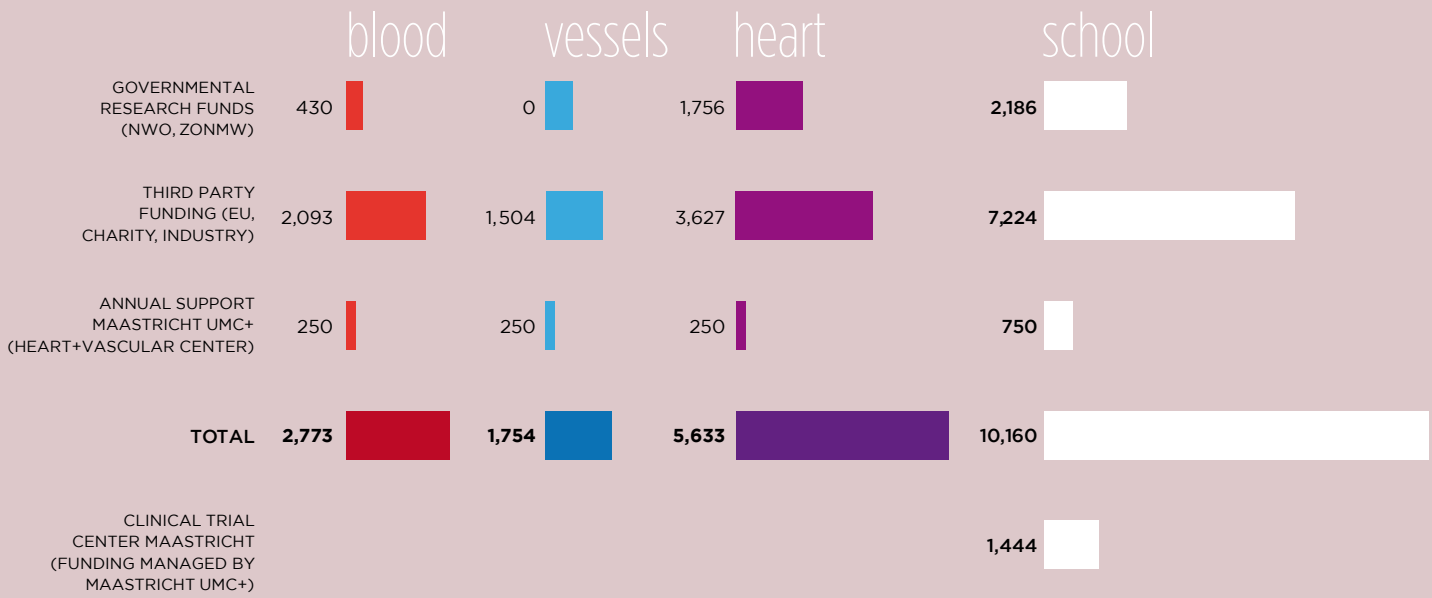


ACADEMIC STAFF **28.1**

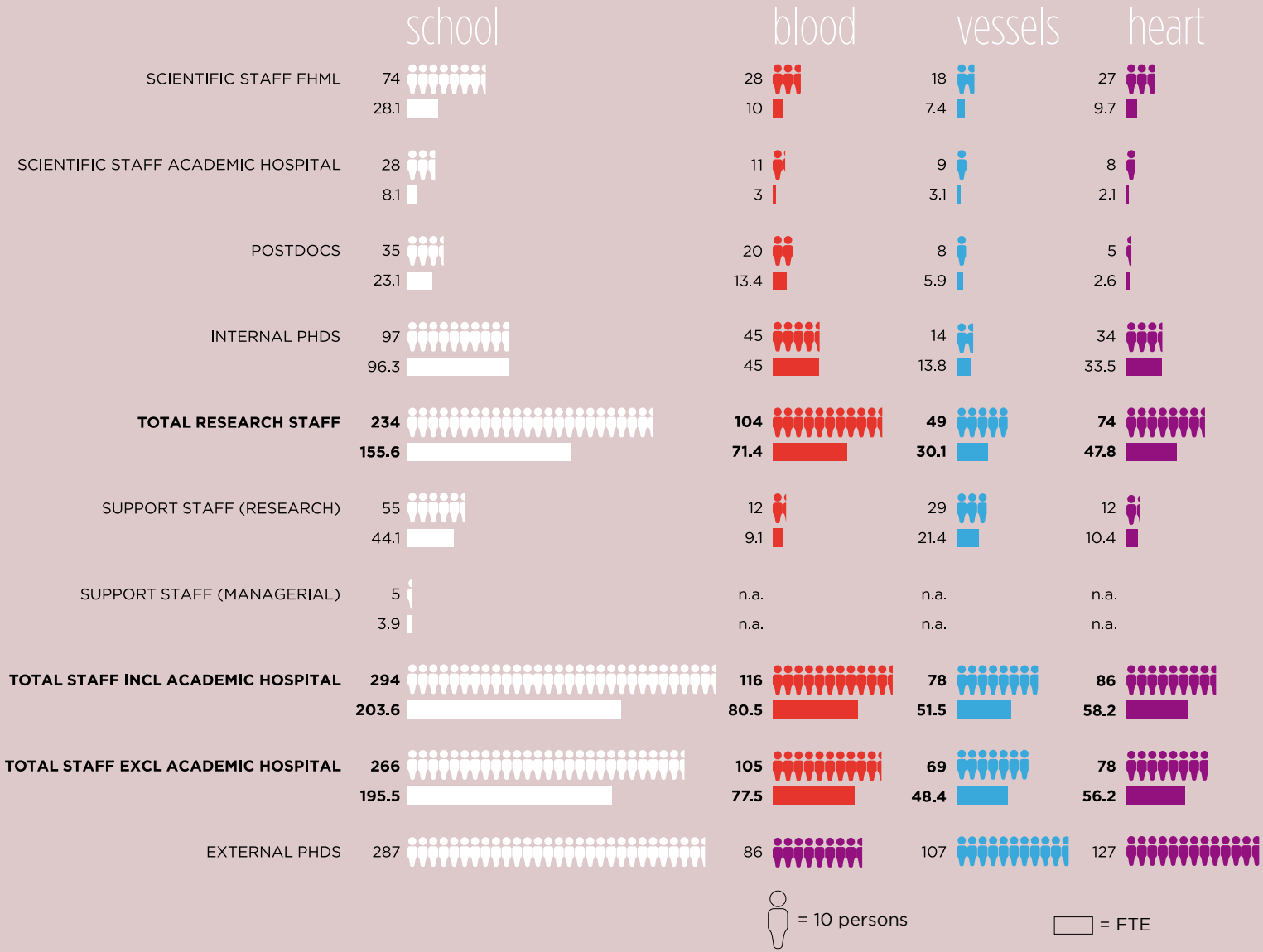
RATIO REFEREED ARTICLES PER FTE ACADEMIC STAFF **23**

Please note that the sum of the publications in the Divisions exceeds the total number of publications at School level, due to a double counting of publications with authors from different Divisions.

NEW CONTRACTS AND GRANTS (K€) IN 2020



SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2020



HIGHLIGHT
DIVISION BLOOD

ROB HOLTACKERS & CASPER MIHL

Advances in cardiovascular imaging: paving the way towards personalised treatment

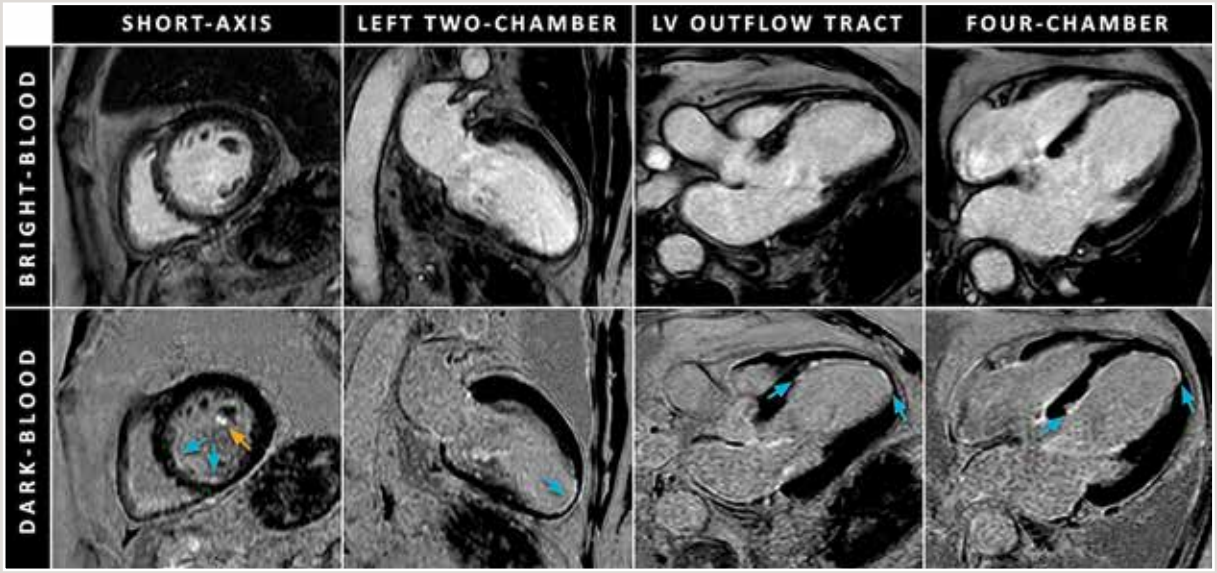
In the past 15 years, cardiovascular disease (CVD) death rates have seen a strong decline, mainly thanks to cardiovascular risk factor control interventions. Nevertheless, CVD remains the leading cause of death worldwide for both men and women [1]. Although overall CVD mortality has now fallen steadily for several decades, age-adjusted mortality rates are rising and an increasing number of individuals with non-fatal CVD live with chronic disabilities and impaired quality of life [2,3]. The associated financial impact on the health care system is huge, with CVD total costs already approaching 4% of the gross domestic product in the United States [4]. In the near future, an increase in morbidity and thus in prevalence is expected, which underlines the need for prevention, early detection and treatment of this growing health care problem [5].

Coronary artery disease (CAD) is by far the largest contributor to CVD, accounting for over 50% of all CVD-related deaths. In recent years, non-invasive cardiac imaging techniques have played an increasing role in the (early) detection of CAD and the assessment of myocardial viability. Both cardiovascular magnetic resonance (CMR) and coronary computed tomographic angiography (CTA) can aid in diagnostic workup and potential treatment of CVD.

In CMR, late gadolinium enhancement (LGE) is a widely used technique that has been extensively validated as a marker of irreversible myocardial damage in clinical and preclinical models. Since its initial validation against histology approximately two decades ago [6], LGE has gained wide acceptance and is now considered the reference standard for the non-invasive assessment of myocardial viability. Myocardial enhancement is strongly associated with adverse outcomes and has proved to be superior to volumes and function.

In current clinical routine, 2D LGE images are acquired during breath-holding, where the normal myocardium appears black, and areas of infarcted myocardium appear bright. However, since the blood pool has a signal intensity that is almost as bright as that of the neighbouring subendocardial infarct tissue, an accurate assessment of the scar-blood barrier is compromised. As a result, the apparent scar volume can be substantially underestimated or even completely obscured.

HIGHLIGHT



In collaboration with King's College London, we aimed to improve poor scar-to-blood contrast by developing a novel, readily available "dark-blood" LGE method [7]. Compared with conventional LGE, dark-blood LGE showed improved scar-to-blood contrast, while maintaining good contrast between scar tissue and normal myocardium (**Figure 1**). In a subsequent study, dark-blood LGE showed superior detection of ischemic scar patterns, improved observer confidence, and increased image quality in a cohort of 300 patients [8]. These findings led to Magna Cum Laude awards from the International Society for Magnetic Resonance in Medicine (ISMRM) and the European Society of Cardiovascular Radiology (ESCR) in 2019. Currently, various centres around the globe have already adopted this novel dark-blood LGE approach in their clinical routine.

FIGURE 1 Conventional bright-blood and novel dark-blood late gadolinium enhancement (LGE) CMR images acquired in multiple cardiac views. The cyan arrows indicate the infarcted region, while the orange arrow indicates an area of intracardiac thrombus. At the septal wall in the LV outflow tract images, dark-blood LGE clearly visualises the scar/blood barrier, while this border cannot be observed using conventional LGE alone. Image adapted from Holtackers et al. with permission [8].

HIGHLIGHT

Another important limitation in the detection of subendocardial scar tissue using conventional 2D LGE techniques is the rather thick (8-10 mm) slices that are routinely acquired. Subtle areas of scarring may remain unrecognised or cannot be accurately assessed. Additionally, such 2D images can only be viewed in the plane in which they were acquired, preventing any options for multiplanar or 3D reconstructions. Although 3D techniques exist that allow for the acquisition of much thinner slices and thus revealing more detail in the acquired images, these are not straightforward for LGE imaging.

The increased spatial resolution, and thus the increased number of slices, comes at the cost of increased scan duration, in which the contrast agent concentration gradually decreases during scanning due to contrast washout. This varying concentration often leads to undesired image contrast, hampering the use of 3D acquisitions with high isotropic resolution for LGE. Therefore, a novel dynamic timing mechanism was developed that compensates for contrast washout and thereby enables 3D LGE imaging with high isotropic resolution and optimal dark-blood image contrast [9]. The results led to another Magna cum Laude award from the ESCR in 2020. Additionally, compared to conventional 2D LGE, where images are acquired during breath-holding, the patient can now breathe freely. This not only leads to increased patient comfort and endurance, but also enables high quality imaging in patients with severe respiratory diseases.

Clinical benefits of the combined high isotropic resolution and optimised dark-blood contrast reside in the improved detection and visualisation of thin subendocardial scar patterns. The importance of accurate scar detection is underlined by a recent study, showing that, compared with recognised myocardial infarction patients, those with unrecognised myocardial infarction were less likely to receive guideline-directed medical therapies and had an increased risk of heart failure hospitalisation [10]. Furthermore, there is increasing evidence that scar tissue should be avoided in left-ventricular (LV) lead placement. Pacing in scar regions can affect cardiac resynchronisation therapy (CRT) by causing regional slowing of conduction. Also, positioning the LV-lead in scar tissue is associated with a diminished clinical response to CRT and with proarrhythmic events [11]. In addition to avoiding scar tissue, there is a preference for the region of latest activation on the LV inferolateral wall, bearing in mind that the rationale of biventricular pacing is to resynchronise the LV.

The demonstrated improved scar demarcation and observer confidence [9] represent promising steps towards improved detection and qualification of complex ventricular or supraventricular scar architectures. The clinical relevance has recently been illustrated in a patient with a huge LV pseudoaneurysm [12]. This may pave the way for improved diagnostic accuracy and prognosis, but also plays an important role in the work-up towards personalised treatment of patients with ventricular or supraventricular tachyarrhythmias.

In addition to LGE imaging, the role of coronary CTA as a non-invasive diagnostic imaging technique in the evaluation of CAD has been well established. High negative predictive value and high sensitivity of coronary CTA have been reported (99% and 94%, respectively), making coronary CTA an ideal tool to rule out CAD in patients presenting with stable chest pain [13]. In addition, the presence of obstructive CAD on coronary CTA has proved to be a strong predictor of the occurrence of coronary events [14].

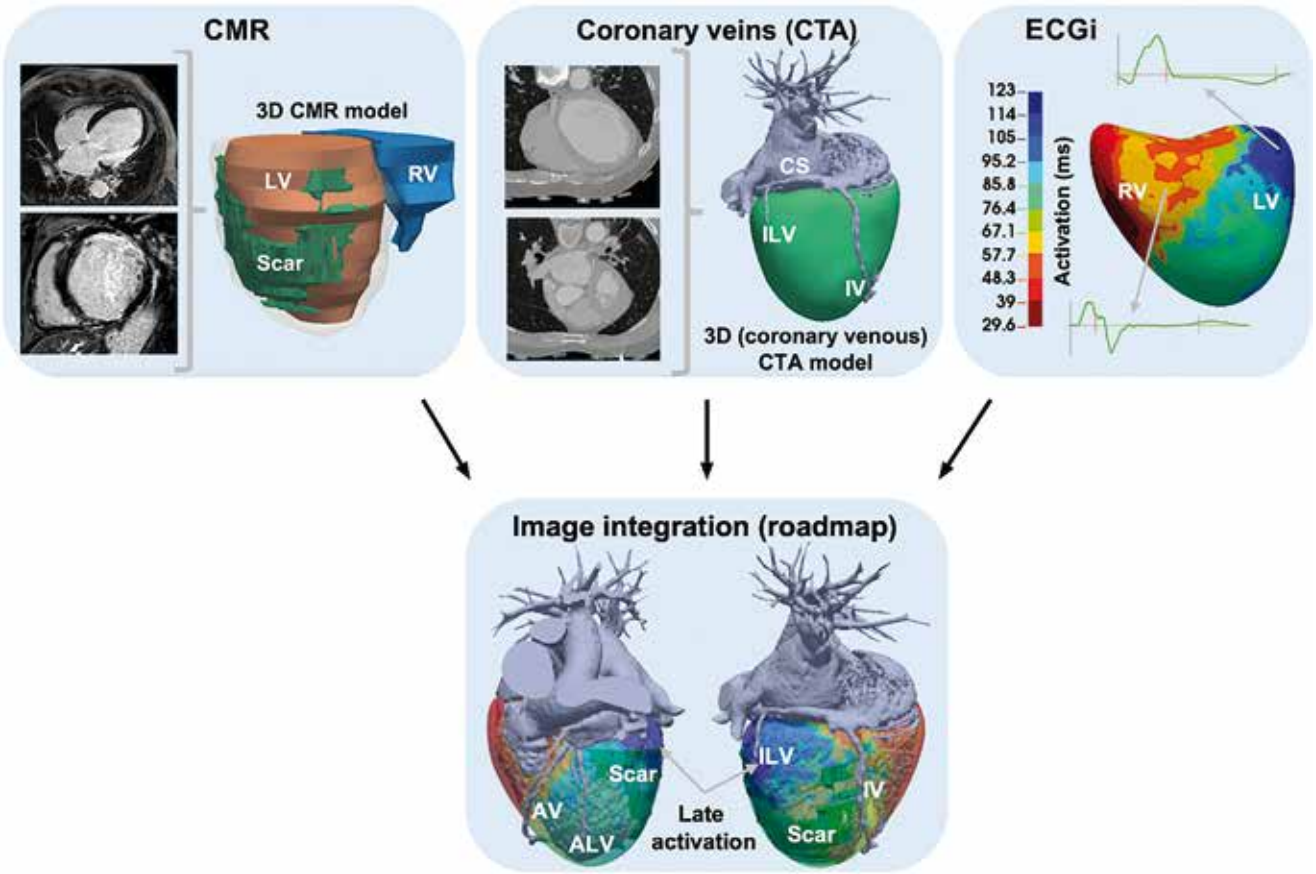

CMR
3D CMR model
LV
RV
Scar
Coronary veins (CTA)
CS
ILV
IV
3D (coronary venous) CTA model
ECGi
123
114
105
95.2
85.8
76.4
67.1
57.7
48.3
39
29.6
Activation (ms)
RV
LV
Image integration (roadmap)
Scar
AV
ALV
Late activation
ILV
IV
Scar

FIGURE 2

FIGURE 2 Integration of LGE CMR, coronary veins CTA, and ECGi to obtain a CRT roadmap. The high spatial and temporal resolution of coronary CTA combined with the excellent soft tissue contrast of CMR prove to be a powerful combination for the assessment and analysis of myocardial substrate and anatomy. Image adapted from Nguyen et al. with permission [15].

In the last few years, however, CTA has broadened its horizon and is now playing an increasingly important role in the pre-interventional work-up as well. A dedicated imaging and injection protocol offers the potential to not only evaluate the coronary arteries, but also to allow for depiction of the venous coronary anatomy. Recently, the feasibility of a patient-tailored lead implantation by integrating the coronary venous anatomy from CTA with focal scar localisation on LGE has been evaluated [15]. This multi-modality CRT-roadmap provides detailed imaging of the coronary veins and scar substrate, as well as high-resolution epicardial electrical activation patterns, facilitating decision-making during implantation (**Figure 2**).

Although multimodality image-guided work-up plays an increasingly important role in personalised treatment, direct image-guided therapy would be even more desirable. The feasibility of real-time CMR-guided electrophysiology (EP) has been demonstrated in both preclinical and clinical studies. The growing availability of MR-compatible EP equipment, including (active tracking) mapping and ablation catheters and ablation systems, has accelerated the clinical implementation of interventional CMR (iCMR) procedures worldwide. In recent years, the Departments of Cardiology and Radiology & Nuclear Medicine have collaborated intensively to enable state-of-the-art iCMR procedures in an existing radiology space (**Figure 3**). In the early months of 2021, the first iCMR procedures for supraventricular arrythmias were successfully performed at MUMC. CMR provides a more detailed visualisation of the cardiac anatomy than conventional fluoroscopy, facilitating the determination of the optimal ablation strategy and decision-making during ablation itself. Additionally, CMR enables per- and post-procedural imaging, which provides information about the tissue characteristics and function during and after treatment. As no harmful X-ray radiation is used for CMR, iCMR can be performed with zero radiation dose, which is beneficial for both patient and EP personnel.

In summary, the continuing technological advances in non-invasive imaging techniques mean that these techniques play an increasingly important role in all facets of the fight against the rising burden of cardiovascular diseases, including early detection, work-up, treatment strategy and planning, treatment itself, post-procedural evaluation, and follow-up.

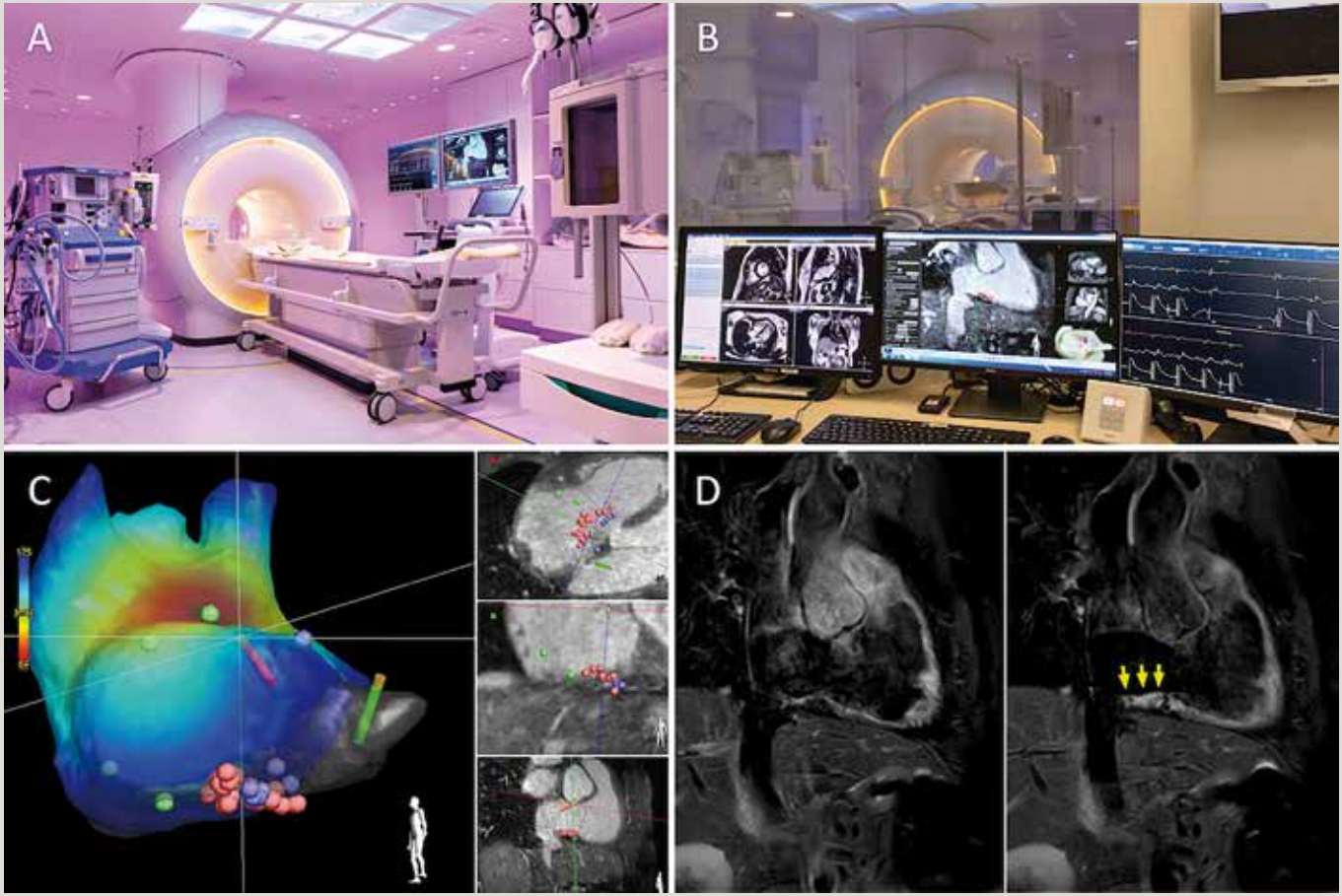


FIGURE 3 Transformation of an existing radiology space into an iCMR suite (A) and control room (B). During the procedure, an electrical colour map of the right atria, including the ablation points, can be projected onto the high-resolution CMR model to confirm the desired bidirectional electrical block (C). Immediately after ablation, T2-weighted MR imaging (D) can be performed to visualise oedema near the ablation area (right, yellow arrows) and compare it with the pre-ablation oedema imaging (left).

