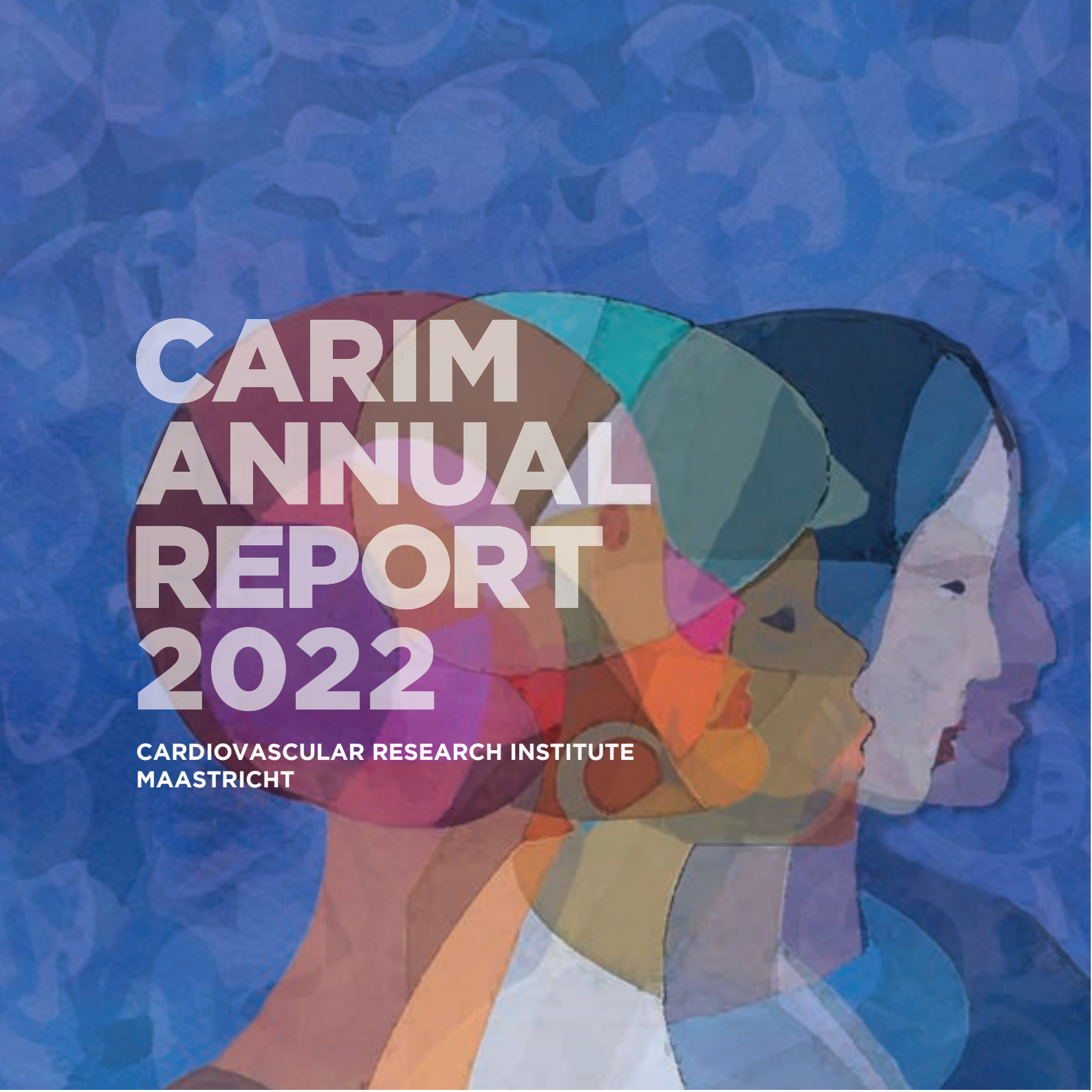

CARIM ANNUAL REPORT 2022

CARDIOVASCULAR RESEARCH INSTITUTE
MAASTRICHT

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MAASTRICHT

CONTENTS

PREFACE

KEEP MEDIOCRITY AT BAY...

With great pride and appreciation I present to you our CARIM Annual Report 2022.

It has been a remarkable and productive year, during which we've gained numerous new ideas and embarked on new avenues. Our core business of sound scientific research and defining new objectives to tackle current complex cardiovascular issues is consistently and gently supported by our Recognition & Reward programme and work and performance pressure reduction plans, all aimed at enhancing the well-being of our students, researchers and support staff.

But the specific fight against work and performance pressure could end up homogenising our diverse and multicultural academic community. The risk is that by using one-size-fits-all rules, we might force important individuals into a uniform and average approach, aiming to apply policies broadly instead of customizing them to personal requirements. This goes against the current approach in science and clinical practice, where we tailor strategies to individual needs.

Creating such mediocrity is deeply ingrained in our Dutch culture. The old Dutch wisdom, "just act normal, that's already crazy enough," might be at the root of this.

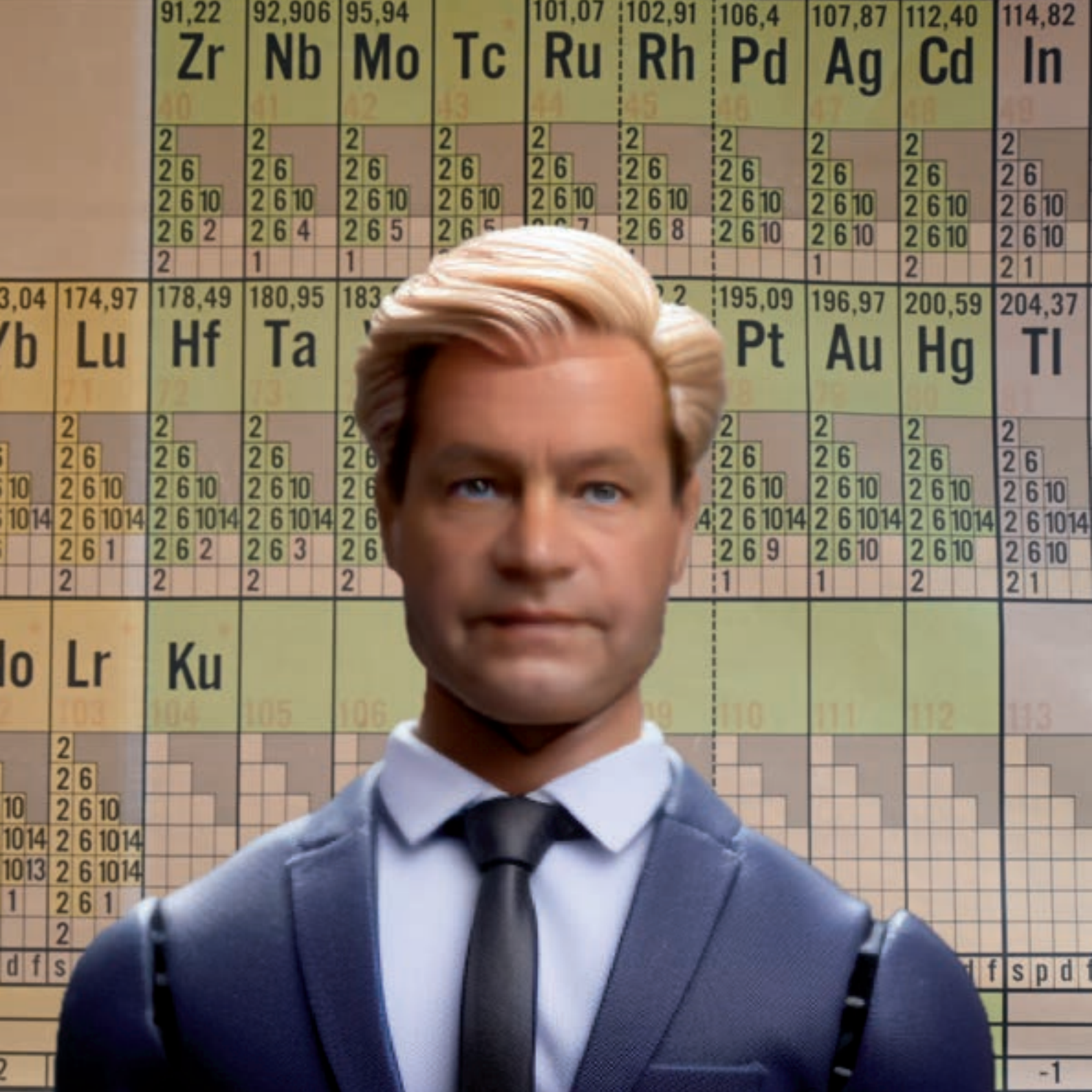
Whether it's prioritising participation over winning (Netherlands Olympic Committee 2023: it will be about stories, not medals), systematically suppressing personal excellence, abolishing *cum laude* distinctions, or dampening enthusiasm for individual achievement out of consideration for those in second place. This is characteristic of our small country with a beautiful diverse and colourful content, currently heading towards mediocrity of dubious hue.

It's not without reason that in Dutch language we have the unique and untranslatable term '*eenheidsworst*' (uniform sausage), and while mediocrity might lead to stability, safety, and tranquillity, in the end it will be sound and dull. And this will certainly be the death blow to science and its output. So let's fight against this, starting first in our academic strongholds.

It's a thin line between 'sound and dull' and 'reliable and reproducible', the latter being the holy grail of any scientific research team. A consistent and dependable scientific output from a team, however, must stem from a blend of diverse and distinct perspectives and personalities within the team, like an incubator where extremes of character and ambition can converge to establish a reliable consensus on scientific conclusions. This is best done by challenging each other through a circular process of critique, discussion, reflection, and adaptation. This process can never materialise within a team of pre-formed '*eenheidsworsten*'. Research teams should harbour an arena for exploding paradigms (Kuhn) and a wood workshop for sawing at the legs of proposed hypotheses (Popper).

For the above to succeed, we need original and ambitious people. What's the current challenge with ambition, why aren't we allowed to run that extra mile anymore?

Is a young medical student better off if the *cum laude* option disappears? If an ambitious student aims to excel through character and seeks that distinct affirmation, is that not a rightful pursuit, one that should not be taken away? Most doctors do not graduate with *cum laude* honours, and this doesn't make them inferior doctors. Most don't even aspire to achieve *cum laude*, and some who hoped for it deal with disappointment, and that's part of growth. It's beneficial, as


91,22 Zr
92,906 Nb
95,94 Mo
Tc
101,07 Ru
102,91 Rh
106,4 Pd
107,87 Ag
112,40 Cd
114,82 In
174,97 Lu
178,49 Hf
180,95 Ta
195,09 Pt
196,97 Au
200,59 Hg
204,37 Tl
Lr
Ku

there will be many more disappointments in life; it's best to develop resilience against them. The fact that some individuals don't reach the bar – whether it's significant or not – doesn't mean the bar should be abolished to the detriment of a minority who strive to clear it and consider it important.

Let us give our students and scientist the right to be different, to make their own ambitious choices, and grant those who seek recognition their right to personal fulfilment, without the patronising and moralising approach of our current culture and society. Let us not all evolve into Barbies and Kens, let us stay different, original, disruptive, and challenging, and let's prevent that mediocrity will make diversity and inclusivity obsolete. Do it your own way, be assertive and proactive: you're good - get better; and pursue your dreams and your passion. CARIM will help you with that.

In our current annual report we salute our young and free-spirited staff members, their personal establishments, drives, and unique views, and we illustrate the budding of a new era of CARIM infrastructure. We have updated our young talent development HS-BAFTA programmes, offering academic time-outs to engage in science, and to go abroad for scientific and cultural exchange. We present to you our runners from SCRUM lab and elaborate on the firm establishment of extensive postdoctoral clinical training through Blood, Vessels, and Heart by CAS-AM, EVC, and DAS-CAM, respectively. We present to you our new bilateral and binational cardiorenal institute AMICARE, it has hatched and already grown out its clothes, and as cherry on the cake we offer you ReGEN Biomedical, our public-private large scale cell factory shedding light on the future of therapy.

All these topics lay in front of you, in our annual report that is packed with division highlights, opinions, new personal grants and contracts, and all awards and prizes bestowed upon our fellow CARIM employees in this exceptional year.

This is CARIM 2022.

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) has established itself over the last decades as a leading research institute in the field of cardiovascular disease in Europe. 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 are 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 divisions. This 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 talent development tracks. The individual PIs are responsible for the financial management of their groups. Cardiovascular scientists from around the world join CARIM because they value CARIM's open communication, close cooperation, stiff ambitions, good technological facilities and a critical learning environment. CARIM is one of the eight research institutes 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 institute 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 2022, CARIM was involved in many European projects including six ITN/DN programmes with a total number of almost 30 Early Stage Researchers allocated to CARIM.

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 independently publish. Past and 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 CVON, Horizon 2020, Horizon Europe, ERA-CVD, Interreg and Leducq Transatlantic Networks. 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. International training is provided by all three divisions leading to three excellent and much acclaimed courses: the Certificate of Advanced Studies in Antithrombotic Management (CAS-AM: Division Blood); The European Vascular Course (EVC: Division Vessels), and the Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM: Division Heart).

KEY FIGURES 2022

ANNUAL BUDGET: **21.5** M€

NEW CONTRACTS AND GRANTS: **8.5** M€

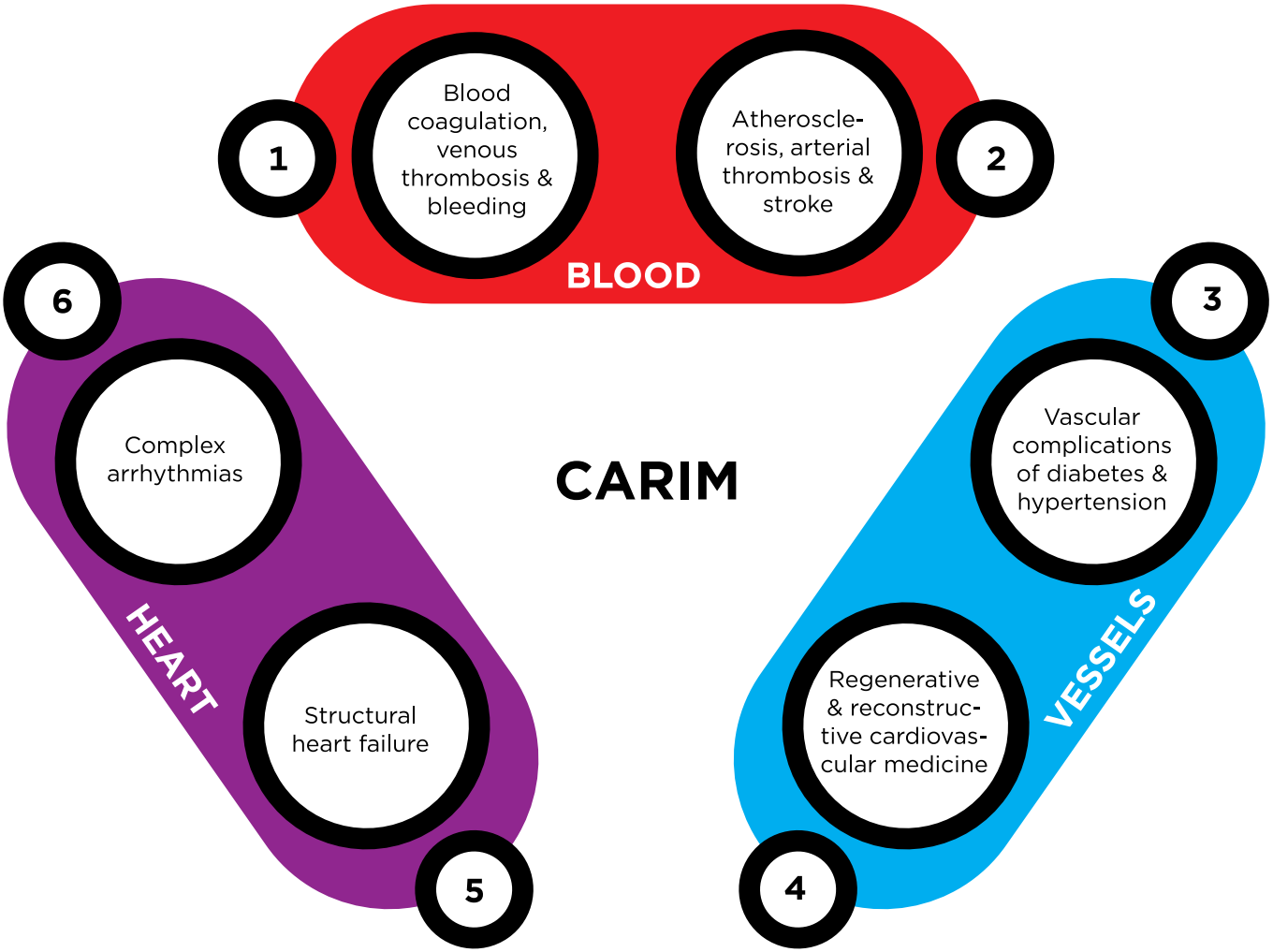
RESEARCHERS: **164.7** FTE (145 INTERNAL PHDS)

TECHNICAL AND SUPPORTING STAFF: **54.1** FTE

DEPARTMENTS/DISCIPLINES: **17**

INTERNATIONAL PEER-REVIEWED JOURNAL ARTICLES (SCI): **1,090**

PHD THESES: **67**


1
Blood coagulation, venous thrombosis & bleeding
Atherosclerosis, arterial thrombosis & stroke
2
BLOOD
6
Complex arrhythmias
HEART
Structural heart failure
5
CARIM
3
Vascular complications of diabetes & hypertension
VESSELS
Regenerative & reconstructive cardiovascular medicine
4

INTERVIEW

JOB VERDONSCHOT

“I can really sink my teeth into a subject”

Job Verdonschot is virtually unstoppable. Whether it is about a boardgame or an application for a Dekker grant, sometimes it’s as if his competitiveness gets the better of him. Not that it bothers him. “On the contrary, I find it hugely rewarding.”

In 2022, it earned him the Dekker Clinical Scientist grant, as well as no less than three awards for his PhD thesis, including the CARIM Dissertation Prize. His research concerns the role of genetics in dilating cardiomyopathy (DCM).

What is dilating cardiomyopathy and how does it develop?

"It's when the heart muscle is dilated, and becomes less able to pump off the blood that enters the heart. If oxygen shortage can be ruled out as a cause, it is referred to as a non-ischemic dilated heart muscle. It can arise from genetic defects, alcohol abuse, pregnancy and other things, like chemotherapy. I'm particularly interested in the genetic factors that cause DCM."

Do patients always know there is something wrong?

"No, not always. The first symptoms are often fatigue, shortness of breath, palpitations, but it can also be discovered by accident during an ultrasound check, without there being any symptoms. And sometimes when people suddenly drop dead on the football pitch, they are later discovered to have had a DCM. That's why you'd want to detect it in time."

Why did your PhD thesis on this subject earn you three awards?

"I was the first PhD candidate in Maastricht to fully concentrate on the genetic component of DCM. The field of clinical genetics has boomed over the last ten years. The diagnostics have been greatly improved, and I've kept a close watch on that development. I was able to check many of the new genes that were discovered in our patient cohort, and could thus identify a few that play a part in the development of DCM. A number of my articles have been cited in the guidelines that are currently used in clinical diagnostics. That gives me greater satisfaction than the awards for the thesis."

Are you at risk if you're a relative of someone who has DCM and a gene mutation?

"That's a question I was often asked by patients in the clinic, and it is a question I hope to answer, or at least partially, using this Dekker grant. First-degree relatives, so children, siblings and parents, have a 50% chance of having the same genetic predisposition if a gene mutation has been found in a patient with DCM. They are currently given the opportunity to be genetically tested, and if they have the mutation, they are sent to a cardiologist to have an ultrasound examination. In nine out of ten cases, they do not yet have cardiomyopathy. They then want to know what the risk is, and we don't really know that. The guidelines recommend yearly ultrasound exams, whereas we don't actually know at all whether that's really necessary for all of them. There have been cases where a massive DCM was detected in someone without any symptoms, but nine out of ten ultrasounds are perfectly normal. So the aim of my research is to be able to predict how large the relatives' personal risk of DCM will be. Some of them may then perhaps only have to have an ultrasound once every five years."

How do you go about researching that?

"In the past we have created a database with ultrasounds, ECGs and DNA samples of around a thousand patients with DCM. We now want to collect the same data from the relatives of all these patients. We know whether the members of this group have also developed DCM by now. New technology enables us to analyse their ultrasounds and ECGs in a different, more accurate manner and detect subtle changes that may indicate an early stage of DCM. And what is the most interesting aspect for me personally: I'm going to check whether a combination of a number of gene

THE FIELD OF CLINICAL GENETICS HAS BOOMED OVER THE LAST TEN YEARS

mutations results in greater risk to the relatives, a so-called genetic risk score."

Did clinical genetics always make your heart beat faster?

"Frankly, I didn't even know about the discipline before I did my research placement with Professor Heymans as part of my medical studies. But it immediately caught my interest. When I switched from the biomedical sciences programme to medicine, I thought I wanted to become a cardiologist, as I'm absolutely fascinated by the heart. But during my clinical placement at the Department of Cardiology, I found out I wasn't really suited to that. I was interested in everything that wasn't acute, but performing a PTCA or emergency cardiac care, that's not for me. I lack the dexterity and the practical insight. I spent most of the second part of my clinical placement at clinical genetics. Now I'm training to become a clinical geneticist, a cardiac geneticist to be precise. DCM nicely combines cardiology with clinical genetics."

Do you have enough time to do research?

"There's never enough time for research, but I can't complain. Clinical genetics is an academic discipline, so as part of your training you have to contribute to the research. That's a luxury compared to, say, trainee cardiologists. For the past six months, I've been able to do research full-time as part of my training programme. I've had the opportunity to instruct PhD students who will continue this project. As of next week, I'll be back at the clinic full-time. That means that clinical tasks will take priority again and it will be difficult to fit in research work. It's a matter of working efficiently so that I'll hopefully have more than one day a week for research, in addition to the leisure time I put in as well. I don't mind that at all. I can really sink my teeth into something and then it's actually mostly relaxing to engage in research."

Does your partner agree with that?

"We're engaged, and my fiancée already has a job, but is still working to complete her PhD thesis. We both spend

THE WAY GENETICS AND CARDIOLOGY, BUT ALSO PATHOLOGY AND IMMUNOLOGY, COLLABORATE HERE IN MAASTRICHT IS UNIQUE

weekends working at the dining table, our computers side by side. That's kind of having fun together, isn't it? But no, we are definitely there for each other and make time for leisure. It's made easier by the fact that we don't have children yet, although we do have two cats that always want to sit with us."

What are your hopes for the future?

"After completing my training in 2025, I hope to get a job as a clinical geneticist here in Maastricht. The way genetics and cardiology, but also pathology and immunology, collaborate here is unique. Colleagues come from all over the country to see how we do things here. This is the best place to be for me. I hope to get a job that combines research with clinical work. In the past year I've already learned how to supervise a team of PhD students, rather than doing everything myself. I very much enjoy working at the interface between research and the clinic, as it allows me to apply my research as much as possible in my everyday clinical work."

Finally: how do you now look back on the process of applying for the Dekker grant?

"The FHML Grants Office helped me write my application as effectively as possible. And I practised my presentation with the CARIM Research Council. Without their help, it would never have had this quality. I knew that five other people had also been invited for an interview for the two grants that were available. So I prepared thoroughly of course. I saw that the members of the interview panel mostly had a genetics background, so I particularly prepared for that type of questions. And then I got very different, very critical questions. I thought I was answering them well, but their reactions gave nothing away. So I didn't feel too good about it. When I got a call from the Dutch Heart Foundation a month later, they said: 'Sorry, but we have some really bad news for you', so I thought, there you go. 'You're going to be very busy, as you've got the grant.' What?! I really had to ask: 'What do you mean, did I get it or not?' It was a great day."

Dr Job Verdonschot completed his medical degree at Maastricht University with first-class honours, and received his PhD there in 2021, based on a thesis entitled 'Causes and consequences of dilated cardiomyopathy: Integrating genotype and phenotype to redefine disease diagnostics and therapeutics'. It won him the CARIM Dissertation Prize, the Ben ter Haar Prize and the Einthoven Dissertation Prize. He is currently training at Maastricht UMC+ to become a clinical geneticist.

INTERVIEW

NIKO DECKERS AND SANDRINE SEYEN

Running SCRUM

They look after the cells at the Stem Cell Research University Maastricht (SCRUM) seven days a week. Each day the cells are evaluated, provided with fresh culture medium, nestled on a little blanket, and handled with the greatest possible care by 'Team Belgium', as they humorously call themselves. Sandrine Seyen and Niko Deckers are the two SCRUM technicians, and they have been working closely together since the lab was opened in September 2022. In addition to their love of the lab, they share a love of running. Outside the lab too.

Sandrine Seyen and Niko Deckers both had a great deal of experience as technicians at a university lab before they started work at SCRUM. Niko had been working in biochemistry for over twenty years, with Professor Schurgers, while Sandrine had worked for over ten years at the cardiology lab led by Professor Volders. "The first time I saw cardiomyocytes with my own eyes was in 2018. I really wanted to understand how the process worked: from white blood cell to stem cell, to, for instance, cardiomyocyte." At her own request, she attended two courses on biology and stem cells and human genetics at Liège University, which provided her with the expertise to start working at the SCRUM lab. Niko: "I learned all I needed to know from Sandrine and from Cengiz Akbulut, who developed a technique for culturing stem cells as a PhD project at Maastricht." Akbulut now leads the SCRUM lab and sometimes lends a hand to take the load off the two technicians.