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INTERVIEW

PIETER VAN PAASSEN

Immunology research in times of COVID

If your primary expertise is immunology of vascular disorders, specifically those of the smaller blood vessels, and even more specifically in relation to organs, the COVID-19 pandemic offers some interesting opportunities. Internist-immunologist Pieter van Paassen saw those opportunities and acted upon them. He consulted with colleagues from CARIM's Biochemistry and Blood Coagulation Departments, and together they came to valuable insights, which will hopefully be translated into medication for severely ill patients with COVID-19.

Pieter van Paassen likes to be honest and realistic in what he has to say. So he first of all would like to tone down the recent story in a local newspaper which portrayed him as "the man who unravelled the way corona virus induces our immune system to overreact." "As a Principal Investigator, I led the project, but of course I'm not doing it on my own. The strength of our work lies particularly in the collaboration with various groups within CARIM: the Biochemistry group of Schurgers, Reutelingsperger and Nicolaes, and the Blood Coagulation group of Spronk and Ten Cate. Other major contributors are the young physician-researchers in immunology, like Matthias Busch, Sjoerd Timmermans and Joop Aendekerk. We had previously already combined our knowledge of the immunology and biochemistry of specific disease entities like vasculitis and thrombotic microangiopathy with theirs, which led to very satisfactory results."

MAJOR LINK IN THE CHAIN

Together, they became the first in the world to argue convincingly how in a corona infection, our innate immune system increases the tendency towards coagulation and damaged vessel walls. This means that less blood is transported to the organs and oxygen deficiencies arise, with all the attendant consequences for the lungs and other organs. An important link in this process is the neutrophil (white blood cell) and its high level of activation by the complement system, which is an evolutionarily ancient but highly effective part of the innate immune system. Normally, neutrophils respond during intense activation, as in the case of severe infections, by expelling part of their nuclear content in a network of fibres. This network contains, among other things, DNA and proteins, which in normal situations eliminate the infecting micro-organisms with minimal damage to the body. “But whereas this normally happens in an organised way, it appears that in patients with COVID-19, especially those who are severely ill, small ruptures arise in the network. This also releases histones into the circulation and the pulmonary tissue, which are highly toxic and activate coagulation. This leads to thrombosis and vessel wall damage, which in turn causes oxygen deficiencies and further immune activation and organ damage.” Their study, in which they described this concept for the first time, was published in the journal *Circulation* last year.

MEDICATION

The Department of Biochemistry has been researching the toxic effects of histones for several years. They developed a drug that neutralises the histones: M6229 (M for Maastricht, plus the postal code of Maastricht University). It has been patented and subsequently licensed to a local company. Together with the immunologists, the research group is hoping to be able to administer the drug to the first COVID-19 patients as soon as it has been approved by the competent authorities, perhaps even in early June.

A second drug which is being investigated by his group is IFX-1, or vilobelimab. Van Paassen has already administered the drug in a research context to patients with vasculitis (inflammation of the vessel walls). It inhibits C5a, a key protein within the complement cascade which plays an essential part in the activation (or overactivation) of neutrophils in COVID-19. “When I noticed the similarities between vasculitis and COVID-19, I contacted the German company which is developing IFX-1. It turned out that they had successfully treated a number of patients in Wuhan in March 2020, and that they were developing a protocol through their contact at the Amsterdam University Medical centre, and we were able to join in immediately.” The results of the phase I study were promising. “The mortality rate was halved, but of course this concerned a small group. Currently the phase III study is in progress, in which we aim to include 360 severely ill intubated patients with COVID-19.”

HECTIC PERIOD

During the interview, Van Paassen is constantly being interrupted by phone calls on COVID-19 patients in the ICU who might or might not be included in his current study, or have to be referred to a follow-up study. This is what it’s like, doing scientific research while as a doctor you are going through what may well be one of the most hectic periods in your career. At the same time this translational research, which is solidly grounded in the clinic, with large cohorts of well-characterised immunological disease entities, usually having vascular bed pathology in common, obviously also gives him a lot of energy. “It’s great to see how this fits in with basic research in CARIM context. In my role as the Principal Investigator for the southern region of ‘the

Netherlands B-cell and Antibody Network', I also try to link the most recent developments in immunological research in the Netherlands to the techniques developed by CARIM's biochemistry group. It's a wonderful challenge to strengthen the links between immunology and biochemistry, partly by involving PhD students."

COMPLEX SYSTEM

But back to COVID-19. Van Paassen emphasises that many questions about the virus remain, and that simply saying that the virus "makes the immune system run riot" is oversimplifying the facts. "As soon as the immune system is discussed outside scientific circles, the story is usually incorrect or at least incomplete. Partly because the system is so complicated. It also plays an important part in repair work within the body, for instance via a subset of the macrophages. So it is not always clear what exactly detecting an 'activated' immune system implies at tissue level. When researchers in Amsterdam autopsied deceased COVID-19 patients, the brain tissues did not contain the virus, but did show the pathological reaction: vascular changes and the tendency towards coagulation. Although this process is initiated by the infection, it then disengages, and if it's insufficiently corrected it can, as it were, influence processes autonomously." He also likens the residual symptoms that many ex-COVID-19 patients experience to a smouldering fire that occasionally flares up again. "Maybe the repair processes are still in full swing, trying to restore tissues to their former healthy status, or maybe the immune system, or parts of it, remains in a state of activation for too long, with its corresponding symptoms. The recovery of affected tissues may take a long time, as is known in the case of the kidneys. The chronic fatigue that people report, for example, is a fairly common characteristic of many viral infections."

COMPLEX PUZZLE

Van Paassen compares the action of the complex immune system with a huge dashboard full of lights. The lights stand for the many different types of cell involved, which communicate with each other through "messenger molecules" like cytokines. "You should imagine that in an undisturbed situation, that is, in a patient who has no infection, no cancer and no stress, the immune system is at rest. Most of the lights are then in stand-by mode. As soon as there is danger, like a virus or a tumour cell, the system awakens. Genetically, this means that the production of the relevant cells and molecules is accelerated. So you see that 'lights' go on all across the landscape. We know that's how it goes in a viral infection. And it appears that in many people who have gone through COVID-19, many of the lights fail to go out. So the immune system remains on the alert." Research will have to show whether this does indeed explain the after-effects. Until that time, Van Paassen is happy to have contributed, in close collaboration with his CARIM colleagues, to solving the COVID-19 puzzle.

Dr Pieter van Paassen studied medicine at Groningen University and was trained to become an internist-nephrologist. In 2001, he switched to immunology, especially because of his interest in the role of the immune system in systemic autoimmune diseases like vasculitis, and in the pathology of organs, especially the kidneys and the heart. He is the chair of the national vasculitis task force. The Netherlands Federation of University Medical Centres (NFU) has recognised the clinical work done by his group as a Centre of Expertise, and the group aims to be shortly recognised as a European Reference Network on Vasculitis. For many years he has led the Nier Werkgroep Limburg (Limburg Renal Registry), which is a treasure trove for research into immune-mediated kidney disorders.

INTERVIEW
JORDI HEIJMAN

NWO Vidi grant and CARIM PhD grant in 2020

2020 was a ‘very productive year’ for Jordi Heijman, as he received both a Vidi grant and a CARIM PhD grant. “I was really ready for that. I obtained my Veni grant in 2015 and now the Vidi, five years later, upon my first attempt. But in the meantime I applied for a dozen other grants which I didn’t get. So perseverance might be the most important quality for a scientist.”

He can still recall the exact date on which the Dutch Research Council NWO issued the press release presenting de Vidi laureates in late 2020: 4 November. “It was the day our daughter was born. It was an induced labour, so I knew in advance that it was going to be a very interesting day.” This new addition to his family (their second child) also marked the expansion of his research group. But more about that later; first we discuss the nature of his research.

RESEARCHER AMONG CARDIOLOGISTS

Since the time of his knowledge engineering studies, for which he did his degree project at the Department of Cardiology at Maastricht UMC+, his research has revolved around computer models of the electrical activity of the heart. These models are intended to clarify the origin of cardiac arrhythmias and possibly improve their treatment. The fact that he opted for a workspace not within the university but among cardiologists at the hospital only increased his commitment to improve patient care. “My research is increasingly moving in the direction of clinical applications, and my talks with people at the coffee machine here are most inspiring in that respect. That’s one of the things that I miss now, with the corona restrictions.”

VENI RESEARCH IN 2015

The research for which he received the Veni grant concerned the role that calcium handling in cardiomyocytes plays in the development of arrhythmias. Calcium plays a major role in these cells as it links the heart’s electric activity to their contraction. If, however, calcium is released spontaneously from intracellular storage organelles at the wrong moment, this can trigger an extra heartbeat, which can initiate arrhythmia. “Part of my Veni research involved identifying the factors that contribute to such spontaneous calcium releases. For instance, we saw that changes in the localisation of ion channels could be one of the causes. When our computer model kept all other factors equal – which is almost impossible in lab experiments but is perfectly possible in models – and only relocated the ion channels to a different part of the cell, this was enough to influence the likelihood of spontaneous calcium releases.”

VIDI 2020 RESEARCH

While one extra heartbeat is usually not such a big problem for a patient, persistent abnormal electric activity (i.e., arrhythmias) are. The question how calcium can influence arrhythmias in the longer term is the subject of the research for which he got the Vidi grant. “The heart is very good at adapting to changing circumstances, for example during exercise or as part of our day–night rhythm. And the ion channels in the cardiac muscle cells play a major role in this.” One of Heijman’s research questions is therefore how electrical signals, via calcium, change the transcriptional regulation of the ion channels.

His computer model studies are always linked to experimental data. “Combining the two can offer better insights. Experimental research cannot yet relocate the ion channels in a cardiac cell, and determine the role of their distribution. But when we look at the cells under the microscope, we do see

IF YOU’RE MOTIVATED, YOU CAN LEARN ANYTHING

that the distribution of some ion channels is altered in certain diseases. We can then simulate such changes in a computer model, which in turn helps to develop better experiments."

For him, everything revolves around the potential applications in patient care, in both the short and longer term. "So fundamental research is also essential, because we can reap the benefits in ten years' time. Let's be honest: many of the drugs currently used to treat cardiac arrhythmias were discovered by accident. So far, we haven't been very successful in developing new medications based on mechanisms. But we've made major steps towards greater insights."

EXPANSION OF THE RESEARCH GROUP

Thanks to the 2020 grants, his research group can now be doubled in size. Over the coming year, three new PhD candidates and a postdoc researcher will be added to the team. Heijman himself will be taking a course in PhD supervision, in order to support them even more effectively. "In my opinion, those who are open to it receive excellent support at Maastricht University. Putting together a team that works together well is a challenge, but I'm very much looking forward to expanding my group. I try to turn the job interviews into real conversations, to allow me to sense whether we really click. To me, open communication is really important for effective selection." The main thing he is looking for is someone's motivation. "I'm not so much interested in whether someone already possesses all the skills. If you're motivated, you can learn anything. If you're really willing to go for it, this is the greatest job you could imagine."

MAKING CHOICES ABOUT AUXILIARY ACTIVITIES

He has to admit, though, that the job is becoming ever more challenging. As the list of his additional tasks continues to grow, from membership of the management team at the Department of Cardiology to that of the Strategic Board of CARIM, he realises that he will have to make choices. "I've always enjoyed doing lots of different things. If I want to become successful fast, the main thing is to focus on publishing high-quality papers, but it's also important to work on your network for the longer term. It's not always possible to predict what the future will bring or how certain activities may contribute. So far I've not been very good at making choices, and have said yes to almost everything I was asked for, just because I enjoy all of it." However, he knows that in the end, he will have to learn to say no occasionally.

WORK–LIFE BLEND

The main reason for learning to say no is not so much the infamous 'work-life balance'. "I'm more interested in the phrase 'work–life blend'. The former suggest a contrast, and that's not how it feels to me. The two go together and I get my energy from both. The flexibility of my job allows me to dovetail my work and family commitments as necessary. I want things to run smoothly at home, and I want to be a good father to my two kids, with a fair distribution of tasks. My wife also works full-time, so the planning is tight, but fortunately I don't need a lot of time for myself besides family and work." Nonetheless, he would like to learn better how to say 'no' over the next few years. Anybody have a vacancy for a nice auxiliary activity in the meantime?

Jordi Heijman studied knowledge engineering at Maastricht University, where he also received his PhD with full honours. His dissertation project was partly supervised by the Department of Cardiology and partly by the Department of Knowledge Engineering, and it earned him the CARIM Dissertation Award. He obtained a Veni grant in 2015, followed by a Vidi grant in 2020. In the same year, he received a CARIM PhD Grant.

GRANTS, PRIZES AND HIGHLIGHTS

03

SCIENTIFIC **HIGHLIGHTS**

IIn 2020, the successful work of our researchers was reflected in 858 scientific publications in peer refereed journals of which 660 Science Citation Index (SCI) articles excluding abstracts and 52 letters to the editor. 36 PhD candidates successfully defended their theses, 2.2 million Euros of funding were received in competition from national science foundations and 7.2 million Euros funding from third money parties, charities, EU framework programmes and industry. In 2020, the average impact factor of CARIM's 660 SCI publications reached 6.1.

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RESEARCH GRANTS AWARDED TO INDIVIDUALS

NWO TALENT SCHEME

The Dutch Research Council (NWO) has awarded a prestigious Vidi grant of 800,000 euros to Dr **Jordi Heijman** (Dept. of Cardiology). Jordi is one of three Vidi laureates from Maastricht University in 2020 (out of a total of 81 awardees selected from 503 eligible proposals) with a proposal entitled 'Time traveling to treat heart rhythm disorders'. Heart rhythm disorders remain a major cause of death. To identify improved therapies, Jordi and his team will use advanced computer models to determine the mechanisms through which heart rhythm disorders become more stable over time, a process involving changes in numerous components of the heart's electrical system occurring over milliseconds to days. Back in 2015, Jordi already received a NWO Veni grant for his research. See pages 32-35 for a full interview with Jordi.

NWO ASPASIA VANESSA VAN EMPEL

Dr **Vanessa van Empel** (Dept. of Cardiology) was awarded an Aspasia grant by NWO. Aspasia is linked to the Vidi and Vici competitions of the NWO Talent Scheme and is intended to accomplish a proportional distribution of female associate and full professors.

NHS DR E DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Pieter Goossens** (Dept. of Pathology) and Dr **Constance Baaten** (Dept. of Biochemistry) both received a grant. Pieter received a Senior Scientist grant of 465,000 euros for his project 'Plaque macrophage heterogeneity and beyond: Profiling the culprit phenotypes'. This grant will allow Pieter to continue his research activities within the Department of Pathology. Pieter is going to study macrophages. These are immune cells which are useful, but which can also be harmful. They can destroy pathogens, but they also increase hardening of the arteries (plaques). There are many different types of macrophage. Using a special new microscope, Pieter will pinpoint, for both men and women, exactly where specific macrophages are located in their plaques and what exactly they do there. He will then investigate how he can alter the behaviour of harmful macrophages. In future, researchers will be able to use this knowledge to develop new drugs against arteriosclerosis.

Constance received a Postdoc grant worth 265,000 euros for her project 'Thrombus architecture: elucidating the roles of adherens, tight and gap junctions'. With this grant, Constance wants to create the basis for a new drug to prevent dangerous blood clots. To this end, over the next few years she will immerse herself in the biology of blood platelets – blood cells that play a major role in forming blood clots and therefore also cause thrombosis. There are already drugs available that can prevent the formation of blood clots, but unfortunately these sometimes have such a strong effect that they cause haemorrhaging. Constance wants to study a new mechanism in the complex process of blood coagulation, to be able to adjust the balance very precisely. See pages 72-77 for a full interview with Pieter and Constance.

ZONMW OFF ROAD GRANT MIRANDA NABBEN

Dr **Miranda Nabben** (Depts. Genetics & Cell Biology and Clinical Genetics) was awarded an Off Road grant from ZonMw worth 100,000 euros for her project entitled 'Amino Acids as an unconventional therapy to treat diabetic cardiomyopathy'. In this out-of-the-box proposal she will investigate the potential of using specific amino acid supplementation to rescue the heart from lipid overload-induced insulin resistance. The study will be conducted using in vivo rodent and in vitro cell models, including primary rodent and human induced pluripotent stem cell-derived cardiomyocytes. The focus of the Off Road programme is on developing an innovative idea into a proof-of-concept, and includes high risk-high gain research.

KOOTSTRA FELLOWSHIPS

In 2020, **Federica de Majo** (Dept. of Molecular Genetics) was granted a Kootstra Talent Fellowship for postdocs for her proposed study entitled 'invEstigation of tissUe-specific penetRance Of laminoPAthies (EUROPA)'. The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific careers. The fellowship aims to facilitate talented researchers to develop their own research ideas and CV, and subsequently help increase their chances of obtaining personal grants at external funding agencies.

CONTRAST YOUNG INVESTIGATOR VOUCHER GRANT MAGDOLNA NAGY

Magdolna Nagy (Dept. of Biochemistry) was awarded with a CONTRAST YTP Young Investigator Voucher worth 50,000 euros for her proposed study entitled 'Effect of the contact activation on ischemia-reperfusion injury in stroke patients'. Her study will focus on dissecting the impact of the intrinsic activation in relation to risk factors for stroke and clinical outcomes and on determining the bridge between contact activation and NETs. This will be carried out in collaboration between Maastricht UMC+ and Erasmus MC. The CONTRAST YTP aims to stimulate and support young researchers in developing and evaluating high quality scientific ideas in stroke research, from fundamental and preclinical research to clinical research.

OTHER AWARDS, PRIZES AND GRANTS

CARIM PHD CALL

In 2020, the following projects were awarded in the CARIM PhD Call:

1) 'DynamX: Next-generation phenotyping of vascular mechanics' from Prof. **Tammo Delhaas**, Dr **Bart Spronck** and Prof. **Leon Schurgers**: Accelerated arterial stiffening increases cardiac workload, and eventually leads to heart failure. Aortic aneurysm rupture is lethal in 4–5 out of 10 cases. What do arterial stiffening and aneurysm rupture have in common, one may ask? Mechanics! In DynamX, we will implement a cross-departmental, cross-species mechanical phenotyping facility to facilitate translational arterial stiffness and aneurysm studies, bridging the gap between biology and mechanics. The recruited PhD candidate will develop two set-ups to study arterial and aneurysm mechanics both in animal and human samples, enabling comparison of human (unknown) mechanical disease phenotypes to specific animal models of arterial disease. DynamX is expected to lead to strong cross-pollination between UM and Maastricht UMC+/HVC and among CARIM labs/facilities in hypothesis generation, clinical data collection, and testing of human samples.

2) 'Virtual patient models for early detection and improved management of atrial fibrillation and its associated adverse outcomes (VIRTUAL-AF)' from Dr **Jordi Heijman**, Prof. **Harry Crijns**, Prof. **Hugo ten Cate** and Prof. **Uli Schotten**: The VIRTUAL-AF project will provide a highly innovative virtual-patient model that can simulate changes in the clinical state (e.g., absence of presence of atrial fibrillation; AF) over the entire lifetime of a cohort of thousands of virtual patients with minute-level resolution. By simulating different AF patterns and integrating the mechanisms of coagulation in this model, the bidirectional interaction between AF and stroke risk can be assessed in virtual clinical trials. VIRTUAL-AF aims to improve early diagnosis and management of AF by identifying screening strategies and will enable in silico analyses of their impact on long-term outcomes.

3) 'High-density, high-coverage mapping to reveal the leading mechanisms of atrial fibrillation' from Prof. **Uli Schotten**, Prof. **Jos Maessen**, Dr **Elham Bidar** and Dr **Stef Zeemering**: With a prevalence of 1-2% in the general population in Europe, atrial fibrillation (AF) is currently the most common sustained cardiac rhythm disorder. Recent advances in improving therapy of AF have been modest with limited efficacy of anti-arrhythmic drugs and ablation therapies, particularly in patients with persistent AF. The development, application, and success rates of both antiarrhythmic drug therapy and ablation strategies strongly depend on insights about the electrophysiological mechanisms of AF. Epicardial mapping has enabled us in previous studies to introduce several novel electrophysiological concepts which contribute to AF development and progression. The main objective of the current study is to robustly identify the main electrophysiological mechanisms of human AF by combining high-density with high-coverage epicardial mapping of the atria.

CARIM-COORDINATED HORIZON 2020 MARIE CURIE ITN PROJECT MINDSHIFT

The MINDSHIFT project, coordinated by CARIM, and lead by Prof. **Thomas Unger** and Dr **Koen Reesink**, was funded by the

European Union within the Horizon 2020 Marie Skłodowska-Curie research and innovation programme to train 15 Early Stage Researchers. MINDSHIFT (Mechanistic Integration of vascular aND endocrine pathways for Subtyping Hypertension: an Innovative network approach for Future generation research Training) is a European joint doctorate programme between CARIM/Maastricht UMC+, University of Glasgow, Université de Paris, Universita Degli Studi Padova, Universidad Autónoma de Madrid and Universidad Complutense de Madrid. The funding will be used to set up a collaborative network of research centres and schools with specific expertise in hypertension, that in the coming years will gather additional fundamental knowledge about the underlying causal mechanisms of hypertension. See pages 66-71 for a full interview with Thomas Unger and Koen Reesink.

Another six European projects in which CARIM participates were granted in 2020:

- A prospective European Validation cohort for stereotactic therapy of re-entrant tachycardia (STOPSTORM) – Prof. Paul Volders (Dept. of Cardiology). H2020-SC1-2020-Two-Stage-RTD
- Rituximab in patients with acute myocardial infarction: a phase 2 placebo-controlled randomised clinical trial (RITA-MI 2) – Prof. Arnoud van 't Hof (Dept. of Cardiology). H2020-SC1-2020-Two-Stage-RTD
- Machine Learning and Artificial intelligence for Early detection of Stroke and Atrial Fibrillation (MAESTRIA) – Prof. Uli Schotten (Dept. of Physiology). H2020 SC1-BHC-06-2020
- RESEarch for healThy AGEING (RESETageing) – Prof. Leon de Windt (Dept. of Molecular Genetics). H2020-WIDESPREAD-2020-5
- Addressing multimorbidity in elderly atrial fibrillation patients through interdisciplinary, tailored, patient entered care pathways (EHRA - PATHS) – Dr Dominik Linz (Dept. of Cardiology). H2020-SC1-BHC-2018-2020
- A diagnostic test to improve surveillance and care of COVID-19 patients (COVIRNA) – Leon de Windt (Dept. of Molecular Genetics). H2020-SC1-PHE-CORONAVIRUS-2020-2-CNECT

ONE AND A HALF MILLION FOR THE MAASTRICHT STUDY

The Maastricht Study, a large cohort study of the Maastricht UMC+ into causes and consequences of type 2 diabetes, has been awarded a subsidy of 1.5 million euros from the province of Limburg as part of the Kennis-As programme. The subsidy is intended for the second phase of The Maastricht Study, in which all participants in the study are re-examined. In October 2020, the first phase of The Maastricht Study, which mainly consisted of generating data and knowledge, was completed. The results provide a good insight into the health of the Limburg population. The data provided by the measurements of 9,000 participants have revealed relationships between type 2 diabetes and other chronic conditions, such as cardiovascular disease, but also depression, dementia and certain eye diseases. The research has resulted in more than ninety scientific publications and 36 PhD programmes.

ZONMW IMDI DOORBRAAK GRANT

Prof. **Hans-Peter Brunner-La Rocca** (Dept. of Cardiology) was awarded with a ZonMW IMDI *'Technologie voor Bemensbare Zorg' doorbraakproject* grant worth 125,000 euros for the project 'AI-based Diuretic self-therapy in Heart Failure (AID-HF)' in collaboration with the MAASTRO group of André Dekker. The project will focus on the development of an AI-based algorithm that enables patients with heart failure to adjust their diuretic therapy according to their individual needs. Explicitly, the advice will be given directly to the patients, which will increase their self-care abilities and their independence. After the development of the algorithm based on existing data, it will be tested prospectively in heart failure patients who use eHealth monitoring.

BAYER IIR LEON SCHURGERS

Prof. **Leon Schurgers** (Dept. of Biochemistry) was awarded with a PRECLINICAL Investigator/Institution Initiated Research (IIR) of 242,797 euros for his proposed study entitled 'Pro-calcifying properties of vitamin K antagonists and potential protective role of Rivaroxaban in the cardiovascular system'. His study will focus on new oral anticoagulants (NOACs) such as Rivaroxaban exerting their activity through direct inhibition of factor-Xa without interference with the vitamin K system. As a future perspective, NOACs may be the preferred anticoagulation therapy in patients with high risk for cardiovascular calcifications (e.g. diabetics or moderate CKD patients) since, theoretically, NOACs should be neutral in terms of calcification induction or acceleration. This study aims at dissecting the specific vasculoprotective activities of NOACs compared to warfarin.

CVON DOUBLE DOSE STEPHANE HEYMANS

Prof. **Stephane Heymans** (Dept. of Cardiology) is principal investigator of the recently funded CVON-Double Dose consortium (Amsterdam, Rotterdam, Utrecht, Groningen and Maastricht). Inherited cardiomyopathies affect tens of thousands of people in the Netherlands and cause severe symptoms and an increased risk of sudden cardiac death. The most common forms are hypertrophic (HCM) and dilated cardiomyopathy (DCM). The central Double Dose hypothesis is that metabolic stress may represents the central pathomechanism of early and late cardiac dysfunction in HCM and DCM. Therapeutically targeting this may prevent or cure cardiomyopathies. The Double Dose programme will establish serum, tissue and iPSC-CMs biobanks from a large set of cardiomyopathy patients. It will provide mechanistic pre-clinical and clinical insight into the link between metabolic stress and cardiomyopathy pathophysiology, and translate these findings to optimise diagnosis and care of cardiomyopathy patients.

DCVA IMPRESS VANESSA VAN EMPEL

Dr **Vanessa van Empel** (Dept. of Cardiology) is co-PI and WP leader of the DCVA consortium IMPRESS. The consortium was awarded 2.5 million euros to improve the diagnostics and care of heart problems in women, the focus will be on patients with microvascular (MVA) or vasospastic (VSA) angina. This will be carried out in collaboration between Maastricht UMC+, Amsterdam UMC and UMC Utrecht. Additionally, the IMPRESS consortium will collect, disseminate and identify existing knowledge ready for implementation on sex and gender differences in CVD through a Knowledge Platform.

INVESTIGATOR INITIATED GRANT (IIG) VOUCHER GRANT SIMONE EUSSEN

Dr **Simone Eussen** (Dept. of Epidemiology) was awarded with an Investigator Initiated Grant (IIG) by the World Cancer Research Fund (WCRF) of 382,128 euros for her project entitled 'Neuro-inflammatory metabolites of the kynurenine pathway during colorectal cancer survivorship: dietary determinants and impact on quality of life, fatigue and depression up to five years post-treatment'. This research will focus on the interrelations between diet and kynurenines, and whether associations between diet and domains of health-related quality of life are mediated by neuro-inflammatory kynurenines.

REGMEDXB POSTDOC PROJECTS

Prof. **Leon Schurgers** (Dept. of Biochemistry) and Dr **Barend Mees** (Dept. of Vascular Surgery) were awarded with two RegMed-XB postdoc projects, centred around molecular mechanisms to develop graft scaffolds using tailored use of iSMC populations, and developing novel techniques to ex vivo or in situ clean coronary vessels from calcification. The first postdoc project (HVC–CARIM; 190,950 euros) involves cleaning and optimising coronary arteries to support revascularisation of the ischemic heart and promote perfusion to tissue-engineering repaired cardiac tissue/valves. The second postdoc project (MERLN and HVC–CARIM) is centred around tissue engineered grafts of biomaterial engineering that will be used for cellular seeding with iSMCs and iECs to be able to revascularise ischemic cardiac tissue. Together, these cardiovascular moonshot projects within RegMed-XB hold promise in opening new opportunities to restore vascular integrity by removing and combat calcification, but also carries considerable novelty in the research field.

ZONMW ZE&GG FLOW GRANT MAARTEN SNOEIJS

Dr **Maarten Snoeijs** (Dept. of Vascular Surgery) was awarded with a ZonMw grant of 465,000 euros for the FLOW project that will evaluate the follow-up of the vascular access for hemodialysis in a multicenter randomised controlled trial. In current clinical care, vascular access flow volume is periodically assessed to detect and treat asymptomatic stenosis. The FLOW project will determine whether it is safe to abandon this practice of active surveillance. Vascular access stenosis will then be treated only when clinical problems of flow dysfunction occur during hemodialysis. The FLOW project will be coordinated by a national team including vascular surgeons, nephrologists, interventional radiologists, dialysis nurses, patient representatives, and health care economists. ZE&GG is part of the ZonMw programme Efficiency Studies that aims for high-quality, accessible, and affordable health care. The programme is a collaborative effort of patients, researchers, practioners and policymakers.

CROWN STUDY

The study 'Cardiovascular Risk Score in Women - the CROWN study' (Prof. **Arnoud van 't Hof**) has received funding from Bayer. The CROWN study aims to investigate the potential value of mammography as screening tool for coronary artery disease in women. The study will include 1,000 women who are presenting with coronary complaints at Zuyderland Medical Centre Heerlen and have been participating in the Dutch breast cancer screening programme. While aspiring to improve risk prediction and clinical outcomes of cardiovascular disease in women, the CROWN study is performed by a multidisciplinary collaboration between cardiologists, gynaecologists and epidemiologists of Zuyderland Medical Centre Heerlen, Maastricht UMC+ and Bevolkingsonderzoek Zuid.

NATTOPHARMA LEON SCHURGERS

Prof. **Leon Schurgers** (Dept. of Biochemistry) was awarded with 49,608 euros from NattoPharma to verify vitamin K deficiency in COVID-19 patients that are well characterised. Patients will be screened for COVID-19 and disease progression will be monitored. Serum and plasma will be collected and used to measure dp-ucMGP (vascular vitamin K status) and Pivka-II (liver vitamin K status) to confirm vitamin K deficiency in COVID-19. This serum will be used to apply in vitro on endothelial cells and vascular smooth muscle cells to investigate the molecular mechanism by which the 'perfect inflammatory storm' in COVID-19 affects the vasculature, or how the diseased vasculature contributes to COVID-19 severity. Furthermore, Leon was awarded with 35,000€/year for 5 years to conduct research in the area of vitamin K, vitamin K – dependent proteins and vitamin K metabolism.

IMCHECK THERAPEUTICS ERIK BIESSEN

The group of Prof. **Erik Biessen** (Dept. of Pathology) has recently started collaborating with Imcheck Therapeutics, a mid-size French Biotech company, focusing on the design and clinical application of new generation antibody-based checkpoint inhibitors. Supported by a 200,000 euros investment, they will deploy their in-house technology platforms to (1) characterise the location of these inhibitors in tumor and cardiac tissue, (2) specify leukocyte subsets that show the highest expression level myeloid subsets and (3) characterise the functional impact of these inhibitors on these cells in culture. This project will provide a firm mechanistic underpinning of the clinical effects observed for these compounds and may unveil new indications, potentially paving the way for more sustained collaboration with this exciting company.

OTHER HIGHLIGHTS

CARIM COMMITMENT AWARD

Dr **Carla van der Kallen** (Dept. of Internal Medicine) has received the CARIM Commitment Award, intended for any CARIM member who has devoted his/her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze medal of the sculptor Marina van der Kooi. "When we think of Carla, one of our precious employees, words like 'connect, facilitate, organise, and empathy' jump to mind. She is the heart and engine of The Maastricht study, keeping it afloat, and volunteering for all difficult tasks to keep it moving. She does this all while always realising the importance of organisation of CARIM's flagship programme The Maastricht Study."

HIGH ROYAL HONOUR HARRY CRIJNS

For his pioneering work in the field of cardiology, Prof. **Harry Crijns** (Dept. of Cardiology) has been appointed Knight in the Order of the Netherlands Lion. The presentation of one of the oldest and highest Dutch civil orders took place during an international mini symposium in honour of his farewell on 26 November. Harry received the decorations from Mayor Mirjam Clermonts-Aretz of Meerssen. Harry also received the Maastricht UMC+ medal from Dr Helen Mertens and the CARIM Commitment Award from Prof. Tilman Hackeng. In addition, the newly installed funding programme in which CARIM doubles one selected crowd funding programme annually the moment it reaches 25 k€ by donating 25 k€ will bear Harry's name in the future: the CARIM Crijns' Crowdfunding Doubler.

JORDAN PRIZE FOR HUGO TEN CATE

Prof. **Hugo ten Cate** (Dept. of Internal Medicine), the outgoing chairman of the board of the Federation of Dutch Thrombosis Services (FNT), was presented with the Jordan Medal during the General Members' Meeting in Hoevelaken. The Jordan Medal is awarded to people who have made an exceptional contribution to FNT and anticoagulant care in the Netherlands. The medal is named after Prof. Jordan, internist and founder of the first thrombosis service in the Netherlands. The prize consists of a crystal glass plaque engraved with the name of the recipient and the date of award. In the almost 50 years of the FNT's existence, the prize has been awarded 16 times. One of the major things that Hugo has taken on in his role as FNT chairman is chairing the steering committee that led to the national integrated anticoagulation care standard (LSKA). This LSKA has given an enormous 'boost' to chain thinking within the anticoagulation world.

WINKLER MEDAL MR CLEAN

Six doctors from three different UMCs, including Prof. **Robert van Oostenbrugge** and Prof. **Wim van Zwam** (Dept. of Neurology), were jointly awarded the prestigious gold Winkler medal by the Dutch Neurology Society on 17 December 2020. They received the prize for the MR CLEAN study into better treatment for patients with a cerebral infarction. The Winkler Medal is a gold commemorative medal established in memory of Dr Cornelis Winkler (1855-1941), Professor of Psychiatry and Neurology and authority in the field of neurology and brain anatomy in the Netherlands. The science prize is awarded every five years to the Dutch person who made the most deserving contribution in the field of neurological science in the five years prior to the award. The special thing is that this time the prize was awarded to a six-man ship.

CROWDFUNDING ROGIER VELTROP

Rogier Veltrop (Dept. of Biochemisty) initiated a successful crowdfunding on the SWOL platform. SWOL aims to promote science which is a crucial building block to achieve a better future for next generations, which is exactly what Rogier is striving for: Understanding cardiovascular diseases leading to personalized medicine therapy to provide heart failure patients with a better future. After a thorough preparation, the campaign was launched in the summer of 2020. The campaign reached a climax when radio performances, many interviews, an initiative of Ruud van der Meijden – finishing a 1000 km long bike race at the Randwyck campus – culminated into a live performance of Rogier at Op1: a popular late night talk show reaching over a million viewers. Hundreds of donations of inspired viewers and (families of) heart patients who supported Rogier's research, raised the financial thermometer to 25,000 euros.

CARIM supported this initiative wholeheartedly and doubled the revenues to 50,000 euros. Rogier continued with a personal story on television (L1) and showed how he is able to make beating heart cells from a tube of blood. The end result of the SWOL crowdfunding campaign was a staggering 81,717 euros just by private individuals. Unfortunately, due to COVID circumstances, a fundraise science event for companies had to be cancelled, but starting January 2021, Rogier continues his fundraising at Health Foundation Limburg to obtain more funding for his pioneering life's work.

PROFESSOR HEIMBURGER AWARD DORITH CLAUSHUIS

Dorith Claushuis (Dept. of Internal Medicine) received the 2020 Professor Heimburger Award for coagulation research for the project 'Bruton's tyrosine kinase inhibition in hemostasis and bleeding'. This project will aim to understand the mechanism of bleeding in patients with BTK inhibitors. This project will be done together with Prof. Johan Heemskerk, Prof. Hugo Ten Cate, Dr Marijke Kuijpers and Bibian Tullemans. The annual global Prof. Heimburger Awards programme recognises the clinical and/or preclinical research of emerging coagulation specialists who are driven to improve the care of patients with bleeding disorders.

COEN STEHOUWER BOARD MEMBER EASD

Prof. **Coen Stehouwer** (Dept. Internal Medicine) was elected as full member (clinician) of the Board of the European Association for the Study of Diabetes e.V. (EASD) with a term of office from 1 January 2021 until 31 December 2024. The aims of the Association are to encourage and support research in the field of diabetes, the rapid diffusion of acquired knowledge and to facilitate its application.

FREDERIK PHILIPS PRIZE ESTELLE NIJSSEN

Estelle Nijssen (Dept. of Radiology) has won the Frederik Philips Prize 2020 with her thesis 'AMACING; AMAastricht Contrast-Induced Nephropathy Guideline project; Evaluation of guideline-recommended prophylaxis to prevent contrast-induced nephropathy'. This prize is awarded annually during the Radiology Days by the Dutch Society for Radiology (NVvR) to the person who has completed the best research in the field of Clinical Radiological Imaging and Intervention Techniques in the Netherlands.

COEN STEHOUWER AND CHRISTIAN WEBER AMONGST MOST INFLUENTIAL RESEARCHERS

Prof. **Coen Stehouwer** (Dept. of Internal Medicine) and Prof. **Christian Weber** (Dept. of Biochemistry) are among the most influential researchers when it comes to the production of multiple highly-cited papers that rank in the top 1% by citations for field and year in the Web of Science™. Each year, Clarivate™ identifies the world's most influential researchers - the select few who have been most frequently cited by their peers over the last decade. In 2020, fewer than 6,200, or about 0.1%, of the world's researchers, in 21 research fields and across multiple fields, have earned this distinction.

MAGNA CUM LAUDE AWARD FOR MRI PHYSICIST ROB HOLTACKERS

During the 2020 online congress of the European Society of Cardiovascular Radiology (ESCR), Dr **Rob Holtackers** (Dept. of Radiology) won the Magna Cum Laude award for the second year in a row. His latest research focussed on the improved visualisation of subendocardial scar patterns in patients with cardiac arrhythmias for which he developed a novel 3D MRI scan technique. A close collaboration between the Departments of Radiology and Cardiology of Maastricht UMC+, the Department of Cardiology of the Antwerp University Hospital, and Philips Healthcare proved crucial to achieve this excellent result.

PÉLERIN AUDIENCE AWARD MICHIEL HENKENS

Michiel Henkens (Dept. of Cardiology) has received the Pélerin audience award in 2020. The 25th edition of the Pélerin physician assistant symposium took place on 7 October. Because of the online edition, all nominees were asked to record a video in which they could explain their research in their own way. All resident physicians, investigators and semi-physicians made unique contributions, which were then assessed by a jury of specialists.

PROFESSORSHIPS

The following CARIM researcher were appointed to professor in 2020:

Erik Beckers (Dept. of Biochemistry) - Professor of Internal Medicine, specialising in Haematology

Jur ten Berg (Dept. of Cardiology) - Professor of Antithrombotic Therapy in Cardiac Catheter Intervention

Paula da Costa Martins (Dept. of Molecular Genetics) - Professor of Molecular Microvascular Biology

Marc Hemmelder (Dept. of Internal Medicine) - Professor of Internal Medicine, specialising in Nephrology

Yvonne Henskens (Dept. of Clinical Chemistry) - Professor of Clinical Chemistry, specialising in Haemostasis

Iwan van der Horst (Dept. of Intensive Care) - Professor of Intensive Care

Judith Sluimer (Dept. of Pathology) - Professor of Cardiovascular Pathophysiology

Kevin Vernooy (Dept. of Cardiology) - Professor of Electrical Management of Heart Failure

HIGHLIGHT
DIVISION VESSELS

MARC HEMMELDER

The COVID-19 pandemic year 2020; perspectives for research in chronic kidney disease

Although COVID-19 affected the entire world population in 2020, there are specific subpopulations that are at higher risk of a more severe disease course. In addition to exposure to the virus and viral load, and to genetic and immunological factors, chronic kidney disease (CKD) has emerged as the most common risk factor for severe COVID-19, as well as the strongest risk factor after age [1-2]. In a cohort analysis of a health analytics platform in the UK consisting of more than 17 million inhabitants with almost 11,000 COVID-19 related deaths, patients with severely impaired kidney function (eGFR <30 ml/min/1.73m^2, also known as CKD stages G4 and G5), patients on dialysis, and patients having had a solid organ transplantation were shown to be extremely vulnerable. Their COVID-19 associated mortality risk was reported to be 3 to 4 times higher than that of the general healthy population in a fully adjusted model including age [2]. This risk of dying is considerably higher than the 1.5-2-fold increase that was observed in established high-risk groups, such as patients with obesity, hypertension or diabetes [3]. Potential mechanisms for the increased susceptibility of patients on dialysis to severe COVID-19 are summarised in **Figure 1**. COVID-19 is also associated with an increased risk of acute kidney injury, which may be accompanied by a need for renal replacement therapy [4]. Continuous dialysis treatment during ICU admission is associated with an increased risk of filter clotting due to heparin resistance caused by increased thrombogenicity associated with COVID-19 [5].

In response to the COVID-19 pandemic, our nephrology division participated in the working group which constructed a large European renal database (ERACODA, the European Renal Association COVID-19 Database). Data were collected to specifically investigate the course and outcome of COVID-19 in patients living with a kidney transplant or on maintenance dialysis therapy who presented at the hospital. In addition to all relevant clinical variables, frailty was scored by the attending physician on a scale of 1–9 according to the Clinical Frailty Scale (CFS), an easily applicable tool to stratify patients according to their level of vulnerability [6]. Of the 1073 patients enrolled during the first wave, 305 (28%) were kidney transplant patients and 768 (72%) were dialysis patients, with a mean age of 60±13 and 67±14 years, respectively. The 28-day probability of death was 21.3% (95%

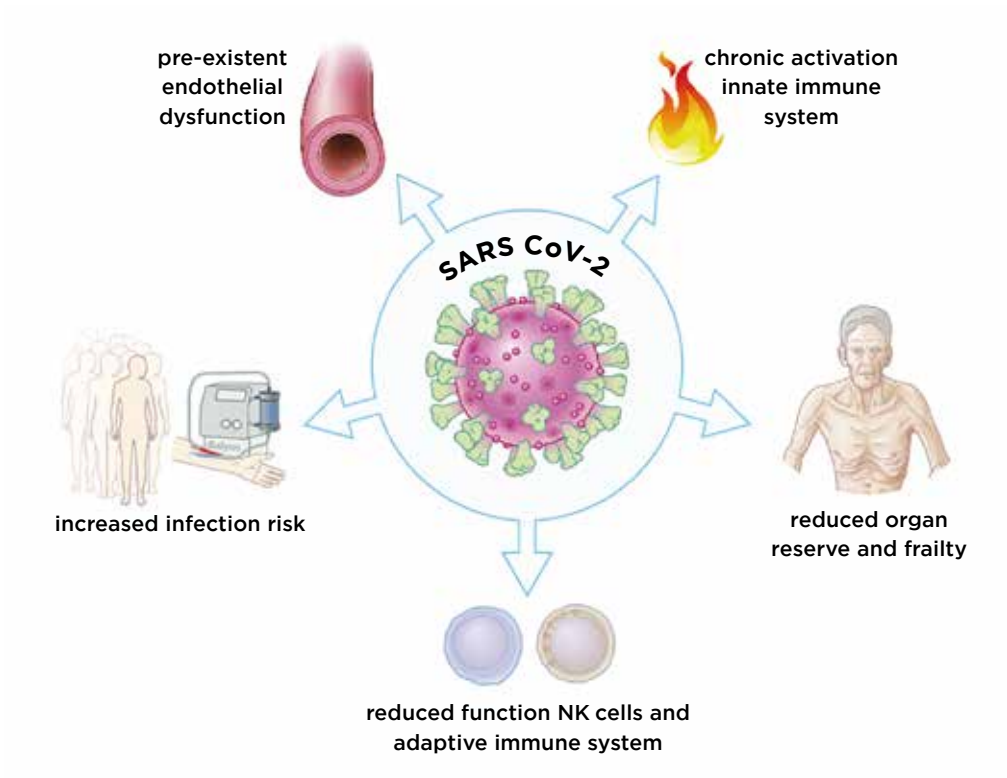

FIGURE 1 Potential mechanisms for the increased susceptibility of patients on dialysis to severe COVID-19.

confidence interval [95% CI] 14.3–30.2%) in kidney transplant and 25.0% (95% CI 20.2–30.0%) in dialysis patients [7]. Mortality was primarily associated with advanced age in kidney transplant patients, and with age as well as frailty in dialysis patients (**Figure 2**). Data from the Dutch Registry of Renal Replacement Treatment (RENINE) demonstrated a comparable mortality of 33% for the dialysis patients in the Netherlands. Similar high COVID-19 mortality rates in dialysis and renal transplant patients have been demonstrated by the European ERA-EDTA registry of kidney replacement treatment [8]. It is remarkable that despite the high fatality rate, just 4% of dialysis patients and 18% of the kidney transplant recipients with COVID-19 were admitted to the ICU. Frailty has been introduced as a key factor for triage of COVID-19 patients in conditions of limited ICU capacity in the Netherlands. In collaboration with CAPHRI, we will use ERACODA data to analyse whether triage by frailty has influenced the discrepancy between high fatality rates and restricted ICU admission of dialysis patients and kidney transplant recipients.