GREAT RESPONSIBILITY

Because of course it is a very special lab, and the two technicians do feel a great responsibility, which at times involves some stress. Generating a 'colony' of stem cells

takes about three to four months, a period during which you need to be fully focused. Niko: “If the culture medium gets contaminated, the whole batch is lost. One time we had a visitor at the lab, and two days later we were in big trouble. So now we don’t allow anyone in anymore, and when we’re working at the cabinet, we don’t even talk to each other. And we clean the whole lab ourselves. But that’s also a bit of a sport, and it really makes the lab our own. It’s just all very critical.” Sandrine: “I normally come in to work on Saturdays, and Niko on Sundays, and then you’re working for an hour or three at least. I sometimes do feel stressed.” Niko: “But when we’re able to work for months on end without any contaminations, and the incubator is full of nice stem cells, I also get a lot of joy out of it.”

PRIMORDIAL CELL

The process of generating stem cells starts with a blood donation. The white blood cells are isolated from the blood sample and stored in a biobank, after which the cells that are to be used to generate stem cells are selected. The cells are provided with nutrients and signalling molecules through the culture medium, whereupon they differentiate into another cell type, into which DNA material can be inserted. This last step enables the cells to programme themselves to become primordial cells, or stem cells. “Such a stem cell can develop into anything”, says Sandrine with great enthusiasm. “Muscle cell, liver cell, cardiomyocyte, etcetera. We ourselves haven’t taken that step yet, since we first wanted to invest a year in setting up the lab, up to the point where we store the stable stem cells in liquid nitrogen awaiting the next step.”

BLANKET

During the process, the cells also produce waste materials, and some cells die. Niko: “The culture medium contains growth factors with a rather short half-life. If we don’t change it every day, the cells will die.” When the plastic plate on which the cells are growing gets overcrowded, part of the colony needs to be removed. “That clump of cells then needs to attach itself to another plate, but they only do so if we first put a little blanket on it. If we don’t, we lose them. You have to apply these procedures very accurately, or they might, for instance, start to differentiate spontaneously, which is not what you want.” Selecting the cells to be used in the further process is also done by hand. By now, the two technicians have become experts at recognising the right shade of grey-brown, together with a reasonably large nucleus, which characterise the right kind of cell. Sandrine: “And also, a good stem cell has a sort of ‘face’, which I think looks like the ‘Ghostface’ from the film ‘Scream’. We mark the cells that have this potential on the plate.” Niko: “And sometimes you see that the cells look the same as they did the day before; that means the development has stopped. It also shows the accidental nature of life. There is no exact scenario, and each cell is different.” Sandrine: “Sometimes cells look absolutely perfect at first, and in the end there’s no colony. While other cells may look less perfect at first, but when we still continue with them, they turn out to be fantastic.”

LAB JOURNAL

In somewhat under a year, they are now working fully in sync. Sandrine: “I immediately get what he’s about to do in the lab without us having to say anything. We’ve developed a lab journal which allows us to follow exactly what the other has done, and we’ve set up a well-organised system for storing the cells.” Niko: “All credit should go to Sandrine for that.” Sandrine smiles: “Yeah, but you’re good at taking the cue!” Niko: “And what’s also important: we can tolerate each other’s playlists. We try out a new, unexpected playlist at the lab each day. That’s going well. Imagine you have to work

SUCH A STEM CELL CAN DEVELOP INTO ANYTHING

together with someone who listens to yodelling music all day! Sandrine: “Yeah, Team Belgium is getting on very well.”

RUNNING MARATHONS

In addition to their passion for generating stem cells, they share another passion, as they discovered when they started working together at the SCRUM lab. Niko: “We both run marathons.” Sandrine: “Well, actually he’s gotten much further than I. I ran my first marathon in April 2023, in Paris”. She’s not just running by herself, but is leading a runners’ club in Liège, with about ninety members. She holds training sessions three to four times a week, and in addition to that she goes cycling with a club on Sundays. “Getting exercise ensures a good balance with the work.” Niko ran his twelfth marathon in Lisbon in October 2022. “I still find it difficult to say it out loud, but I suspect it may have been my last. My knee is beginning to play up, and I’m also have been playing padel since a year and a half. But I do so enjoy running, it’s a kind of philosophy. Sometimes I think of absolutely nothing for a whole hour while running. That’s fantastic.”

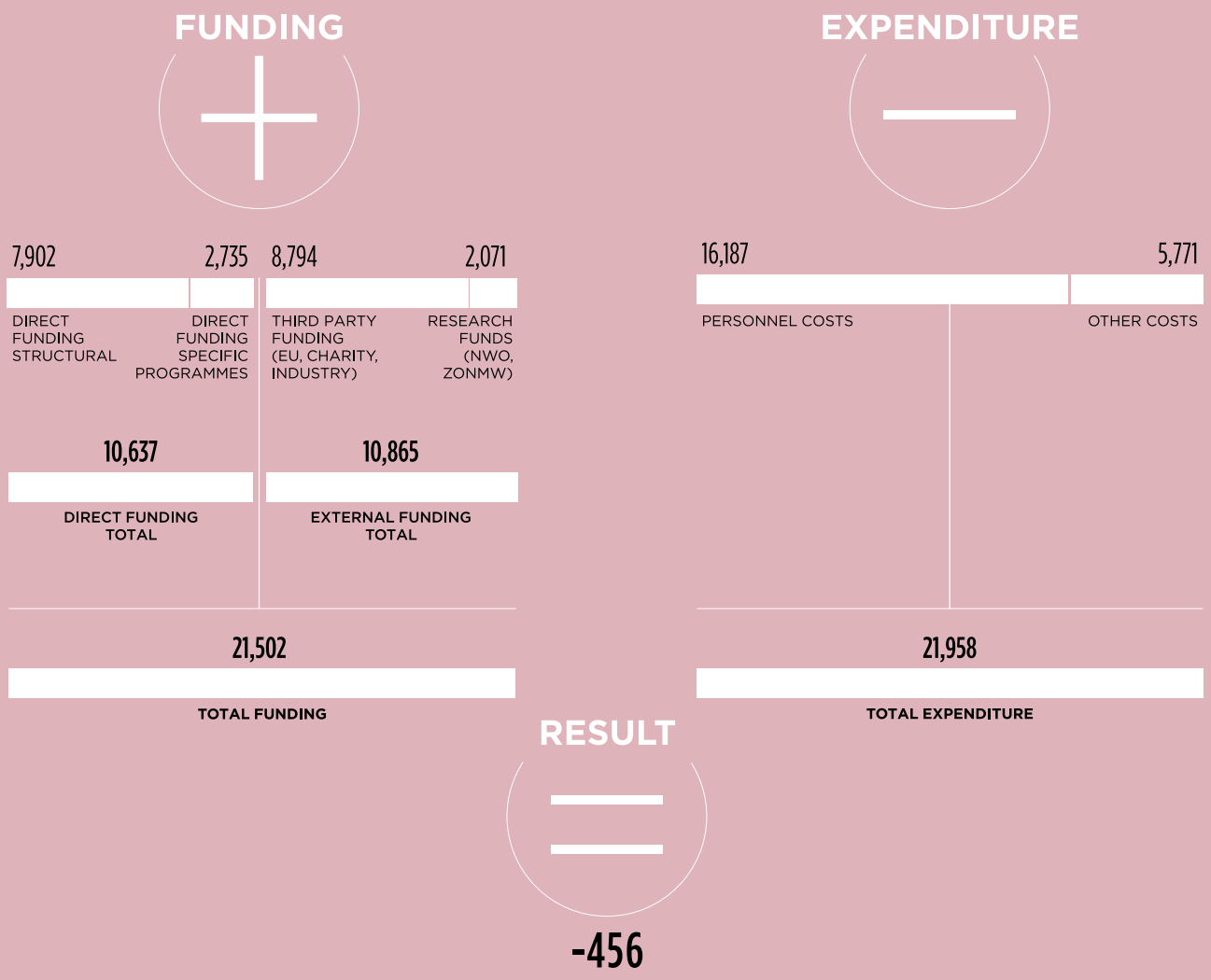
Sandrine Seyen studied medical biology, specialising in biotechnology, at the Haute Ecole André Vésale in Liège (Belgium). She started her career at the University of Liège, and worked as a quality control technician at GlaxoSmith-kline in Rixensart (Belgium). In 2010, she joined the Department of Cardiology in the group led by Professor Paul Volders, where molecular biology became her main area of research. Next to this, she has been working as a technician at the SCRUM lab since its opening in September 2022.

Niko Deckers studied chemistry, specialising in environmental sciences at the Katholieke Hogeschool Limburg (KHLim) in Belgium, and biochemistry at Hogeschool Zuyd (Heerlen). During this BSc Biochemistry track, he started an internship at the lab of Professor Chris Reutelingsperger in 1999, and has been working there ever since. In 2009, Professor Leon Schurgers joined the ‘Reutelingsperger’ research group, and he recently took over as Principal Investigator. As Niko’s new supervisor and director of SCRUM, he asked Niko to join the SCRUM lab and to build and run the lab together with Sandrine.

FACTS AND FIGURES

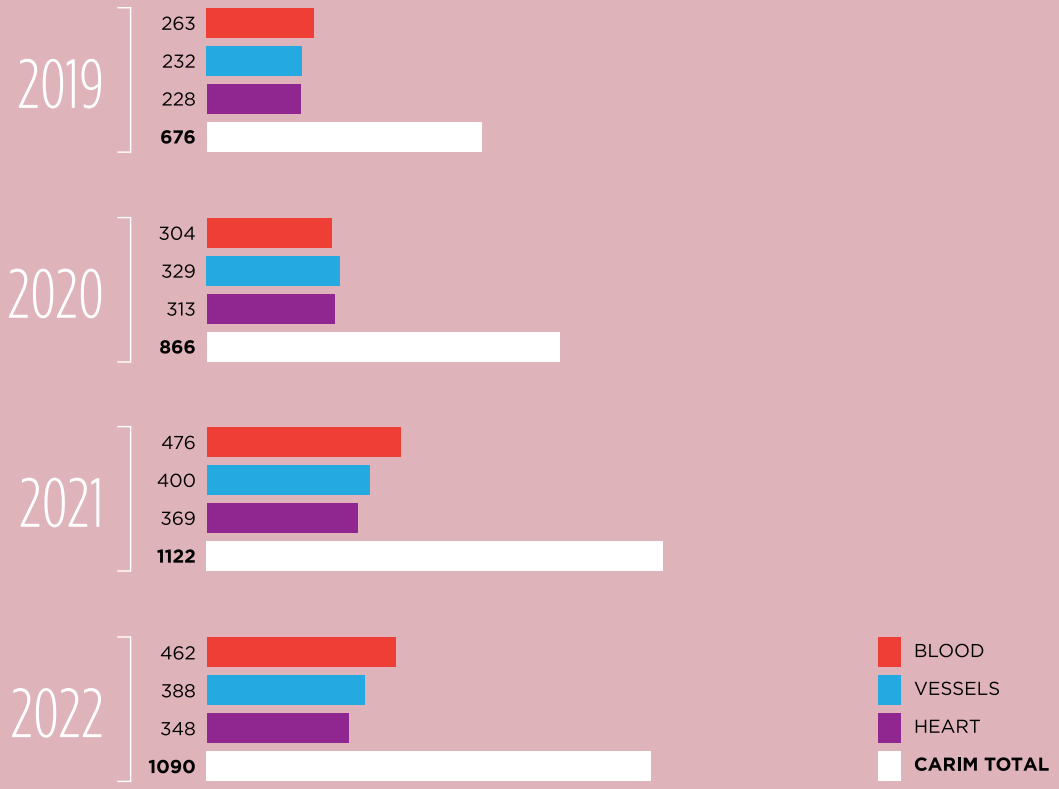
02

FUNDING AND EXPENDITURE (K€) AT INSTITUTE LEVEL 2022



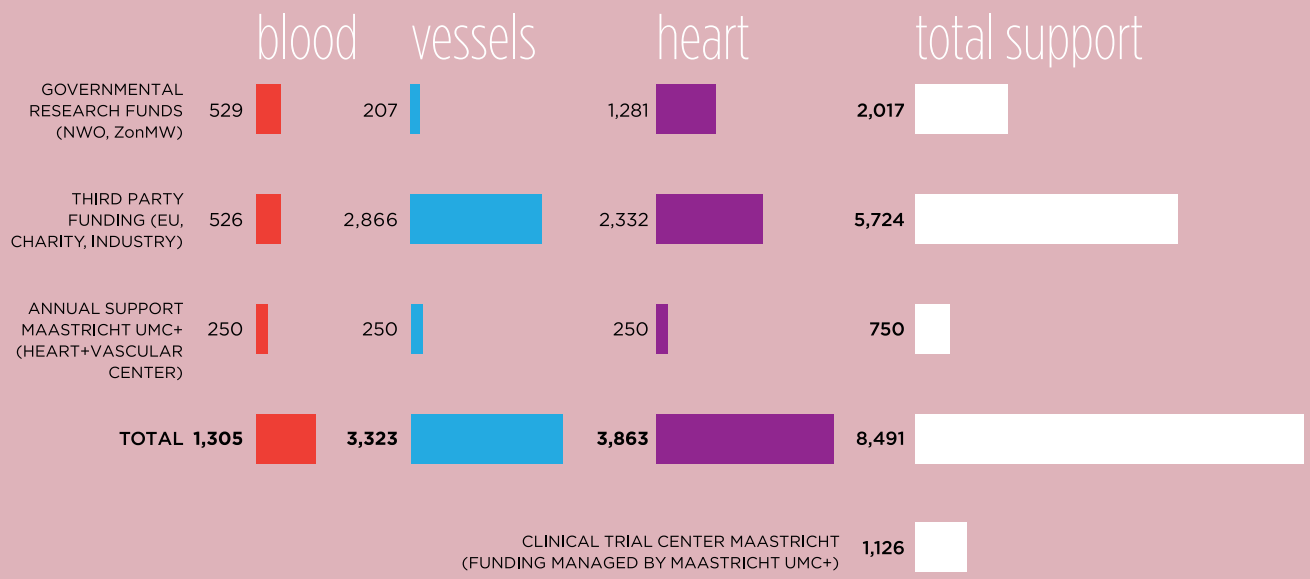
RESEARCH OUTPUT IN 2022

SCI JOURNAL ARTICLES

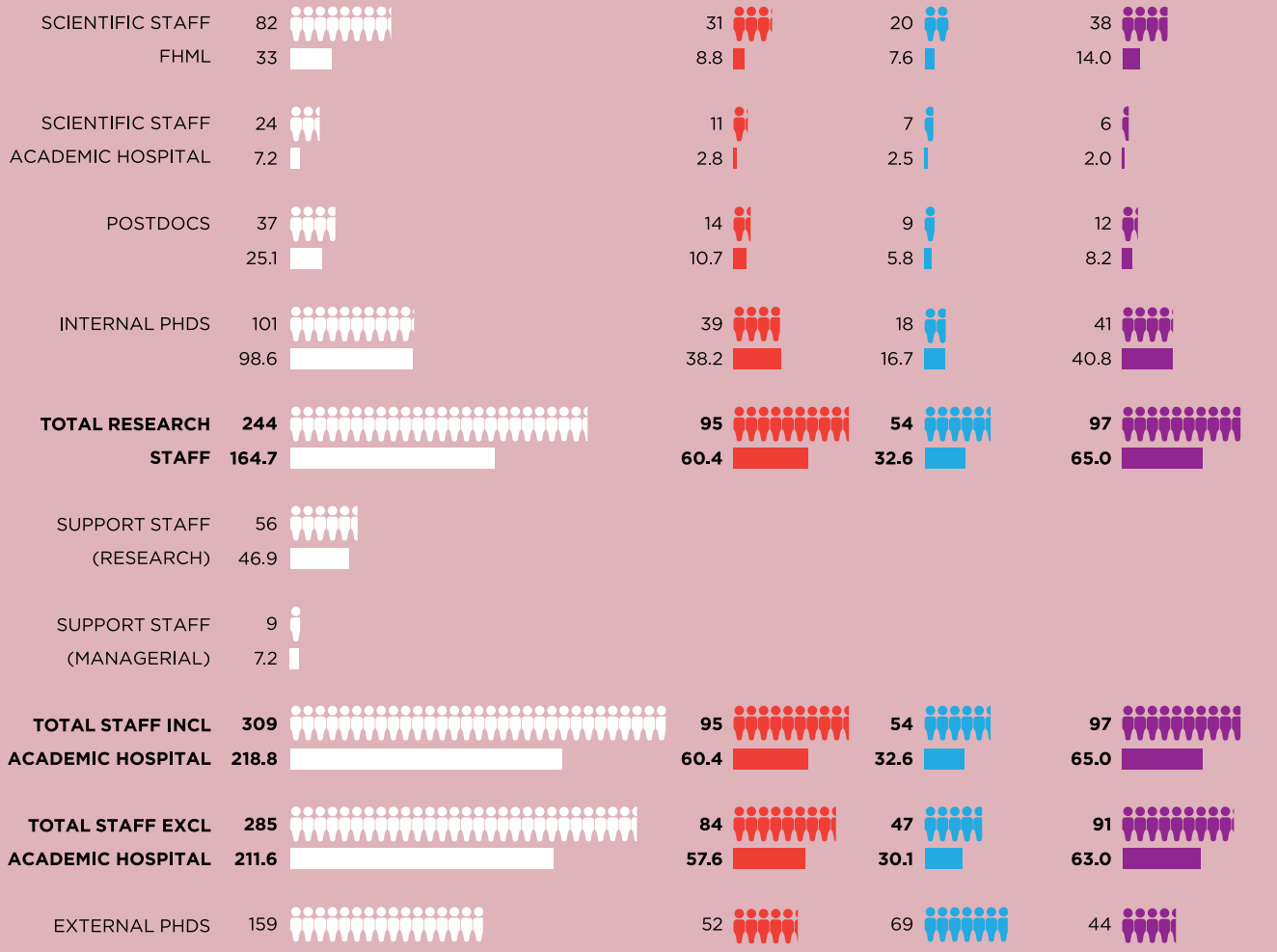


Note: the sum of publications in the divisions exceeds the total number of publications at Institutional level due to double counting of publications with authors from different divisions.

NEW CONTRACTS AND GRANTS (K€) IN 2022



SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2022



Note: the sum of staff in the divisions does not add up to the number at institute level due to double affiliations and separate institute-central appointed staff

= 10 persons = FTE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4,67905.07,0,0,0,0,30
4,66938.9,0,0,0,0,30
49,86421.04,0,0,0,0,30

INTERVIEW

DOMINIK LINZ

#Tele-care

2022 was a good year for cardiologist Dominik Linz.
He obtained a professorship at the University of Copenhagen and since 2022, the teleconsultation approach for cardiac arrhythmia assessment developed by his team is being reimbursed by the large Dutch health insurer VGZ.

Even better, based on the Maastricht project, the Dutch Healthcare Authority has given all Dutch hospitals the opportunity to negotiate reimbursement agreements for using digital devices for rhythm monitoring around teleconsultations. #Wow, he might have tweeted to his over four thousand followers on Twitter.

Apart from much misery, the Covid pandemic has also boosted creativity. This was true as well for the team led by Dominik Linz, who would characterise himself as a doctor doing a lot of scientific research. Since there were certain periods where patients could not come to the hospital to have an electrocardiogram made, the team developed TeleCheck-AF. To use this tele-care approach, patients have to download an existing app, Fibricheck, onto their smartphone. Using the smartphone's camera, with flash, it can then digitally measure their heart rhythm in a fingertip. The results are directly transferred to the cloud at Maastricht UMC+, providing three measurements a day for seven days. "If patients have been monitoring their atrial fibrillation for a week before they come and see their cardiologist, the consultation at the outpatient clinic passes off very differently than when they passively have an ECG made at the hospital, as they used to do. They're much more involved, and the feedback provided by the app also teaches them to recognise when their cardiac rhythm is irregular."

APART FROM MUCH MISERY, THE COVID PANDEMIC HAS ALSO BOOSTED CREATIVITY

SIX THOUSAND PATIENTS

These measurements not only enable doctors to see whether the rhythm is regular, but also whether a patient has atrial fibrillation or another arrhythmia. During the Covid pandemic, over 40 European centres joined the system, and since then, over two hundred thousand measurements of six thousand patients have been collected. This has provided the researchers with new materials for research. What other information can be gained from the data using new algorithms? "The waveform of the digital pulse measurement contains a lot of extra information. New algorithms using artificial intelligence enable us, for instance, to see the difference between an extrasystole coming from the atrium and one coming from the ventricle of the heart. In the future we might also be able to derive signs of heart failure, or other diseases, from the digital data." The team not only concentrates on the technology, but also invests much time in communication with patients. The target group is often advanced in years, and some of them have little experience with smartphones. But even the oldest patient, aged 92, can now handle the app. And what you often see is that the older people often keep up the measurements more conscientiously than the younger ones.

VIRTUAL-SAFARI

Linz emphasises that it is always the doctor who remains responsible for the treatment and for correctly integrating the data into the care provided. "Even the best app cannot determine whether a patient will get better or not. But if doctors get a better understanding of how best to use the information, patients will also benefit." Tele-care, using

mHealth (mobile health), has become popular since Covid. Linz also developed the 'VIRTUAL-SAFARI' pathway for people who may be suffering from sleep apnoea. The latter is one of his areas of special interest: the relation between sleep apnoea and atrial fibrillation. Maastricht UMC+ now handles the diagnostics entirely remotely, whereas before, people used to have to sleep at the hospital for a night. Patients just sleep at their own home, and use a wristwatch, an oxygen meter and a sensor on their chest, all connected to their smartphone. "The data arrive in the cloud, the pulmonologist examines them and uses tele-consultation to inform the patient whether treatment is necessary."

LOWER REIMBURSEMENT

Until recently, a major challenge was the reimbursement rate for mHealth. The rates are lower than those for the traditional treatment, which in the long run hampers the introduction of these new forms of care. Together with the Dutch health insurer VGZ, the hospital's purchasing department, in consultation with the cardiologists, came up with an 'optional temporary reimbursement structure', which compensates for the 'downgrade' applied to teleconsultations for atrial fibrillation. "This gives the hospital more time to systematically chart the implementation of mHealth and eventually adjust the reimbursement mechanisms." The plan was adopted by the Dutch Healthcare Authority, so that all Dutch hospitals can now make use of this compensation scheme. "It was a lot of work, but it's a nice example of the way research can yield benefits for patient care within a short period of time." This is precisely the interface where Linz feels at home and to which he likes to contribute. "Even though doctors who engage in research are often a bit crazy. There's never enough time. Clinical work is done when you go home, but research work is never done. I'm glad they do take that into consideration at Maastricht. My research days are designated CARIM days." The PhD candidates and postdocs who work on his projects are also employed by CARIM, and he can use his CARIM network for expertise regarding artificial intelligence and complex modelling calculations. "For me, this makes the added value of such a research institute very real."

OVER 40 EUROPEAN CENTRES JOINED THE SYSTEM, OVER TWO HUNDRED THOUSAND MEASUREMENTS OF SIX THOUSAND PATIENTS HAVE BEEN COLLECTED

PROFESSOR

While Linz is 'well on his way to become a professor' (focusing on complex care for patients with atrial fibrillation) at Maastricht, he was already appointed professor at the University of Copenhagen in 2022. After completing his PhD at Maastricht, he trained as a cardiologist at Homberg/Saar in Germany. There he did a lot of animal experiments on the mechanisms of atrial fibrillation. When he then left for Adelaide in Australia for a fellowship, the research infrastructure moved to the University of Copenhagen, with which he had already collaborated regularly before, in

I THINK IT'S USEFUL TO USE SOCIAL MEDIA, AND ESPECIALLY TWITTER, TO PROMOTE YOUR PUBLICATIONS AND NEW TECHNIQUES

particular with Thomas Jespersen. "I then became a visiting professor at Copenhagen. This was converted to a full professorship in 2022, after we received a large grant from the Novo Nordisk Foundation. In Denmark, large companies like Novo Nordisk can fund scientific research through a foundation which is independent of the company. Eighty percent of all cardiovascular research in Denmark is funded in this way", says Linz. The 3.5 million euro grant over seven years helped to fund his professorship.