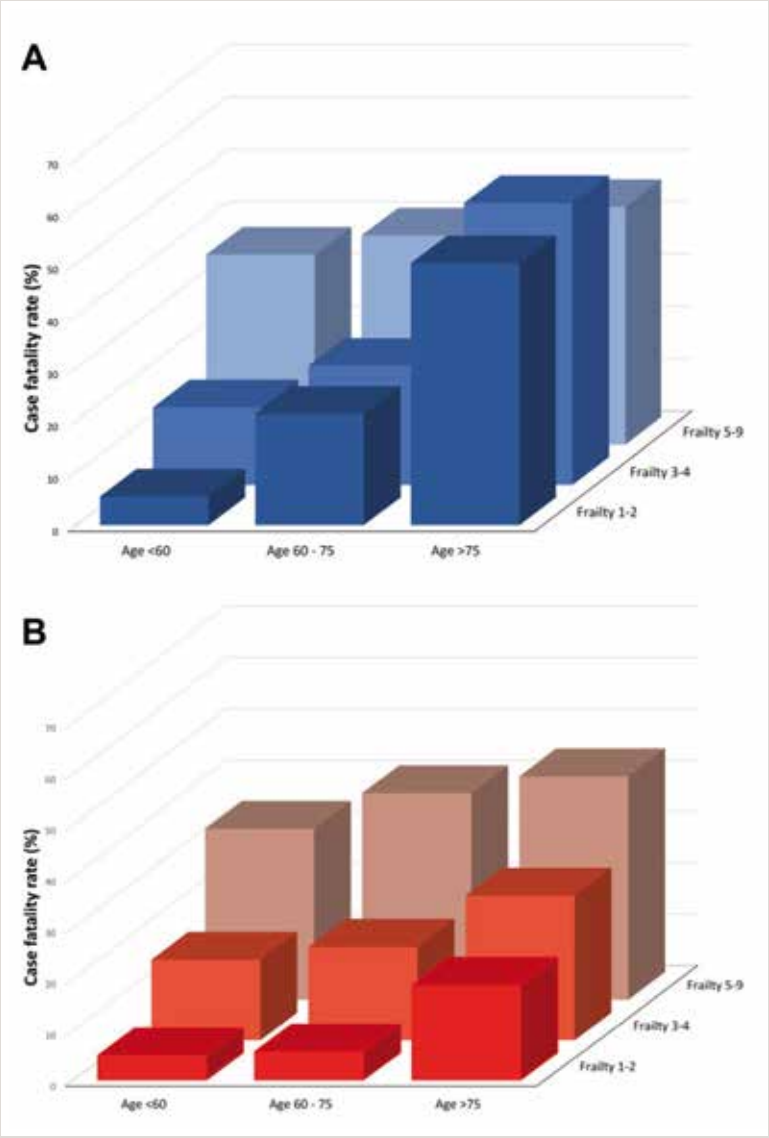

FIGURE 2 Relationship between age, clinical frailty score and 28-day case-fatality rate in (A) kidney transplant and (B) dialysis patients with COVID-19. Age and clinical frailty scores are subdivided into three clinical classes.

Considering their high risk of a serious course of COVID-19, it is essential to prioritise the patients with CKD for SARS-CoV-2 vaccination [9]. So far, none of the trials with presently available vaccines have included patients on dialysis or after kidney transplantation [10-11]. It is well known that the efficacy of vaccination against other viruses, such as hepatitis B and influenza, is considerably lower in patients with severely impaired kidney function and in patients on dialysis or with a kidney transplant. Explanations include the immunosuppressive properties of waste products that accumulate in case of renal function impairment and the use of immunosuppressive agents [12]. All Dutch UMC nephrology divisions cooperate in the REnal patients COVID-19 VACcination (RECOVAC) consortium, which will perform two studies to analyse SARS-CoV-2 vaccination in CKD. Firstly, a small short-term study will analyse specific immunological B- and T-cell responses after SARS-CoV-2 vaccination in patients with CKD stage G4-G5, dialysis and kidney transplant patients. Secondly, a large prospective observational national cohort study on long-term efficacy in preventing

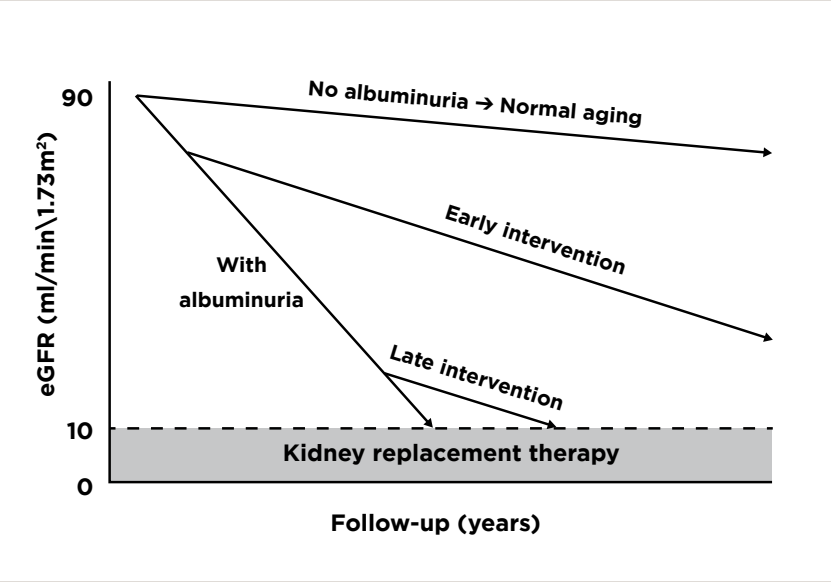

FIGURE 3 Schematic presentation of kidney function decline over the years and the effect of late versus early intervention to prevent the need for kidney replacement therapy. Adapted from Gansevoort and de Jong (2009).

COVID-19 and safety after SARS-CoV-2 vaccination (the LESS CoV-2 study) will be started. This study will involve 24 000 patients with CKD G4-G5, dialysis or kidney transplant who are currently being vaccinated. In addition, IgG-antibody response will be measured 28 days and 6 months after the second vaccination in 3 subgroups of 4000 patients. The LESS CoV-2 study, which will be coordinated by our nephrology division, and will yield more insights into the protection level of SARS-CoV-2 vaccination in these high-risk populations and the prognostic value of antibody responses.

CKD has a major effect on global health, both as a direct cause of global morbidity and mortality and as an important risk factor for cardiovascular disease [13-14]. The Global Burden of Disease, Injuries, and Risk Factors Study (GBD) showed a high prevalence of CKD of 9.1% in the global population, which is comparable to the prevalence of diabetes mellitus [13, 15]. Impaired fasting plasma glucose, high blood pressure, high body-mass index, a diet high in sodium, and lead were identified as risk factors for CKD. CKD directly contributed 58% of the disability-adjusted life years (DALYs) due to impaired kidney function, whereas 41% (38·2 to 44·4) were contributed by cardiovascular disease DALYs and less than 1% (0·003% [0·002 to 0·004]) by gout DALYs. Considering the additional impact of the COVID-19 pandemic in patients with CKD, future research in the nephrology division will focus on more timely detection of CKD as well as interventions to slow the progressive course of CKD and prevent long-term cardiovascular and renal complications (**Figure 3**).

CKD is defined as a decrease in kidney function measured by glomerular filtration rate (GFR) or evidence of kidney damage (even with normal GFR) such as albuminuria, abnormal urine sediment or structural abnormalities, persisting for more than 3 months [16]. Diagnosis and treatment of primary or secondary renal diseases in patients with CKD is the first step. In the case of progressive CKD, the next step involves optimised renal and cardiovascular

prevention by dietary salt intake reduction, optimised blood pressure and dyslipidaemia management, as well as renin-angiotensin inhibition in case of albuminuria [17]. One innovative life style intervention may be to increase dietary potassium intake, which mitigates the detrimental effects of high dietary sodium intake by a significant natriuretic response, analogous to taking a loop or thiazide diuretic, resulting in blood pressure lowering without the accompanying risk of hypokalemia [18]. Data of the Maastricht Study in a population with a mean eGFR of 88 mL/min/1.73m2 and mean albuminuria of 6.7 mg/24 hours showed that only lower potassium intake, but not sodium intake, was nonlinearly associated with higher cardiac biomarkers [19].

Previous studies suggest that screening for CKD in high-risk and elderly populations is a cost-effective approach to reducing progression to ESKD and CKD mortality [20-21]. The majority of subjects (65%) found by screening to have increased albuminuria also had hypertension, diabetes or hypercholesterolemia. In two-thirds of these subjects, these abnormalities had not yet been diagnosed [22]. Our nephrology division will participate in the Check@Home consortium to screen a population of people aged 50-75 years with home testing for increased albuminuria, to facilitate early detection of as yet undiagnosed risk factors for CKD and cardiovascular disease, and to improve health outcomes.

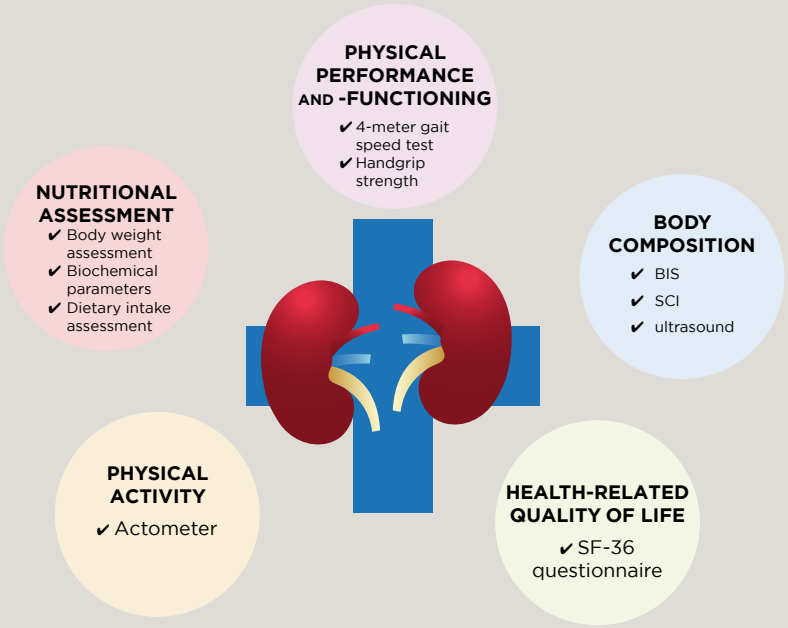

FIGURE 4 Multidimensional functional assessment of patients with CKD. BIS= bio impedance spectroscopy; SCI = serum creatinine index.

The nephrology division will also focus on the multidimensional assessment of the cardiovascular, nutritional and functional status of patients with advanced or end-stage CKD, as shown in **Figure 4**. Pronounced abnormalities in vascular structure and function, such as pulse wave velocity, deteriorate progressively in patients on dialysis [23]. A study will be performed to assess frailty by this multidimensional approach in patients with CKD stage G3-G5. In view of the impact of frailty in an aging population with CKD, a longitudinal assessment may detect whether interventions earlier in the course of CKD deliver favourable cardiovascular and renal outcomes as well as more instruments for patients to improve their own health-related quality of life.

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INTERVIEW

THOMAS UNGER AND KOEN REESINK

Innovative Training Network MINDSHIFT
funded by the European Commission

Entire libraries have been filled with information about the role of hormonal metabolism in hypertension. Similarly, Maastricht researchers have published enough papers on vascular problems in hypertension to fill another library. However, the relationships between these two phenomena are still a gap to be filled on the bookshelves. And what may be even more important: young researchers need to be trained to 'carry the flag of hypertension research'.
A European grant of four million euros, supporting the joint efforts of six universities and nine non-academic partners, has enabled the start of the multidisciplinary MINDSHIFT research programme, coordinated by some of the top scientists at CARIM.

The first version of the grant application scored a solid 8 out of 10 points. That was a pleasant surprise for Koen Reesink, who coordinated the research proposal together with initiator Thomas Unger. “It was a surprise that we were able to secure funding for hypertension research, which is not exactly a novel field of research.” Unger: “It was swimming a bit against the stream. Hypertension does not currently exist on the EC programmes, because we can treat it with drugs. Yes, we can prevent 40% of strokes by controlling hypertension. That’s great. A 15% reduction of heart disease, that’s fine, but we would like to have more, for instance to prevent people going into kidney failure.” And so Unger and his colleague Gian Paolo Rossi from Padua put their heads together. The niche that the MINDSHIFT project addresses is that of the interrelationships between the hormonal and vascular systems that play a role in hypertension. Such knowledge is not yet available nor integrated in the diagnosis or treatment of hypertension.

THIRD TIME LUCKY

When it came to writing the second version of their application, one year later, all six academic consortium partners got together to flesh out the following points: What elements can each of the centres contribute? And wherein then lies the innovative value? What are the challenges? The second application scored a solid 9 out of 10, but that was still not enough to secure the grant. Reesink: “We then also started intense discussions with the nine non-academic partners, using individual agendas to build our collective agenda. That’s how we explored what gives us an edge and what we can achieve together. It then became very concrete and that’s what we needed: for such grant applications you won’t get away with a series of platitudes on paper. And when they ask for ‘coherence’, that means that literally all elements in your proposal must connect with each other, which is an extreme challenge. The third and final version of our application got a score of 92.6%.” And so 2020 saw the approval for the project, which also represents

THE FINAL AIM OF THIS PROJECT IS A EUROPEAN HYPERTENSION SCHOOL, WHICH UNITES YOUNG SCIENTISTS WHO WORK IN HYPERTENSION RESEARCH TO WORK TOGETHER

an investment in the European research climate. “We’re developing a network that will continue after the four years of this project.”

EUROPEAN HYPERTENSION SCHOOL

Thomas Unger explains: “The final aim of this project is a European hypertension school, which unites young scientists who work in hypertension research to work together. This project is a valuable part of the path to go there.” Unger laid the foundation for this network over 40 years ago. In 1979, he co-founded the European Council for Cardiovascular Research (ECCR) – then called “European Blood Pressure Group” – which has always been committed to advancing future cardiovascular research by training the next generation researchers.

Reesink: “These ITN (Innovative Training Networks) grants focus on the future workforce in Europe. So the key aim is to train fifteen early stage researchers (ESRs: PhD candidates), all of whom will be supervised by several academic partners and also gain work experience with the non-academic partners. Of course, the research context must be highly relevant: I think that bringing together endocrine and vascular knowledge on this scale is fairly unique.” Unger: “You can fill a library on the role of the hormone system and the vascular system, but the interactions between these two, from the molecule to the organ and in relation to our patients’ condition, are not well understood. We are dealing with a very complicated issue; you cannot expect a single clear cause of hypertension, unfortunately.”

STEP BY STEP

All PhD projects will start in the autumn of 2021, and MINDSHIFT should be completed by December 2024. A major challenge, according to Reesink, will be to ensure

WE’RE DEVELOPING A NETWORK THAT WILL CONTINUE AFTER THE FOUR YEARS OF THIS PROJECT

that the formal frameworks do not obstruct the creativity and innovation they seek through collaborations. Reesink: “Science is rather competitive. It shapes the future, as a PhD candidate, as a group, as an institution, and as a network. So you go for it together and then if you obtain a new finding or develop a novel tool: who owns it? How do you share the ownership? How about risks or negative findings? That’s also a discussion we enter into with our industrial partners.” The coordinator radiates energy as he lists the challenges. “That’s what gets me out of bed in the morning. Even though it’s not an easy task, and sometimes I lose heart. But time and again you discover that you’re not facing it alone, and that you still manage to take the next step.”

BUILDING ON PREVIOUS EXPERIENCE

A major advantage is the experience that CARIM gained from a previous ITN project called INTRICARE. Tara de Koster was responsible for the project management in that

project, and has now also assumed this task for MINDSHIFT. Reesink: “She is extremely talented and works with me on the daily coordination.” Thomas Unger also coordinates, but focuses on the bigger picture: “You can compare it rather to a presidential role. Not responsible for the daily details, that’s what Koen and Tara are doing an excellent job with.” Reesink: “And Thomas has been carrying the flag of hypertension research for the last 40 years, which is invaluable. It is the passion, the humour, and the knowledge that he wants to pass on. Thanks to him, the research continues to build on what’s already there. He can spot what may look new but was already studied thirty years ago. And he sees how new methodologies may enable us to still take it a step further. He’s very good at that.”

EVERYONE’S VOICE IS HEARD

One interesting challenge that Reesink sees is to make the network operate smoothly. “Hypertension is a kind of network illness. The individual components are not necessarily diseased, but together they are. It’s similar with a network: we’re all good people, but the question is how we can work together well.” One partner in the programme is the Recess College, with which Reesink worked on leadership development. The College will offer such training to both the PhD candidates and supervisors in MINDSHIFT, which makes for a rather unique programme, in addition to the research approach. What do you do as a PhD candidate if your supervisor may not seem interested in your ideas? How do you bring out the best in the young researchers you are supervising? Reesink: “I think it’s important that people regularly meet and interact, despite the deadlines and the stress. That’s also what we want to achieve with this network: making sure everyone’s voice is heard.” Unger adds: “We want to educate people to be firm and to carry the flag of hypertension research, wherever they may go. In turn, young people also educate us with their ideas. In science, the best ideas occur to you mainly between the ages of 20 to maybe 40, and later you dwell on that work and you gain wisdom. I’m a ‘wise and old man’ now, I’ve just turned 70. But I still write articles and in June 2020, I was the first author of the recent guidelines for hypertension from the International Society of Hypertension (ISH). That’s not something you can do at a younger age. So, every age gives you a chance to do something that makes sense. And I look forward to our collaboration in MINDSHIFT.”

EVERY AGE GIVES YOU A CHANCE TO DO SOMETHING THAT MAKES SENSE

THE NICHE THAT THE MINDSHIFT PROJECT ADDRESSES IS THAT OF THE INTERRELATIONSHIPS BETWEEN THE HORMONAL AND VASCULAR SYSTEMS THAT PLAY A ROLE IN HYPERTENSION

MINDSHIFT (Mechanistic Integration of vascular aND endocrine pathways for Subtyping Hypertension: an Innovative network approach for Future generation research Training) is an Innovative Training Network funded by the European Commission. More information at: www.eumindshift.eu

Thomas Unger is Emeritus Professor of Pharmacology and Experimental Medicine and was the scientific director of CARIM from 2012 to 2017. Previously he was director of the Institute of Pharmacology and founding director of the Centre for Cardiovascular Research (CCR) at the Charité in Berlin.

Koen Reesink is assistant professor at the Department of Biomedical Engineering, and started his career at Maastricht University with a PhD in 2002. In 2008, he received a Veni grant from NWO, and in 2012, he worked at Imperial College London for six months, where he still holds an honorary research fellow position.

INTERVIEW

CONSTANCE BAATEN AND PIETER GOOSSENS

Laureates of the Junior and Senior Dekker grants

If the Dutch Heart Foundation awards you one of its Dekker grants, they call you personally. That is, if they can reach you, in both the physical and figurative sense of the word.
One of the laureates we interviewed was so busy working at her computer that the message initially did not get through to her.
The other was visiting a Belgian zoo where he had no signal.
Fortunately, just like top researchers, the Dutch Heart Foundation is very tenacious, and it all worked out in the end.

It is almost like a scene from a film, with Pieter Goossens spending the day at a zoo with his family, on the very day when the Heart Foundation phones those lucky enough to receive a Dekker grant. “Around midday, a colleague texted me to ask if I had heard from them yet. I texted back: ‘No, but the day is not over yet.’ I spent the rest of the day walking around the zoo with my phone in my hand.” No phone calls came in. So at the end of the day, as he returned to his car, he was convinced that his application had failed. It was then he saw that his phone had logged ten missed calls from the Dutch Heart Foundation. “Apparently the reception in the zoo was poor,” he smiles. Goossens was the recipient of a Senior Scientist Dekker grant of 465,000 euros. And when Constance Baaten at last managed to detach herself from her concentrated work on the computer, it finally dawned on her that she had been awarded a Postdoc grant of over 250,000 euros.

What does this grant mean to you?

Baaten: “It’s a great honour, but also a boost to your career. The Dekker grant enabled me to regain my position at Maastricht. Before that I had only a postdoc research appointment at Aachen, and now I’m combining the two positions: one day a week at Aachen and four at Maastricht. I studied here, and also did my PhD and more here, so I was hoping to return. Because of the congenial atmosphere, but also because the research topic I’m interested in fits in perfectly with my current position.”
Goossens: “For the last few years I’ve been working as a postdoc in Maastricht, and liking it a lot, but I was unable to obtain a permanent appointment. Thanks to this grant, and another one I secured, I can now start my own research group. I’ve engaged two PhD candidates. And the Dekker grant enabled me to start my tenure track in the autumn of 2020, putting me on the path towards a permanent position. I now have four years to prove myself.”

Do you have any idea what was the key to your success?

Baaten: Although you do get feedback on your application from the reviewers, from which you can find out what they’re looking for, I couldn’t say what clinched it. I did get some help from the university: tips on how to frame the application, and presentation training with the research council. So you’re better prepared for the interview.”
Goossens: “I tend to be more nervous for these practice interviews than for the real interview at the Heart Foundation. Your colleagues take a different view of you: they know you and your techniques, and their questions are far more challenging. I think my research is a bit more basic than the typical Heart Foundation project. So I’ve mainly tried to show them the possibilities it could offer in the longer term.”

IT’S A GREAT HONOUR, BUT ALSO A BOOST TO YOUR CAREER

What exactly are you going to research with this grant?
Goossens: "Macrophages are a type of immune cells that I've been working on all through my career. We know that they play an essential role in the origin and progression of atherosclerotic plaques. And also that macrophages can fulfil all kinds of, sometimes contradictory, functions within a plaque. They can make it grow or rupture, but can also stabilise it or make it shrink. In recent years it has also been shown that cells and molecules in the immediate environment largely determine what form a macrophage adopts. So it's on this basis that it decides what it's going to do. And there are so many different types present in a plaque, each with their own functions and agenda. One plaque may harbour more macrophages of a particular type than another. So far, nobody has succeeded in visualising all these different types of macrophages simultaneously. That means you can't properly study the balance within the plaque. Over the last few years, I've developed a microscopy technique that does make this possible, called multispectral immunofluorescence. This enables us not only to see which types are present, but also where they are situated in the plaque and whether they are concentrated or spread out, and what molecules are present there that can control their identity. We've already tested this in murine plaques, but also in spleen and liver, and now we're going to apply this technique to human plaques. Once we know what functions these macrophages fulfil, it will be interesting to eliminate one of these types or steer them in a different direction. So far, all macrophages are being targeted, including those that are harmless. Macrophages are a kind of shapeshifters among immune cells. I often jokingly say that our body is merely a vehicle to transport macrophages, as they control just about everything in our body. They're present in all organs and they do different jobs in different places, which makes it a very interesting cell type to base a career on."

APPARENTLY THE RECEPTION IN THE ZOO WAS POOR

But you, Constance, undoubtedly consider platelets the most interesting phenomenon in our bodies?
Goossens, jokingly: "Platelets are not even cells."
Baaten, laughing: "They have no nucleus, unlike macrophages, but I do indeed find platelets the most interesting objects. I study the role of platelets in the formation of blood clots, so in thrombosis. Mine is a three-year project and I'll be examining the structure of such clots. Normally, platelets don't interact with each other, but they do so during clot formation. When you look at other tissues, you see that cells there are linked together by junction proteins. For a long time, it was thought that blood clots were a random accumulation of platelets, but in recent years, research has shown that they do have a structure. In the first part of my project, I'll be looking at the macrostructure, so the general structure of the clot, and then later I'll zoom in to see how they're attached. I'll also study how this process works under the influence of anticoagulants, which are prescribed to people, for instance, after a cerebral infarction or a heart attack. I want to find out how such an anticoagulant changes the structure of a blood clot, which should give us insights into the way the therapy works, as well as its side-effects. I'll be studying this using microscopy techniques in thrombi I'll be creating in vitro."

If the Dutch Heart Foundation awards
you one of its Dekker grants,
they call you personally.
That is, if they can reach you, in both the
physical and figurative sense of the word.

What motivates you as a scientist?

Goossens: "I just wouldn't know what else to do. As a kid, I wanted to become an inventor, but that's too general. While revising for an exam I had a kind of Aha! experience. About how the human body works, and how everything is connected, and that's the thrill I keep looking for. I want to understand things and discover things for myself. The moment when you're looking through a microscope and realise: I'm the first in the world to see this. That's marvellous. And after that you're left with more questions than before, and it's that constant search that keeps me going. As long as I can still reasonably manage to obtain grants, I enjoy getting on with it."

Baaten: "My feelings exactly, that curiosity. Wanting to know how something works. This feels like just the right kind of career for me so far. Applying for grants is part of the game, and it never makes me think 'Perhaps it's time I switched to something else'."