GOOD COMBINATION

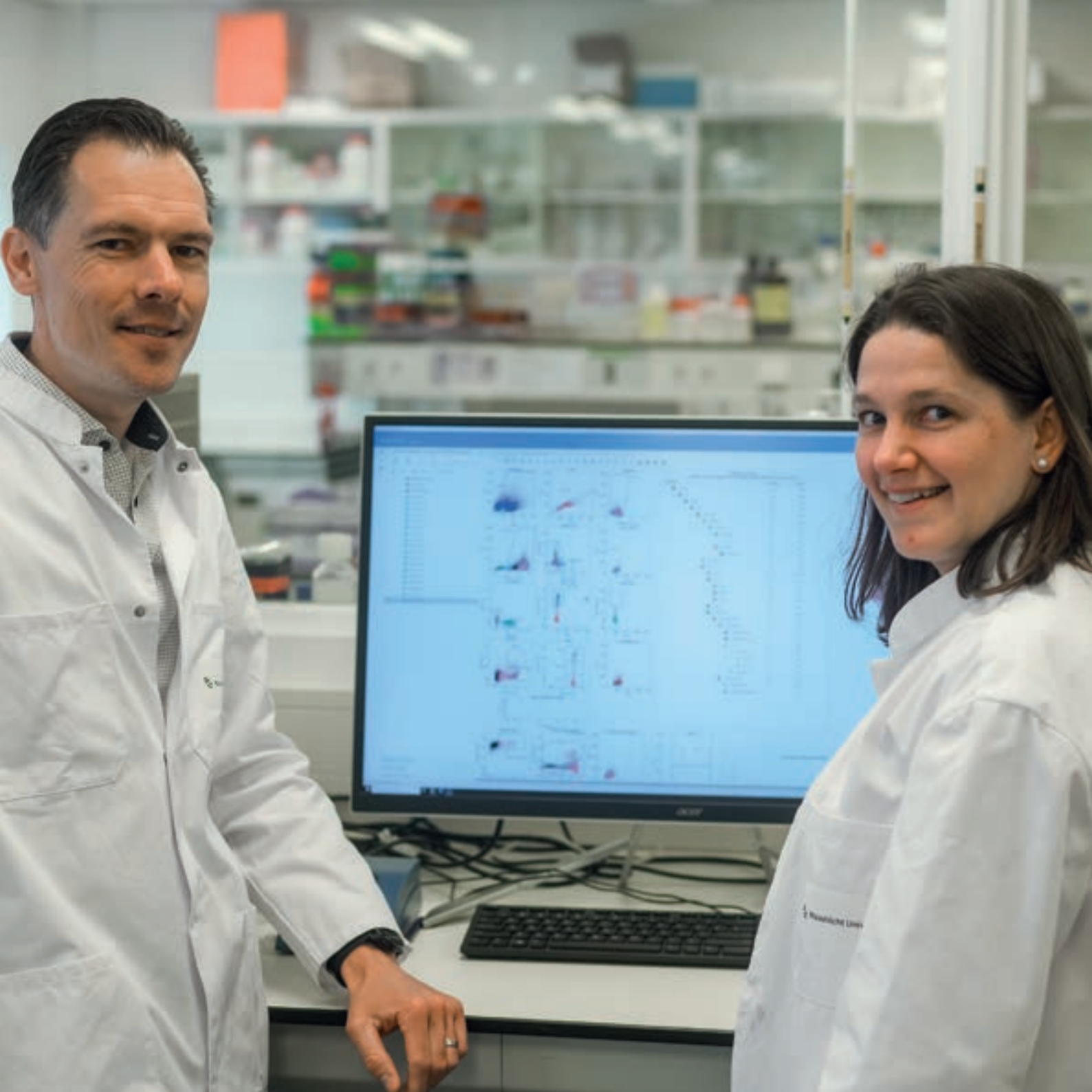
Together with Thomas Jespersen, Linz is leading the Copenhagen research group on sleep apnoea and atrial fibrillation. "Thomas concentrates on basic research, while I focus more on clinical/translational work, which is a good combination. We're hoping to further extend the collaboration between Maastricht and Copenhagen in the future." Linz spends one week a month in Copenhagen, which according to him combines well with his work as Head of Electrophysiology and at the catheterisation room in Maastricht. "Research work is easier to plan than clinical work," he smiles. His wife is also a doctor, and understands what it's like, and especially what he is like. "That also helps and motivates me."

TWITTER

During his three-year stay in Australia, he became acquainted with Twitter as a communication platform for cardiologists. When he started his account (@Dominik_Linz) he had thirty followers; by now this has grown to four thousand. "When I came to Maastricht, some people there were a bit sceptical about it. That's changed since the European Society of Cardiology and the European Heart Rhythm Association have started to use it as a platform for research information." Linz is a member of the EHRA's E-communication Committee, which provides a lot of information to cardiologists about how to use Twitter effectively. They have organised webinars on how to set up a profile and how to tweet, and even wrote a paper about it. "I think it's useful to use social media, and especially Twitter, to

promote your publications and new techniques. If your publications are being very rarely opened on a website, you can boost your coverage up to 500-fold by using social media effectively. TeleCheck-AF started with three Dutch centres, and by using Twitter (#TeleCheck-AF) we reached 80% of the other participating centres. So part of the success of the project is based on social media communication." And so, things have come full circle.

Dr Dominik Linz is a clinician-scientist, who received his PhD from Maastricht University in 2013 and completed his Cardiology training in Homburg/Saar, Germany, in 2017. From 2017 till 2019, he joined the group of Prof. Prash Sanders as Associate Professor and clinical EP-fellow in Adelaide, Australia. Since 2019, he is a staff member and Head of Clinical EP at the Heart+Vascular Center, Maastricht UMC+, and since 2022, he holds the full Professorship of Lifestyle Factors in Cardiac Arrhythmia at the Department of Biomedical Sciences (BMI) at the University of Copenhagen, Denmark.



HIGHLIGHT
DIVISION BLOOD

LIEVE TEMMERMAN
KRISTIAAN WOUTERS

Phenotyping cells from every colourful angle

Inflammation is at the core of cardiovascular disease development. The interplay between inflammation and cardiovascular pathologies has been a research focus for many groups within CARIM, including the Departments of Pathology and Internal Medicine. We have studied immune cells and their contribution to cardiovascular disease in a variety of experimental models, as well as their interplay with metabolic comorbidities such as diabetes or fatty liver disease. Translation of experimental findings is achieved though fruitful collaborations with the Maastricht UMC+ Department of Vascular Surgery. This department provides excised human carotid plaques to continuously expand our Experimental Vascular Pathology (EVP) human plaque biobank, a fantastic resource to validate our results and find new leads or targets. In addition, the framework of The Maastricht Study offers excellent prospects to validate experimental findings in humans.

The famous CANTOS trial proved a few years ago that inflammation is a valuable target to reduce cardiovascular risk. However, it has also shown that targeting inflammation is not successful in all patients, and that generic inhibition of key inflammatory mediators entails a risk of severe infections[1].

The more our knowledge advances, the more it becomes apparent that we need to be precise about the specific immune cell subtype we study. For example, cross-presenting $CD8\alpha^+$ dendritic cells (DC), a small and specialised DC subset, do not contribute to atherosclerotic plaque development or progression[2]. In contrast, another small DC subset, plasmacytoid DCs, protect against atherosclerosis by fine-tuning T-cell responses[3]. Clearly, only precise measurements and targeting of such populations individually make it possible to understand their roles in the disease process. This is also illustrated by the current advances in single-cell RNA sequencing, which continues to identify novel tissue-specific immune cell subsets and their activation states.

Based on these insights, we have developed an *in vitro* high content screening system to measure multiple functions of

cells in order to functionally phenotype primarily human immune cells and study CVD-relevant processes. Secondly, we have been able to expand our capabilities to substantially increase the number of characteristics that can be analysed.

MULTIPARAMETER FUNCTIONAL PHENOTYPING

Macrophages are crucial in atherogenesis as well as for cardiac repair. At the same time, they are extremely sensitive to contextual cues and readily adapt to their environment. New subtypes and activation states are continuously being described and defined by new markers, harnessing new potential homeostatic or pathological functions. At EVP, we aim to understand how macrophages operate in the complex context of cardiovascular disease. In collaboration with the Departments of Biochemistry and Physiology, we have acquired a BD Pathway 855 High Content Analysis fluorescent microscope within the framework of an NWO ZonMW programme entitled '*Meer Kennis Minder Dieren*', and an Interreg VlaN Trans-Tech Diagnostics programme. Erik Biessen and Lieve Temmerman have used this microscope to design a multiparameter functional screening tool at 96- or 384-well level for primary human macrophages: the Macroscreen. Probe-based functional tests (phagocytic activity, apoptosis, oxidised LDL uptake, cell shape, oxidative stress, etc.) were combined with multiplex ELISA data and metabolic activity measurements to obtain a complete fingerprint of the macrophages' functional profile. As a proof of concept, we exposed human macrophages to 30 different cocktails of inflammatory compounds and performed the Macroscreen. In accordance with recent growing insights, these different exposures induced high functional diversity in macrophages, far beyond the conventional pro- versus anti-inflammatory, so-called M1-M2, subsets, which was mirrored at a transcriptional level (**Figure 1**).

In real life, however, macrophages are never exposed to just one or two compounds, but rather to a cocktail of hundreds of molecules. Following a heart attack, massive cardiac oedema occurs, bringing resident and newly recruited macrophages in close contact with a traumatic context made up of cellular debris, inflammatory markers and other danger signals. Using the Macroscreen, we compared macrophages exposed to serum from patients who had had an acute myocardial infarction (AMI) with cells exposed to healthy control serum (**Figure 2A**). We found that the AMI serum context programmes macrophages to make them better suited for debris cleanup and repair, by increasing their phagocytosis capacity and tuning inflammatory pathways like interleukin-6 secretion. (**Figure 2B**) RNA-sequencing of these macrophages allowed us to construct a regulatory network of the transcription factors driving the AMI serum-induced changes (**Figure 2C**). We identified gene modules specifically correlating with patient prognosis (ejection fraction, infarct size, end diastolic volume) four months after infarction.

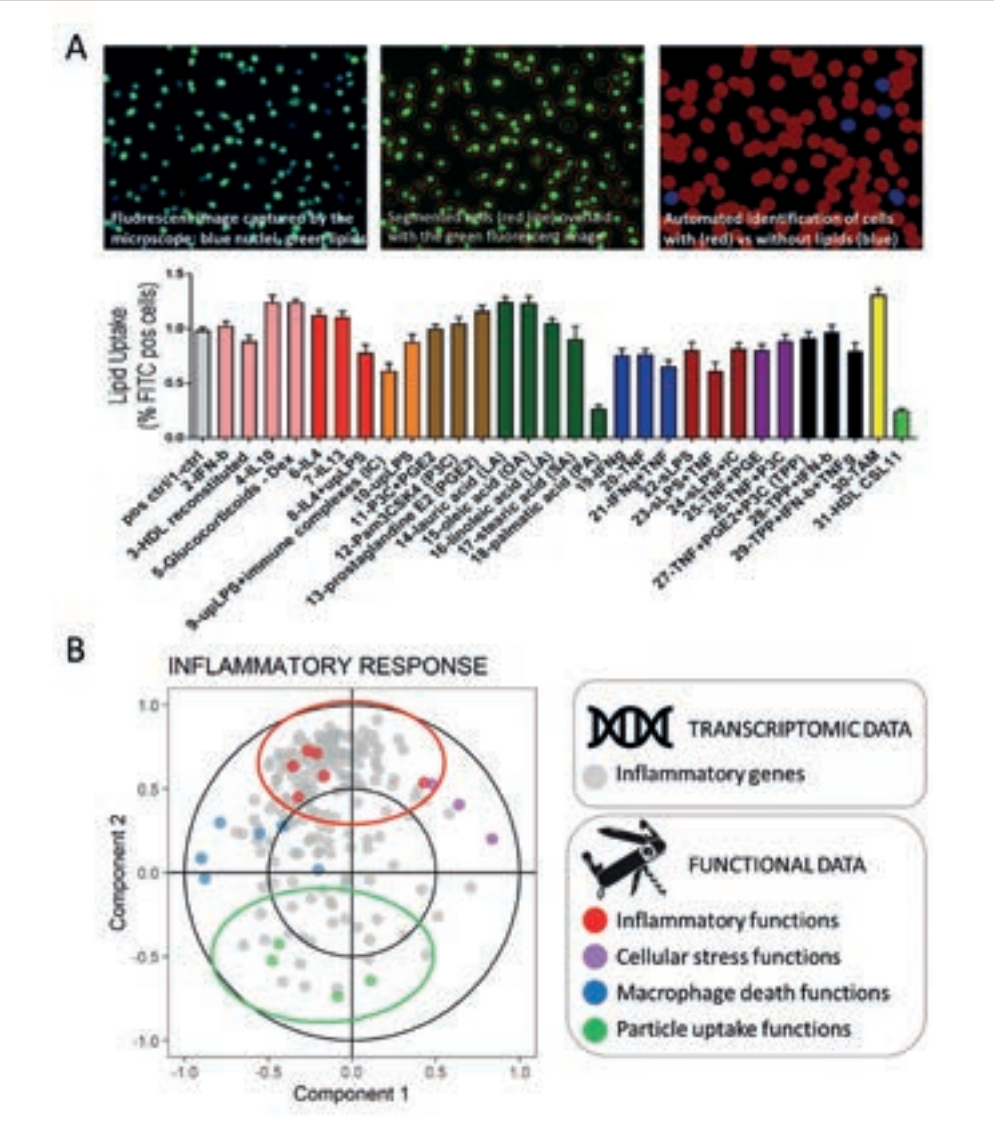


FIGURE 1 Measuring functional diversity in macrophages
(A) Lipid uptake assay. Human primary macrophages incubated with Bodipy-cholesterol-loaded oxidised LDL particles were imaged in de BD Pathway and analysed using Cell Profiler. (B) Gene set enrichment analysis (Hallmark Gene Set from the Broad Institute) of genes implicated in inflammation and their relation to macrophage functional behaviour.

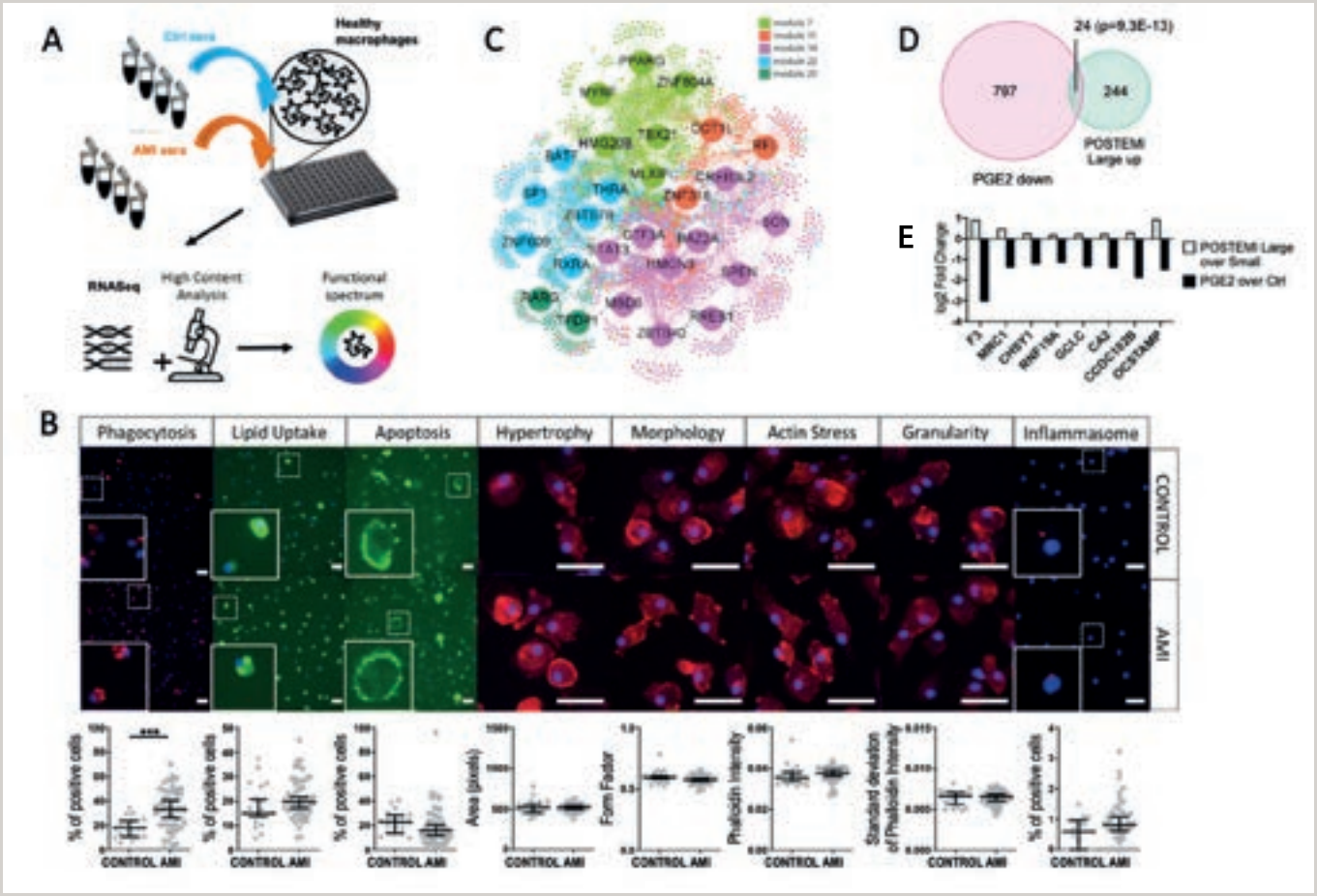


FIGURE 2 Macrophages are reprogrammed by the AMI context.
(A) Schematic study design. (B) High content screening images with image cytometry data graphs in macrophages exposed to AMI serum versus control serum. (C) Regulatory network showing the top 1% drivers of gene expression clusters (colour-coded) correlating with cardiac performance 4 months after AMI. (D) Overlap between PGE2 downregulated and "bad prognosis" (POSTEMI Large) upregulated genes (Hypergeometric testing; p=9.36E-13). (E) Log2-fold changes for the POSTEMI-Large top-ranked differentially expressed genes (p<0.001) shows reversal of "bad prognosis" programme.

Once we had pinpointed the 'good prognosis' versus the 'bad prognosis' macrophage profile, we were able to use this information to interrogate the LINCS1000 cell perturbation database, a repository of gene expression profiles of cells exposed to known drugs and compounds. We found that prostaglandin E2 receptor agonists phenocopied the 'good prognosis' expression profile of our AMI serum-exposed macrophages. Next, we stimulated macrophages with PGE2 and were able to confirm that Prostaglandin E2 receptor agonists have the potential to reverse detrimental reprogramming of monocyte-derived macrophages by AMI (**Figure 2D-E**).

Conceptually, our work, recently published in *Advanced Science*,[4] proposes that there is a therapeutic window for drug interventions for a short period after a heart attack, to modify the post-infarction traumatic context and induce macrophages to switch to a reparative mode and improve prognosis. Interestingly, the concept we describe here is widely applicable, as macrophages are omnipresent and often control tissue repair after insult, infection, or injury. For example, we are now continuing these studies with macrophages exposed to serum from COVID-19 patients. The serum was obtained from patients during the acute phase of their SARS-CoV-2 infection. Preliminary data reveal that macrophages strongly respond to the high-risk COVID-19 serum environment, with repercussions for respiratory health after 3-6 months. However, more detailed and high-throughput immunophenotyping is needed to visualise and study these diverse phenotypes beyond the *in vitro* Macroscreen model setup.

MULTISPECTRAL ANALYSIS OF CELLULAR HETEROGENEITY

Largely initiated by Kristiaan Wouters (Department of Internal Medicine), CARIM has invested in the latest development in flow cytometry: spectral flow cytometry (Cytek Aurora). Unlike conventional flow cytometry, which uses sets of filters to measure certain bandwidths of fluorescent signals, this novel technique can measure the complete spectral signature of a specimen. This offers two main advantages over conventional flow cytometry techniques. (1) It can determine the fluorescent spectrum of the specimen itself, solving autofluorescence issues which previously severely hindered analysis and phenotyping of complex cells like macrophages or fibroblasts or of complex tissues like liver or atherosclerotic plaque. (2) Many more fluorophores (40+) can be combined in one assay, allowing heterogeneity at the single cell level to be analysed in much greater detail and with high throughput (>10,000 cells per second).

To illustrate the power of this novel technology, we have recently set up a 26-marker immunophenotyping assay for human blood cells, allowing us to measure many immune cell subsets and their activation status. Another exciting prospect of spectral flow cytometry is that it allows correction for autofluorescence, which is specifically present in several primary tissues. Sabine Daemen and Kristiaan Wouters recently developed a new approach to identify and correct for autofluorescent signatures in the mouse liver, to measure hepatic immune cell populations more accurately (**Figure 3**). Atherosclerotic plaque specimens also contain high levels of autofluorescence, which has often precluded the successful identification and quantification of plaque cell subsets. Currently, Lieve Temmerman and Renée Tillie at EVP

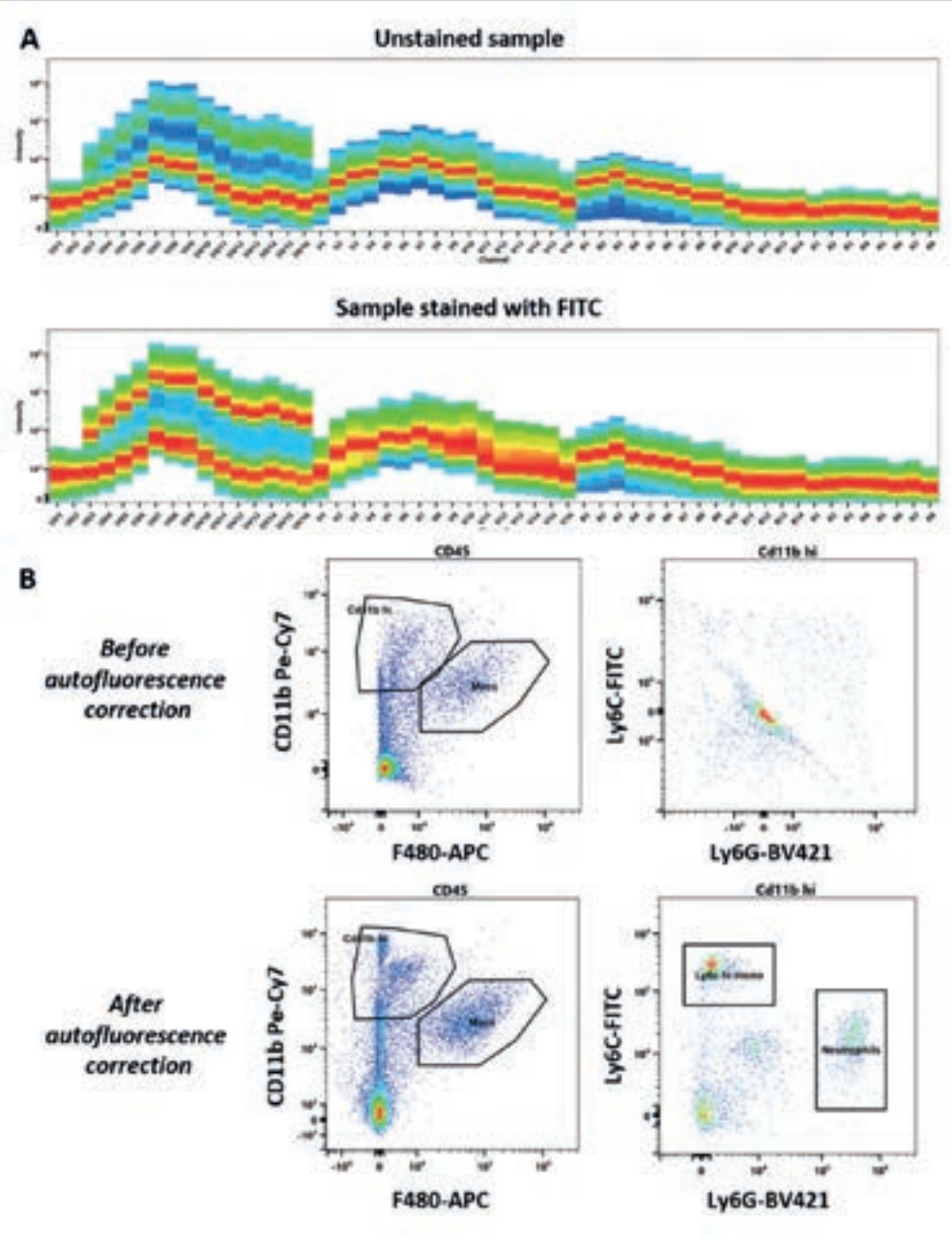


FIGURE 3 Improved detection of hepatic macrophage subsets after correction for multiple autofluorescent signatures. (A) Cytek Aurora spectra of unstained liver sample with high autofluorescence versus a liver sample stained with FITC. The spectrum of the unstained cells is almost indistinguishable from the stained sample. (B) Flow cytometry plots of live, single, CD45 cells isolated from a mouse liver. The high autofluorescence in liver cells leads to an inability to distinguish the immune cell subsets of interest, however this can be overcome by accurate autofluorescence correction.

are setting up a 24-colour panel to analyse atherosclerotic plaque cell populations, while at the same time measuring their metabolic activation profile.

To make this complex technology more accessible for all CARIM researchers, Kristiaan has developed a 'universal background panel' to identify the main leukocyte populations in human blood while leaving the most common fluorophores (FITC, APC, PE etc.) available for specific subset or activity markers of interest to each researcher. This ensures consistency across studies in CARIM and enables users to plug in their specific marker panel of interest, facilitating panel design. In addition, the facility has several antibodies available that can be used in a 'cost per assay' manner to reduce the costs of pilot-testing antibody panel development.