Goossens: Doing science means you also have to be able to deal with setbacks. When three quarters of your experiments end in disappointment, you must be able to take courage from the ones that do succeed."

Baaten: "That's what makes it especially wonderful when things work out."

Goossens: 'People who can't deal with that don't last very long in this type of work. You have to have the right mental makeup to keep going."

What does CARIM mean to you?

Goossens: "When you get to start your own research group, it's very convenient that the expertise about practical matters like fund-raising, HR and finances is available. And you have direct access to everyone who's working on a similar subject at Maastricht. I've become more and more aware of the presence of CARIM."

Baaten: "During your PhD project, CARIM is simply a part of it, and you attend lectures and courses. But also when you're applying for grants, there's a lot of help and support available. The institute is very accessible when you need something, so that's gratifying."

Why Maastricht?

Baaten: "I find the atmosphere at Maastricht very easy-going and pleasant, and in my view it's very important to feel at home in your work. To me, the same goes for Aachen."

Goossens: "I've so far worked in Brussels, Ghent, Marseille and Maastricht, and it was while I was in France that I really realised I wanted to return to Maastricht. There's an open atmosphere here, and it's not too big. And being Flemish, I like to be around people who say what they think. You're not having to deal with hidden agendas here, but on the other hand people here are not as direct as those from places like Amsterdam. There they sometimes appear to drawing you out, and that's a bit too much for me. This is the happy medium."

Pieter Goossens studied biomedical science at the Vrije Universiteit Brussel, and received his doctorate at Maastricht University in 2012; his thesis was entitled 'A fatal attraction: Macrophage recruitment to the atherosclerotic plaque'. After a postdoc period at Marseille, he returned to Maastricht in 2016.

Constance Baaten studied molecular life sciences at Maastricht University, where she also received her doctorate in 2018; her thesis was entitled 'Acquired alterations in platelets: Insight into impairment and recovery of platelet function'. She was then given a postdoc position at University Hospital RWTH Aachen, where she is still working, in conjunction with a postdoc position at UM she obtained in January 2021.

EDUCATION AND TALENT DEVELOPMENT

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of its students. Clinical and preclinical staff of CARIM is intricately involved in the development and execution of the education programmes of the FHML Bachelor and Master studies of Biomedical Sciences, Medicine, and the Physician-Clinical Investigator Programme (MSc/MD). CARIM is also involved in the education programme of the Faculty of Science and Engineering.

In addition, CARIM's staff is involved in the design of a contiguous and state-of the-art PhD (doctoral) training programme. The content of the PhD education programme has been developed by CARIM's top researchers, while 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.

RESEARCH MASTER

In the Biomedical Sciences programme, master's students are informed about CARIM and the programmes of the other FHML Schools during the start of the master. Members of the CARIM staff actively participate in the design and execution of the teaching programme in the second and third course. Students can attend school-specific lectures and parallel programmes organised by school researchers. In the second semester, they may become acquainted in more detail with School specific practical research. In this respect, CARIM offers students the opportunity to do a junior research internship in the field of cardiovascular biology at one of CARIM's laboratories. In the second year, the students that are attracted to cardiovascular research can do their senior research internship and master thesis in CARIM. These internships are also accessible for students from other master programmes, provided that they have an adequate background. All too often successful master students subsequently pursue their scientific career as PhD candidates within CARIM.

PHD PROGRAMME

Our PhD programme is accessible for talented and motivated students graduated from national and international Medical and Basic Sciences Masters. At the end of 2020, in total 288 (internal as well as external) PhD candidates attended our PhD programme. In 2020, 53% of our PhD candidates came from abroad, creating an exciting multicultural and international atmosphere. The translational nature of CARIM's research is exemplified by the mix of PhD candidates with a background in medicine or in the basic sciences. The principal goal of the four-year PhD training programme is to support PhD candidates in developing themselves into independent and productive researchers in the cardiovascular field. To ensure high quality PhD training, CARIM offers frequent interaction of PhD candidates with skilled and experienced supervisory teams, thereby providing a stimulating and critical environment to further develop research skills. We also offer our PhD candidates a broad range of possibilities to attend general and school specific courses, to attend seminars and master classes. PhD candidates are stimulated to visit symposia to present their own research on national and international podia. In 2020, 59 new PhD candidates started their trajectory at CARIM, of which 30 were employed at Maastricht University.

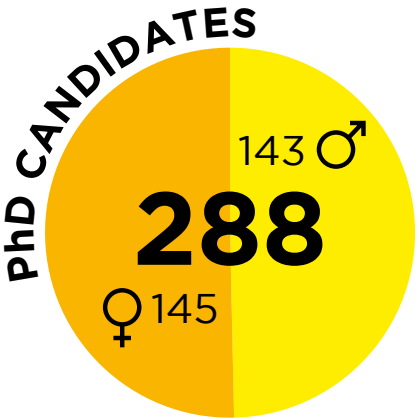
POSTGRADUATE PROGRAMME

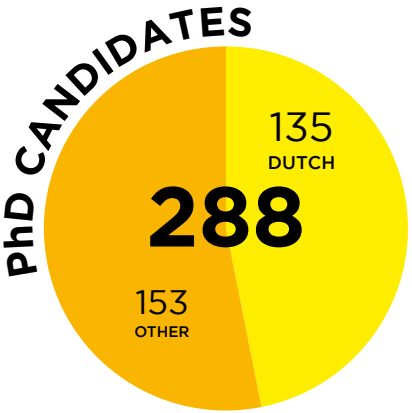
One of the key needs identified by the European Society of Cardiology is the training of future leaders in arrhythmia management and research. For this purpose, a unique two-year postgraduate educational programme entitled 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM) has been established. DAS-CAM trains the future leaders in cardiac electrophysiology by integrating state-of-the-art cardiac arrhythmia management with leadership skills, biostatistics and health technology assessment. DAS-CAM is a collaboration between Maastricht University, the European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA). It consists of eight modules (six of which take place in Maastricht) each chaired by two expert anchor persons supported by the Scientific Program Committee. Researchers from CARIM play a major role in the DAS-CAM programme, with four CARIM Principal Investigators serving as anchor persons and several CARIM researchers involved as members of the Scientific Program Committee and guest lecturers. In addition, a number of DAS-CAM participants will continue to be affiliated with CARIM through a PhD research project. The first successful PhD conferral of a former DAS-CAM participant at Maastricht University took place on 2 October 2020.

The second DAS-CAM cohort started in 2019 and enrolled 30 cardiac electrophysiologists from 18 countries. Originally, four modules, including the final graduation, were scheduled for 2020. The January module could take place as scheduled. Thereafter, the DAS-CAM programme adapted to the new circumstances: a virtual event was held in the summer to discuss cardiac arrhythmia management and leadership during COVID-19. One of the remaining modules was held in a hybrid format in October 2020 and the final two modules have been postponed to 2021.

PHD STATISTICS

In 2020, 24 PhD candidates finished their theses within our institute and twelve theses were externally prepared.





CARIM THESES 2020

Hermans B
Title: Diagnosing Long-QT Syndrome, Simple but not easy
Supervisors: Prof. T. Delhaas, Prof. L.A.F.G. Pison (UHasselt)
Co-supervisor: Dr P.G. Postema (AUMC)
10 January

Zhou TL
Title: Blood Pressure Variability: causes and consequences
Supervisors: Prof. C.D.A. Stehouwer, Prof. A.A. Kroon
Co-supervisor: Dr R.M.A. Henry
15 January

Geraets Y
Title: Metabolic phenotyping of the pressure-overloaded Heart - Focus on model development
Supervisor: Prof. J.F.C. Glatz
Co-supervisors: Dr M. Nabben, Dr J.J.F.P. Luiken
24 January

Demand J
Title: Oxygen sensors in atherosclerosis
Supervisors: Prof. E.A.L. Biessen, Prof. C.D.A. Stehouwer
Co-supervisor: Prof. J.C. Sluimer
30 January

Kusters Y
Title: Unraveling Obesity's Road to Diabetes and Cardiovascuar Disease: Contributors to Insulin Resistance, Beta-cell Dysfunction and Vascular Dysfunction
Supervisors: Prof. C.D.A. Stehouwer, Prof. C.G. Schalkwijk
Co-Supervisor: Dr A.J.H.M. Houben
20 February

Atcharayam N
Title: Duchenne Muscular Dystrophy: The NIMHANS Experience
Supervisors: Prof. T. Delhaas, Prof. B.W. Kramer
23 April

Fontaine M
Title: The MacroScreen Platform – Capturing Cardiovascular Disease Inflammation In Vitro
Supervisor: Prof. E.A.L. Biessen
Co-supervisors: Prof. J.C. Sluimer, Dr L. Temmerman
14 May

Beurskens D
Title: Extracellular histone H3: biomarker and therapeutic target for the prevention of tissue damage
Supervisor: Prof. C.P.M. Reutelingsperger
Co-supervisor: Dr G. Nicolaes
2 July

Stifft F
Title: Novel Insights for Improvement of Tacrolimus Therapy
Supervisor: Prof. J. van Hooff
Co-supervisor: Dr M. Christiaans
3 July

Van Gorp R
Title: Oral anticoagulants as double-edged sword: balancing between coagulation and calcification
Supervisors: Prof. L.J. Schurgers, Prof. C.P.M. Reutelingsperger
8 July

Van der Vorm L
Title: Unravelling von Willebrand Factor: Active VWF in conditions of (un)balanced haemostasis
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr B. de Laat, Dr J. Remijn
10 July

Elbatrik M
Title: Network pharmacology for mechanistically redefined comorbidities
Supervisor: Prof. H.H.H.W. Schmidt
Co-supervisor: Dr A.I. Casas Guijarro
26 August

CARIM THESES 2020

Josefs T
Title: Diabetes-related factors and atherosclerosis regression
Supervisors: Prof. C.G. Schalkwijk, Prof. E.A. Fisher (NYU School of Medicine)
Co-supervisor: Dr K. Wouters
3 September

Van Dongen D
Title: Pre-hospital risk stratification in suspected Non ST-elevation acute coronary syndrome
Supervisor: Prof. A.W.J. van 't Hof
Co-supervisors: Dr J.P. Ottervanger, Dr R.J. Slingerland (Isala, Zwolle)
3 September

Smulders M
Title: Diagnostic evaluation of chest pain. The role of non-invasive cardiac imaging
Supervisors: Prof. H.J.G.M. Crijns, Prof. J.E. Wildberger
Co-supervisors: Dr S. Bekkers, Dr B. Kietselaer (Zuyderland Medisch Centrum)
4 September

Goldhoorn R-J
Title: Endovascular treatment of acute ischemic stroke in clinical practice
Supervisors: Prof. R.J. van Oostenbrugge, Prof. W.H. van Zwam
4 September

Sun A
Title: Role for phosphatidylinositol 4-kinase IIIß in cardiac metabolic diseases
Supervisor: Prof. J.F.C. Glatz
Co-supervisors: Dr J.J.F.P. Luiken, Dr D. Neumann
8 September

Wang S
Title: Vacuolar H+-ATPase as target to restore cardiac function in the diabetic heart
Supervisor: Prof. J.F.C. Glatz
Co-supervisors: Dr J.J.F.P. Luiken, Dr M. Nabben
8 September

Vroemen W
Title: Cardiac Troponin T; It's all in the shape of you
Supervisor: Prof. O. Bekers
Co-supervisors: Dr D. de Boer, Dr W. Wodzig
11 September

Wolf M
Title: Evolution and technological advances in ablation of complex atrial and ventricular arrhythmias
Supervisors: Prof. H.J.G.M. Crijns, Prof. M. Duytschaever (AZ Sint-Jan, Brugge)
2 October

Jaminon A
Title: Key role for VSMCs in vascular remodeling and calcification
Supervisors: Prof. L.J. Schurgers, Prof. C.P.M. Reutelingsperger
2 October

Prisco S
Title: The role of Aldosterone and PTH in Human Primary Aldosteronism and Vascular Calcification
Supervisors: Prof. L.J. Schurgers, Prof. T. Hackeng, Prof. G.P. Rossi (Padua)
8 October

Li W
Title: Microvascular dysfunction, physical activity, and cardiometabolic disease
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr A.J.H.M. Houben, Dr M.T. Schram
22 October

Cuijpers I
Title: A novel paradigm for heart failure with preserved ejection fraction. Working towards understanding the pathology of HFpEF
Supervisors: Prof. S. Heymans, Prof. E.A. Jones (KU Leuven)
28 October

CARIM THESES 2020

Rensma S
Title: Causes and consequences of microvascular dysfunction Focus on the brain
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisor: Dr T.T. van Sloten
29 October

Petsohonsakul P
Title: Role of vascular Remodeling in Atherosclerosis and Aortic Aneurysm; Vascular calcification as a hallmark of increased vascular smooth muscle cell oxidative stress
Supervisors: Prof. L.J. Schurgers Prof. C.P.M. Reutelingsperger
Co-supervisor: Dr B.M.E. Mees
2 November

Muralidhar K
Title: Renal protection off pump coronary artery bypass grafting
Supervisors: Prof. J.G. Maessen, Prof. L. Vincent (Narayana Health City, Bangalore)
Co-supervisor: Dr Y. Ganushchak
10 November

Sang Y
Title: Innovation and standarization of near-patient platelet function assays
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr B. de Laat, Dr M. Roest
11 November

Bennis F
Title: Machine learning in medicine - Big pictures require small, but crucial strokes
Supervisors: Prof. T. Delhaas, Prof. B.W. Kramer
Co-supervisor: Dr P. Andriessen (Maxima Medisch Centrum, Veldhoven)
13 November

Vonhögen I
Title: Bridging the gaps of microRNAs in Obesity
Supervisors: Prof. L.J. de Windt, Prof. P. da Costa Martins, Prof. M.E.A. Spaanderman
Co-supervisor: Dr M. Muri (Malága, Spain)
17 November

Notten P
Title: Ultrasound-accelarated catheter-directed thrombolysis for the prevention of postthrombotic syndrome
Supervisors: Prof. H. ten Cate, Prof. M.J.H.M. Jacobs
Co-supervisor: Dr A.J. ten Cate-Hoek
26 November

Krasznai A
Title: Optimizing the perioperative period in the treatment of varicose veins
Supervisor: Prof. C.H.A. Wittens
Co-supervisor: Dr L.H. Bouwman
27 November

Gaudino M
Title: The Radial Artery for Coronary Artery Bypass Grafting
Supervisors: Prof. R. Lorusso, Prof. J. G. Maessen
Co-supervisor: Dr M.C.G. van de Poll
1 December

Schönleitner P
Title: Dynamic Regulation of Subcellular Calcium Handling in the Atria; Modifying Effects of Stretch and Adrenergic Stimulation
Supervisors: Prof. U. Schotten, Prof. H.J.G.M. Crijns
Co-supervisor: Dr G. Antoons
15 December

Zelis N
Title: Predicting adverse outcomes in older medical emergency department patients
Supervisor: Prof. P.W. de Leeuw
Co-supervisors: Dr. P.M. Stassen, Dr J. Buijs (Zuyderland MC Heerlen)
16 December

Ter Woorst J
Title: Outcome in cardiac surgery: differences between men and women
Supervisor: Prof. J.G. Maessen
Co-supervisors: Dr A.H.M. van Straten (CZE), Dr M.A. Soliman Hamad (CZE)
16 December

DISSERTATION PRIZE 2019

Dr **Debbie Beumer** (Dept. of Neurology) received the CARIM Dissertation Award 2019 for her thesis 'Insights in acute endovascular treatment in ischemic stroke'. Debbie was one of the coordinative researchers from the Mr Clean study, which was a prospective blinded open randomised trial on the safety and efficacy of IAT (Thrombectomy) with acute stroke. She was shared first author on the world famous New England Journal of Medicine paper describing the trial results. In addition of this landmark study, many relevant sub-group analyses were taken up in her thesis, as well as pre-trial clinical data that led to successful design of Mr Clean. Debbie has been a coordinative PhD candidate all the way, leading to a high impact study with equal output.

KNOWLEDGE TRANSFER

CARIM COURSES

Due to the COVID-19 pandemic, the annual CARIM Course Week that usually takes place in June was cancelled.

CARDIOVASCULAR GRAND ROUNDS AND CARIM SYMPOSIUM 2020

The Cardiovascular Grand Rounds Maastricht and the yearly CARIM symposium are means to update the knowledge of our PhD candidates, our researchers and other external people with interest in the field of cardiovascular research.

At the start of 2020, the successful Cardiovascular Grand Rounds Maastricht lecture series hosting national and international experts, was initially continued on a weekly basis. These lectures take place on Friday during the morning meetings, with breakfast provided, and are of very high scientific level, worthy of an early rise. The lectures were interrupted during the first wave of the pandemic, but resumed after the summer break in an online format. Also in the new format, the lectures have been well attended and have addressed a wide range of topics relevant to all CARIM divisions. The Cardiovascular Grand Rounds are organised by Prof. **Blanche Schroen** and Dr **Jordi Heijman** (Dept. of Cardiology). For the current programme please visit our website.

CARIM's hybrid annual symposium was held in Maastricht and online on 25 November, as it was not possible to have the entire CARIM community together due to the corona measures. An interesting afternoon programme was organised that could be followed online via livestream. Our

recent laureates presented their research and a session on diversity and inclusivity was organised. The poster session was held in a different format than usual. Nominated PhD candidates and/or researchers recorded short videos in which they presented their research. The recordings were judged by a committee and the winner from each division presented their research on 25 November.

The Robert Reneman Lecture that takes place during the annual CARIM Symposium is named in honour of the founding scientific director of CARIM. The Robert Reneman Lecture is given by a renowned scientist in the field of cardiovascular diseases and is awarded with a bronze sculpture of Caius Spronken. This year's Robert Reneman Lecture was presented by Prof. Harry Büller. Harry Büller, MD, PhD is a professor of Internal Medicine at the

Academic Medical Center in Amsterdam. He is specialised in Vascular Medicine. Dr Büller earned his MD and PhD at the University of Amsterdam. After graduating, he completed his research fellowship in haemostasis and thrombosis in the Departments of Medicine and Clinical Epidemiology and Biostatistics at McMaster University in Hamilton, Ontario, Canada in 1981 and 1982. In 2008, he was appointed Honorary Professor of the Royal Netherlands Academy of Arts and Sciences. He authored and co-authored more than 740 scientific articles of topics in his field. He supervised 52 PhD candidates as a promotor. In December 2019 he retired.

Finally, the CARIM Commitment Award (see page 52), Dissertation prize (see page 86) and the video prizes were awarded. The following videos were awarded with a prize:

- Division Blood: ultrasound-accelerated CAtheter-directed thrombolysis Versus Anticoagulation for the prevention of post-thrombotic syndrome: The CAVA-Trial by Pascale Notten;
- Division Vessels: Microvascular dysfunction: contribution to stroke, dementia and depression by Thomas van Sloten;
- Division Heart: Heart sounds for cardiac resynchronization therapy optimization by Hongxing Luo.

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2020

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2020. Some of them are presented below.

The **Cardiorenal Seminars** is a joint lecture series of CARIM and the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. **Joachim Jankowski**) and offers a platform for international top scientists in the field of vascular biology and nephrology to present their recent work. The lecture series is alternately held in Aachen and Maastricht. In 2020, eight keynote lectures were given by Dr Caroline Cheng (UMC Utrecht, 23 January), Prof. Matthias Taupitz (Charité Berlin, 13 February), Prof. Stephan Rosenkranz (University of Cologne, 27 August) Prof. Christoph Wanner (University Hospital Wuerzburg, 3 September), Prof. Nikolaus Marx (University Hospital Aachen, 24 September), Prof. Peter Stenvinkel (Karolinska Institutet Stockholm, 29 October), Prof. An De Vriese (Ghent University, 12 November) and Prof. Carsten Wagner (University of Zurich, 17 December).

The three-monthly **Maastricht Immunology Seminar Series** bring together researchers from Maastricht that are interested in immunology and inflammation. These informal meetings are ideal to expand local networks, and to share research techniques and experience. Each seminar, an external speaker is invited and two PhD candidates or postdocs from Maastricht present their research. The meetings are organised by Dr **Kristiaan Wouters** (Dept. of Internal Medicine) and Dr Lotte Wieten (Dept. of Transplantation Immunology). The organisation Committee

also contains PhD candidates from different research schools: **Xiaodi Zhang** (Dept. of Internal Medicine), Nicky Beelen (Dept. of Transplantation Immunology), Ines Reis (Dept. of Molecular Genetics), and Marina Damas (Dept. of Psychiatry and Neuropsychology). In 2020, we unfortunately only had one meeting in March, due to the COVID-19 situation. This was a special edition where the latest advances in flow cytometry were introduced by Sebastiaan van Bockstael from Cytek. He presented the state-of-the-art spectral flow cytometry technology. This led to a demo of this technology in September after which CARIM decided to invest in this exciting new technology, and a 4 laser Aurora spectral analyser has been purchased.

From 12-14 February, the 4th meeting of the EU-CardioRNA COST Action was hosted by Dr **Emma Robinson** and Prof. **Blanche Schroen** (Dept. of Cardiology) at Maastricht UMC+, supported by CARIM. EU-CardioRNA is a pan-European network with the aim of catalysing multidisciplinary research collaborations to foster our understanding of the role of transcriptomics in cardiovascular disease (CVD). It is an initiative of the H2020 funded European Cooperation in Science and Technology (COST) Association. The Maastricht meeting played host to more than 85 guests from 33 different countries both in and outside Europe, including Estonia, Slovakia, Bosnia-Herzegovina, Malta and Singapore. Two themes of the meeting were 'Cardiac aging and associated comorbidities' and 'Novel alternative approaches to studying CVD' and scientific sessions as well as roundtable discussions were tailored around these topics. Prof. Tilman Hackeng gave an opening welcome to attendees on 12 February and opening and closing keynote lectures were given by Prof. Leon de Windt (Dept. of Molecular Genetics) and Prof. Eva van Rooij (Hubrecht, Utrecht) respectively.

The yearly **Scientific Meeting of The Maastricht Study** took place on 5 November. To celebrate the 10th anniversary of The Maastricht Study, the theme of the symposium was 'The Maastricht Study 2010-2020: A decade of deep-phenotyping'. Because of the COVID-19 measures the symposium was organised as an online event with over 150 participants of whom ~125 from The Netherlands and ~30 from elsewhere in the EU.

First, Dr Miranda Schram took us back to the first 10 years of the Maastricht Study. The session was continued with last year's successful new format of duos of senior and junior researchers where the senior researcher provides an outline of the topic and the junior researcher presents recent results. This year's duos were Dr Annemarie Koster and Evelien Vandercapellen who focussed on physical activity in the prevention of type 2 diabetes, Dr Simone Eussen and Kim Maasen who presented research on the assessment of diet using food frequency questionnaires with focus on dicarbonyls and advanced glycation end-products, Prof. Martijn Brouwers and Yuri Foreman who focussed on metabolism and continuous glucose monitoring, and Dr Jaap Janssen and Laura Vergoossen who presented their work on functional brain imaging and white matter in type 2 diabetes. This session was closed by Dr Carla van der Kallen who looked forward to The Maastricht Study 'phase 2' in which participants of The Maastricht Study are invited for a full round of re-measurements. The keynote lecture was delivered by Dr Nishi Chaturvedi, Professor of Clinical Epidemiology at University College London, who educated us on current developments in epidemiology, deep-phenotyping and observational cohort research.