Currently, the Departments of Internal Medicine and Pathology are working towards combining Macroscreen functional profiling data with *in vivo* phenotypic data using spectral flow cytometry, so phenotype can be truly linked to function. Overall, thanks to the active collaborations between these departments, we now have at our disposal a fantastic toolset to truly investigate cellular heterogeneity and grasp the associated functional implications.

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INTERVIEW

ANOUK GULPEN
RENSKE OLIE
RENÉE BRÜGGEMANN

A matter of planning

For a moment, Renske Olie hesitated when she received the invitation for this group interview. Asking three women to talk about the challenging combination of doing a PhD project while starting a family, and perhaps completing a medical specialist training as well: was that not kind of stereotyping? Anouk Gulpen and Renée Brüggemann had fewer objections. “I want to show younger colleagues that this combination is definitely feasible”, says Gulpen. Together, they come up with four tips.

Renske Olie was the only one of the three who already had a permanent job as an internist when she started her PhD project. “I had my eldest, who is now eleven years old, during the final year of my training. At age thirty, that was a deliberate decision. The second was born eight years ago, when I was already working as a medical specialist. I had already entertained the idea of doing scientific research before, but it only materialised when I returned from maternity leave after having my second child.” Renée Brüggemann was in the final stages of her training when the Covid pandemic started, which was also when she became pregnant for the first time. “Social life was largely suspended, and time became available for other things; so I might as well put that to good use. My eldest is now eighteen months, and I’m expecting my second child at the end of July. Before my delivery, I thought I’d be able to complete my PhD thesis during my maternity leave, but that proved to be somewhat optimistic. I managed to complete it eighteen months later, fortunately before my second child arrived, as that was one lesson I had learned.” Anouk Gulpen started her PhD project while training to become an internist. During the first year, she was able to devote all her time to her research work at the Department of Biochemistry, after which she combined it with her internist training at Maastricht UMC+ and later at the Elkerliek hospital in the town of Helmond, where she currently works. “My children are now six, four and half a year old. When I defended my PhD thesis, I was 36 weeks pregnant with my youngest. That went well under the circumstances.”

Why did you want to do a PhD?

Olie: “As I was already working as an internist at thirty, I thought to myself: do I want to keep this up until retirement, or do I want to progress? And although at the hospital there is no obligation to do a PhD, if you want to get on in your career, then a PhD is an obvious next step. It opens doors, for instance to join scientific advisory committees, or national guideline committees.”

Gulpen: “I wanted to develop further, in the field of science as well, in addition to working as a medical specialist. Job opportunities for internists are relatively limited, so doing a PhD thesis seemed like a good investment for the future.”

Brüggemann: “Up to and including my fourth article, I still told myself that I wasn’t working on a PhD thesis. In the end, it was almost done, and my boss said: ‘Perhaps you should get a PhD after all.’ You also hear stories of people who are working on a PhD project and no longer feel like completing it. This way, the cloud of having to finish it is no longer continuously hanging over your head.”

Olie: “That’s more or less how I got into it as well. If you start out calling it a PhD project, you put too much pressure on yourself, whereas if you say you’re going to do some scientific research and will just see how far it gets you, there’s not so much pressure. This way it remained a fun thing to do, as I really wanted to do it myself. Nobody was telling me it had to be finished before a particular date, which meant I was more intrinsically motivated and enjoyed the work more. And if my family needed more attention at a particular time, I was there for them too.”

Tip 1 Do not call it a PhD thesis from the start

Gulpen: “Although for me it was a conscious decision to start a PhD project. In a way, I actually needed the pressure to complete it, to ensure I made it to the finish line.”

To what extent was it actually a matter of family planning?

Gulpen: "I was thirty and still in my specialist training when I had my first, and fairly soon afterwards came my second child. That was a conscious decision. I then started to work as a medical specialist in Helmond, moved to Brabant with my family and also still had to complete my PhD thesis. So my wish to have a third child had to be put on hold for a while. Once we had found some breathing space again and had settled down, we found we still wanted it. Of course, you never know how the process is going to develop and what other opportunities will present themselves. That's how you can end up defending your thesis while heavily pregnant. There was, however, a large difference between my pregnancies: in my experience your life is a bit less hectic and more ordered when you're a trainee than when you're a medical specialist. That may sound strange, but that's how it was with me."

Olie: "If you wait until you've fully completed your training, you're often around 32 years old. Some women might find that too old. Also, while you're in training, you have job security. After your maternity leave, the lost time just gets added. Whereas if you've just started work as a medical specialist, you might get a one-year contract, and they don't appreciate it too much if you're pregnant and can't do shifts for half of that year."

Brüggemann: "That's right. After I had just had my first, I was given a six-months contract, followed by a one-year contract to replace a sick colleague. I wanted a second child, but that seemed impractical at that time. It is definitely a factor, even if that's not how it's supposed to be. You're not going to go on leave for four months during a one-year contract when you know they've hired you because they're understaffed."

Tip 2 Having children while you're still in training is not such a bad idea

What were the greatest obstacles on your career path?

Brüggemann: "There's never been anyone holding me back, but I found the biggest problem to be the accumulation of tasks. Or rather my own expectations, the fact that I wanted to do everything perfectly."

Olie: "That's absolutely the case. You try to give 100% in your work and be there 100% for your children, and then you try to combine those two so you end up having only 75% to give to both. I remember at one time I was on the phone with my work as I was on duty, using earbuds, while at the same time putting my child to bed, as my husband was doing a night shift. That doesn't really work. You think you're cleverly combining things, whereas you're really doing both things imperfectly. That's something I've learned: it's better to make a clear choice between being at work and being a mum at home. Nowadays I prefer to be at the hospital when I'm on duty, or at home with the kids without a phone or a computer at hand."

Tip 3 Home is home and work is work

Gulpen: "I try to keep home and work separate, but in practice that doesn't always work out completely, as my youngest is now sitting beside me in a baby rocker while I'm doing this interview."

Brüggemann: "Babies do sleep a lot, don't they, as I said to my PhD supervisor before my maternity leave. So I thought I'd be able to finish my research project at the same time. That proved to be a complete underestimation; it was just impossible to combine the two. When the child eventually started to sleep more regularly, it became easier. But no golden tip, alas."

What factors were helpful?
Gulpen: “Careful planning. Organising your work and home situation carefully with your partner, so that you both have enough time to work as well as to relax.”

Brüggemann: “That’s one thing, yeah. That and continuously discussing what gets priority when. If, for example, an article needs to be finished, the little one spends an extra day with grandma. And last year when we were buying a house, that was top of the agenda for a while. In the last few weeks, my thesis defence took priority, so the washing was stacked up to the ceiling.”

Olie: “In my situation, the absence of hard deadlines was once again a great help. If my family needed some more attention for a while, that was no problem at that moment.”

Tip 4 Don’t try to do everything perfectly at the same time

Talking about family life: do you and your partner evenly share the household tasks?
Olie: “When I go away to a conference for a week for my work, everyone asks: How does your husband cope? They never ask how I cope when he’s away. Whereas he probably spends more time on household chores and the kids than I do, at some moments. But for some reason they always look at the woman: how do you cope if the school staff are having a study day? If the children take a fall at school and their lip is bleeding, it’s me the school phones. I have to admit, we have divided up the tasks in a rather traditional way, in that I buy the presents for the children’s parties, make sure they’ve got their gym gear with them and have them take an empty shoe box to school for a crafts project. But that’s partly a matter of character: I’m a bit more organised than my husband, so it’s just more practical if I’m on the Whatsapp groups for school, the field hockey club, dance classes and korfball. While my husband does more of the shopping and takes care of things around the house and garden.”

Gulpen: “We have a joint week calendar, so that everybody knows what we’ve got planned. I’m often the one who writes the children’s practical things on the calendar, and I often lay out the stuff they need, but my husband takes care of other tasks, in the house and the garden. You divide up the tasks in a way that works best for you.”

I FOUND THE BIGGEST PROBLEM TO BE THE ACCUMULATION OF TASKS

Where do you see yourselves in ten years' time?

Olie: "I'm fairly settled. I've had a permanent appointment here for the past ten years and I enjoy it. But I definitely want to stay involved in research, supervise my own PhD students and develop that further. I've found out that I like that combination. That's the advantage of working at the academic hospital here, that you're able to combine research, teaching and patient care, and focus on what you enjoy most."

Gulpen: "I enjoy contributing to the improvement of health care. I'm on two national boards, which is very interesting additional work. I have a permanent appointment, so I needn't worry about that, but I want to put myself in a good position. Things are not really quiet right now; these are the classic years of hard graft."

Brüggemann: "I've only just received my doctorate, so I haven't looked much further into the future yet. What I definitely want is a permanent appointment. I like teaching, which I'm able to do at the academic hospital. That's my first priority, and we'll see what comes next. First thing coming up is of course my second child; so no, I'll be busy enough for a while yet."

Dr Renske Olie has been working as an internist specialising in vascular medicine at HVC. She trained as an internist at the Elisabeth Hospital in Tilburg and at Maastricht UMC+. Her research concerns the effects of various anticoagulants in patients with cardiovascular disease. She received her doctorate on 20 March 2023, based on her thesis entitled 'Personalized antithrombotic treatment in high-risk patients with coronary artery disease'.

Dr Anouk Gulpen has been working as an internist specialising in vascular medicine at the Elkerliek Hospital in Hemond since 2020. Since 2021, she has been leading the thrombosis services at the Bernhoven hospital in the Oss-Uden-Veghel area (province of Noord-Brabant), and since 2022 also those of the Eindhoven region. She completed the UM's Masters programme for Medical Doctor–Clinical Investigator, after which she trained to become an internist at Maastricht UMC+. She received her doctorate on 9 September 2022, based on her thesis entitled 'Direct oral anticoagulant care: Focus on management and monitoring'.

Dr Renée Brüggemann has been working at Maastricht UMC+ as an internist specialising in geriatric care since 2022. She trained there and at Zuyderland hospital in Heerlen, and received her doctorate on 4 April 2023, based on her thesis entitled 'Unraveling hypercoagulability in COVID-19 and optimizing VTE management in the frail nursing home population'.

GRANTS, PRIZES AND HIGHLIGHTS

03

SCIENTIFIC HIGHLIGHTS

In 2022, the successful work of our researchers was reflected in 1,090 international peer-reviewed journal articles (SCI). 67 PhD candidates successfully defended their theses, 2.0 million Euros of funding were received in competition from national science foundations and 5.7 million Euros funding from third money parties, charities, EU framework programmes and industry.

SCHOLARLY IMPACT

22.5% of CARIM's publications belong to the top 10% and 3.7% to the top 1% publications in its field. With an overall CNCI (Category Normalized Citation Impact) of 2.1, CARIM's publications are cited 2.1 times more often – on average – than the expected average for comparable publications. All research lines are above world average in their contribution to the top 1% and top 10% of publications. The percentage of publications published open access has increased at CARIM, with 21.9% of the total output being available in a journal under an open license in 2015 to 62.3% in 2022. When taking green open access publications into account, 81.7% of CARIM's publications of 2022 falls under open access.

	NUMBER OF DOCUMENTS*	AVERAGE CNCI	NUMBER OF PAPERS IN TOP 1%	NUMBER OF PAPERS IN TOP 10%	% OF PAPERS IN TOP 1%	% OF PAPERS IN TOP 10%
Blood	506	1.8	19	133	3.8	26.3
Vessels	484	2.1	18	96	3.7	19.8
Heart	416	2.8	27	100	6.5	24.0
CARIM total	3,566	2.1	133	803	3.4	22.5

*The number of documents and citation impact for separate divisions (2019-2020 only) and the research institute (2015-2020)

RESEARCH GRANTS AWARDED TO INDIVIDUALS

NHS DR E. DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Job Verdonschot** (Dept of Cardiology) and Dr **Magdolna Nagy** (Dept of Biochemistry) both received a grant. Job was awarded a Clinical Scientist grant of €245k for the project 'It's all in the family! A dedicated care pathway to improve early recognition of relatives at risk for the development of dilated cardio-myopathy'. The grant will allow him to boost his research focusing on helping the family members of patients with dilated cardiomyopathy. Hereditary heart muscle diseases can cause severe heart failure and/or cardiac arrest. If the patient has been diagnosed with a hereditary cause, first-degree relatives are also advised to have their heart checked regularly. Job wants to be able to better predict which first-degree relatives run a high risk of becoming ill and which relatives have a low risk and can therefore be reassured. See pages 12-17 for a full interview with Job.

Magdi received a Postdoc grant of €280k for the project 'Elucidating the mechanism and impact of contact activation in acute ischemic stroke'. With this, she can conduct research on cardiovascular diseases in the coming years. Magdi's research focuses on safer drugs for patients who have had a stroke. Many of them are prescribed drugs to prevent blood clots. Blood clots can lead to another cerebral infarction. However, these drugs can have nasty side effects. They can cause bleeding, sometimes even to a dangerous level.

FELLOWSHIPS ROB HOLTACKERS

Dr ir **Rob Holtackers** (Dept of Radiology & Nuclear Medicine) received a Kootstra Talent Fellowship from the FHML/ Maastricht UMC+ with his proposed study 'Interventional cardiac MRI: a new strategy for improved diagnostics and treatment of cardiac arrhythmias'. The Kootstra Talent 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.

Rob also received a Niels Stensen Fellowship from the Porticus foundation, which enables him to gain research experience at a top university or scientific institute abroad. Although 1.5 T and 3 T systems are the current clinical field strengths used for MRI, the staggering recent progress in hardware, software, and methodology help making low-field systems (<1.5 T) more powerful, more cost-effective, and more widely accessible. By overcoming the past limitations of low-field systems, high-performance low-field MRI will challenge the existing clinical field strengths of 1.5 T and 3 T.

In addition, given its reduced costs of purchase, instalment, and maintenance, and advantages in system siting, it will facilitate the more global dissemination of MRI to the benefit of a larger patient pool and reach geographical regions that have not traditionally had easy access to MRI. Rob's visit to the University Hospital in Lausanne (CHUV) will allow him to work with such a unique high-performance low-field MRI system, which is currently not available in the Netherlands, and to perform research at the highest level in this field.

OTHER AWARDS, PRIZES AND GRANTS

Three research teams coordinated by CARIM researchers received funding from ZonMw within the Open Competition programme. Each research team received €750k on average.

AVF FAILURE IN RENAL FAILURE - Prof. Andy Baker (Dept of Pathology)

Worldwide, an estimated three million patients with end-stage renal disease are treated with hemodialysis for survival. Hemodialysis requires access to the blood vessels to transport the patient's blood to the dialysis machine. An arteriovenous fistula (AVF), in which an artery is directly connected to a vein, is therefore created surgically, usually in the arm. However, this intervention often fails, posing a huge clinical problem for this patient population. This problem will only increase in the coming years due to an increase in patients with diabetes and end-stage renal disease. Therapies to prevent AVF failure are lacking because it is unclear why the AVF fails. Therefore, Andy's team wants to better understand this process and develop therapies for AVF surgery to prevent AVF failure. This will improve the outcomes of AVF surgery.

NEW THERAPEUTIC TARGETS FOR DCM? - Prof. Erik Biessen (Dept of Pathology) and Prof. Stephane Heymans (Dept of Cardiology)

In the Netherlands, 80,000 people suffer from dilated cardiomyopathy (DCM), a disease that causes life-threatening arrhythmias and heart failure, often at a young age, with major emotional and economic consequences. Less than half of patients respond to current standard treatment. DCM is a heterogeneous disease, in which the hereditary form is characterized by metabolic changes. It is unclear whether these metabolic changes directly lead to fibrosis and inflammation, or indirectly, via certain cell types in the heart, the macrophage, known to control fibrosis, inflammation and heart function. Based on their expertise in macrophage biology, clinical DCM pathophysiology and knowledge of advanced single-cell technology, Prof. Erik Biessen and Prof. Stephane Heymans aim to define new therapeutic targets for treatment of genetic DCM.

RECOVERY PROCESS OF THE HEART AFTER INFARCTION? - Dr Matthijs Blankesteijn (Dept of Pharmacology & Toxicology)

After a heart attack, part of the heart muscle cells are replaced by scar tissue. This scar tissue does not contribute to pump function, which can cause heart failure, a condition with a 5-year survival of only 50 percent. The core idea of the research team, led by Dr Matthijs Blankesteijn, is that the repair process of the heart after an infarction must be adjusted by reducing scarring and giving the heart's natural ability to repair the damage. Recent research in zebrafish shows that their hearts contain this natural ability to regenerate, preventing scarring. With a team of experts in the field of repair processes and biomaterials, Matthijs wants to develop a material that on the one hand supports the infarct area and thus prevents rupture, and on the other hand releases medicines to stimulate the natural repair process.

Prof. **Casper Schalkwijk** (Dept of Internal Medicine) received a grant of €100k from the European Foundation for the Study of Diabetes (EFSD). This grant will be used to further study DNA modifications by methylglyoxal. Methylglyoxal is a key mediator in the association between hyperglycaemia and vascular disease. In addition to protein modifications, methylglyoxal can also react with nucleosides to yield methylglyoxal-DNA. So far, the impact of methylglyoxal-DNA on vascular function is unknown. The objective of this project is to determine the role of methylglyoxal-DNA in the development of CVD in diabetes. The impact from a clinical point of view is that methylglyoxal-DNA can be a novel promising biomarker to predict CVD in diabetes and a new therapeutic target to decrease CVD burden in diabetes.

CARIM researchers from the Dept of Biomedical Engineering (Prof. **Joost Lumens,** Dr **Nick van Osta** and **Tim van Loon**) have been awarded an NWO Take-off phase 1 grant to embark on a valorization feasibility study. Through their research in the field of Computational Cardiology, they have conceived the idea of 'Insilicor – The Cardiovascular Digital Twin Platform'. This pioneering technology harnesses the power of artificial intelligence and biophysical modeling to integrate existing functional cardiac measurements into a virtual representation known as the 'Digital Twin', offering unparalleled insights into crucial functional aspects of a patient's heart that are presently inaccessible or can only be obtained by using invasive measurements. While the valorisation of this idea is still in its early stage, this grant will enable the development of a robust business case, and will be utilized for tasks such as defining the user journey, devising a market strategy, conducting further prototype validation, and crafting a comprehensive business plan. By the summer of 2023, the objective is to determine the feasibility of transforming this idea into a viable business venture.

Diabetes is one of the fastest growing non-communicable diseases worldwide and among the leading causes of disability and death. Improvements in treatment and care were made over recent decades, yet it requires a breakthrough to address any future challenges. The new research project MELISSA (Mobile Artificial Intelligence Solution for Diabetes Adapted Care), a collaboration of twelve partners from seven countries coordinated by Prof. **Bastiaan de Galan** (Dept of Internal Medicine) will leave its mark in introducing Artificial Intelligence (AI)-based solutions. Funded through the European Union's Horizon Europe Framework Programme for Research and Innovation, the project will receive €5.9 mln over the next four years. In addition, the Swiss government will contribute €1.8 mln in funding for the Swiss Associate Partners. MELISSA is coordinated by CARIM who will work closely on managing the project with Debiotech, the University of Bern and Eurice.

Two research projects have received a Public-Private Partnership (PPP) Allowance in 2022: CELLSYSTEMICS, coordinated by Dr **Koen Reesink** (Dept of Biomedical Engineering) and CARDIOIDS, coordinated by Prof. **Leon de Windt** (Dept of Cardiology). PPP Allowances are awarded to Top consortia for Knowledge and Innovation (TKI) for research projects with particular utilisation focus. Such consortium should comprise one or two academic/ knowledge institutes and one or more private partners who also contribute to the project budget by in-kind or cash.

The CELLSYSTEMICS project develops a platform for characterisation of cellular system dynamics for tissue disease stageing and programming for repair, and is part of the Human Measurement Models programme, funded by Health-Holland, Top-Sector Life Sciences & Health, to the Association of Collaborating Health Foundations (SGF), and by ZonMW. The eight consortium partners are: Maastricht UMC+, TU/e Faculty of Electrical Engineering, Optics11Life, Confocal.nl, HCM Medical BioSPX, STEMCELL Technologies and Contact-group Marfan Nederland. CELLSYSTEMICS capitalises on the Heart+Vascular Center/CARIM initiative and investments from Biomedical Engineering (Dr Koen Reesink), Cardiothoracic Surgery (Dr Elham Bidar) and Biochemistry (Prof. Leon Schurgers) to form a long-term research infrastructure around thoracic aortic aneurysm, cell-matrix interaction, and cell-based disease modeling and therapy.

In CARDIOIDS two- and three-dimensional cultures of patient-derived stem cell heart muscle cells will be compared with a unique mouse model harboring the same inherited heart disease mutation to determine their functionality and predictive behavior with the existing models and clinical data. These 3D cardiac organoids are expected to be a superior tool for drug screening, offering the opportunity to discover new therapies for serious heart diseases.

A collaborative project of CARIM and AstraZeneca, led by Prof. **Stephane Heymans** (Dept of Cardiology), aims to identify new DCM patient subgroups, and unravel the underlying pathophysiologic pathways to come to new therapeutic targets. First data within the unique prospective Maastricht DCM cohort identified distinct phenogroups based upon clinical, imaging and genetic data. Cardiac RNA profiles pointed to a decisive - yet unexplored enrichment of metabolic - inflammation-fibrosis pathways in these phenogroups. In a DCM-Precise (Precision medicine in dilated cardiomyopathy) collaboration they now aim to uncover specific pathways and key targets in the control of cardiac function and arrhythmias. This represents an opportunity to repurpose or discover new therapeutic leads/ targets for DCM subgroups in general, and identify new targets for orphan drugs in genetic DCM.

The CARIM commitment award of 2022 went to **I'mCARIM board members 2021, Myrthe van der Bruggen, Renée Tillie, Valeria Saar-Kovrov, Kim Maasen, Adele Ruder,** for their unprecedented efforts to further improve the well-being among CARIM's PhD candidates, and creating an illustrated PhD guide with facts, figures, and important info to safely cross a PhD trajectory. In addition, they designed a CARIM recruitment video that will surely result in a motivated start of many new PhD candidates arriving at CARIM, as well as attracting new ones.

CARIM COMMITMENT AWARD WINNERS

2015	Rob van der Zander
2016	Frits Prinzen
2017	Peter Leenders, Agnieszka Brouns-Strzelecka, Nicole Bitsch, Helma van Essen, Jacques Debets (MF)
2018	Koen Reesink
2019	Kristiaan Wouters; Tara de Koster
2020	Carla van der Kallen; Harry Crijns
2021	Stella Thomassen
2022	Myrthe van der Bruggen, Renée Tillie, Valeria Saar-Kovrov, Kim Maasen, Adele Ruder (I'mCARIM); Marc van Bilsen

The team of Dr **Dominik Linz** and Dr **Justin Luermans** (Dept of Cardiology) has received one of the ten grants for transmural cardiac care from ZonMw and the Dutch Heart Foundation. This grant of €75k will be used to further develop integrated care and collaboration between general practitioners and the Dept of Cardiology of Maastricht UMC+ for patients with atrial fibrillation. Within this integrated care approach there will be a major role for mobile health to early detect atrial fibrillation and to optimise treatment of atrial fibrillation and concomitant treatment of relevant comorbidities. Therefore, within this project a pilot will be held within four general practitioner offices to test and refine this mobile health approach, which will be starting soon. See pages 28-33 for an interview with Dominik.

The EmbRACE network under the supervision Prof. **Uli Schotten** (Dept of Physiology) and Prof. Michiel Rienstra (University Medical Center Groningen) has received €2.5 mln from the Dutch Heart Foundation to study the underlying mechanisms that lead to the development of atrial fibrillation. It is the follow-up to the successful RACE V study. Atrial fibrillation is the most common heart rhythm disorder. In the Netherlands, 360,000 people have atrial fibrillation; in addition, an estimated 80,000 people who unknowingly have this condition. It can lead to complications such as stroke, heart failure and death. The risk of this increases if someone suffers more from the consequences of atrial fibrillation. It is therefore important to prevent this. Addressing the underlying risk factors and disease processes is a key goal of the new research programme. The underlying mechanisms for the onset and progression of atrial fibrillation are complex and not yet fully understood. They may be important for the treatment of atrial fibrillation. Although it is not yet known exactly how the bosom becomes diseased, it is already known that high blood pressure, obesity, heart failure and diabetes are important risk factors. The research programme will therefore map the various underlying mechanisms of atrial fibrillation, both in men and women.

This year's Harry Crijns Research Grant of €25k was presented to **Vital Houben** during the CARIM annual scientific symposium for his project 'GADGET'. The goal of GADGET is to further optimise and personalise cardiac rehabilitation, exploring potential benefits and possibilities of accelerometers in telerehabilitation. The grant was

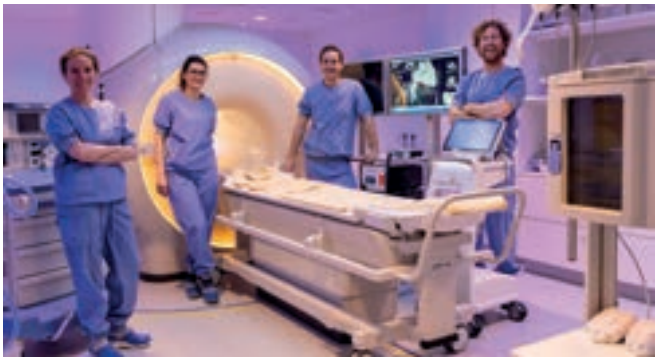
awarded for the first time in 2021 by the Cardiovascular Research Fund of Health Foundation Limburg to a promising young researcher in the field of cardiovascular disease. The Grant was instituted as a tribute to Prof. Harry Crijns, who was chair of the Department of Cardiology of Maastricht UMC+ until December 2020 and board member of CARIM. Throughout his long and successful career in translational and clinical cardiology, Prof. Crijns made innumerable contributions to cardiovascular science, particularly in the field of atrial fibrillation. Harry Crijns has played an important role in shaping cardiovascular research at the local, national and European level and has had a major impact on the careers of many assistants and colleagues and on the lives of many patients.

Dr **Miranda Nabben** and Dr **Joost Luiken** (Dept of Genetics and Cell Biology), together with researchers Jeroen Bogie and Jerome Hendrix from Hasselt University, have been awarded a grant from an application round to promote collaboration between the Universities of Maastricht and Hasselt. The project proposal aims to study the common role of the fatty acid transporter CD36 in two different diseases: Diabetic Cardiomyopathy (Maastricht) and Multiple Sclerosis (Hasselt). Particular emphasis is placed on a specific post-translational modification of CD36, called palmitoylation, which the researchers hypothesise that this process is altered in both diseases. Both research teams will synchronise their techniques to study CD36 palmitoylation in both diseases. The award involves the appointment of a joint PhD candidate for a period of four years who will work partly in Maastricht and partly in Hasselt.

In collaboration with Profs. Paul Proost and Pedro Marques (Dept of Microbiology Immunology and Transplantation) from the KU Leuven, Dr **Ingrid Dijkgraaf** and Prof. **Tilman Hackeng** (Dept of Biochemistry) have been granted an award to appoint a joint PhD candidate to investigate the molecular mechanism(s) of the tick-derived evasin protein family. Moreover, the therapeutic potential of evasins to treat acute liver injury will be evaluated. Therefore, evasins will be modified to optimize their pharmacokinetics and pharmacodynamics. In addition, Dr Dijkgraaf and Prof. Hackeng have been granted a joint PhD project with Hasselt University. In this Maastricht-Hasselt project, a collaboration with Prof. Markus Kleinewietfeld (Dept of Immunology and Infection), structure-activity relationship studies on tick protein Salp15 will be performed. The therapeutic potential of Salp15 in (auto)immune diseases will be assessed by investigating the mode of action and effects on human CD4+ T cells.

Dr ir **Rob Holtackers** (Dept of Radiology & Nuclear Medicine) and his iCMR team have won the Team Science Award from NWO. The Team Science Award rewards the most inspiring and successful team of researchers from various disciplinary fields, who jointly take on a scientific challenge in which their individual strengths and expertise demonstrably reinforce each other. The iCMR team aims to improve the treatment of patients with cardiac arrhythmias by treating them while inside an MRI scanner. By combining their diverse expertise, the team uses basic science, biomedical technology, and patient care to achieve their objective. The jury valued the complementarity of the disciplines in their team and the combination of scientific and technological expertise. The route taken by the team to translate elementary science and technology into patient care

resulted in an impactful application. The prize money of €10k is intended for activities with relation to the team.



Prof. **Frits Prinzen** (Dept of Physiology) received the Maastricht UMC+ medal at the end of his valedictory lecture due to his retirement from UM. This medal is awarded to officials who have had significant significance for Maastricht UMC+ or with special merits outside their own discipline. The 'Electromechanics of the Heart' professor was awarded the medal because of his scientific career, his contributions and dedication to teaching during 44 years of service at the university and his collegiality.

Dr **Ben Janssen** (Dept of Pharmacology & Toxicology) was awarded the Wynand Wijnen Education Prize during Maastricht University's 46th Dies Natalis. The Wynand Wijnen prize is awarded to staff members who have made an exceptional contribution to education at Maastricht University. "We should take note of the unique situation that Ben was nominated twice to win this award, both individually and as part of a collective. It's almost inevitable that Ben Janssen was rewarded for his efforts".

Dr **Estelle Nijssen** (Dept of Radiology & Nuclear Medicine) was awarded the Dissertation Prize 2021 for her thesis 'AMACING: Evaluation of Guideline-Recommended Prophylaxis to Prevent Contrast-Induced Nephropathy' during the Dies Natalis.

Dr **Matthijs Cluitmans** (Dept of Cardiology) received the WCN Research Prize 2022 during the annual WCN congress in Amsterdam. Matthijs pitched his 2021 Science Translational Medicine paper to the jury and an audience of ~200 cardiologists. His team's work highlights the importance of (concealed) recovery abnormalities in patients who survived

'unexplained' sudden cardiac arrest. By combining noninvasive mapping with experiments and computer models, they improved the understanding of the trigger-substrate interaction leading to these arrhythmias. The WCN is the Working Group Cardiological Centers Netherlands, which is an organisation that binds all Cardiology centres (academic and peripheral) in this country. The WCN Research Prize is awarded to young scientific researchers, selected by a multi-disciplinary jury, to encourage cardiovascular research.

On Thursday 13 October, in honour of World Thrombosis Day, Dr **Arina ten Cate-Hoek** (Dept of Internal Medicine) received the Virchow Prize 2022. The prize was awarded by the DGA (*Deutsche Gesellschaft für Angiologie - Gesellschaft für Gefäßmedizin*), the joint professional association for

angiologists, phlebologists and vascular surgeons of the three German-speaking countries (Germany, Austria, and Switzerland). She receives the prize for her scientific work in the field of Post Thrombotic Syndrome and in particular for research into the effectiveness of compression therapy and the direct impact of her work on various guidelines.

Dr **Philippe Vangrieken** (Dept of Internal Medicine) received the Prof. dr. J. Terpstra Award 2022 during the annual Dutch diabetes symposium. The main objective of this prize is to stimulate young researchers who conduct research in the field of diabetes mellitus. The Prof. dr. J. Terpstra Young Investigator Award amounts to €10k. The winner will also receive a matching memento with inscription.

Floor Pinckaers (Dept of Neurology) has received the Pélerìn award for her research on dual-energy CT after endovascular stroke treatment. The award was presented during the annual Pélerìn Symposium that took place on 5 October 2022. The annual Pélerìn physician assistants symposium is the ideal opportunity for physician assistants, physician researchers and semi-doctors to draw attention to scientific research carried out from Maastricht UMC+.

During the ARTERY22 conference that was held in Nancy, France from 19-22 October 2022, **Berta Ganizada** (Dept of CTC) and **Cindy van Loo** (Dept of BME) both received an award. Berta gave an oral presentation on her current work on histomorphometric analysis of cell and matrix components of ascending thoracic aortic aneurysm for which she got rewarded with the second place Young Investigator Award. The aim of her project is to identify an early-stage screening markers for patients with thoracic aortic aneurysm. Cindy van Loo received a Research Exchange Grant for her research proposal in collaboration

with the lab of Jason Au at the University of Waterloo in Canada. This enables her to investigate the mechanical properties of aortic and carotid artery tissue of human donors.

OTHER HIGHLIGHTS

On Thursday 20 October, **AMICARE**, the Aachen-Maastricht Institute for Cardiorenal Disease, was opened in Aachen. In this research institute, researchers from Maastricht UMC+ and RWTH Aachen University work together to unravel the relationship between heart and vascular problems and kidney disease. It is one of the first European institutes in which researchers from different countries from different disciplines will collaborate so intensively on this medically urgent problem. The research institute focuses on translational research that aims to translate fundamental research results into applications for the patient. This means that on the one hand the researchers will continue to investigate the mechanisms and causes of the convergence of heart, vessel and kidney problems. On the other hand, the scientists also expect to be able to accelerate research into the early recognition and treatment of this syndrome with AMICARE, for example with medication. See pages 62-67 for an interview about AMICARE with Heidi Noels and Erik Biessen.

Prof. **Christian Weber** (Dept of Biochemistry) was identified by Clarivate™ (Web of Science) as one of the world's most influential researchers: the select few who have been most frequently cited by their peers over the last decade. In 2022, fewer than 7,000, or about 0.1%, of the world's researchers, in 21 research fields and across multiple fields, have earned this exclusive distinction.

Prof. **Coen Stehouwer** (Dept of Internal Medicine) is ranked among the Top Scientists for 2022 by Research.com. For the 2022 edition of the ranking, more than 65,700 scientist profiles on Google Scholar and Microsoft Academic Graph

have been examined with several indicators and metrics reviewed in order to consider each scientist's inclusion in the ranking.

On 1 January 2022, Dr **Dominik Linz** (Dept of Physiology) became Professor of Lifestyle Factors in Cardiac Arrhythmia at Department of Biomedical Sciences (BMI) of the University of Copenhagen as part of the research theme 'Physiology of Circulation, Kidney and Lung'. Dominik Linz was awarded a DKK 25 mln Novo Nordisk Foundation (NNF) Young Investigator Award in 2021 for the project 'Arrhythmia mechanism-tailored assessment of sleep-disordered breathing in atrial fibrillation'. He is now joining BMI to establish a research group focusing on the investigation of the mechanisms underlying atrial fibrillation (AF) in sleep-disordered breathing (SDB). The objective is to develop and validate a mechanism-driven assessment of SDB for a personalised guidance of SDB treatment in patients suffering from AF. Dominik will combine his clinical work at Maastricht UMC+ with his professorship in Copenhagen.

Prof. **Leon the Windt** (Dept of Cardiology) has been elected Chair of the Talent Program in the steering board of the Dutch CardioVascular Alliance (DCVA). To secure continuity in high quality and innovative research, the DCVA invests in identifying and nurturing the most talented cardiovascular researchers, which will become the leaders of the future in national and international research consortia, or have a strategic position in a non-academic sector. The alliance aims to strengthen the funding landscape, by initiating grants to fill gaps in the current offering from junior to senior scientist.

The **Stem Cell Research University Maastricht (SCRUM)** that was initiated by CARIM in collaboration with FHML, was opened in 2022. SCRUM is the latest core facility of FHML and will provide service for the generation of induced pluripotent stem cells (iPSC). In this new core facility, iPSCs provide a solution for research with cells from hard-to-reach tissues such as heart, vascular tissue or brain tissue. These iPSC have the potential to grow into different types of somatic cells. SCRUM is an example of Maastricht University's social commitment to the 3R initiative. iPSC research provides an endless supply of cells, from same genetic origin, that can serve to test drugs and genetic intervention treatments, without using animal models. See pages 18-21 for an interview with Sandrine Seyen and Niko Deckers about running the facility.

Dr **Chahinda Ghossein-Doha** (Dept of Cardiology) has been named this year's 'Top Woman of Limburg province'. She received the title at a ceremony in Weert on 22 September 2022 organised by the *Topvrouwen* Limburg Foundation. Chahinda is a cardiologist in training at Maastricht UMC+ and a researcher at CARIM and GROW. Her research focusses on cardiovascular diseases in women, particularly in relation to their pregnancy. She is committed to this women-specific issue through her work as a cardiologist and scientist, and through the Queen of Hearts foundation, which she has founded. Chahinda aims to give the topic more exposure and to break existing taboos. She is the author of a book about the impact of pregnancy complications on women and she organises projects in which science, music and art come together.

A CARIM team existing of **Sandrine Seyen, Kelly Nies, Sophie van de Walle, Tilman Hackeng, Elham Bidar** and **Cengiz Akbulut** coached by **Boy Houben** participated in the '*Prominentenroeien*' organised by the WMC Maastricht (Maastrichtsche Watersportclub). They succeeded in beating some of the racing shell teams, made it to the finals, and won the cup for the '*sloep*'.

PROFESSORSHIPS

1 July 2022: Andy Baker (Dept of Pathology) – Professor of Translational Cardiovascular Sciences

INTERVIEW

HEIDI NOELS AND ERIK BIESSEN

From virtual to real institute

AMICARE, the Aachen-Maastricht Institute for Cardiorenal Disease, was opened in Aachen in October 2022. In this institute, researchers from Maastricht UMC+ and RWTH Aachen University work together to unravel the relationship between cardiovascular problems and kidney disease. It is one of the first European institutes in which researchers from different countries and from different disciplines collaborate so intensively on this medically urgent problem. Two members of the founding team, Erik Biessen and Heidi Noels, gave an interview.

ONE OF THE ASSETS OF AMICARE IS THAT IT OFFERS JUNIOR RESEARCHERS MORE OPPORTUNITIES TO SHAPE THEIR CAREERS

How did AMICARE come about?

Erik Biessen: "It was through my previous collaboration with IMCAR, the Institute for Molecular Cardiovascular Research at University Hospital RWTH Aachen, that I came into contact, around 2014, with the Aachen Professor Joachim Jankowski. Our shared interests and our complementary expertises, soon resulted in a part-time position at Aachen for me and at Maastricht for him. That's how the collaboration between our two institutes gradually got off the ground. We soon started the IMCARIM lecture series, with guest speakers from renal and cardiovascular research. The aim was to strengthen the ties between the research teams, and to encourage interaction. Soon after, other CARIM and IMCAR staff also obtained dual positions at both universities, such as Heidi Noels and Leon Schurgers. We attended each other's staff meetings and actively collaborated on joint projects, but we still felt something was missing."

Heidi Noels: "PhD students had already been supervised by teams from both Aachen and Maastricht for a number of years, working towards a double doctorate. That in itself already brought the scientific research to a higher level, as they were able to use the expertise of both teams. But it was a virtual institute; what we lacked was joint labs in a physical institute, to strengthen the collaboration. That idea had already arisen in 2017, and the plan was developed further with the support of both universities."

Why was Aachen chosen as the location for the institute?

Noels: "The ideal location would of course be on the border between the two countries, but that's not a realistic option. There is already a joint Aachen-Maastricht institute which is located on the Dutch side of the border, called AMIBM, so it was fitting to build AMICARE on the Aachen campus. The labs are currently used by the team led by Dr Emiel Van der Vorst, who also holds a dual position at both universities."

Biessen: "One of the assets of AMICARE is that it offers junior researchers more opportunities to shape their careers, not only because they can benefit from the grant options in both the Netherlands and Germany, but also regarding content: although cardio-renal problems are clinically urgent, integrated studies in this field are scarce. Traditionally, cardiologists and nephrologists each approach the disease process mainly from the perspective of their own background and expertise. That's why we need to bring these two disciplines closer together, so as to better understand kidney diseases and cardiovascular disorders. That's also where there are opportunities for medical research, and I think AMICARE is one of the few institutes where the various disciplines from different countries are extensively working together on this problem."

To a lay person, it sounds almost unreal that these two disciplines until recently did not really collaborate.

Biessen: "That's right. Traditionally, cardiologists and nephrologists have often operated separately where research is concerned. Especially if compared to oncology, where cross-fertilisation between disciplines is already much more common. Worldwide, such cross-disciplinary collaboration has not yet really been achieved within the cardio-renal field."

Noels: "It's not until recent years that high interest has been paid to the relation between failures of these two organs. Accordingly, in the last few years, the number of publications regarding cardio-renal research has been rising, and we contribute to that."

Biessen: “The way the institute has been set up is also unusual: it ranges from very fundamental to applied patient-based research. So, it covers the entire trajectory. AMICARE will also harbour a clinical study centre, where patients can take part in clinical research, for instance to test the effectiveness of new drugs. Having this whole research pipeline under one roof is absolutely one of the strengths of AMICARE.”

What will be the next step?

Noels: “The current lab space covers about 140 square metres, and an additional 3,600 square metres are planned in a new building on the RWTH campus. That will be opened in late 2025, enabling us to physically collaborate even better. Part of the new extension will house the new clinical study centre. And of course, translating research findings to patient care will require collaboration with pharmaceutical and biotechnology companies. These discussions are ongoing.”

Biessen: “In a way I’m glad the institute is being set up in Aachen, partly as this offers much more opportunity for future expansion, as this would be much more difficult to realise in a short timespan, in the Netherlands. The campus structure at RWTH Aachen is shaped for and allows such a dynamic strategy.”

AMICARE expects to be able to accelerate research into the early recognition and treatment of cardio-renal disease, for example with medication. Industry probably plays an important role here?

Biessen: “What we see worldwide is increasing partnerships between the academic community and the industry, which is a win-win situation for both parties, and offers universities more opportunities, not only in terms of research funding, but also for joint steps towards translating research findings to clinical care. That’s something universities often have less experience with. What makes it interesting for industries is that they get involved in the basic research process, thus giving them first access to research findings. I strongly believe in such partnerships, which you also see at Cambridge, for instance. Of course, we have to safeguard our integrity as researchers, but I’m confident about that at AMICARE.”

Noels: “And in the meantime, the joint research programme is showing steady progress.”

What other projects should we think of?

Noels: “Kidneys are very important organs, as they remove waste products from the blood. If you have kidney failure, the waste products accumulate in the blood, which can negatively affect cellular processes in organs. We call these harmful substances uraemic toxins, and several AMICARE teams, including those led by Professors Hackeng, Schurgers, Jankowski, Marx and Van der Vorst, and of course Erik’s and my own, are investigating their link with vascular disorders like atherosclerosis, inflammation, arteriosclerosis etc.”

Biessen: “Within AMICARE, some intensive collaborative clinical projects are underway, which, among other things, investigate the effects of vitamin K supplements on the elasticity of blood vessels. It’s particularly the patients with kidney function problems whose vessels are less elastic, which in turn affects the functioning of the heart. This clinical study is coordinated by Professor Floege from Aachen and Professor Schurgers from Maastricht. And then there are more basic research projects, in which we study the accumulation of toxic substances in the blood of patients with advanced kidney failure. Dr Van der Vorst is focusing on the AHR protein, which

is activated by these toxic substances, and may as such play an important part in aggravating arteriosclerosis and arterial inflammation."

Where do you hope AMICARE will be in ten years' time?

Biessen: "I hope that by then it will be a viable institute which has offered new opportunities to young talents, so they can build good careers in the Netherlands, Germany or even further afield. But I also hope that the intensive collaboration in the workplace will have led to cross-fertilisation and eventually to new targets for interventions in people with reduced kidney function who are at high risk of developing cardiovascular diseases. If we have managed to achieve that, even if only partially, I'll be a happy man."

Noels: "The number of joint doctorates and research teams working within AMICARE, but also the collaboration with industries, is an important indicator of success. Plus of course the interaction with patients. We like to keep them informed of research developments, but we also regard their experiences as valuable for the researchers. This kind of interaction is also an important success factor for us."

Prof. Erik Biessen has been working at Maastricht University since 2007, leading the Experimental Vascular Pathology group and researching the role of inflammatory processes in the development of cardiovascular diseases. In addition, he has held a part-time position at the Institute for Molecular Cardiovascular Research at RWTH Aachen University since 2015. After having studied molecular sciences at Wageningen University and obtaining a doctorate at Groningen University in 1989, he worked at Leiden University for 20 years, where he was made Professor of Therapeutic Gene Modulation in 2015. Key words in his research work include systems medicine, bioinformatics, multispectral analysis and macrophage biology.

Dr Heidi Noels has been working at RWTH Aachen University since 2008, where she has led the Experimental Cardiovascular Pathobiochemistry group of the Institute for Molecular Cardiovascular Research since 2011. Since 2020, she has also been affiliated with CARIM's Department of Biochemistry. Her group focuses on the identification and characterisation of pathological inflammatory mechanisms underlying the development of cardiovascular disease, as well as the increased risk of cardiovascular disease in patients with chronic kidney disease. She studied at KU Leuven, where she received her doctorate in 2008. She was awarded her Habilitation at RWTH Aachen University in 2021, where she also received the venia legendi in Experimental Cardiovascular Medicine.

WHAT MAKES IT INTERESTING FOR INDUSTRIES IS THAT THEY GET INVOLVED IN THE BASIC RESEARCH PROCESS, THUS GIVING THEM FIRST ACCESS TO RESEARCH FINDINGS

HIGHLIGHT
DIVISION VESSELS

PHILIPPE VANGRIEKEN

Advanced Glycation Endproducts Unleashed: driving hypertension, opening therapeutic avenues, and probing biomarker possibilities

ADVANCED GLYCATION ENDPRODUCTS

Traditionally, the formation of advanced glycation endproducts (AGEs) is viewed as a post-translational modification of proteins by reduced sugars that accumulate slowly on extracellular and long-lived proteins throughout life. Formation of AGEs can be regarded as a naturally occurring process resulting from normal metabolism, but increased under hyperglycaemic conditions as well as under conditions of increased oxidative stress, hypoxia and hyperlipidaemia (1). AGEs are not inert and are known to contribute to the development of pathological conditions through various mechanisms. One such mechanism involves the abnormal cross-linking of extracellular matrix proteins, which leads to arterial stiffness. Our understanding of this process owes much to the excellent experimental work conducted in the late 1990s by Professor Harry Struijker-Boudier and other researchers at CARIM (2, 3).

In addition to AGE-induced cross-linking, the binding of AGEs to AGE receptors activates specific genes in various cell types and contributes to the development of pathological conditions. Recent attention has focused on the rapid formation of AGEs, facilitated by methylglyoxal (MGO), a highly reactive compound which plays a key role in the generation of glycation adducts on cellular and short-lived extracellular proteins, lipids, and DNA (1). MGO, primarily produced as a by-product of glycolysis, is believed to be the most potent glycation agent. Organisms possess a defence mechanism called glyoxalase, with glyoxalase 1 (GLO1) as a key enzyme converting MGO to D-lactate (**Figure 1**).

Our research group has made significant contributions to the current understanding of the impact of rapid AGE formation by MGO. Through comprehensive studies encompassing basic science, cohort studies (including The Maastricht Study), and randomized controlled trials, we have demonstrated the detrimental effects of MGO and MGO-derived AGE accumulation on the vascular system. Consequently, our ongoing research focuses on biomarkers, pathophysiological pathways, and prevention of vascular complications related to MGO and the glyoxalase system. To highlight the relevance of MGO in hypertensive disorders, and how they may serve as potential therapeutic targets and biomarkers, we here demonstrate its impact on preeclampsia, a condition

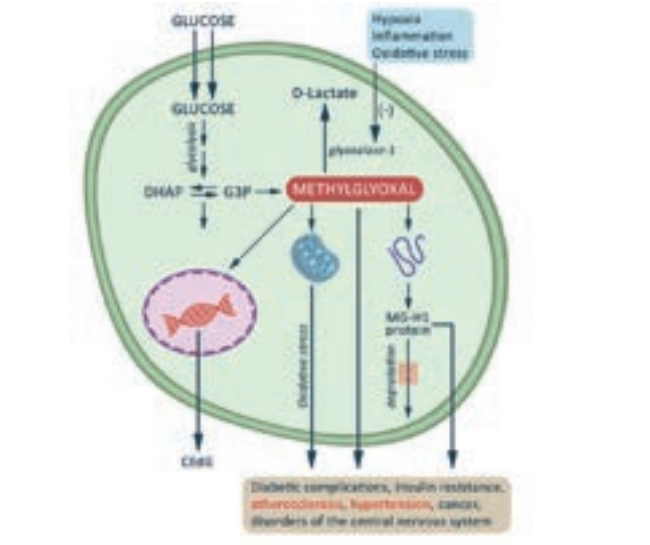


FIGURE 1 Basic biochemistry of methylglyoxal (MGO). MGO is derived from glycolysis by conversion of dihydroxyacetone phosphate (DHAP) and glycerol 3-phosphate (G3P) into methylglyoxal. MGO is detoxified by the glyoxalase pathway into D-lactate. MGO accumulation leads to the formation of MGO-protein-derived hydroimidazolone 1 (MG-H1) and MGO-DNA-derived N(2)-carboxyethyl-2'-deoxyguanosine (CEdG), as well as to mitochondrial dysfunction resulting in the induction of oxidative stress, ultimately contributing to the development of pathological conditions.

characterized by hypoxia, inflammation, oxidative stress, and vascular dysfunction.

PREECLAMPSIA

Preeclampsia is a pregnancy-related disorder that affects approximately 5-8% of all pregnancies and is characterized by hypertension and proteinuria after the 20th week of gestation. Preeclampsia can have serious consequences for both the mother and the foetus, including preterm delivery, low birth weight, and in severe cases, maternal organ failure and death. The exact cause of preeclampsia is not fully understood, but it is thought to be caused by abnormal placentation, resulting in decreased blood flow and oxygen delivery to the placenta, which in turn results in hypoxia, triggers a systemic inflammatory response, and causes endothelial dysfunction (4, 5).

PLACENTAL TROPHOBLAST CELLS

The trophoblast, a specialized cell type forming the outer layer of the placenta, plays a crucial role in placental development and a healthy pregnancy. It invades and remodels maternal spiral arteries, facilitating nutrient and oxygen exchange between mother and foetus. However, impaired trophoblast invasion in preeclampsia leads to incomplete artery remodelling and reduced placental blood flow. This results in placental hypoxia, oxidative stress, and the release of placental-derived factors into the maternal circulation, contributing to the maternal syndrome of preeclampsia (6, 7). These factors initiate a cascade of events, including vasoconstriction and endothelial dysfunction, which are key features of preeclampsia (5, 8).