On 26 November, a **special mini-symposium** was organised on the occasion of **Prof. Harry Crijns' retirement.** Due to

the COVID restrictions, only a small group of participants could be present at Chateau St. Gerlach, with the others participating online. After a short introduction by Dr Jordi Heijman, who moderated the event on behalf of the organising committee, Prof. Crijns received a special royal distinction (‘*Ridder in de Orde van de Nederlandse Leeuw*’) from Mayor Mirjam Clermonts-Aretz of Meerssen, as well as the Maastricht UMC+ distinction from Dr Helen Mertens. The scientific part of the symposium comprised four lectures from renowned collaborators: Prof. Uli Schotten (Maastricht) discussed the mechanisms of atrial fibrillation, Prof. Isabelle van Gelder (Groningen) presented an overview of the famous RACE trials, Prof. Jan Tijssen (Amsterdam) explained the role of cardiovascular biostatistics in state-of-the-art atrial fibrillation research, and Prof. John Camm (London) discussed antiarrhythmic drug therapy. These presentations highlighted some of the many topics that Prof. Crijns has contributed to during his scientific career. Prof. Gerhard Hindricks (Leipzig) and Prof. Kevin Vernooy (Maastricht) explained that these topics will also be included in a special issue of the EP Europace journal on ‘Innovations and Paradigm Shifts in AF Management’, with contributions from numerous local, national and international collaborators. The symposium concluded with speeches by Profs. Martin Paul, Michael Jacobs, and Tilman Hackeng. Prof. Hackeng also gave Prof. Crijns the CARIM award for all his contributions to CARIM during twenty years in Maastricht.

WORLD THROMBOSIS DAY 2020

On 13 October 2020, the **6th World Thrombosis Day (WTD)** was celebrated worldwide. Six years ago the International Society on Thrombosis and Haemostasis decided to dedicate the birthday of the German physician Rudolf Virchow (1821-1902) to increase awareness on thrombosis among the general population. CARIM’s Department of Biochemistry together with Maastricht UMC+ uses this day to bring their research results to the general public and inform our society on important signs that predict or coinicide with this dangerous and prevalent disease. Different from other years for reasons of COVID-19, we took our 2020 campaign to an online format from our University Studios. In preparation for this, flyers and info charts were distributed, and newspaper articles in newspapers and hospital magazines were published. World Thrombosis Day 2020 was again organised by Lidewij Bos, Dionne Braeken, Stella Thomassen, Hugo ten Cate, and Tilman Hackeng.

The theme for World Thrombosis Day 2020 was evident. The way that COVID-19 impacts all three research areas in CARIM: blood, vessels and heart made CARIM and her researchers very well suited to tackle important COVID-19 research objectives. After a thematic introduction by Prof. Tilman Hackeng, people could enjoy clear lectures by Dr Kristien Winckers on COVID-19, a blood-curdling change, describing the effects of COVID-19 on blood clotting and increased risks on pulmonary emboli. Next, Drs. Anne-Marije Hulshof presented on COVID-19 behind the scenes; a lab

journey, in which she presented potential clinical assays to measure COVID-19 thrombotic complications in blood and blood plasma. Dr Pieter van Paassen, internist-immunologist, informed us on corona crisis: excess harms, in which COVID-19-induced inflammatory responses damages vessel walls (see pages 28-31). Finally, a powerful interview took place between Drs Bram Kremers and a patient with COVID-19 and thrombosis, with touching personal and family experiences.

World Thrombosis Day 2020 registered 271 attendees, and due to overwhelming positive feedback it was concluded to be a great succes.

From left to right: Dr Pieter van Paassen, Drs Anne-Marije Hulshof, Dr Kristien Winckers, Prof. Tilman Hackeng

CARIM'S DEVELOPMENT TALENT PROGRAMME

Early recognition of talent is one of the key strategies of CARIM to coach and prepare gifted young academics for their future academic career. CARIM stimulates and supports talented students and staff by offering grants for research fellowships at each step of their career, be it at Bachelor, Master, postgraduate, PhD or postdoc level. These grants will be enabled through our 'Harry Struijker-Boudier award for talented academics' (HS-BAFTA). The HS-BAFTA is intended for three groups of young scientific researchers.

1. HS-BAFTA TALENTED FUTURE PHD CANDIDATES

The fellowship is intended for:

a. Talented Bachelor students in Health, Medicine or Life Sciences, who have demonstrated to be able to combine their studies with an active involvement in scientific research. It can be used to interrupt their study and to perform a research project within CARIM for 6-12 months during their Bachelor phase.

b. Talented Master students in Health, Medicine or Life Sciences, who have demonstrated to be able to combine their studies with an active involvement in scientific research. It can be used to interrupt their study and to perform a research project for 6-12 months within CARIM during their Master phase.

c. Postgraduates to bridge the time between graduation and the start of an official contract as a PhD candidate within CARIM. The fellowship must start within the first year after graduation and is open to students not yet contracted by or enrolled in a PhD programme.

The fellowship amounts to max. € 21,000 (in accordance with scale 7-0) and € 3,000 for exploitation costs and is meant for a period of max. 6 months. For Ba/Ma students the regular curriculum should be interrupted to perform the research project within CARIM. The PI concerned has to match an equal amount of money for the candidate for an equal period of max. 6 months. This brings the max. total annual amount for the HS-BAFTA on € 48,000 for a total of 12 months.

2017 William van Doorn

2018 Jasper Demandt

2019 Mohamed Kassem

2020 Anne-Marije Hulshof, Yentl Brandt

2. HS-BAFTA TALENTED PHD CANDIDATES

The fellowship is meant to support PhD candidates who want to spend time abroad during their PhD in order to gain experience and improve their chances in receiving a personal grant (i.e. Rubicon; Veni; Dr E Dekker) after their PhD. The fellowship amounts to € 7,500 based on actual costs of max. € 1,000 for (extra) living allowance per month and travel costs, for a period of max. 6 months. The fellowship can be performed during any period within the PhD trajectory.

2018 Mueez Aizaz, Jens Posma

2019 Federica de Majo, Cengiz Akbulut, Walid Chayouya, Rogier Veltrop, Valeria Lo Coco, Rob Holtackers

2020 Stefan Reinhold, Anouk Geraets, Job Verdonschot, Raquel Videira, Jorik Simons, Anne Willers

3. HS-BAFTA TALENTED POSTDOCS (FORMER POSTDOCTORAL TALENT FELLOWSHIP)

The fellowship is intended for recently graduated CARIM PhD candidates. The fellowship is meant to keep top CARIM talents connected to our institute by giving the opportunity to go abroad, thereby establishing international cultural and scientific exchange and gaining the experience required for acquiring personal grants. Therefore, a main requirement for this fellowship is that approximately 9 months (max. 12) shall be spent at a partner institute outside the Netherlands to acquire (further) foreign experience and strengthen the international network of the candidate and PI(s) involved. The candidate should use this year for setting up international collaborations and writing a proposal for a postdoc position (i.e. Rubicon; Veni; Dr E. Dekker) and will be judged on his intentions of performing research of this grant from within CARIM.
The ultimate goals are either to acquire or increase international research experience, to broaden the laureate's professional network, and to enhance chances of obtaining prestigious grants in order to strengthen the personal and professional ties to Maastricht University and specifically CARIM.

2016 Stijn Agten

2017 Robin Verjans

2018 Mitchel Bijnen

2020 Federica de Majo

ROBERT RENEMAN LECTURE

The Robert Reneman Lecture takes place during the annual CARIM Scientific Symposium, and is named in honour of the founding Scientific Director of CARIM. The Robert Reneman Lecture is given by a renowned scientist in the field of cardiovascular diseases and is awarded with a bronze sculpture of Caius Spronken.

1993	M. Verstraete	Leuven, Belgium
1994	J. Sixma	Utrecht, NL
1995	P. Vanhoutte	Courbevoie, France
1996	W. Schaper	Bad Neuheum, Germany
1997	P. Davies	Philadelphia, USA
1998	M. Pfeffer	Boston, USA
1999	Y. Nemerson	New York, USA
2000	V. Fuster	New York, USA
2001	M. Schneider	Houston, USA
2002	F. Rosendaal	Leiden, NL
2003	A. Zeiher	Frankfurt, Germany
2004	P. Poole-Wilson	London, UK
2005	D. Wagner	Boston, USA
2006	S. Wickline	St. Louis, USA
2007	J. Molkentin	Cincinnati, USA
2008	B. Furie	Boston, USA
2009	K. Walsh	Boston, USA
2010	J. Lusis	Los Angeles, USA
2011	W. Ouwehand	Cambridge, UK
2012	D. Kass	Baltimore, USA
2013	J. Yudkin	London, UK
2014	P. Reitsma	Leiden, NL
2015	S. Hatem	Paris, France
2016	S. Laurent	Paris, France
2017	J. Griffin	San Diego, USA
2018	M. Giacca	Trieste, Italy
2019	V. Ramachandran	Boston, USA
2020	H. Büller	Amsterdam, NL

PROFESSORSHIPS

HEIN WELLENS VISITING PROFESSORSHIP

The Hein Wellens Visiting Professorship is endowed by the St. Annadal foundation to stimulate clinical research in the field of cardiovascular disease. The purpose of this chair is to give renowned scientists the opportunity to teach and apply their knowledge at CARIM. The chair is named after Prof. Hein Wellens (1935-2020), a Dutch cardiologist who is considered to be one of the founding fathers of the cardiology subspecialty of clinical cardiac electrophysiology. From 1978 until 2002, Prof. Wellens held a chair at Maastricht University as Professor and Head of the Department of Cardiology.

2004 - 2005	J. Narula	Irvine, USA
2007 - 2008	M. Krucoff	Durham, USA
2008 - 2010	Y. Rudy	St. Louis, USA
2010 - 2011	R. Kim	Durham, USA
2011 - 2013	K. Mayo	Minneapolis, USA
2013 - 2014	M. Stoll	Münster, Germany
2016 - 2017	A. Zaza	Milano, Italy
2020	Th. Münzel	Mainz, Germany

CARIM-HVC CHAIR

The programme is founded and funded by the CARIM together with the HVC and aims at strengthening the translational cardiovascular axis.

2020 - 2022	C. Hughes	University of California at Irvine

STICHTING TER BEVORDERING VAN CARDIOVASCULAR ONDERZOEK EN ONDERWIJS

2020	P. Kirchhof	University Heart and Vascular Center UKE Hamburg

THE H.C. HEMKER CHAIR

The H.C. Hemker Chair is founded in honour of the founder of the Department of Biochemistry, Professor Coen Hemker. The foundation encourages multiple visits to the department per year to initiate and/or maintain a scientific relation between research groups.

2014 - 2018	R. Ariëns	Leeds, UK
2017 - 2019	S. Watson	Birmingham, UK

EDMOND HUSTINX CHAIR

The Edmond Hustinx Chair, funded by the Edmond Hustinx Foundation, was attached to CARIM from 1998-2008. This chair focussed on research in the area of molecular and chemical aspects of cardiovascular diseases. CARIM was able to appoint internationally recognised top scientists to this chair.

1998	P. Williamson	University of Massachusetts
1999	J. Bassingthwaigthe	University of Washington
2000	M. Safar	Hôpital Broussais, Paris
2002	M. Galli	Ospedali Riuniti, Bergamo
2004	M. Kockx	University of Antwerp
2005	P. Bock Vanderbilt	University Medical School
2007 - 2008	S. Dimmeler	Molecular Cardiology, University of Frankfurt

VAN DE LAAR PROFESSORSHIPS ON BIOCHEMISTRY OF HAEMOSTASIS AND THROMBOSIS

The Van de Laar chair is endowed by a private donation from the Van de Laar Foundation, to enable renowned professors to perform work visits to the Department of Biochemistry to give lectures and to interact with researchers from the Department of Biochemistry in creating an international network for the mutual benefit of performing research on the biochemistry of thrombosis.

2016	C. Weber	Ludwig Maximilians University Munich
2017	K. Mayo	University of Minnesota at Minneapolis

SINT ANNADAL FOUNDATION

2014-2019	J. Hoorntje

OTHER VISITING PROFESSORSHIPS

2016 - 2022	A. Baker	University of Edinburgh

HIGHLIGHT
DIVISION HEART

DOMINIK LINZ

The European mHealth project TeleCheck-AF

The Division Heart of CARIM is renowned for translational research projects focusing on pathophysiology and treatment of atrial fibrillation (AF), which is the most common sustained heart rhythm disorder in humans. Patients with AF are considered vulnerable, which is why monitoring of vital parameters, particularly heart rate and rhythm, is crucial to guide treatment decisions. A ventricular rate above 110 bpm during AF may lead to symptoms such as palpitations and dyspnoea, and may contribute to the development of heart failure (tachy-cardiomyopathy), resulting in increased hospitalisation rates [1]. Under normal circumstances, patients with AF receive a face-to-face consultation in the outpatient clinic (AF-Clinic). Prior to the consultation, an electrocardiogram (ECG) is made, so that heart rate and rhythm information is available. However, during the coronavirus disease 2019 (COVID-19) pandemic, face-to-face outpatient appointments were rapidly converted into teleconsultations, to protect our AF patients from being infected with COVID-19. In fact, the proportion of patient contacts managed by teleconsultations at the Maastricht University Medical Centre (MUMC+) increased from fewer than 1% in 2019 to 76% in 2020. This means that instead of seeing our patients with ECG information, we were calling them without any clinical data about heart rate and rhythm, and it became clear that this made decision making about treatment difficult.

To date, several mobile health (mHealth) technologies are available for remote heart rate and rhythm monitoring [2-3]. However, some of these mHealth solutions are based on a single-lead ECG and require a handheld device or smartwatch, which is not available to every patient. An alternative for ECG is the photoplethysmography (PPG) technology [3]. At the clinic, PPG is routinely used in finger pulse oximeters to measure oxygen saturation. Additionally, PPG can determine blood volume pulse variations in the local arterioles of the fingertip by measuring the amount of reflected light, for example using the built-in camera of a smartphone (**Figure 1**) [4]. The PPG technology can be tried with the patient's own smartphone by downloading the FibriCheck® app and scanning the QR code or filling in the invitation code "CARIM".

Although current guidelines state that PPG technology alone cannot be used to diagnose AF [1], validated algorithms applying machine learning techniques are available to detect AF with an overall sensitivity and specificity of 94.2% and 95.8%, respectively [5]. Therefore, heart rate and rhythm

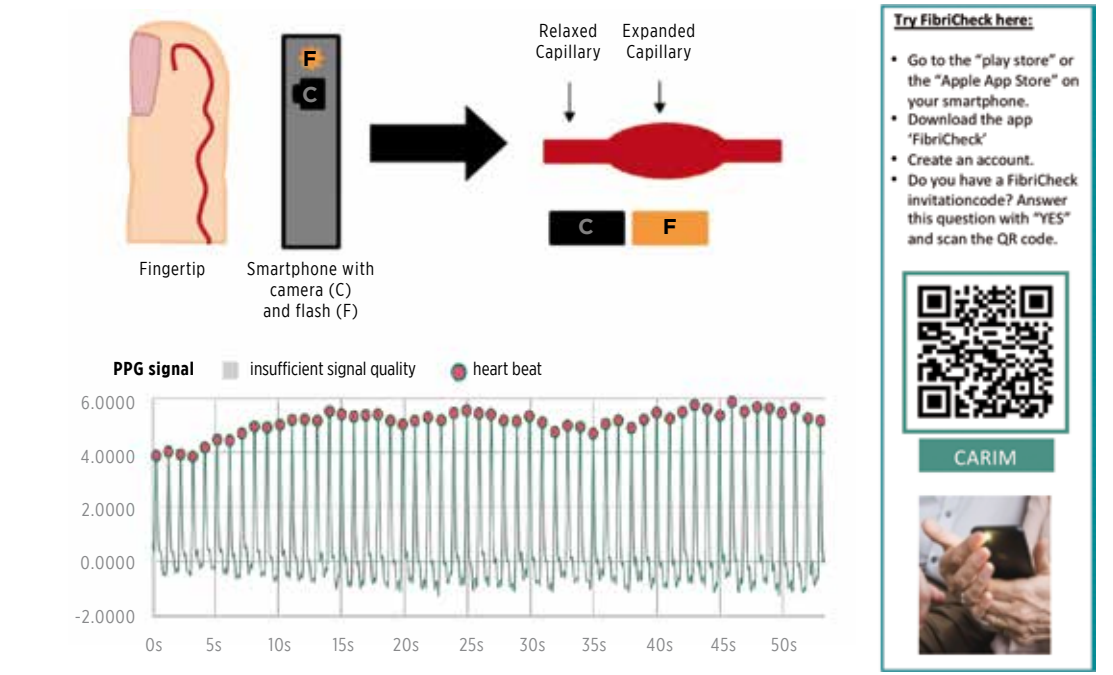


FIGURE 1 The principle of photoplethysmography (PPG) rhythm recording: a light source (e.g. the flashlight of a mobile phone) shines light onto the capillaries in the fingertip. The reflected light is then detected by a photodetector (e.g. the camera of a smartphone). The variations in reflected light intensity mirror the blood pulse variations (below) and can be used for rate and rhythm assessment. The PPG app FibriCheck® can be downloaded and activated by scanning the QR code or filling in the invitation code 'CARIM'.

assessment by PPG technology can be of great value to support the remote management of patients in AF outpatient clinics who have been diagnosed with AF by ECG before.

Just downloading an app makes it possible to literally turn a smartphone, which is nowadays available to almost everybody, into a medical device to provide vital information required to remotely treat our patients [6]. At the beginning of the COVID-19 pandemic, we started to contact our AF patients one week prior to a scheduled teleconsultation and instructed them to download an app called FibriCheck® (Conformité Européenne (CE) marked; www.fibricheck.com). The patients were educated and instructed to perform three heart rate and rhythm recordings a day for one week prior to the teleconsultation, and additional measurements in case of symptoms. All recordings were instantly transmitted to a secure cloud system, which was accessible to the physician at the time of the teleconsultation [6]. We called

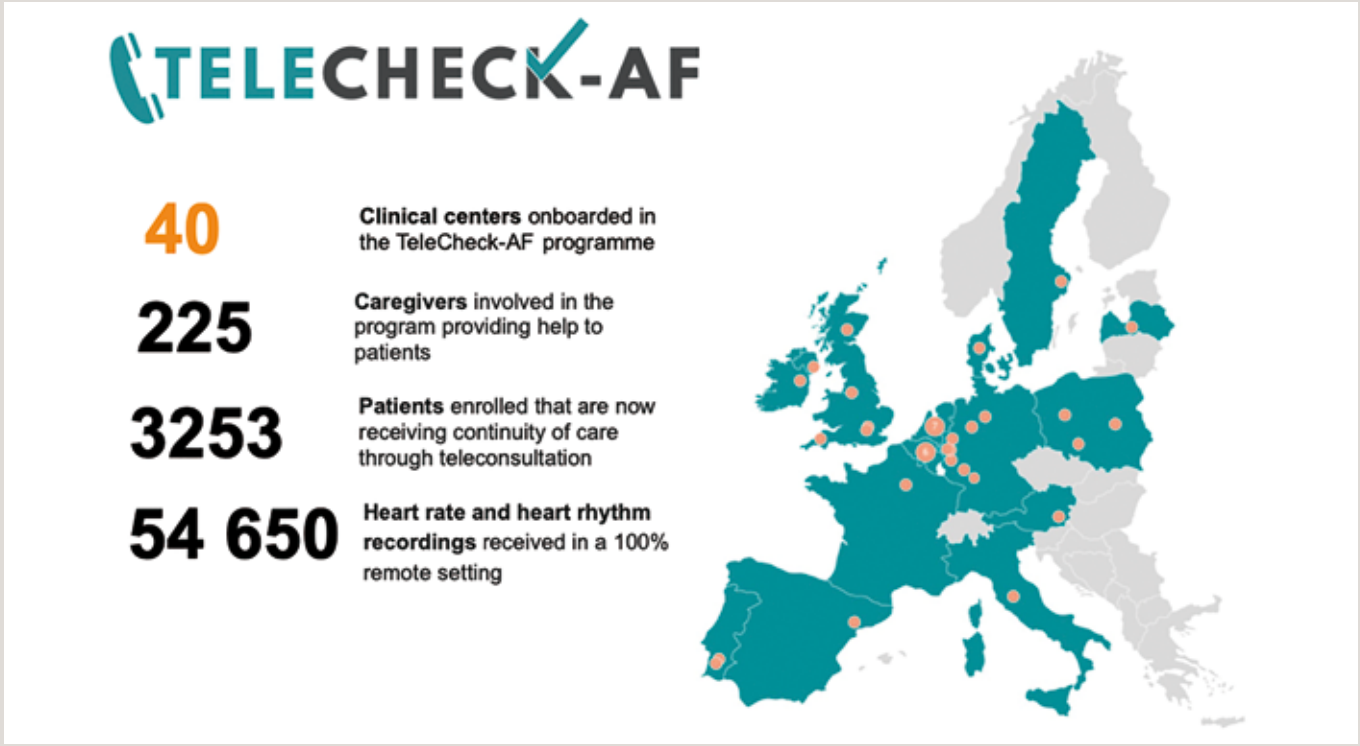


FIGURE 2 Numbers for TeleCheck-AF and regional distribution of centres participating in TeleCheck-AF.

this on-demand mHealth intervention: TeleCheck-AF [7]. TeleCheck-AF incorporates three important components: (i) a structured teleconsultation ('Tele'); (ii) an app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'); and (iii) comprehensive AF management ('AF').

We described the TeleCheck-AF approach in a Standard Operating Procedure manuscript [6] and started to communicate about our mHealth approach via social media (using the Twitter hashtag #TeleCheckAF). Within one month, we set up the TeleCheck-AF mHealth cloud infrastructure at an additional 39 centres in 14 European countries. In total, over 3000 patients have now been managed remotely by the TeleCheck-AF approach outside the hospital via teleconsultation (**Figure 2**) [8].

To assess how mHealth is being used within the European TeleCheck-AF project, we are currently performing a retrospective analysis of the majority of the participating centres [8]. Overall, most centres were university hospitals (64%)

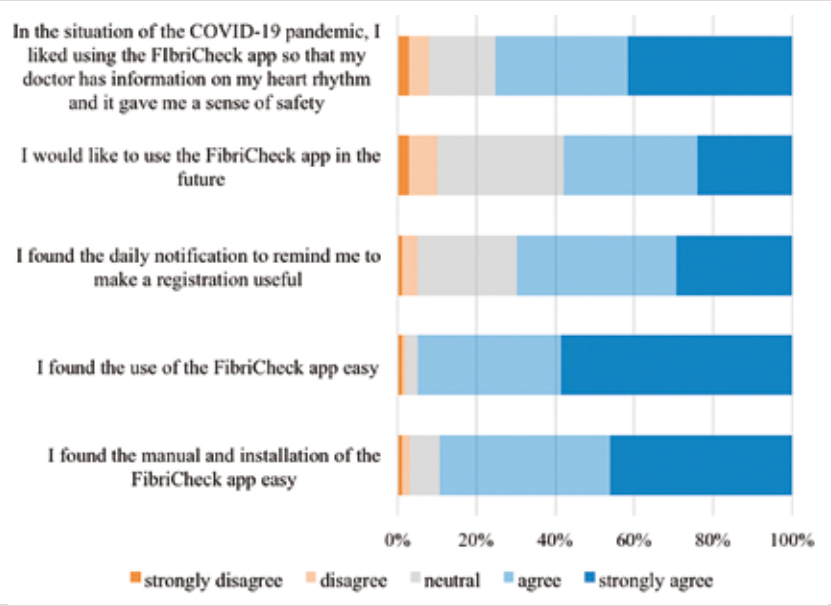


FIGURE 3 Patient experience survey on TeleCheck-AF (n=850 patients). Adapted from reference [8].

and the remaining (36%) were specialised public cardiology or district hospitals. The majority (>80%) of centres reported no problems (concerning cloud access, patient compliance or quality of recordings) during the initial implementation of the TeleCheck-AF approach. Centres agreed that the on-boarding process of their centre in the TeleCheck-AF project was simple, and access to the patient measurements via the stand-alone cloud infrastructure was trouble-free and possible from the first day on. They also agreed that on-demand remote heart rate and rhythm assessment for the purpose of teleconsultation supported their medical decision making, that their patients responded positively to using the app for seven days, and that they felt comfortable about interpreting PPG recordings.