PLACENTAL GLYCOLYSIS IN PREECLAMPSIA

Our previous research showed a metabolic shift in the placenta and trophoblast cells in preeclampsia, characterized by increased glycolysis in response to hypoxia. This adaptation is believed to compensate for oxygen deficiency in preeclampsia (4, 7). However, increased glycolytic activity can lead to the accumulation of metabolic by-products, including MGO, which is believed to contribute to maternal dysfunction and placental-induced complications such as

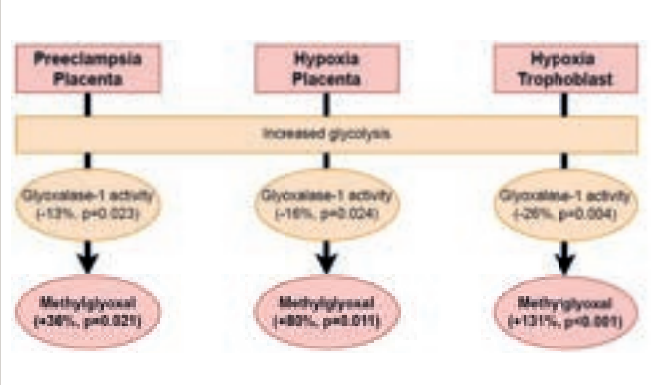


FIGURE 2 Results overview. Increased glycolysis, decreased glyoxalase-1 activity, and increased methylglyoxal levels in preeclampsia placentas and placentas and trophoblast cells after exposure to hypoxia.

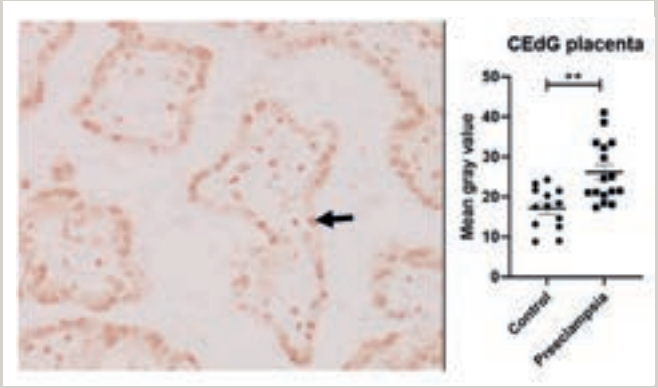


FIGURE 3 Immunostaining of CEdG in the placenta. Cross-sectional view of placental villous tree structure surrounded by trophoblast cells. Example nuclei positive for CEDG are indicated by a black arrow. CEdG: N(2)-carboxyethyl-2'-deoxyguanosine.

vascular oxidative stress (5). Using UPLC-MS/MS, we recently identified elevated MGO levels in preeclamptic placentas and trophoblast cells exposed to hypoxia (**Figure 2**). Furthermore, we observed reduced activity of the GLO1 enzyme – which is responsible for detoxifying MGO and preventing the formation of AGEs – in preeclamptic placentas and in placentas and trophoblasts cultured under hypoxic conditions (**Figure 2**).

In addition to its reactions with proteins and other biomolecules, MGO can form stable adducts when it reacts with nucleotides. One prominent example is the formation of N(2)-carboxyethyl-2'-deoxyguanosine (CEdG), a DNA adduct generated by MGO. Using immunohistochemistry analysis, we observed a pronounced accumulation of CEdG levels primarily in placental trophoblast cells affected by preeclampsia, indicating the main location of MGO (**Figure 3**).

ADVANCED GLYCATION ENDPRODUCTS IN PLASMA IN PREECLAMPSIA

In addition to the observed elevation of placental glycolysis and its reactive by-product MGO, we also found an accumulation of MGO-derived hydroimidazolone 1 (MG-H1), the most abundant form of AGEs in the maternal circulation. Remarkably, an increase in plasma MG-H1 levels was observed as early as the end of the first trimester (**Figure 4**). This accumulation of MG-H1 may contribute to the pathogenesis of preeclampsia, as MG-H1 has been implicated in the promotion of endothelial dysfunction (9). Upon formation, MG-H1 can initiate a range of cellular signalling pathways that result in oxidative stress, inflammation, and endothelial dysfunction. AGEs including MH-H1 can bind to the AGE receptor (RAGE) on the surface of endothelial cells and trigger the release of pro-inflammatory cytokines, or on smooth muscle cells, leading to intracellular signalling

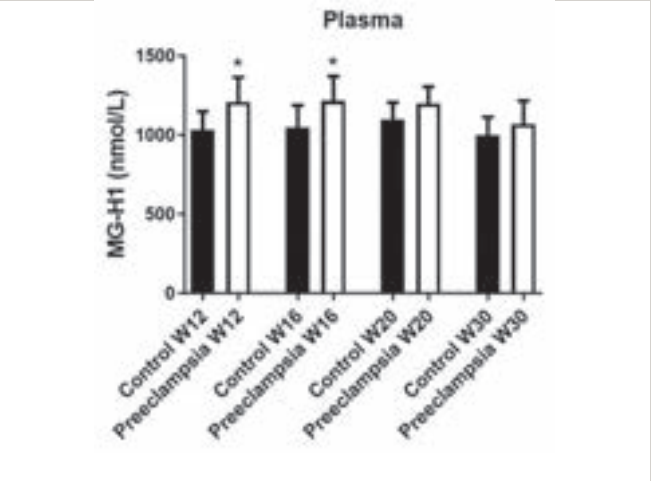


FIGURE 4 Plasma levels of MG-H1 in healthy women vs preeclampsia. Plasma samples were screened for MG-H1 levels at gestational ages of 12, 16, 20, and 30 weeks. MG-H1: MGO-derived hydroimidazolone 1.

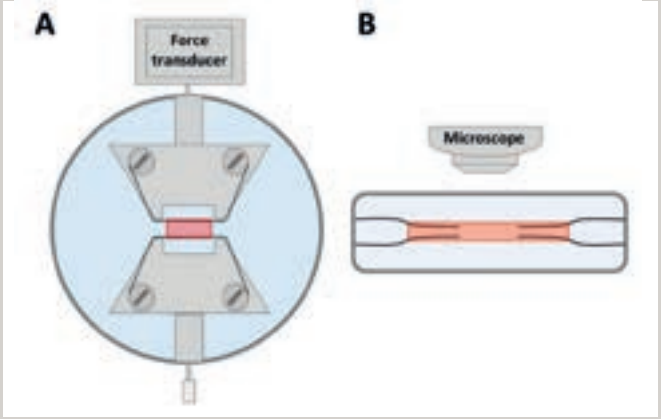


FIGURE 5 Schematic representation of the wire myograph (A) and pressure myograph (B) setting. For the wire myograph setting (A), two stainless steel wires are led through the lumen of the artery in a buffer solution and connected to a displacement device and an isometric force transducer. Contractile responses are expressed as the increase in wall tension (force increase / twice the segment length; N/m). For the pressure myograph setting (B), an isolated artery is mounted onto two glass cannulas in a buffer solution and connected to a pressure servo controller with a peristaltic pump to ensure a controlled internal pressure and flow. A video dimension analyser measures the lumen diameter (expressed as diameter change [μm]).

cascades that promote vasoconstriction. In addition, MGO and MG-H1 can induce the production of reactive oxygen species (ROS) by endothelial cells and decrease the bioavailability of nitric oxide, a key mediator of vascular function (1). Collectively, these effects culminate in impaired vasodilation and increased vascular permeability.

PLACENTAL-DERIVED FACTORS LEADING TO HYPERTENSION AND ENDOTHELIAL DYSFUNCTION

Using wire myography (**Figure 5A**), a technique involving the mounting of small placental blood vessel segments onto wires, our study revealed that factors released from the placenta under hypoxic conditions trigger increased vascular contraction, which is mediated via the angiotensin receptor type 1 (AT1) and endothelin receptor type 1 (ET-1). Additionally, we discovered that these placental factors also exert sustained effects, including increased sensitivity of blood vessels to contractile agents like thromboxane A2 and enhanced proliferation of arterial smooth muscle cells, ultimately resulting in increased arterial media thickness (5, 8). Notably, these effects could be prevented by quercetin, a quencher of MGO. Interestingly, AGEs have

also been implicated in elevating vasoactive compounds like endothelin-1 and angiotensin II, potentially contributing to hypertension in preeclampsia. Furthermore, using pressure myography (**Figure 5B**), which entails the cannulation of blood vessel segments onto a pressure myograph system, we demonstrated that hypoxia-induced placental factors lead to increased endothelial permeability, which also could be prevented by the MGO quencher quercetin (5, 8).

NEW PROGNOSTIC AND THERAPEUTIC PROSPECTS FOR PREECLAMPSIA

Our study revealed elevated levels of plasma MGO-AGEs in women with preeclampsia, as early as the end of the first trimester (**Figure 4**). These findings suggest that MGO-AGEs could serve as valuable early biomarkers for predicting preeclampsia development and monitoring disease progression. Additionally, our recent discoveries shed light on the potential involvement of MGO and MGO-derived AGEs in the placental-maternal cardiovascular axis in preeclampsia by contributing to an increased release of placental vasoactive compounds, leading to hypertension and structural changes in the vascular wall, targetable by MGO quenchers. Interestingly, not only quercetin but also compounds such as aminoguanidine and pyridoxamine have demonstrated efficacy in quenching MGO, reducing AGE formation, and alleviating oxidative stress (1). Trials are necessary to evaluate the effectiveness of these compounds in the prevention and treatment of hypertensive diseases, including preeclampsia.

Collectively, our findings provide a foundation for exploring a new promising field of early biomarkers as well as therapeutic targets for the management of preeclampsia.

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INTERVIEW

MARTIJN BROUWERS

Food for thought

Whereas in CARIM's 2015 annual report Martijn Brouwers openly wondered whether it was his responsibility as a researcher to communicate the results of his work to the general public, these days it's a regular thing for him. "My current research is very well suited to it, and I also consider it part of my job as a professor." He gave his inaugural address in 2022, and some of his major publications were picked up by the media. "We keep saying it over and over again: fructose from fruit juices and soft drinks is bad for you, we have to do something about this, and a tax on sugar is one solution."

As a physician and researcher, Martijn Brouwers is interested in the relation between fatty liver and systemic complications like type 2 diabetes, cardiovascular diseases and polycystic ovary syndrome (PCOS) in women. He also wants to find out the role of fructose in these conditions. He engages in epidemiological research – using the findings of The Maastricht Study to establish a link between fructose intake and the amount of fat in the liver – as well as interventional research – what happens if you remove all fructose from the diet? At the same time, he also includes genetic aspects. "Some people's genetic make-up means that their body is somewhat less able to process fructose. Last year, we published an article in the journal *Gut* saying that these people have a slightly lower risk of bowel cancer. That was picked up by the news site Nu.nl. We subsequently showed that these people also have a lower risk of fatty liver, diabetes, hypertension and cardiovascular diseases. That was published in *Diabetes Care*, and is more evidence that fructose is bad for you."

HALF OF THE STORY

In order to get a better grasp of the mechanism involved, his research group also uses experimental models. These show that if you block the processing of fructose in the early stage of the uptake process, this protects against fatty liver. "But if you block it one step further along the chain, it paradoxically leads to more fat accumulation. This means that the conventional view that fructose causes fatty liver simply by being converted into fat in the liver, is only half of the story. Because if you block the fructose metabolism somewhere along the way, it cannot be converted into fat, but you still get this intrahepatic fat accumulation. Apparently, fructose does something else in the liver. We think that it acts as a signalling molecule that causes the liver to start taking up glucose, which can also be converted into fat."

EVOLVING INTO A SIGNALLING MOLECULE

Fructose thus appears to be on the one hand a source of energy, which can be converted into fat in the liver, while on the other hand it also gives off a signal in the liver. "This fascinating question is also something I discussed in my inaugural address: why should fructose have to give off a signal?" To answer this question, Brouwers has to go back in time, to try and understand why the human body evolved in such a way that fructose became a signalling molecule. "Nowadays, we have completely shaped our surroundings to our own preferences, giving us access to as much fructose and other sweet stuff as we want, all through the day. But about 10,000 years ago, there was only one time a year when fructose was available: in late summer and autumn, when the trees were laden with fruit. And in that same period, food was abundant. So perhaps that's how it became a signal for abundance: there's a lot of food available, which we have to store in large quantities in our liver. There it's converted into fat that can be stored in our adipose tissue as a buffer for the winter." He is aware that this hypothesis is difficult to prove, but he thinks it is plausible. "If fructose acts as a signal of abundance, which stimulates the body to store, you can then imagine why it's not a good idea to continuously ingest fructose. Our present surroundings no longer match the make-up of our bodies. This evolutionary mismatch might contribute to the development of fatty liver, the first stage of nonalcoholic fatty liver disease, with all the systemic consequences I mentioned earlier."

FRUCTOSE FROM FRUIT

When he puts out the advice to replace sugar-containing soft drinks by 'light' products or water, he invariably gets online reactions from the public that fructose is also present in fruits, and so cannot be intrinsically bad. He would also like to understand why fructose from fruit appears to be less harmful

than fructose from things like soft drinks. Lab experiments have shown that when fructose comes in very gradually, the intestines process a large proportion of it, which therefore does not reach the liver. If the same quantity enters the gut in one go, more of it reaches the liver. “We think that that is what makes it unhealthy. Whereas you swallow a soft drink fairly rapidly, eating things like an apple takes longer. Maybe that’s why fructose from fruit has less harmful consequences.” In a partial test of this hypothesis, healthy individuals are currently given a specific amount of fructose at different times and in various forms: an entire apple, a pulped apple, apple juice and a solution of fructose in water. The researchers then measure the fructose levels in the blood. “We’re expecting higher peaks with the soft drink than with the apple.”

MULTIPLE TASKS

Brouwers well remembers how, on the occasion of receiving the Junior Specialist Dekker grant in 2015 at a Dutch Heart Foundation workshop on ‘societal quality’, he wondered whether it was his responsibility to communicate his research to the general public. Was this not rather the grant provider’s responsibility? “It took time for me to realise that this is also one of your tasks as an academic. And since I’ve been appointed a professor, I’ve become even more aware that you have a responsibility towards society. Times have also changed. Societal impact is now playing a more important role in science. But I still don’t think that every research project should make the papers at any cost. Your subject has to be suitable and you have to have a clear message. Our current research does lend itself very well to it. We keep repeating the same message: fructose from fruit juices and soft drinks is bad for you, we have to do something about it, and a tax on sugar is one of the possible solutions. You see that in countries where such a tax has already been introduced, like the United Kingdom, manufacturers are adapting their products, people are consuming less sugar and the state has extra revenues to spend on health-related initiatives. In an ideal world you could, for example, introduce a lower VAT rate on fruit and vegetables. But it’s not easy to steer people towards healthier behaviour in that way.”

IN THE FOOTSTEPS OF …

Since he has been appointed professor, he has noticed that he is more often asked to take up various auxiliary functions, and he has to say no sometimes, “as that’s better for me, my family or the quality of my work. Balancing all my roles is a never-ending struggle, though I’m not at all unique in that respect. It works better in some periods than in others. Being head of the clinical division of Endocrinology & Metabolic Diseases is a challenge, not only during the Covid period, but also for the future: how can we keep healthcare accessible for a population that’s ageing and has more health issues?” Apart from social and scientific responsibilities, being a professor also carries a responsibility for teaching. “It feels like a privilege that I am responsible for monitoring the quality of teaching in the field of hormonal diseases at Maastricht University. It’s especially when I look at those who did this before me, professors Arie Nieuwenhuijzen Kruseman and Nicolaas Schaper, that I find it very special to be allowed to follow in their footsteps.”

Prof. Martijn Brouwers received his doctorate at Maastricht University in 2007, based on his thesis entitled ‘Hepatic steatosis in familial combined hyperlipidemia’, after which he started training to become an internist. Having specialised in endocrinology and inborn errors of metabolism, he has been working as an internist-endocrinologist at Maastricht UMC+ since 2012. In 2022 (after a two-year delay due to the Covid pandemic) he presented his inaugural address on the occasion of accepting the Chair of ‘Internal Medicine, in particular Endocrinology and Metabolic diseases’.

EDUCATION AND TALENT DEVELOPMENT

04

INTRODUCTION

CARIM offers a flexible and integrated education and training programme that suits the individual ambitions of its students and PhD candidates. 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 master programmes offered at FHML, students are informed about CARIM and the programmes of the other FHML research institutes during the start of the master phase. Members of the CARIM staff actively participate in the design and execution of the teaching programme in Master courses. Students can attend institute specific lectures and parallel programmes organised by researchers. In the second year, students who are attracted to cardiovascular research can do their senior research internship and master thesis at CARIM. These internships are also accessible for students from other master programmes, provided that they have an adequate background. Successful master students subsequently can 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 beginning of 2022, in total 365 (internal as well as external) PhD candidates attended our PhD programme. In 2022, 58% of our PhD candidates came from abroad, creating an exciting multicultural and international atmosphere. To advance cardiovascular knowledge and the treatment of cardiovascular disease CARIM considers basic and clinical research equally important, and stimulates their interaction. 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 PhD training programme is to support PhD candidates in developing themselves into independent and mature 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 institute specific courses, to attend seminars and master classes, and provide support of a buddy (senior PhD candidates) and a coach (senior staff member). PhD candidates are stimulated to visit symposia to present their own research on national and international podia. In 2022, 35 new PhD candidates started their trajectory at CARIM.

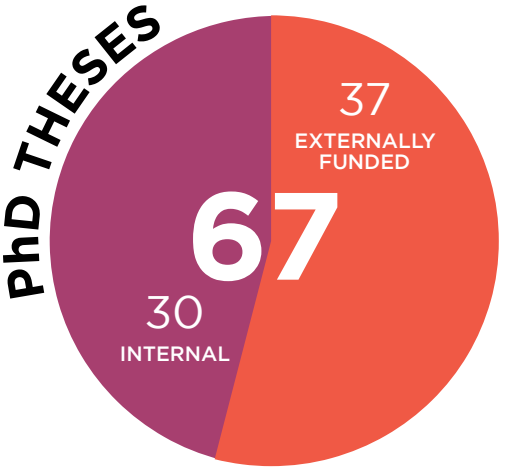
POSTGRADUATE PROGRAMMES

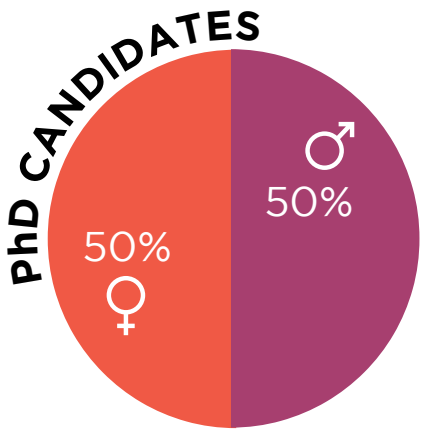
The expertise of the three CARIM divisions is transferred to colleagues from far and wide in three different clinical postgraduate programmes in collaboration with the Heart+Vascular Center: CAS-AM (Blood), EVC (Vessels) and DAS-CAM (Heart). CAS-AM (Certificate of Advanced Studies in Antithrombotic Management) is especially designed for physicians who are active in the management of patients with thromboembolic diseases and have the ambition to improve their knowledge and skills in order to become leading professionals in antithrombotic management. The EVC (European Vascular Course) aims to provide outstanding training and education for Arterial, Venous, Vascular Access and Cardiovascular specialists. DAS-CAM (Diploma of Advanced Studies in Cardiac Arrhythmia Management) trains the future leaders in cardiac electrophysiology by integrating state-of-the-art cardiac arrhythmia management with leadership skills, biostatistics and health technology assessment. All three professional development courses are supported by national and international societies. CAS-AM is endorsed by the International Society on Thrombosis and Hemostasis (ISTH) and the European Congress on Thrombosis and Haemostasis (ECTH); EVC is endorsed by the Aortic Association and Vascular International; and DAS-CAM is endorsed by European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC). For an interview with the organizers of the programmes, see pages 108-113.

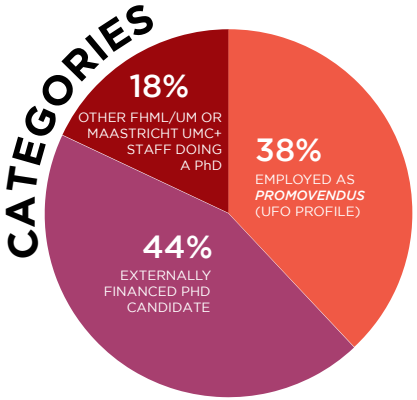
FIGURE CARIM divison structure with professional education

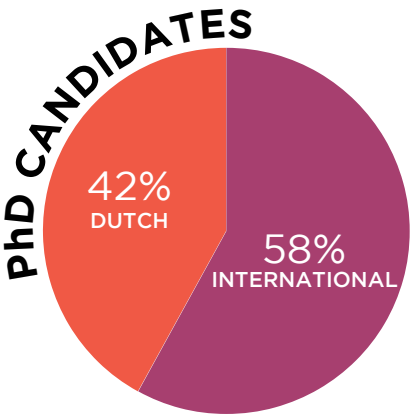
PHD STATISTICS

In 2022, 30 internally funded and 37 externally funded PhD candidates finished their theses within our institute. The male/female ratio within the group of PhD candidates appointed to CARIM at the start of 2022 is 50/50. Almost 60% of our PhD candidates come from abroad.









CARIM THESES 2022

Gennaro Martucci
Title: Challenges in Extracorporeal Membrane Oxygenation: Precision Management to Improve Survival
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Dr G.M. Raffa (ISMETT, Palermo, Italy)
17 January

Li Li
Title: Platelets in thrombosis and haemostasis: synergy with thrombin generation
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr D. Huskens, Dr M. Roest
24 January

Frank van der Heide
Title: Neurodegeneration and microvascular dysfunction - causes and consequences
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr R.M.A. Henry, Dr J.S.A.G. Schouten
26 January

Maria Abbattista
Title: Venous thromboembolism in women - A focus on unusual sites, pregnancy and thrombophilia
Supervisors: Prof. H. ten Cate, Prof. P.M. Mannucci (University of Milan)
Co-supervisor: Dr I. Martinelli (Fondazione IRCCS Ca' Grande, Milan)
11 February

Harilaos Bogassian
Title: New Insights into the Evaluation of Broad QRS Complexes: Relevance for Arrhythmia Management
Supervisors: Prof. H.J.G.M. Crijns, Prof. M. Zarse (Luedenscheid, Germany)
Co-supervisors: Dr J. Heijman, Dr D. Linz
15 February

Stan van der Beelen
Title: Catch FXIa
Supervisor: Prof. T.M. Hackeng
Co-supervisors: Dr S.M. Agten, Dr B.M.E. Mees
17 February

Ricardo Cerqueira de Abreu
Title: Extracellular Vesicles as Platforms for Therapeutic microRNA delivery
Supervisors: Prof. P. da Costa Martins, Prof. L. da Silva Ferreira (University of Coimbra)
Co-supervisor: Dr H. Fernandes (University of Coimbra)
21 February

Francesca Torresan
Title: Excess aldosterone as a mechanism of resistant salt sensitive arterial hypertension
Supervisors: Prof. A. Kroon, Prof. GP Rossi (University of Padova, Italy), Prof. M. Iacobone
21 February

Mieke Karel
Title: Platelets at the intersection of thrombosis and inflammation: establishing innovative methodologies
Supervisor: Dr J.M.E.M. Cosemans
Co-supervisors: Dr M.E. Kuijpers, Dr R.R. Koenen
22 February

Grzegorz Wasilewski
Title: The calcium paradox the role of vitamin K in the bone-vascular axis
Supervisors: Prof. L.J. Schurgers, Prof. C. Reutelingsperger
22 February

Annemiek Dickhout
Title: Painting proteins to study cardiovascular pathology
Supervisor: Prof. T.M. Hackeng
Co-supervisors: Dr R.R. Koenen, Dr I. Dijkgraaf
24 February

Francesco Londero
Title: Lung oligometastatic disease: redefining cancer pathogenesis from a surgical perspective
Supervisors: Prof. S. Gelsomino, Prof. J.G. Maessen
Co-supervisor: Dr A. Morelli (AOUD Santa Maria della Misericordia, Italy)
8 March

CARIM THESES 2022

Justine Ravaux
Title: Pacemaker Dependency after Permanent Pacemaker Implantation Following Cardiac Surgery and Transcatheter Aortic Valve Implantation
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Dr S. Kats
10 March

Vincent Nijenhuis CUM LAUDE
Title: Transcatheter Aortic-Valve Implantation: Antithrombotic Therapy and Individualized Treatment Strategies
Supervisors: Prof. J.M. ten Berg, Prof. A.W.J. van t Hof
11 March

Bibi Martens
Title: Computed tomography of the abdomen: From one size fits all to custom-made
Supervisor: Prof. J.E. Wildberger
Co-supervisors: Dr C. Mihl, Dr E.C. Nijssen
17 March

Valeria Bisogni
Title: Studies on Blood Pressure Variability and Pathogenic Mechanisms of Cardiovascular Risk in Secondary Hypertension
Supervisors: Prof. A.A. Kroon, Prof. G.P. Rossi (University of Padova, Italy)
Co-supervisor: Prof. C. Letizia (University of Rome, Italy)
21 March

Shruti Bhargava
Title: Identification and characterization of the mediators of the calcification paradox
Supervisors: Prof. L. Schurgers, Prof. J. Jankowski (RWTH Aachen University)
21 March

Lars Bolt
Title: Implications in the treatment of peripheral arterial disease - Focussing on endovascular and non-invasive strategies
Supervisor: Prof. G.W.H. Schurink
Co-supervisor: Dr L.H. Bouwman (Zuyderland Medisch Centrum)
31 March

Nick van Osta
Title: Making it Personal - Model-based Cardiac Tissue Characterization in Arrhythmogenic Cardiomyopathy
Supervisors: Prof. J. Lumens, Prof. T. Delhaas
31 March

Erik de Loos
Title: PECTUS EXCAVATUM improvements in surgical care
Supervisor: Prof. J.G. Maessen
Co-supervisors: Dr Y. Vissers (Zuyderland Medisch Centrum), Dr K. Hulsewé (Zuyderland Medisch Centrum)
7 April

Lina Wübbeke
Title: Challenges in the treatment of chronic limb threatening Ischaemia
Supervisor: Prof. G. Schurink
Co-supervisors: Dr B. Mees, Dr J. Daemen
8 April

Kim Maasen
Title: Dietary dicarbonyls: friends or foes of human health?
Supervisors: Prof. C. Schalkwijk, Prof. C. Stehouwer
Co-supervisor: Dr M. van Greevenbroek
13 April

Cristina Altrocchi
Title: Cellular models of cardiac channelopathies
Supervisor: Prof. P. Volders
Co-supervisor: Dr C. Moreno Vadillo (National Institute of Neurological disorders and Stroke, USA)
14 April

CARIM THESES 2022

Juliane Hermann
Title: MALDI mass spectrometric imaging methods for localization and identification of pathophysiological relevant regulators in tissue samples
Supervisors: Prof. L. Schurgers, Prof. J. Jankowski (RWTH Aachen University), Prof. V. Jankowski (RWTH Aachen University)
25 April

Jens Posma
Title: Coagulation Factor Xa as Driver of Cardiovascular Diseases
Supervisor: Prof. H. ten Cate
Co-supervisor: Dr H. Spronk
9 May

Qiuting Yan
Title: The dynamics of thrombin generation
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr B. de Laat, Dr R. de Laat-Kremers (Synapse Research Institute Maastricht)
10 May

Rob Holtackers CUM LAUDE
Title: Visualising the invisible: Dark-blood late gadolinium enhancement MRI for improved detection of subendocardial scar
Supervisors: Prof. J.E. Wildberger, Prof. M.E. Kooi
Co-supervisors: Prof. A. Chiribiri (Kings College, London), Prof. C van de Heyning (University Hospital Antwerp)
13 May

Sjoerd Timmermans
Title: The syndromes of thrombotic microangiopathy: towards a true etiology-based approach
Supervisors: Dr P. van Paassen, Prof. C. Reutelingsperger
Co-supervisor: Dr J. Damoiseaux
13 May

Shailesh Samal
Title: Immune Mechanisms and Potential Immunological Treatment in Atherosclerosis
Supervisors: Prof. Chris Reutelingsperger, Prof. Leon Schurgers, Prof. Johan Frostegard (Karolinska Institutet Stockholm)
16 May

Sofia Beghi
Title: Genetic variants in calcium calmodulin pathway in association with cardiovascular disease: Focus on the potential role of CaMKK1 in heart and vessels
Supervisors: Prof. L. Schurgers, Prof. A. Buschini (Parma University, Italy)
Co-supervisors: Dr E. Bidar, Dr E. Natour
23 May

Marieke Gimbel
Title: Antiplatelet therapy in elderly patients with an acute coronary syndrome
Supervisors: Prof. J. ten Berg, Prof. A. van 't Hof
23 May

Nikolaos Taxiarchis Skenteris
Title: Interplay between inflammation and calcification in cardiovascular diseases
Supervisors: Prof. E. Biesen, Prof. C. Reutelingsperger
Co-supervisors: Dr Hildur Arnardottir (Karolinska Institutet Stockholm), Dr Ljubica Perisic Matic (Karolinska Institutet Stockholm)
31 May

Judith de Ruijter-van Dalem
Title: Tailored therapy in type 2 diabetes unintended effects of glucose lowering agents
Supervisors: Prof. M.C.G.J. Brouwers, Emeritus Prof. F. de Vries
Co-supervisors: Dr A.M. Burden (ETH Zurich), Dr J. H.M. Driessen
2 June

Luise Klein
Title: Protection of the preterm brain against inflammatory stress A promising role for stem cell-based therapy and Annexin A1
Supervisors: Prof. D. van den Hove, Prof. L. Schurgers, Prof. C.P.M. Reutelingsperger
Co-supervisor: Dr T.G.A.M. Wolfs
2 June

CARIM THESES 2022

Jaap Selig
Title: Quality of contemporary anticoagulation management in atrial fibrillation
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr M.E.W. Hemels (Rijnstate ziekenhuis Arnhem), Dr R. Pisters (Rijnstate ziekenhuis Arhnem)
8 June

Pauline van Paridon
Title: Markers of Hypercoagulation in Cardiovascular Disease in the General Population
Supervisors: Prof. H. ten Cate, Prof. P. Wild (Johannes Gutenberg Universität Mainz)
Co-supervisors: Dr H.M. H. Spronk, Dr M. Panova- Noeva (Johannes Gutenberg Universität Mainz)
9 June

Pomme Simons
Title: Unravelling the triangular relationship between polycystic ovary syndrome, cardiometabolic disease and de novo lipogenesis
Supervisors: Prof. M.C.G.J. Brouwers, Prof. C.D.A. Stehouwer
Co-supervisor: Dr O. Valkenburg
15 June

Joost Brouwers
Title: Platelet-rich fibrin interactions in oral implantology
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr J. A. Remijn (Meander Medical Center Amersfoort), Dr B. de Laat (Synapse Research Institute Maastricht)
23 June

Dennis Krist
Title: Novel laser energy applications for the treatment of cardiac arrhythmias
Supervisor: Prof. U. Schotten
Co-supervisors: Dr D. Linz, Dr S. Zeemering
5 July

Raquel Figuinha Videira
Title: Transcription Factors, microRNAs and Extracellular Vesicles at the crossroad of right and left heart failure
Supervisors: Prof. P. da Costa Martins, Prof. I. Falcao-Pires (Porto University, Portugal)
11 July

Stephanie Mezger
Title: Molecular signatures of myocardial infarction: a multidisciplinary analytical approach
Supervisors: Prof. R.M.A. Heeren, Prof. O. Bekers
Co-supervisors: Dr B. Cillero-Pastor, Dr A. Mingels
12 July

Anne Pirson
Title: Endovascular treatment for acute ischemic stroke patients. Exploring predisposing factors and expanding indications
Supervisor: Prof. W. van Zwam
Co-supervisors: Dr J. Staals, Dr W. Schonewille (Sint Antonius ziekenhuis)
14 July

Marina Heuschkel
Title: Multi-omics discovery of novel molecular pathways in cardiovascular calcification
Supervisor: Prof. L. Schurgers
Co-supervisor: Dr C. Goettsch (UK Aachen University)
7 September

Rianneke de Ritter
Title: Sex differences in causes and consequences of type 2 diabetes
Supervisor: Prof. C.D.A. Stehouwer
Co-supervisors: Dr C. van der Kallen, Dr S.J.S Sep (UMC Utrecht), Dr S. Peters (The George Institute for Global Health, London)
8 September

Anouk Gulpen
Title: Direct oral anticoagulant care Focus on management and monitoring
Supervisors: Prof. H. ten Cate,
Co-supervisor: Dr A.J. ten Cate-Hoek, Prof. Y.M.C. Henskens
9 September

CARIM THESES 2022

Florit Marcuse
Title: Clinical care optimization for patients with a thymic tumor: With special interest in myasthenia gravis and thymic epithelial tumors
Supervisors: Prof. J.G. Maessen, Prof. M.H.V. De Baets
Co-supervisor: Dr M.M. H.Hochstenbag
16 September

Spencer Keene
Title: Beyond airflow obstruction: multicomponent COPD prognostication in personalised care
Supervisors: Prof. F. Franssen, Prof. P. Abab (University of Birmingham)
Co-supervisors: Dr J. Driessen, Dr R.E. Jordan (University of Birmingham)
20 September

Hongxing Luo
Title: Heart sounds: From animal to patient and Mhealth
Supervisors: Prof. F.W. Prinzen, Prof. T. Delhaas
Co-supervisor: Dr R.C. Cornelussen
22 September

Nikki Pluymaekers CUM LAUDE
Title: Cardioversion of atrial fibrillation revisited
Supervisor: Prof H.J.G.M. Crijns
Co-supervisors: Dr J. Luermans, Dr D. Linz
23 September

Justas Simonavičius
Title: The relationship between the use of loop diuretics, congestion and heart failure outcome: in search of novel tools of congestion detection and grading
Supervisor: Prof. H.P. Brunner-La Rocca
Co-supervisors: Dr C. Knackstedt, Dr S. van Wijk
30 September

Gina Perrela
Title: Platelet Glycoprotein VI in the Regulation of Thrombus Growth
Supervisors: Prof. J. Heemskerk, Prof. S. Watson (University of Birminghan)
Co-supervisors: Dr M. Thomas (University of Birmingham), Dr M. Nagy
4 October

Armand Linkens
Title: The impact of dietary advanced glycation endproducts - Relevance to glucose metabolism, vascular function, and gut microbiota
Supervisors: Prof. C. Schalkwijk, Prof. C. Stehouwer
Co-supervisors: Dr A. Houben, Dr S. Eussen
5 October

Andreia Pinheiro Vilaca
Title: Targeting the heart: Extracellular vesicles and beyond
Supervisors: Prof. L. de Windt, Prof. L. da Silva Ferreira (University of Coimbra)
Co-supervisor: Dr H. Agostinho Machado Fernandes (University of Coimbra)
18 October

Elisa D'Alessandro
Title: Atrial fibrillation and hypercoagulability: A two-way street with many side-roads
Supervisors: Prof. H. ten Cate, Prof. U. Schotten
Co-supervisor: Dr F. van Nieuwenhoven
20 October

Billy Scaf
Title: Atrial fibrillation and hypercoagulability: A two-way street with many side-roads
Supervisor: Prof. U. Schotten
Co-supervisors: Dr H. Spronk, Dr S. Verheule
20 October

CARIM THESES 2022

Michiel Henkens
Title: Improving diagnosis and risk stratification of cardiomyopathies across the ejection fraction spectrum: The past, present and future
Supervisor: Prof. S. Heymans
Co-supervisors: Dr J.A.J. Verdonschot, Dr M.P. Hazebroek, Dr V.P.M. van Empel
24 October

Laura Willemsen
Title: Thrombosis and Hemostasis in Coronary Artery Bypass Grafting Surgery
Supervisor: Prof. J.M. ten Berg
Co-supervisor: Dr C.M. Hackeng
10 November

Anne Tavenier
Title: Towards optimal platelet inhibition and pain relief in ST-elevation myocardial infarction
Supervisors: Prof. A.W.J. van 't Hof, Prof. J.M. ten Berg
Co-supervisors: Dr R.S. Hermanides (Isala Zwolle), Dr J.P. Ottervanger (Isala Zwolle)
17 November

Chang Lu
Title: Computational strategies in cardiometabolic diseases: a portal to deeper mechanistic understanding
Supervisor: Prof. E.A.L. Biessen
Co-supervisors: Dr J.M.H. Karel, Dr P. Goossens
24 November

Dawid Kaczor
Title: Inflammatory actions of chemokines and extracellular vesicles in pathological tissue remodeling
Supervisors: Prof. T.M. Hackeng, Prof. R. Kramann
Co-supervisor: Dr R.R. Koenen
28 November

Jorn Brouwer
Title: Reducing the risk of transcatheter aortic valve implantation
Supervisors: Prof. J.M. ten Berg, Prof. A.W.J. van 't Hof
Co-supervisor: Dr M.J. Swaans (St. Antonius Ziekenhuis Nieuwegein)
1 December

Cengiz Akbulut
Title: Spatiotemporal developmental regulation of arteriosclerosis
Supervisors: Prof. L. Schurgers, Prof. R. Kramann (RWTH Aachen University), Prof. S. Sinha (University of Cambridge)
2 December

Anne Raafs
Title: Atrioventricular imaging to predict outcome in dilated cardiomyopathy: Towards a multimodality approach
Supervisor: Prof. S.R.B. Heymans
Co-supervisors: Dr C. Knackstedt, Dr M.R. Hazebroek, Dr J.A.J. Verdonschot
6 December

Myrthe van der Bruggen
Title: Multi-model assessment of arterial stiffness: focus on methylglyoxal
Supervisors: Prof. T. Delhaas, Prof. C.G. Schalkwijk
Co-supervisors: Dr K.D. Reesink, Dr B. Spronck
8 December

Vincenza Gianfredi
Title: An epidemiological approach to depression: social networks, physical activity and diet
Supervisors: Prof. N.C. Schaper, Prof. A. Odone (University of Pavia)
Co-supervisors: Dr A. Koster, Dr M.T. Schram
19 December

CARIM THESES 2022

Jingnan Huang
Title: Platelet proteomic progress and retraining mechanisms in glycoprotein VI-mediated thrombus formation
Supervisors: Prof. J.W.M. Heemskerk, Prof. H. ten Cate, Prof. A. Sickmann (Leibniz-Institut für Analytische Wissenschaften-ISAS)
Co-supervisor: Dr A. García (Universidade Santiago de Compostela)
20 December

Paolo Meani
Title: Left Ventricular Unloading in Extracorporeal Life Support
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen, Prof. M. Ranucci (University of Milan)
22 December

DISSERTATION PRIZE 2021

The CARIM Dissertation Prize 2021 has been awarded to **Job Verdonschot** for the thesis 'Causes and Consequences of Dilated Cardiomyopathy: Integrating Genotype and Phenotype to Redefine Disease Diagnostics and Therapeutics'. Job provided a very comprehensive PhD thesis at the link between geno- and phenotyping in patients with dilated cardiomyopathy. The thesis was awarded the judicium *cum laude*. In the same year, the Dutch Clinical Genetics Society recognized the excellence of his research with the Ben ter Haar Award and the Dutch Society for Cardiology granted him the Einthoven Dissertation Prize (2022). Both are very prestigious awards in their respective fields.

KNOWLEDGE TRANSFER

CARIM COURSES

From 13-17 June, the annual CARIM Course Week took place. The week consisted of parallel courses, covering several aspects of CARIM's research and a social programme organised by I'mCARIM, the organisation of CARIM's PhD candidates. In 2022, two courses were organised by CARIM researchers: 'Vascular inflammation and thrombosis' and 'Drug discovery and development'. Almost 40 PhD candidates participated. Furthermore, the course 'Advanced Microscopy and Vital Imaging', which is accessible to CARIM PhD candidates, was organised.

The aim of the course 'Vascular inflammation and thrombosis' was to increase the PhD candidates' horizon on basic and clinical concepts in vascular biology and thrombosis and will introduce them to (*in vitro* and *in vivo*) technologies frequently used in this field. At the end, they were acquainted with available facilities and technologies in our atherothrombosis cluster (e.g. flow cytometry, animal models, lesion analysis, transcriptomics, microscopy etc.), but also have mastered to implement these technologies to the benefit of their own research.

The 'Drug discovery and development' course has provided insights into the drug development process from the identification and validation of a therapeutic target to the final approval of the drug candidate. The goal of this course was to improve the PhD candidates' understanding of drug discovery and to give them the keys to build their expertise.

CARDIOVASCULAR GRAND ROUNDS AND CARIM SYMPOSIUM 2022

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.

In 2022, the Cardiovascular Grand Rounds Maastricht lecture series, hosting national and international experts, was successfully continued on a bi-weekly basis. These lectures traditionally take place on Friday during the clinical staff's morning meeting from 8 am until 9 am and are of a very high scientific level. Since the Covid pandemic, these lectures take place in a hybrid format, with options to attend in-person in the Cardiology morning meeting room or online via Zoom. Through both options, the lectures have been well attended and have addressed a wide range of topics relevant to all CARIM divisions. The Cardiovascular Grand Rounds are made possible by several grants, including one from '*Stichting ter bevordering van Cardiovasculair Onderzoek en Onderwijs*'. They are currently organised by a working group representing all CARIM divisions, with Prof. Blanche Schroen and Dr Jordi Heijman acting as the primary scientific contacts. For the current programme and the composition of the organising committee, please visit the CARIM website and/or follow us on the UM's CARIM intranet page. To facilitate involvement of our young researchers, I'm CARIM recently started to actively promote the lectures in their network and helps steering workshops with the speakers.

The CARIM annual scientific symposium was held on Wednesday 16 November. During the morning programme, our NWO and Dutch Heart Foundation laureates presented their research. In the afternoon, a session on regenerative medicine with internal and external speakers was organised. As in previous years, a substantial part of the programme was the poster session, in which scientists of the institute presented their recent research findings.

The Robert Reneman Lecture that is given 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. In 2022, the Robert Reneman lecture was presented by Prof. Peter Stenvinkel, professor and senior lecturer at Department of Renal Medicine of Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden. He has published more than 620 original publications and reviews and over 30 book chapters on various aspects of inflammation, wasting and metabolism in chronic kidney disease patients. In addition, Peter Stenvinkel is the world expert on biomimetics, providing lessons from nature for contemporary ways to improve human health.

Finally, the CARIM prizes were awarded and the CARIM priori were drawn by lot. As of January 2022, Simon Schalla and Jolanda Gulpen are part of the CARIM Executive Board for one year. The following posters were awarded with a prize:

- Division Blood: Renée Tillie: Partial myeloid inhibition of key glycolytic enzyme PFKFB3 increases hepatic steatosis and inflammation, but does not affect atherosclerosis;
- Division Vessels: Pim Bouwmans: Impact of immunosuppressive therapy and type of SARS-CoV-2 vaccine on antibody response in patients with chronic kidney disease or on kidney replacement therapy;
- Division Heart: Tim van Loon: Digital twin of the failing heart: a platform for *in silico* research and diagnostic support.


CARIM
16
NOVEMBER
CARIM
SYMPOSIUM
2022

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2022

Complementary to the Cardiovascular Grand Rounds Maastricht and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2022. 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 2022, eight keynote lectures were given by Leon Schurgers (Maastricht UMC+, 20 January), Joshua Hutcheson (Florida International University, 17 February), Leon de Windt (Maastricht UMC+, 17 March), Susanne Sattler (Imperial College London, 28 April), Andreas Herrlich (Washington University School of Medicine, 12 May), Philip Wenzel (Johannes Gutenberg University Mainz, 23 June), Katja Simon (Max Delbrück Center Berlin, 29 September) and Alexander Bartelt (Ludwig-Maximilians-University Munich, 1 December).

As CARIM acquired a 10x chromium platform for single cell/nuclear sequencing, which is open to use by all FHML scientists, two workshops organised by Prof. **Judith Sluimer** (Dept of Pathology) on **single cell sequencing** were organised in 2022. During the first workshop on 31 March, participants learned about practical steps in cell isolation, loading and sequencing analysis and explored the possibilities the sequencing data analysis could bring them. The other workshop 'Bioinformatics analysis of single cell sequencing data' on 25 October trained participants for the next step. Participants learned how to process their sequence file in the programme 'Cell ranger', cluster similar cells together with 'Seurat', and identify differentially expressed genes.

On Friday 11 March, the inaugural lecture '*Bloedarmoede is Bloedrijkdom*' of Prof. **Erik Beckers** took place.

From 23 until 25 March, the **4th Maastricht Consensus Conference on Thrombosis (MCCT)** was organised jointly with the TICARDIO project (Horizon 2020 ITN) in which CARIM is involved as well. The theme of the conference was 'Blood coagulation and beyond' and expresses the importance of blood coagulation elements as regulators of haemostasis, but also in a range of diseases: from myocardial infarction and stroke, to cancer, sepsis and other major morbidities. One essential feature of the blood coagulation system is that it is not confined by boundaries: clotting regulates beyond the vessel wall, at the cellular level. In the 4th MCCT meeting faculty, students and other participants were assembled to together sketch outlines for future research. TICARDIO PhD candidates were actively involved in discussion panels.

On 22 September, Prof. **Frits Prinzen** (Dept of Physiology) held his valedictory lecture '*Minder is meer*'. Preceding the lecture, a symposium was organised in which topics related to his research were addressed.

On 24 September, the 14th edition of the event ***'Loop met je Dokter'*** was organised by the Health Foundation Limburg, in collaboration with doctors from Maastricht UMC+, Zuyderland and regional general practitioners. The walking event allows patients to engage in a different, informal way where doctors show the importance of a healthy lifestyle by setting a good example themselves. Several CARIM

members acted as team captains. In total, €51,118 was raised for groundbreaking research into cardiovascular diseases.

On 6 October, a hands-on **Social Media workshop** was organised in collaboration with the FHML/Maastricht UMC+ Marking & Communication team. In this workshop, the importance of social media but also the pitfalls were discussed, the different channels and purposes were explained and attention was paid to the participant's own social media. Dr Dominik Linz (Dept of Physiology) shared his experience with Twitter.

From 11 until 13 October, the Flow Cytometry Course was organised by Dr **Kristiaan Wouters** (Dept of Internal Medicine) and Dr Lotte Wieten (GROW). The first day (afternoon) beheld a theoretical course with a general introduction to flow cytometry, the latest technological advances in spectral flow cytometry and information on the flow cytometry tools and possibilities at Maastricht. The second and third day involved hands-on practical sessions to learn to use the flow cytometers and to get acquainted with data acquisition, analysis, and troubleshooting.

On 13 October, CARIM together with the HVC organised a programme round **World Thrombosis Day** to draw special attention to thrombosis. This year, special attention was paid to risk factors of thrombosis. In the afternoon there was a well-attended information market, where information could be found about thrombosis, a healthy lifestyle (nutrition, exercise and stopping smoking) and (putting on) compression stockings. In the afternoon, four speakers provided insights into various factors related to thrombosis:

- Prof. Hugo ten Cate: Risk factors for thrombosis
- Dr Arian van der Veer: The contraceptive pill and thrombosis
- Ruth Willems: Cancer and thrombosis
- Melanie Acampo-de Jong: Thrombosis medication

In addition, Aaron Iding interviewed patient Lianne Kaanen, who suffered a thrombosis and pulmonary embolism at the age of 16.

On 18 October, a large CARIM community convened in Lumière Cinema for CARIM's first 'diversity and inclusivity' event: '**Picture a scientist**'. The identically-named documentary, that can also be watched on Netflix, is about issues that women encounter while being a scientist. The documentary contains quite challinging stories, but is also about how more subtle forms of harassment can have major impact. Or as a scientist in the movie said: a ton of feathers still weighs a ton. The response of all present was almost subdued. The subsequent discussion was led by UM's diversity officer Dr Constance Sommerey and by FEM (Female Empowerment Maastricht) chair Dr Aurélie Carlier, and was helped by a Wooclap interactive question and answer presentation on the large screen. People responded anonymously with comments like: "I am shocked about how unaware I am of the issue", and shared personal stories like "I was told postdocs cannot have children". One of the attendees framed the event as bringing the topic of (gender) discrimination 'out of the shadows', and this was a feeling shared by many. During the drinks afterwards, conversations on the topic continued. The event was organised by CARIM's diversity and inclusivity working group consisting of Judith Cosemans, Tara de Koster, and Blanche Schroen (2022).

CARIM'S DEVELOPMENT 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 programme 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 to 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. Talented future PhD candidates in Health, Medicine or Life Sciences, 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 covers the candidate's full salary for 6 to 12 months including bench fee. For Ba/Ma students the regular curriculum should be interrupted to perform the research project within CARIM.

2017 William van Doorn

2018 Jasper Demandt

2019 Mohamed Kassem

2020 Anne-Marije Hulshof, Yentl Brandt

2021 Daniek Meijs

2022 Peter Deissler

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 up to 6 months supplemental living allowance per month and travel costs.

2018 Mueez Aizaz, Jens Posma

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

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

2021 Kim Maasen, Job Stoks, Jordi Kocken, Renée Tillie, Rachel van der Velden

2022 Jerremy Weerts, Shaiv Parikh, Mitch Ramaekers, Deepak Balamurali, Vanessa Bröker, Bob Knapen, Maurits Sikking

3. HS-BAFTA TALENTED POSTDOCS

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 fellowship covers the candidate's full salary for 12 months including bench fee. 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

2021 Jens Posma

2022 Mohamed Kassem

HS-BAFTA winners 2022

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
2021	B. Casadei	Oxford, UK
2022	P. Stenvinkel	Stockholm, Sweden

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
2022	P. Stenvinkel	Karolinska Institute Stockholm, Sweden

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 focused on research in the area of molecular and chemical aspects of cardiovascular diseases. CARIM was able to appoint internationally recognised top scientists to this chair.

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

I'MCARIM 2022

I'MCARIM 2022

I'mCARIM is a committee formed by a group of enthusiastic PhD candidates, who represent all PhD candidates at CARIM. We organise social and networking activities, provide input to improve the PhD programme and advise the CARIM Executive Board and Faculty Board on relevant issues.

Like the rest of the Netherlands, CARIM came back to life after the Covid restrictions were lifted in 2022. This meant that for the first time in several years, PhD candidates were able to meet and socialise in person. On the other hand, some challenges remain within the new remote working culture, and the social ties between students of different departments have been a bit less intensive since the pandemic.