Of the 850 patients included in the retrospective patient experience analysis, one-third were in the 60-69 years age range, the oldest patient being 92 years old. Patients agreed that the app was easy to use (94%) and easy to install (89%). The app gave patients a sense of safety (74%). More than half of the patients (58%) agreed or strongly agreed that they would like to use the FibriCheck® app in the future. The results of the patient experience survey are presented in **Figure 3**.

We are currently tracking the treatment decision and management pathways of patients within the TeleCheck-AF project. In total, more than 50 000 PPG measurements were recorded by more than 3000 patients, who have been characterised in an electronic Case Record File. In collaboration with all TeleCheck-AF investigators and with the University of Adelaide (Australia) and the University of Copenhagen (Copenhagen), we will apply signalling processing and machine learning approaches, to test whether PPG signals incorporate features beyond heart rate and rhythm which may help to predict at an earlier stage, or even to prevent, onsets of arrhythmias or hospitalisations and emergency department presentations due to heart failure decompensations and high symptom burden.

In the future, smart wearable devices and smartphone apps used by our patients will provide more and more biometric information, which may guide our treatment decisions. However, despite the rapid progress of technology, there

is still a significant gap between what we know and how we apply this knowledge in clinical practice. One focus of TeleCheck-AF is to identify and address existing challenges in the implementation of mHealth use in AF management. In addition to supporting the development of suitable mHealth infrastructures in the hospital, we are refining integrated care mHealth pathways to incorporate mHealth solutions in existing outpatient infrastructures and to provide patient education to support empowerment and self-care [9].

Another focus is that of steering the discussion about mHealth reimbursement models and privacy considerations. As scientists, physicians and society, we need to make sure that the new technology is accessible and user-friendly for all patients, to ensure digital equity in mHealth and throughout modern medicine.

The TeleCheck-AF project is an example of an Integrated Clinical Research Project, which contributes to patient care during the COVID-19 pandemic and opens up several research opportunities, covering the complete translation axis from new innovative technology and algorithms to clinical implementation and reimbursement discussions. Additionally, lessons learned from the TeleCheck-AF project will help us to develop and refine infrastructures for future digital multicentre trials. We thank the TeleCheck-AF team in Maastricht, all national and international TeleCheck-AF investigators and all our patients for joining us on this exciting digital journey!

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PHD POLICY - BACK TO THE FUTURE

MARC VAN BILSEN

INTRODUCTION

Over the years, the evaluation of our PhD training programme has become an increasingly important aspect of the 6-year self-assessment cycle of research schools. More or less in parallel to this, the policy regarding PhD training has undergone major changes at the national, faculty as well as school level.

Generally speaking, we are inclined to consider the status quo as a given and we try to deal with it as best as possible. However, once in a while it is good to take some time to look back and to try and track down which processes have actually led to the *status quo*. Sometimes this can be useful in shaping the future, and this certainly also applies to the *status quo* regarding PhD policy.

In 2010, I accepted the request of the then Scientific Director to become the PhD coordinator at CARIM. Hence, after approximately a decade, it is good to reflect on CARIM's PhD policy in the context of the external developments and to look forward to the challenges and opportunities that lie ahead of us.

HISTORICAL LANDMARKS - THE AIO SYSTEM AND THE RESEARCH SCHOOL SYSTEM

The introduction of the AIO ('research assistant in training') system at the Dutch universities in 1986 signified a seminal change in PhD policy. The major reason for introducing this system was the recognition that scientific research was crucial for the Dutch knowledge economy and that the training of more PhDs was an important pillar in strengthening this knowledge economy. Another reason was that at that time, PhD trajectories were too non-committal and, as a consequence, took excessively long. Accordingly, the main purposes of the AIO system were to increase the number of PhDs and to get more grip on PhD trajectories.

The AIO system was also one of the reasons to create the so-called research schools in 1991. The introduction of the AIO system had increased the need for well-structured research training programmes. At the same time, it was felt that the research at Dutch universities needed a quality incentive and more coordination. These developments led to the founding of research schools, one of them being CARIM. Research schools were defined as 'Centres of high-quality research offering structured training to young researchers'. The combination of the AIO and research school constructions forced faculties and schools to develop concrete plans to specify the training & education part of their PhD programmes.

FROM SALARY VERSUS TRAINING TOWARDS SALARY AND TRAINING

Of course, as is inherent in Dutch nature, the AIO system had to be cost-effective as well (more PhDs for the same amount of money). To reduce the costs it was argued that AIOs were 'in training' for a certain percentage of their appointment (especially in the first years) and that 'training time' did not have to be rewarded in the form of salary. In practice, this meant that the salary of AIOs was substantially cut, to barely above the minimum wage level in the first year of appointment.

Only in 2003, with the introduction of the UFO (University Job Classification) system for all university employees, was the principle of salary cuts for AIOs abandoned. From then on, AIOs were paid a salary more in line with other academic staff and were considered full-fledged university employees. Furthermore, the term 'AIO' was replaced by 'PhD candidate'. At the same time, it was felt that training-on-the-job was insufficient to become an independent researcher and that PhDs should still be able to increase their knowledge, skills and competences through courses, workshops and practical training.

From a historical perspective, therefore, the status quo is largely the result of two historical developments, which, on the one hand, have meant that university-employed PhDs are now considered full-fledged employees (according to UFO system), and that, in the other hand, they receive ample and appropriate training (inherited from the AIO system and the Research School system).

DURATION OF PHD TRAJECTORIES

Ever since the introduction of the AIO system the average time it takes for a PhD candidate to complete their thesis has hardly declined, and still stands at about five instead of four years. Basically, all measures to get more grip on the PhD trajectories had only modest effects on the average duration. There are both pros and cons to a prolonged PhD trajectory. The five years of PhD training result in highly qualified researchers who outperform PhDs from other countries, and PhDs evidently benefit from this when applying for a postdoc position abroad. On the other hand, the extended time is sometimes considered disadvantageous when a PhD is looking for jobs outside academia. Also, from a financial point of view, a shorter duration leads to a higher PhD turnover and is therefore preferred by the universities.

In line with this, the FHML has also taken various initiatives to try and reduce the average duration of PhD trajectories. To this end a 'carrot and stick' policy was developed. In case a PhD candidate succeeds in completing his/her thesis within the allotted four years, the supervisor receives a financial incentive. In contrast, if it takes more than four years, the supervisor has to pay the salary for the extra time needed. PhDs are no longer allowed to complete their thesis in their own time (while receiving unemployment benefit). In addition, to better monitor the training, supervision and progress of PhD candidates, the FHML implemented a web-based system, referred to as PhD-TRACK.

THE HISTORY OF PHD-TRACK

When I started as PhD coordinator in 2010, CARIM's PhD programme had eroded gradually, and I was asked to revitalise the programme and to bring it more in line with recent developments at the national and international level. In practical terms, this resulted in the CARIM Research Education Supervision plan, the so-called CARES plan, in which the plans for each PhD candidate's PhD programme had to be concretised and laid down in a personal research plan, an education plan and a supervision plan. In parallel with this, the course programme offered by CARIM was renewed, putting more emphasis on state-of-art cardiovascular research topics instead of department-related topics.

At the same time, to get a better grip on PhD trajectories, developments at the faculty level were aimed at harmonising the PhD programmes in the individual schools. This resulted in the well-known PhD-TRACK web-based application to monitor the progress of PhDs in a more standardised manner across all FHML schools. This meant that we already had to abandon the CARES plan in 2015. The good thing is that

important elements of the CARES plan were incorporated in TRACK, most notably the personal research plan (PRP). The education and supervision parts of the CARES plan merged into the training & supervision plan (TSP) of TRACK. For FHML, PhD-TRACK has become the principal tool to monitor the progress and success of PhD trajectories in each school, as well as a source of information for planning and control overviews.

THE BURDEN OF MONEY

For each successful PhD defence, universities receive a substantial amount of money from the government. This makes the PhD system part of the revenue model of universities: the more PhDs receive their degree, the more income.

The FHML has fully adopted this revenue model. These days a substantial part of the money that schools receive from the FHML (via the so-called *'Toewijzing Integrale Middelen'*) is based on how the FHML schools perform in terms of the number of PhD theses completed, relative to other schools. Other performance indicators, such as the number and quality of publications and the number and type of grants acquired, have become irrelevant. The way this funding model works in practice is that FHML schools compete for the number of completed PhD trajectories.

In my view this is an unhealthy situation. In practical terms, this implies that each school strives to get as many PhDs enrolled as possible and to have them complete their theses within as short a time as possible, at least within four years. It has created a system in which quantity (number of PhD theses) is the decisive factor. In line with FHML policy, the number of PhD theses has indeed increased substantially over the years, and at CARIM too, the number of PhDs has grown significantly. As show in **Figure 1** the number of PhDs employed by the university has shown a steady increase over time. Most notably, however, the number of PhDs who are not employed by the university ('external' PhDs) has risen dramatically over the last decade. By now, the total number of PhDs far exceeds the number of staff researchers. When expressed in full time equivalents (fte) the numbers become even more staggering: more than 300 fte of PhDs versus 60 fte of scientific staff and post-docs. These numbers illustrate that PhDs have become the cornerstone of CARIM's research effort.

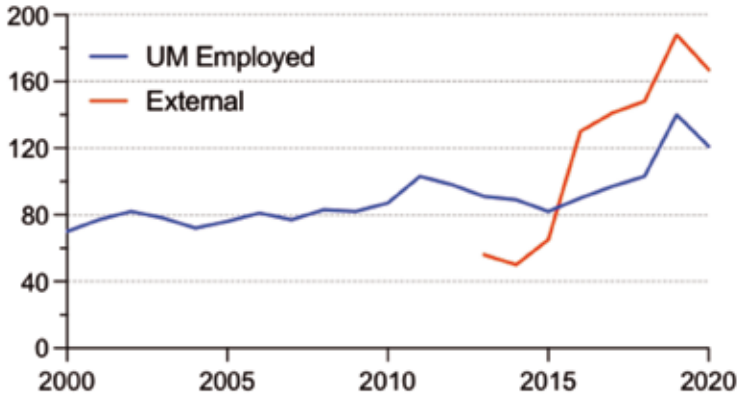


FIGURE 1 NUMBER OF PHD CANDIDATES AT CARIM
Development of the numbers of UM-employed and non-UM-employed (external) PhD candidates at CARIM. Before 2013 the number of external PhDs was not systematically monitored.

WHAT IS CARIM'S REASON TO EXIST?

The historical context of why research schools were founded also means we have to ask ourselves: why do we exist as CARIM? Is it our principal goal to generate high-quality scientific output (mainly via the efforts of PhDs), or alternatively, is it our goal to train PhDs (with scientific output being a major by-product). The most probable (and politically correct) answer is 'both'. In daily practice, however, the focus is on scientific output. To some extent this is appropriate, as most of our funding agencies primarily ask for scientific deliverables. However, if we consider training to be an important task of a research school, then we should also recognise that training PhDs is a crucial element of CARIM's existence and that this training can be at odds with the generation of scientific output. Training PhDs requires time and money (attending courses, course fees in some cases) which goes at the expense of pure research.

SCIENTIFIC RESEARCHER VERSUS ACADEMIC PROFESSIONAL?

This discussion should also take another aspect into account. What is the purpose of training PhDs? Do we train them to become independent researchers? The current definition according to the UM regulations for obtaining a doctoral degree (2020) is still identical to that formulated as part of the Dutch Higher Education & Research Act (1992). It states that the goal of obtaining a PhD degree is to write a thesis that serves as evidence of the competence needed to practice science independently. According to this definition, CARIM's task is to train scientific researchers.

However, we cannot ignore the fact that as a consequence of the PhD revenue model, far more scientists are being trained than academia can absorb. As early as 2011, a paper addressing this issue appeared in Nature (Cyranoski et al., Nature 2011). In this opinion paper the current system was aptly referred to as 'The PhD factory'. Indeed, in practice only about 30% of all PhDs end up in academia, and the majority of PhDs pursue a career outside academia.

Up to now, the PhD programmes have always been seen as tools to enable PhD candidates to develop into independent researchers. Given that only 30% will end up in academic research, is this still fair? More recent developments try to give a broader scope to PhD trajectories. According to this point of view, PhD programmes should enable the candidates to develop into academic professionals, with the acquirement of academic skills and an academic mode of thinking being given a more central role. This would put PhD candidates in a better position to pursue a career outside academia. These kinds of issues are currently also on the agenda as part of the Recognition & Awards initiative (position paper VSNU *'Ruimte voor ieders talent'* 2019) and are likely to have consequences for PhD trajectories as well as the contents of PhD theses.

CARIM'S PHD POPULATION AND CAREER PERSPECTIVES

Taking a closer look at the next career step of CARIM's PhDs (**Figure 2**), it is indeed evident that only 32% continue their career in academic research. By contrast, a considerably larger fraction (44%) end up in health care (reflecting the high number of PhDs with a medical background in CARIM). The remaining 24% find a position elsewhere. In my view scientific research should be considered a critical element of becoming a health care professional. This notion is also substantiated by the emphasis that is put on scientific training as part of the Medical Master programme at UM. Accordingly, about three quarters (32% + 44%) of CARIM's PhDs will benefit directly from a proper training

as a scientific researcher. In that sense, the current CARIM training goals still suit the majority of CARIM's PhDs.

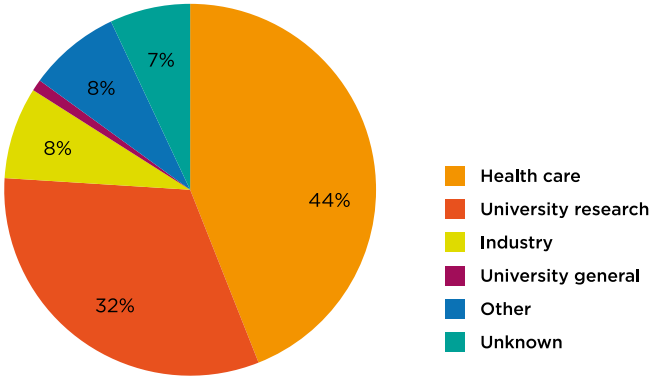


FIGURE 2 CAREER PERSPECTIVES
Positions after acquiring a PhD degree (Source: ERC report 2019).

CHALLENGES AND OPPORTUNITIES

As outlined above, the status quo regarding PhD policy is largely based on developments at the national (AIO system, research school system, UFO system) and faculty levels (number of PhDs as sole performance indicator). As CARIM we have to accommodate these, largely external, developments as best we can.

The rapid rise in the number of non-UM-employed PhDs is of some concern though, as the FHML's PhD system was developed primarily with UM-employed PhDs in mind. As of 2020, the relation between external PhDs and the UM is formalised in a so-called hospitality agreement. But what can and should we ask from a PhD who will graduate at Maastricht, but who works at and is employed by a spin-off company or a university hospital in India?

Within the given boundaries, there is probably room for improvement. For CARIM it might be worthwhile to identify at an early stage – for instance at the end of the second year – those PhDs who are talented and would like to pursue a career as basic or clinical scientist (a kind of tenure-like system for talented PhDs). For these PhDs, the time to obtain a PhD degree should be more flexible, giving them extra time if needed to complete promising studies. For those who do not aim at a career in academia, the goal would be to complete their programme within the official four years. During the second half of the PhD trajectory, they should be allowed to invest a certain amount of their time in the acquirement of skills that are useful in their prospective work environment.

Finally, current national developments may also affect the boundaries set by FHML. For instance, the recent discussions about Recognition & Rewards at the UM and FHML aim to put greater emphasis on quality over quantity. If taken seriously, this should also imply that the Recognition & Reward policy has to be translated into the FHML's financing model, thereby giving a wider meaning to performance indicators.

ARTS & SCIENCES

RACHEL TER BEKKE

Arts & Sciences

It was through her supervisor Paul Volders that cardiologist Rachel ter Bekke, then at the beginning of her PhD project, came into contact with his sister, the process artist Claudia Volders. The two immediately clicked, and decided to examine how art and science can reinforce each other for the benefit of heart patients. This led to the birth of the 'HeArt Project', in which science and visual arts work side-by-side to promote holistic patient care. "It has opened my eyes to the added value offered by art for both patient care and research."

"I was doing research in the context of the WORM study, which involved mapping a large family with a hereditary genetic defect that predisposes for sudden cardiac arrest. Having this hanging over them like Damocles' sword has a huge impact on all those involved. It was then that I met Claudia, and she started to ask all kinds of questions that made me stop and think, like: 'Do you actually really see each individual patient? Can you smell that mutation? Shall we go to the origin of their family tree and symbolically dig up some earth there? Let's turn the family tree, which comprises 16 generations and 6,000 real people, into music!' Together we decided to use the emotional and connecting power of art to translate complex scientific findings into humane and holistic patient care. We use art as an intuitive vehicle to promote creativity and the communication between doctor and patient."

Holistic patient care

"How can we use art to understand patients better? Art can connect multiple layers of consciousness and activate consciousness levels. This not only teaches patients to deal with their disease better, but will enable doctors to learn to understand and support them in a very different way. This is a completely virgin territory, very different from what we doctors are used to. It is not just trying to achieve certain functional parameters, or particular blood levels, but seeing the person as a whole and treating them as such. Unfortunately, current patient care practice does not allow enough time for this; it won't work within the usual 15 minute consultation slot. Still, I'm convinced that only a holistic approach will enable us to really move forward, in other words, improve our insight into diseases and improve patient care. Art is a universal medium for this."

The HeArt Project

"The HeArt Project revolves around the patient's experience. Claudia had previously made works of art involving scientific figures and tables that were printed on cloth. We then used these as covers for the tables in the waiting room of the Cardiovascular Centre (HVC). Patients were invited to write on them, whatever they wanted. That turned it into a genuine street-art poem, straight from the heart and filled with emotion. No patient satisfaction study could come close to this! Patients came into my office with tears in their eyes, touched by this wonderful initiative. Art provided a gateway into the patient's inner well-being. One elderly gentleman who participated in the WORM study wrote a moving letter about the impact this art & science project had

WE USE ART AS AN INTUITIVE VEHICLE TO PROMOTE CREATIVITY AND THE COMMUNICATION BETWEEN DOCTOR AND PATIENT

on him. His letter is now part of the composition banner that is on display the at the HVC's outpatient department. It's still very emotional to read it."

Coping with disease through art: HeArt-Ma'at!

"After this pilot stage, we were convinced that art can offer added value to both doctors and patients. Together with the departments of Medical Psychology and Psychiatry (Maastricht UMC+), Clinical Neuropsychology (Faculty of Psychology & Neuroscience, School for Mental Health & Neuroscience) and Data Science and Knowledge Engineering (Faculty of Science & Engineering), we're now working on a follow-up project, called HeArt-Ma'at. This will involve using art as a diagnostic and therapeutic means to better understand patients and help them deal with their disease. More acceptance and peace, less stress, which can alleviate illness. Think of people who have had a near fatal arrhythmia and have been resuscitated. They have looked death in the eye. They're usually treated by having an ICD implanted, in addition to medication. Medically speaking, we're done; the guidelines have been followed. But the person with the ICD is entering an invisible new reality, full of the fear of death, fear of a shock, and concern from their loved ones. It's not surprising that many of them experience high levels of anxiety, depression and even panic. That in turn causes high activation of the sympathetic nervous system, increased risk of arrythmias and even ICD shocks. It's for these people that we want to develop an art-based intervention, using art objects in a virtual environment to encourage them to cope better with their disorder. The better they cope, the lower their stress levels and the lower the mortality rates. That's our target. At the same time, healthcare professionals will be able to understand and support their patients better. It's a large project, which is still being developed, and for which the first subsidies have now been obtained. We have also started to cooperate with international partners like Abertay University and the University of Dundee."

Art & Science

"This is just the beginning. Integrating art into patient care and research will lead to creative cross-fertilisation and create room for out-of-the-box thinking and crossing boundaries. This will yield results for patients as well as researchers: in 2019 I received the CARIM Dissertation Prize for my PhD thesis, which allowed scope for art as well as science. I'm very proud of that."

Rachel ter Bekke studied medicine at Antwerp University and has worked as a cardiologist-electrophysiologist at Maastricht UMC+ since 2013. She received her PhD at Maastricht University in 2018, based on her thesis entitled 'Ventricular arrhythmogenesis in the genetically-susceptible heart: time to change concepts of mechanisms and management', for which she was given a CARIM Dissertation Prize in 2019. In the same year, she obtained a Veni grant for her research into the relationship between electrical and mechanical drivers of ventricular arrhythmias.

doi:10.1093/eurheartj/ehaa615

Obituary
Dr Hein Wellens MD PhD

On 9 June 2020, Dr Hein Wellens passed away, at the age of 84

Hein was Professor Emeritus of Cardiology at Maastricht University, the founder of academic Cardiology in Maastricht, and department head from 1977 until 2000. On the occasion of his retirement in 2000, a book was published to commemorate his 33 years in clinical cardiology and arrhythmology,[1] including the first 10 years (1967–77) at the Wilhelmina Gasthuis in Amsterdam. In all these years, Hein and colleagues made countless seminal contributions to our understanding of human cardiac electrophysiology and arrhythmia management, e.g., by authoring>700 scientific papers, book chapters, and books.

As a dedicated family man, friend to many, former cricket player, and lover of jazz, he also enjoyed many other aspects of life.

Hein was honoured as an ESC GoldMedallist in 2002.

His first short paper 'The Treatment of Auricular Fibrillation Using Direct Current Discharge (Cardioversion)' in 1967, and his PhD thesis 'Electrical Stimulation of the Heart in the Study and Treatment of Tachycardias' in 1971 marked the beginning of a long list of innovative concepts that underpin modern cardiac electrophysiology. All his contributions impacted heavily on our field and read as chapters of an established textbook. Yet, while best recognized for advancing our knowledge of the electrocardiogram, cardiac arrhythmias, electrophysiology, and sudden death, Hein Wellens was also a visionary.

Dedicated to bringing academic research to the highest possible level, he was one of the founding fathers of the Cardiovascular Research Institute Maastricht (1988). He strongly promoted translational research and multidisciplinary collaborations. In his role as Director (1993–2003) of the Interuniversity Cardiology Institute of the Netherlands (now Netherlands Heart Institute), he had the means to connect people, supporting them to excel in cardiology. Hein had a nose for young talent. Among the things that cheered him most was the success of his protégés.

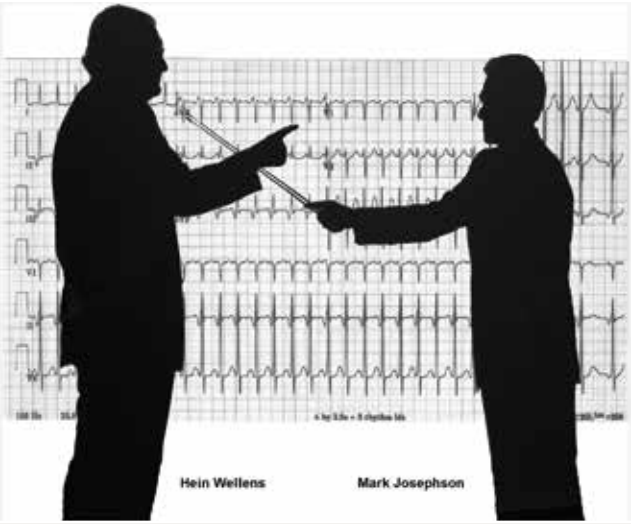
He supervised many PhD candidates and trained numerous medical specialists. The list of persons visiting Maastricht from abroad for a clinical or research fellowship is long. All of them found their way to respectable positions and credit Hein for contributing to this. Thus, he had a far-reaching influence on colleagues and professional organizations. Many of us stand on his shoulders.

His scientific legacy is nicely illustrated by a photo taken at the doctoral-degree ceremony of Daniel M. Johnson at Maastricht University in 2013, when five generations of PhDs climbed the stairs, with four being (co)supervisor of the next in line.

Hein was a passionate physician who concentrated his efforts in patient care, persisting and persevering to find solutions for people in need. He could become somewhat impatient if clinical progress was delayed by medical incompetence, expecting his own high standards from others. His adage 'What You Do Not Know, You Do Not See' was a way of emphasizing the importance of first-hand knowledge in clinical practice.

Many have commended his skills as an educator; Hein had an absolute gift for teaching. Complex arrhythmias were pedagogically reduced to logical elements and as an attendee you could be amazed how he made intricacies so simple. He entertained large crowds and small groups alike, and the teacher in him would always involve the audience, often with the use of an interactive voting system. Famous were his courses on complex cardiac arrhythmias with best friend Mark Josephson, which were organized for 35 consecutive years (1981–2016) and continuously received very high ratings.

From 2017, Hein Wellens contributed to the educational program 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM), a joint initiative of Maastricht University Medical Center, the European Heart Academy, and the European Heart Rhythm Association. Together with Jeronimo Farre´, he led DAS-CAM Module 1 'Towards an Optimal Use of the ECG in Cardiac Arrhythmia Management'.



One of the key needs identified by the European Society of Cardiology is the training of future leaders in arrhythmia management and research, from a broad view of society and economic perspectives. DAS-CAM serves that goal. In January 2017, Hein addressed the DAS-CAM participants on one aspect of leadership, stating–with that typical pose of his and a stern look over his glasses–: 'To become a leader you need luck. You need to be at the right place, at the right time, and with the right support'.

The above characterizations exemplify that Hein Wellens maintained a very active publication, teaching, and consulting schedule after stepping down from office, until shortly before his demise. In hindsight, his valedictory lecture 'The Future of the Cardiologic Patient' in 2000—partly an act of frustration about mandatory retirement—was the start of a long epilogue. In fact, >250 publications of his hand saw the daylight only after he retired, and some are still in press! Many of us would consider these post-retirement achievements a very decent yield of an entire academic career.

As the years imposed their relentless burden, Hein often quoted Bette Davis: 'Getting old ain't for sissies'. It was a way to soft-pedal his physical constraints and re-concentrate on his 'hobby' again. Until that, inevitable final episode came.

Hein Wellens was one of the truly great cardiologists of our time. He will be remembered as a genial and remarkable man who persisted in following developments in his discipline throughout his life. Somebody with a genuine interest in other people and a family man and friend who will be missed so dearly. We have all lost a seminal figure.

Paul G A Volders and Harry J G M Crijns.
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REFERENCE

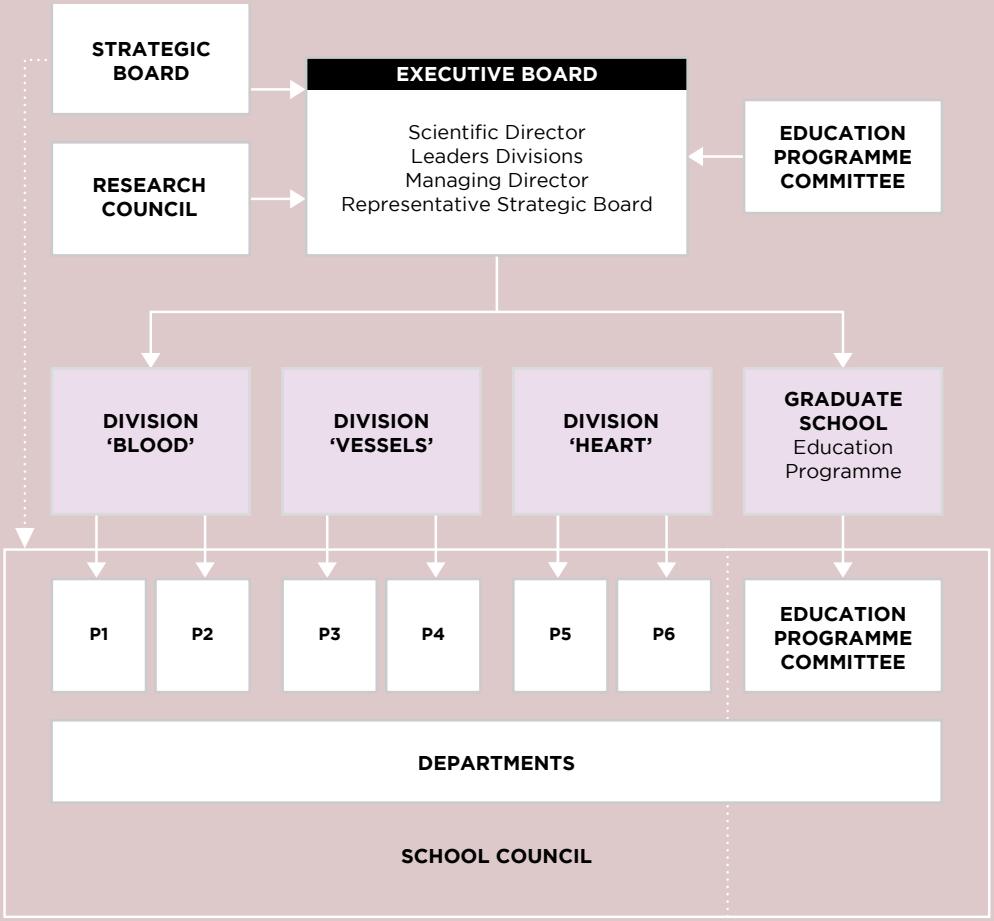
1. Smeets J, Doevendans P, Josephson M, Kirchhof C, Vos M, eds. *Professor Hein J.J. Wellens: 33 Years of Cardiology and Arrhythmology.* Dordrecht, The Netherlands: Kluwer Academic Publishers, 2000.

Five generations of PhDs. 8 March 2013. From left to right: Daniel Johnson, Marc Vos, Hein Wellens, Anton Gorgels, Paul Volders

ORGANISATION

05

ORGANISATION



The Scientific Director has the final responsibility for the research institute, including the organisation and management of the research programme, the scientific output, the training of Master's and graduate students and post-doctoral fellows, the financial management and the public relations of the institute. The Scientific Director is assisted by the Managing Director, who takes care of the financial, legal and human resource issues and the secretary to the Board, whom together represent the Management Team (MT). The MT meets weekly. Together with the three leaders of the divisions and a representative from the Strategic Board, the MT constitutes the Daily Board of the institute. The Daily Board meets monthly to discuss and decide upon issues at strategic and operational level. The Daily Board is advised by the Strategic Board, Education Programme Committee (EPC) and the Research Council.

The Strategic Board (SB) is in place to advise and support the Scientific Director in managing long-term policy. The SB is also a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive international scientific environment. The Strategic Board meets regularly to discuss issues such as grant programmes, national and international collaboration networks, interdisciplinary communication and CARIM's visibility in the national and international cardiovascular fields.

The EPC coordinates both the PhD and master's training programmes and advises the Executive Board on all issues regarding these educational programmes. The chairperson is also CARIM's PhD coordinator and advises the Daily Board on all issues regarding the PhD programme. Within CARIM, the PhD coordinator works closely with the CARIM Office, policy advisor and Scientific Director.

The Research Council advises the Executive Board and PIs on the quality of research proposals and meets regularly to discuss and guide grant applications. In 2019, the CARIM Grants and Incentives Team was established to boost grant applications by activating researchers and research teams, keeping track of submitted, granted and rejected applications and discussing calls and opportunities.

The School Council consists of all PIs and Department Heads and meets four times a year. The School Council is informed by the Executive Board on ongoing matters and advises the Scientific Director on research within the school and the related education programmes.

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- Prof. Paul Volders, Dept. of Cardiology
- Prof. Christian Weber, Dept. of Biochemistry
- Prof. Joachim Wildberger, Dept. of Radiology
- Prof. Leon de Windt, Dept. of Cardiology

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CARIM OFFICE

The CARIM Office consists of specialists that support the organisation and its researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Riet Daamen (until April 2021), Esther Willigers and Barbara Przybylski (from February 2021) are responsible for administrative issues, including supporting the executive management. The controller of CARIM is Lynn Lemeer. The Finance Department of Maastricht University provides support on accounting the CARIM research projects with Henny Kerckhoffs, Esther van Heel, Yves Filot (until August 2020), Johan Noordijk (from July 2020) and Hans Slenter (from October 2020). Mechteld Ostendorf and Anke Neekmann of the Human Resources Department of Maastricht University are dedicated to CARIM. In legal affairs, Cindy Schröder, Monique Soons-Smeets and Suzanne ten Hoeve support CARIM. Willem Wolters is responsible for funding acquisition. Managing Director Wouter Hankel is the head of the CARIM office. Former Managing Director Rob van der Zander was a special advisor to the management of CARIM (until the summer of 2020). The research in CARIM's divisions involves the research activities of employees working in 17 (six basic and eleven clinical) departments of Maastricht UMC+.

6
BASIC DEPARTMENTS

- Biochemistry
- Biomedical Engineering
- Epidemiology
- Genetics & Cell Biology
- Pharmacology & Toxicology
- Physiology

11
CLINICAL DEPARTMENTS

- Anesthesiology
- Cardiology
- Cardio-Thoracic Surgery
- Clinical Chemistry
- Internal Medicine
- Intensive Care
- Neurology
- Pathology
- Radiology & Nuclear Medicine
- Vascular Surgery

INTERVIEW

HARRY CRIJNS EN KEVIN VERNOOY

Management change at the
Maastricht UMC+ Cardiology Department

Since February 2021, Kevin Vernooy has been filling the chair vacated by Harry Crijns. That is literally how it still feels to him at the time of this interview, in late March. Vernooy is now in charge of the Department of Cardiology at Maastricht UMC+, over two years after Crijns saw that he was a suitable successor. “Just pick up the book called ‘What are the characteristics of a born leader?’ and you see that’s Kevin. That was not so hard to see.” The two men look back and ahead.

Originally, the plan was that Harry Crijns would not retire until August of 2021, but altered regulations meant that this was moved forward to December 2020. “That came as a bit of a shock, as there was still so much that needed to be done!” As he says this, he also realises that this would probably have been his feeling at any moment. “It wasn’t a big task showing Kevin the ropes, as that was a natural process that had been underway for some time.” Both men look back with pleasure on all the Friday afternoons when they used to get together over the past few years. “Around five o’clock he would enter my room asking; ‘Any news?’ and we’d then catch up. It took some getting used to when I was no longer sitting in that chair. The Friday five o’clock moment felt a bit empty then.” Vernooy: “I still phone him occasionally. About simple things, like a particular budget and what should be done with it, but also about more complicated stuff, discussions with colleagues, which often have a history attached to them. I then ask for ‘parental advice’: How would you deal with this? If I have to take a difficult decision, I like to consult a few people. And then it’s nice to be able to call someone who can say what the best thing to do is, without a hidden agenda of his own.”

A SUITABLE HEAD OF DEPARTMENT

Vernooy still remembers clearly how Crijns approached him saying: “I think you would be a suitable successor when I retire.” “Since I knew that his retirement was approaching, I had of course already given it some thought. And I was eager to take this step, as I very much enjoy combining research, clinical work and management. As head of the department you have even more opportunities to make your mark and to get things done. In view of the Cardiology Department’s recent history, I thought it was best to have another cardiac rhythm expert as the head. It was an opportunity I had to take.” Crijns had seen for some time with what flexibility his intended successor had led the Arrhythmia Section of their department. “People were very pleased with it. I didn’t even hear any more grumbling by the die-hards and it was running much more smoothly than when I was leading it. He is good tactically, and he knows what people can do and how to inspire and connect them. That’s the most important thing of all, I think. Furthermore, he has a comprehensive view of the field, is enthusiastic and is good at taking decisions. He has achieved a high scientific level and is known internationally and by the medical industry. Those are the qualities that make a good head of the department.”

A GOOD BALANCE

Since Vernooy has spent most of his life, training and career in Maastricht, he did not feel out of his depth when the time came. He spends three days a week on research and management, while working two days a week in the clinic as an electrophysiologist. “I consider myself too young to spend all my time on management, and I like doing cardiovascular interventions. I think this is a good balance. But that’s only made possible by having some helping hands at the department, as it’s a large team.” Crijns: “My clinical work gradually dwindled. I haven’t done any cardiac catheterisations in the last ten years, although I did still do outpatient consultations one day a week. But Kevin should definitely keep up the interventions, to maintain his international profile. And I think it’s possible, too, as he’s surrounded by many friends. And that’s quite important. When I arrived in 2001, things were different. There were many people who felt that things should stay as they were. So over the past few years I was very happy with the support I got for my approach in the management team.”

I WOULD LIKE TO ENHANCE THE TIES BETWEEN CLINICAL AND PRECLINICAL RESEARCHERS, AS I THINK WE CAN LEARN FROM EACH OTHER AND STRENGTHEN EACH OTHER

TOUGH JOB

Looking back on it, the first few years as head of the department were not easy for Crijns. “People thought I wasn’t a good leader, as they felt I didn’t intervene enough. On the other hand, I felt that things had to change, and that means impinging on hallowed institutions. I’m not going to name any names, but there were people with established positions, and I wasn’t fully aware that trust is something you have to earn. I managed to get there in the end, but those first few years were not really much fun. At that time it was just a tough job and a lot of hard work! It got better later on, otherwise I wouldn’t have kept it up for so long. The job also involves meeting many pleasant people with whom you are able to do cutting-edge things. That’s very enjoyable and satisfactory.”

PROUD

The list of achievements over his long career is huge. It is available in a reader-friendly version on the Maastricht UMC+ website, in the press release about the royal honour that was bestowed upon him when he retired in November. “Yeah, you really have to put together such a list, or you won’t get the decoration”, he jokes. “I pity the person who had to compile the list, but some of the items are actually true… What I’m most proud of with hindsight is that I was valued as the head of the department. That’s what I sensed. There were also scientific results, not only for me but for the entire department. And an important achievement, and Kevin played a major role in this, is that we’ve made cardiac rhythm a signature topic for the department again. And here he is, carrying on the torch.” He still appears a little stunned by the mini-symposium at which he was presented with the decoration. “It was more of a maxi-symposium than a mini-symposium. Incredible. And so now we’re entering a new era.”

THREE ROLES COMBINED

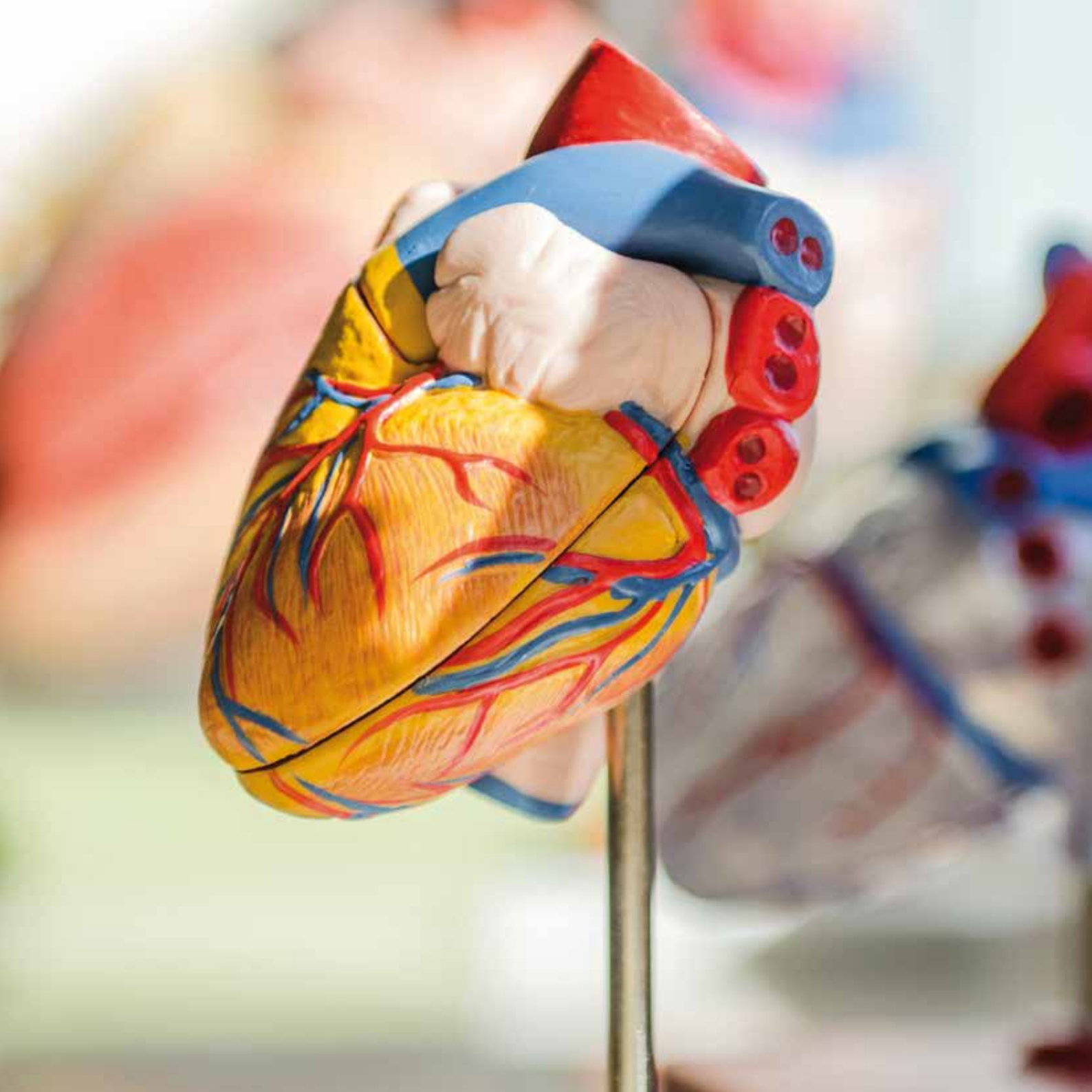
Vernooy is happy to have taken over the torch at this time. “For instance, the collaboration with the regional Zuyderland hospital has never been as good as it is now, and Harry played a major role in this. And the same is true for the other clinical disciplines with which we collaborate closely at our hospital. We all really need each other to be able to offer effective patient care. We have to hold on to that in the future.” He is looking forward to further raising the department’s profile in terms of organisation and focus. At the same time he realises that it is almost impossible to fulfil all three roles, those of clinician, scientific researcher and manager, equally well. “Harry is a great researcher. I have made my mark as a researcher, and I find the many projects

I'm involved in very inspiring, but I don't think I can match Harry's level. But a large part of the success is often the result of facilitating the research. I hope to make a difference there." In this respect, he is hoping to shift more of the cardiological research towards CARIM. "The links with CARIM are good, but could be even more prominent. Sometimes a cardiologist involved in research hardly ever comes into contact with the university side, whereas all the clinical research is also CARIM. I would like to enhance the ties between clinical and preclinical researchers, as I think we can learn from each other and strengthen each other."

Currently, Harry Crijns is still appointed for scientific research one day a week. "Life has become a lot more quiet, but I still do something each day. I also still have a formal admission at the Cardiology Department, what used to be called a zero-hours appointment. So I'm still sort of a member of staff, although Kevin might see that differently," he jokes. Vernooy: "I'm still looking for people who want to do COVID care!" "I'm up for that", smiles Crijns.

Harry Crijns studied at the University of Amsterdam, and became a cardiologist in 1987, specialising in cardiac arrhythmias. In 2001, he was appointed Full Professor of Cardiology at Maastricht University and head of the Cardiology Department. He retired in November 2020, and on this occasion he was made a Knight of the Order of the Netherlands Lion, one of the oldest and most prestigious Dutch civilian orders. He has built up a national and international reputation in the field of cardiac arrhythmias, and atrial fibrillation in particular.

Kevin Vernooy obtained both his degrees and his PhD at Maastricht University. At Maastricht UMC+, he specialised as a cardiologist-electrophysiologist. He became a member of the staff of the Cardiology Department in 2011, and since 2014 he has led the Arrhythmia Section. In 2020 he was made a full professor occupying the chair of 'Electrical treatment of heart failure.' About a year later, he took over from Harry Crijns as Head of the Department of Cardiology.



FACES

BLOOD P1 BLOOD COAGULATION, VENOUS THROMBOSIS & BLEEDING


AARON ISAACS


ALMA MINGELS


ARINA TEN CATE-HOEK


CECILE MAASSEN


ELISABETTA CASTOLDI


ERIK BECKERS


FRAUKE SWIERINGA


GERRY NICOLAES


HANS IPPEL


HENRI SPRONK


HUGO TEN CATE


INGRID DIJKGRAAF


JOHAN HEEMSKERK


JUDITH COSEMANS


JUR TEN BERG


KANIN WICHAPONG


KRISTIEN WINCKERS


MARIJKE KUIJPERS


MONIKA STOLL


OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENSKE OLIE


RORY KOENEN


STEVEN MEEX


STIJN AGTEN


TILMAN HACKENG


YVONNE HENSKENS

FACES

BLOOD P2 ATHEROSCLEROSIS, ARTERIAL THROMBOSIS & STROKE


BAS BEKKERS


CARINE PEUTZ


CASPER MIHL


CHRIS REUTELINGSPERGER


CHRISTIAN WEBER


DIETBERT NEUMANN


ED ERINGA


ELINE KOOI


EMIEL VAN DER VORST


ERIK BIESSEN


FELIX MOTTAGHY


GOSIA FURMANIK


JACK CLEUTJENS


JOACHIM JANKOWSKI


JOACHIM WILDBERGER


JUDITH SLUIMER


LEON SCHURGERS


LISETTE UNGETHUM


MARC VAN ZANDVOORT


MARJO DONNERS


NICO DECKERS


PETRA LUX


PIETER GOOSSENS


PIETER VAN PAASSEN


REMCO MEGENS


ROBERT VAN OOSTENBRUGGE


SIMON SCHALLA


SUZAN WETZELS


SYLVIA HEENEMAN


WERNER MESS


WIM VAN ZWAM

FACES

VESSELS P3 VASCULAR COMPLICATIONS OF DIABETES & HYPERTENSION


BASTIAAN DE GALAN


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


FRANK DE VRIES


HANS VINK


ILJA ARTS


JULIE STAALS


KRISTIAAN WOUTERS


MARLEEN VAN GREEVENBROEK


MARTIJN BROUWERS


MIRANDA SCHRAM


MARC HEMMELDER


NORDIN HANSSEN


RONALD HENRY


SEBASTIEN FOULQUIER


SIMONE EUSSEN


THOMAS UNGER


THOMAS VAN SLOTEN


YVETTE DERKS

FACES

VESSELS P4 REGENERATIVE & RECONSTRUCTIVE CARDIOVASCULAR MEDICINE


BAREND MEES


ELHAM BIDAR


IWAN VAN DER HORST


GEERT WILLEM SCHURINK


JOS MAESSEN


MARK POST


MICHAEL JACOBS


PEYMAN SARDARI NIA


ROBERTO LORUSSO


SANDRO GELSOMINO

FACES

HEART P5 STRUCTURAL HEART FAILURE


BEN JANSSEN


BLANCHE SCHROEN


CHRISTIAN KNACKSTEDT


EMMA ROBINSON


GUIDO HAENEN


HANS PETER BRUNNER-LA ROCCA


LEON DE WINDT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MARK HAZEBROEK


MARTINA CALORE


MATTHIJS BLANKESTEIJN


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SANDRA SANDERS-VAN WIJK


SEBASTIEN FOULQUIER


STEPHANE HEYMANS


VANESSA VAN EMPEL


WARD HEGGERMONT

FACES

HEART P6 COMPLEX ARRHYTHMIAS


ARNOUD VAN 'T HOF


AURORE LYON


BART SPRONCK


BAS BEKKERS


CHANTAL MUNTS


DOMINIK LINZ


FRANS VAN NIEUWENHOVEN


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cover photo by Andrea Piacquadio, image design Muis Mücher
page 19 photo by Chris Montgomery (on Unsplash)
page 76 photo by Antoine Barrès (on Unsplash)
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GRAPHIC DESIGN
Muis Mücher, Maastricht

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Drukkerij Hendrix

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