To celebrate the lifting of restrictions, some I'mCARIM social activities were revived. In 2022 we went bowling together with all PhD candidates participating in the CARIM course week, got together to discuss science during the Young Investigator Rounds, and organised a workshop on how to print a beautiful looking thesis. All these events combined shared learning opportunities with some time to casually socialise and network, in order to contribute to the social interaction within our research institute. However, hybrid working also has positive aspects, as we showed with our online Career Event. Hosting this event online, in collaboration with NUTRIM (Institute of Nutrition and Translational Research in Metabolism), meant that we could invite speakers from all over the world and increased the accessibility of the event for many PhD candidates.

In 2021, I'mCARIM and CARIM together made considerable efforts to make new PhD candidates feel more welcome in our institute. To this end, the buddy system was introduced, in which new PhD candidates were matched with senior PhDs from different departments. This buddy programme was fully operational this year. In addition, a PhD guide booklet and video about the programme within CARIM were launched this year, with great success! In honour of these steps, I'mCARIM was awarded the CARIM Commitment Award on the 2022 CARIM symposium. We are very honoured and happy to have received this acknowledgement!

We are also very happy to have the opportunity to contribute to all the important projects described above, which promote the professional development of fellow PhD candidates and offer them support. Moreover, we think it is important to stimulate social interactions among CARIM PhD candidates in a way that is both educational and fun. If you share our enthusiasm, do not hesitate to contact us, as I'mCARIM is always open to new members! Let us make 2023 an even better year.

I'mCARIM 2022
Adele Ruder
Valeria Saar-Kovrov
Renée Tillie
Elias Wieland
Minke Rijpkema
Joana Maria Alves da Silva


INTERVIEW
CAS-AM
DAS-CAM
EVC

The power of interaction

The transfer of the expertise of the three CARIM divisions (Heart, Blood and Vessels) to colleagues from far and wide takes place through three different postgraduate programmes. Although their set-up differs, what they all share is a team of enthusiastic course instructors, a high standard of quality, and Maastricht as the place to be. In order of seniority, starting with the youngest, those involved are happy to tell more.

CERTIFICATE OF ADVANCED STUDIES IN ANTITHROMBOTIC MANAGEMENT (CAS-AM)

Target group: Young physicians (maximum about 20) with an ambition to set up a centre of expertise on anticoagulation.

Design: Five days of live sessions in Maastricht in November and April, with self-study in between.

Arine ten Cate: "For a long time, the range of available anticoagulants showed little change, until around 2010, when the direct acting oral anticoagulants, in no less than four different types, came on the market. That made the work more complicated, and meant that the subject was insufficiently covered in medical training. This led to the idea for a course which would discuss complex antithrombotic care, using the format of the Maastricht educational system of problem-based learning (PBL). In addition, there is a need to train new leaders in the field, who can propagate in-depth research but are also able to set up centres of expertise on anticoagulation. In short: how to become a high-profile managing expert, with a high-quality network? One of the sources of inspiration for us was DAS-CAM."

Henri Spronk: “The second batch will start in November 2023. The first group consisted of eighteen people from ten European countries. This international character makes it fun and enriching. We had about as many trainers as candidates, all renowned experts in the field. Many of them were not yet familiar with PBL, so they were given a crash course. This educational system greatly encourages contacts among the participants.”

Hugo ten Cate: “Afterwards, the candidates reported that the main added value of the course was also that it provided them with a network. In the summer of 2023, this group organised an informal evening during the annual conference of the International Society for Thrombosis and Haemostasis, where they could meet again. And all trainers are looking forward to joining in the next edition, even though they receive no fee. They’re highly motivated.”

Arina ten Cate: “Some are cardiologists, others haematologists or internists, but the team of trainers also includes biochemists and pharmacologists. They also learn from each other as well. The course participants appreciated the direct contact with the trainers and were very happy to ‘finally meet a particular colleague in the flesh.’ The very fact that we value these low-threshold, personal contacts so much is the reason why 20 participants is the maximum.”

Hugo ten Cate: “How to effectively organise anticoagulation care has long been a well-known challenge in the Netherlands as well. In an ideal situation, you would organise this by region. Not every doctor needs to be an expert in this, but if each European region eventually has one of these experts, you’re well on the way.”

Henri Spronk: “Especially because this type of care is switching from generic to personalised care. One third of the mortalities in the Netherlands are caused by consequences of a thrombotic event, which includes heart attacks and strokes. We now know more different types of thrombosis than we used to, we know more about the complex interactions between organs, and there are more anticoagulants available than ever before.”

Arina ten Cate: “The students continue to work out their ambitions in their portfolios. That was an eyeopener to many of them too; it gave them directions for the future. Which is a good thing, as young clinicians often have little time to reflect.”

Hugo ten Cate: “Securing the necessary funding for the course is a major challenge, for which we need sponsors. It’s important for us to situate the course at Maastricht, as there is so much expertise available here, and after all it was a Maastricht idea. Online is not really an option to us: everything depends on the interaction.”

Arina ten Cate-Hoek is Associate Professor of Clinical Epidemiology and Medical Director of the Anticoagulation Clinic, as well as the medical coordinator of the Maastricht Thrombosis Expertise Centre.

Hugo ten Cate is Professor of Clinical Thrombosis and Haemostasis at Maastricht University.

Henri Spronk is Associate Professor of Biochemistry at Maastricht University.

DIPLOMA OF ADVANCED STUDIES IN CARDIAC ARRHYTHMIA MANAGEMENT (DAS-CAM)

Target group: 32 experienced cardiac electrophysiologists, certified by the European Heart Rhythm Association (EHRA), who have the ambition to become leaders in their field.

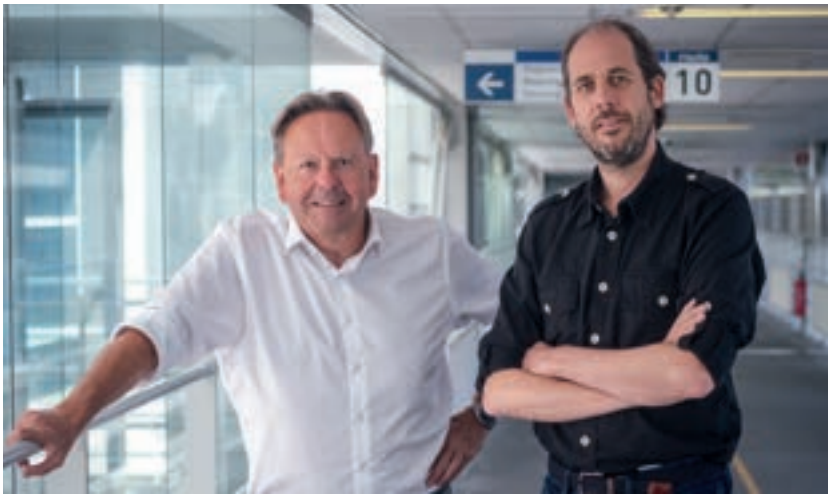
Future set-up: four times 2.5 days of live sessions over the course of one year, including three in Maastricht and one in Nice.

Ever since its inception in 2017, Jordi Heijman has been a member of the Scientific Programme Committee of DAS-CAM, whose founding father, Harry Crijns, has been the course director for the three editions there have been since then. “Now that Harry has retired, he is gradually also handing over these tasks. The idea was that Kevin Vernooy, Paul Volders and I would jointly take over his tasks in the fourth edition.” As matters now stand, this idea needs some slight adjustments, as is clear from Heijman’s biography below.

“The only thing that’s constant is change, is how I would sum up DAS-CAM”, smiles Heijman. The advent of the Covid pandemic meant that the second edition had to be done largely online, and in the course of the current edition it turned out that their project partner EHRA wanted substantial changes to be made. “They wanted to develop a three-tier educational programme: basic, advanced and leadership training. They asked us to develop the third tier as ‘DAS-CAM 2.0’.” Crijns’ successors got together to write a plan, which was approved by EHRA. “This means there will be a re-start of DAS-CAM in September 2024, in a somewhat different format. We’ve put the programme, as it were, in a pressure cooker in order to extract its essence. It’s sometimes good to be forced to cast a critical eye at your own programme. And in that situation, it’s very helpful that we, as the Scientific Programme Committee, get together for over an hour each week to prepare and improve the next module. That has enabled us to develop DAS-CAM 2.0 in a short period of time.”

Whereas so far, DAS-CAM was a 2-year programme comprising eight modules, DAS-CAM 2.0 has four modules in one year. While the lectures offering medical content have been shifted to the ‘advanced’ tier, everything that is needed to become a future leader in the field has been retained. This includes leadership skills, health technology assessment and quantitative biostatistics methods. “Since the course is now presented annually, it means we can serve twice as many people as before. The maximum number of participants in one group has been set at 32, as we strongly believe the participants’ own contributions and interactions are important.” As with all of such programmes, industry sponsoring is indispensable. “You always have to strike a balance: what can you offer the industry, and when is there an added value for the programme? Some companies want to have a representative who can be present at the course, and can develop informal relationships with future leaders in the field. Others find it important that we visit their training centre with a group. If that offers us added value in terms of content, that’s fine with us.” It’s all to serve the higher goal: continuing to share the Maastricht expertise in the field of arrhythmias with participants from all over the world for the years to come.

Jordi Heijman is Associate Professor of Cardiology at Maastricht University and will remain so until January 2024. After that, he will be a professor and chair of Medical Physics & Biophysics at the Medical University of Graz, Austria.



EUROPEAN VASCULAR COURSE (EVC)

Target group: Anyone who treats vascular patients or vascular diseases, from lab technicians to dialysis nurses to specialists and trainees and more.

Set-up: annual, three-day event for 1,500–2,000 participants at the MECC in Maastricht

Twenty years ago, Michael Jacobs was one of the initiators of the EVC, which has been held in Maastricht annually since 2009. “There is an important need, not only for theoretical training, but especially for practical training in our field”, says the founding father and director. “In our discipline, conferences are more common than courses. We offer 300 workshops, where people can train their skills in a hands-on approach. That’s necessary, as the treatment of cardiovascular diseases is increasingly done with minimally invasive endovascular methods through the groin, rather than by ‘traditional surgery’. As a result, there is a need for training both these new techniques, as well as open surgery skills, which are still regularly required in practice. This partly explains the success of our course.”

In recent years, Barend Mees has been assisting Jacobs, who is gradually scaling down some of his tasks. Mees: “Simulation training has become an integral part of training programmes for surgeons, and this goes for vascular surgeons as well. Of course, you also learn a lot from

practical work in your training programme, but this can vary greatly, depending on where you do your training. Even within the Netherlands, there are differences between hospitals offering training programmes, in terms of how much manual skills training you've had when you finish training. In addition, new endovascular devices or new techniques come onto the market each month, and we also include that in our EVC. We objectively compare the various options in a workshop: these five plugs are available to seal a blood vessel; what are the advantages and disadvantages of each, and how do you use them."

Jacobs: "Participants of the latest edition came from 53 different countries. That's good publicity for Maastricht. Pauwels Congress Organisers takes care of the organisation for us, but I myself also deal with things like logistics, contracts, participants and catering." Mees: "That's what may also explain the EVC's success, Michael's close involvement and attention to detail."

Jacobs: What we're aiming at is ongoing educational innovation. This year, Barend will be going to Singapore to check out a method to practise endovascular surgery on human cadavers. I've no idea whether that will be the future, but it's an interesting option. In addition, we keep aiming at a wide range of training courses and case discussions, with which we can continue to attract the more experienced specialists who are seeking in-depth training. And despite the size of the event, we all feel like we're a family."

Mees: "Maastricht is not that large, so course participants also meet each other after the course in the city. And besides, the four EVC programme leaders (arterial, venous, vascular access and cardiac) invite the experts in the field to their homes for an evening. This creates a very special and intimate atmosphere."

Jacobs: "The event is paid for by the participants' fees, a small grant and especially sponsoring by the industry. In recent years it's been difficult to secure the funding. Last year, for instance, we saw an industry partner leave that had been supplying us with aorta models for twenty years. Covid forced us to cancel one year, whereas we still had our overheads. Company budgets are under increasing pressure. The fact that our course is Medtech-approved does help, but it's hard work."

Mees: "During the Covid pandemic we went digital for the first time. We had eight green-screen studios set up at the MECC and offered a two-day programme with only workshops. We developed a kit comprising a vascular model, which we sent to participants' homes together with devices (stents, balloons), and which they could practise hands-on in front of their computer. Like, folding a stent into a home-built aorta. That was great! We even had an online competition between teams from the US, UK, Germany and Italy, to see who could complete a complex vascular catheterisation in the shortest time. That allowed us to retain our sponsors and raise enough money for that year. In the future we might expand our community-building and social-media efforts. When you see a Spanish EVC participant posting a message on LinkedIn saying 'I was at the Olympics of vascular surgery', that really says it all."

Michael Jacobs is Professor of Surgery and Medical Director of the Heart & Vascular Centre of Maastricht UMC+.

Barend Mees is Assistant Professor of Vascular Surgery and a vascular surgeon at Maastricht UMC+.

HIGHLIGHT
DIVISION HEART

HANS-PETER BRUNNER-LA ROCCA

Precision medicine performed by the patient – Towards future care

During the last decades, medicine has seen a tremendous evolution. This is clearly reflected by the fact that 30 years ago, a patient aged over 80 was considered very old, whereas nowadays the same is said about patients aged 90 years or over. Still, this evolution of medicine also has its downside. The resources required, in terms of costs as well as the number of healthcare professionals needed, have been increasing significantly. This increase has been further boosted by the aging population, which implies that there are more people in need of medical care, whereas the number of people who are expected to pay for it is stagnating or in some countries even declining. The result is an imminent collapse of our healthcare system and an inability to provide high quality medical care to everybody. In fact, waiting times for procedures, or even just to see a qualified physician, are already dramatically rising in some countries. Although prevention will help delay the development of diseases – which is highly desirable – it is not sufficiently effective to solve the problem. Nor will concentration of care be sufficient. The way to adequately address this problem is to prevent unnecessary care by personalising it and by having medical care provided by the cheapest but most motivated care provider – i.e. the patients themselves!

Chronic diseases account for the use of up to 90% of the total healthcare resources[1]. One of the most relevant chronic diseases is heart failure[2]. Despite considerable advances in treatment, this disease is still associated with significant morbidity and mortality, as well as with significantly reduced quality of life. Since the prevalence of heart failure increases sharply with age, its prevalence is expected to further increase to 3% of the population by 2025, which means 20 million patients in Europe. It is the most common cause of hospitalisation in patients aged ≥65 years, resulting in high economic burden, viz. about 2% of the total healthcare budget in Western countries. Since almost all patients with heart failure have additional diseases, i.e. co-morbidities[3], treating heart failure also means treating multiple chronic diseases. This makes heart failure the ideal candidate to address the problem of limited resources and to develop solutions for the future care of chronic diseases.

HIGHLIGHT

PATIENT SELF-CARE

The project entitled 'PAtient Self-care uSIng eHealth In chrONic Heart Failure' (PASSION-HF), supported by INTERREG-NWE (total budget €10 mln)[4], aims to initiate a paradigm shift in the care of heart failure and eventually of other chronic diseases[5]. The principal concept is to develop an avatar-driven application called 'DoctorME', which enables patients with heart failure to perform self-care. This will involve not only monitoring and education, as is done by current eHealth or mHealth applications, but also medical decision-making such as changes to drug therapy for heart failure. More specifically, DoctorME is intended to replace healthcare professionals such as cardiologists and general practitioners, at least in part. Thus, DoctorME will provide medical decisions directly to patients, without direct involvement of healthcare professionals. The decisions are based on algorithms that incorporate the current European guidelines for the diagnosis and treatment of heart failure[6]. In the future, the decisions will be supported by artificial intelligence and include algorithms based on the precision medicine approach described below.

The principle is explained in **Figure 1**. Patients will collect information about their current clinical status, which may include symptoms and signs of heart failure, but also data from e.g. wearables and lab results, if required. Based on this information, as well as the medical history from healthcare records and individual preferences, the guideline-based algorithms, in combination with artificial intelligence, will provide treatment advice. If this advice is of low complexity, it will be communicated directly to the patient as a treatment decision. If the advice is highly complex or uncertain, it will remain a recommendation that needs to be reviewed by a healthcare professional. The outcomes will be collected and fed back to the system. Eventually, the system will 'learn' from the decisions made, supplemented by results from external training cohorts. It will be monitored by the healthcare professionals (e.g. through random sampling) and by experts. Novel guidelines will be implemented as required. DoctorME will first be trained for heart failure, including the most common and relevant co-morbidities, allowing its broad application and subsequent extension to other chronic diseases as the primary diagnosis.

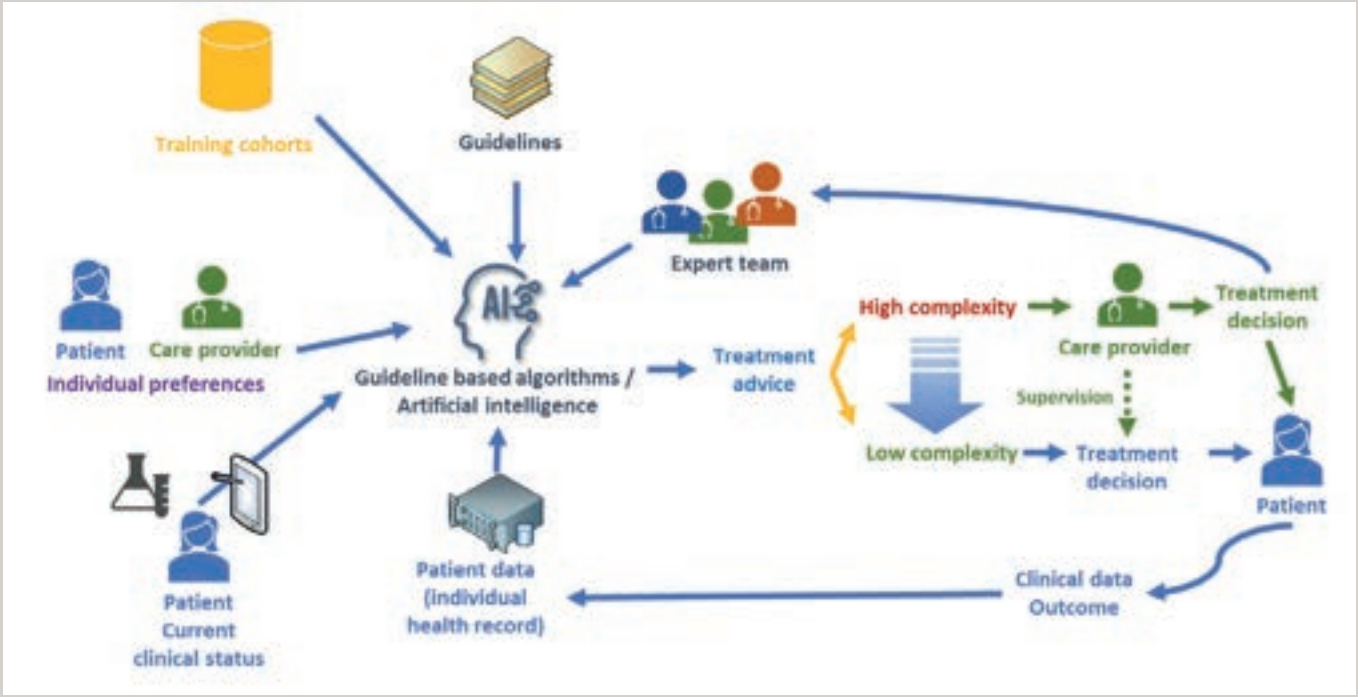


FIGURE 1 Hybrid concept for the paradigm change in chronic heart failure treatment, including artificial intelligence (AI), supported self-care and targeted involvement of medical care providers. It requires effective multi-level diagnostics for patients and comprehensive individual datasets. Depending on complexity, treatment decisions are offered to the patients directly or by healthcare professionals (care providers). Adapted from[5].

There are important aspects that need to be considered and addressed. They include patient acceptance and the fact that the front-end device must basically enable all patients with heart failure to use DoctorME, even if they are not familiar with computer technology[7]. Moreover, patients need to be motivated to use the device, which may be achieved, for example, by the introduction of serious gaming. Linking DoctorME to medical health records of patients will be essential, which means there are legal aspects and privacy issues to be considered. Obviously, this list is not complete, but it is beyond the scope of this article to address them all.

The first version of DoctorME will be made available as a decision-support system, the aim being to introduce it into the care system in 2024. This may enable, for instance, general practitioners to make treatment decisions at the level of

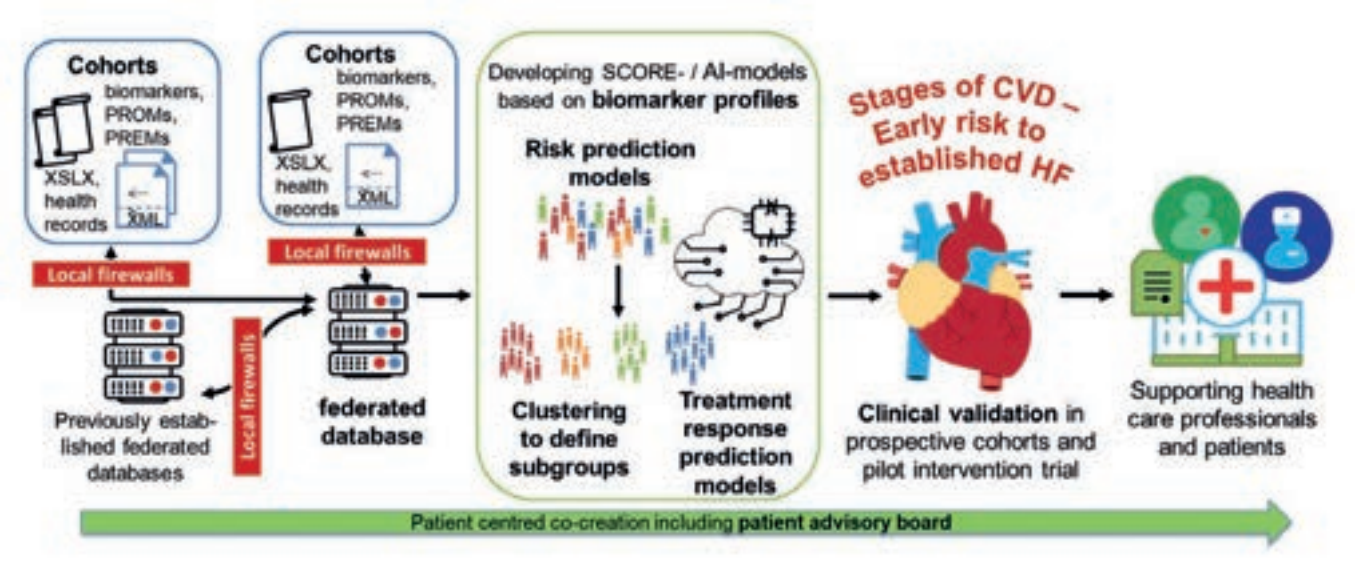


FIGURE 2 Scope of IHI project on precision medicine. For description, see text.

heart failure specialists, particularly in regions where access to specialists is limited. The requirements will be less than for the fully autonomous version of DoctorME. The latter will be further developed in parallel, and then tested in a large randomised controlled trial (RCT). In fact, it is expected that DoctorME will outperform the current standard of care, enabling broad implementation in clinical practice.

TOWARDS PRECISION MEDICINE IN CARDIOVASCULAR DISEASE

With few exceptions, treatment of cardiovascular disease (CVD) follows a one-size-fits-all approach. This approach considers the evidence from large RCTs for specific purposes (e.g. hypertension or heart failure with reduced ejection fraction [HFrEF]) but does not distinguish further between patients who benefit from a specific therapy and those for whom the same treatment offers no added value or may even be harmful. Countless publications about risk prediction claim to eventually provide evidence for a more personalised treatment approach. However, such models hardly influence the management of patients and are certainly not sufficient for a precision medicine approach. Few studies go beyond simple risk prediction. For instance, a meta-analysis of patients with HFrEF revealed that, overall, patients with atrial fibrillation do not benefit from β-blockers, though they may well be beneficial for certain subgroups[8]. The results of this study that used machine learning cluster analysis are promising but will not have any impact on the

treatment of patients, as validation by an independent prospective study is lacking.

As coordinator of a large consortium, I have submitted a proposal to a Horizon IHI call to address this issue. It has been recently approved for funding (€22 mln) and the grant agreement process is currently underway (start of project expected in October 2023). The basic principle of the project is depicted in **Figure 2**. A large number of existing data from registries and interventional trials including a total of approximately 1 million subjects from early risk for CVDs, patients with CVD to establish heart failure will be collected in a federated database. The data include different types of biomarkers, treatment and outcome. The federated data will allow AI modelling across the different studies for better phenotyping of patients to define new clusters of CVD and better risk prediction. However, the project will take an important next step, by modelling the prediction of treatment response in individual subjects based on biomarkers. As mentioned above, however, this will not be sufficient to change medical practice. Therefore, the second part of the project will validate the findings in new and ongoing studies. The most promising model will be prospectively tested in an intervention trial, in which the individual treatment of patients will be based on their individual biomarker profiles. This study may then be used as a blueprint for other models and help to define novel care pathways, representing precision medicine.

My ultimate aim is to combine these two large projects to achieve individualised self-care by patients. This will result not only in more personalised care to improve outcomes while reducing side effects, but also in a substantial reduction of the use of resources required to provide care for chronic diseases.

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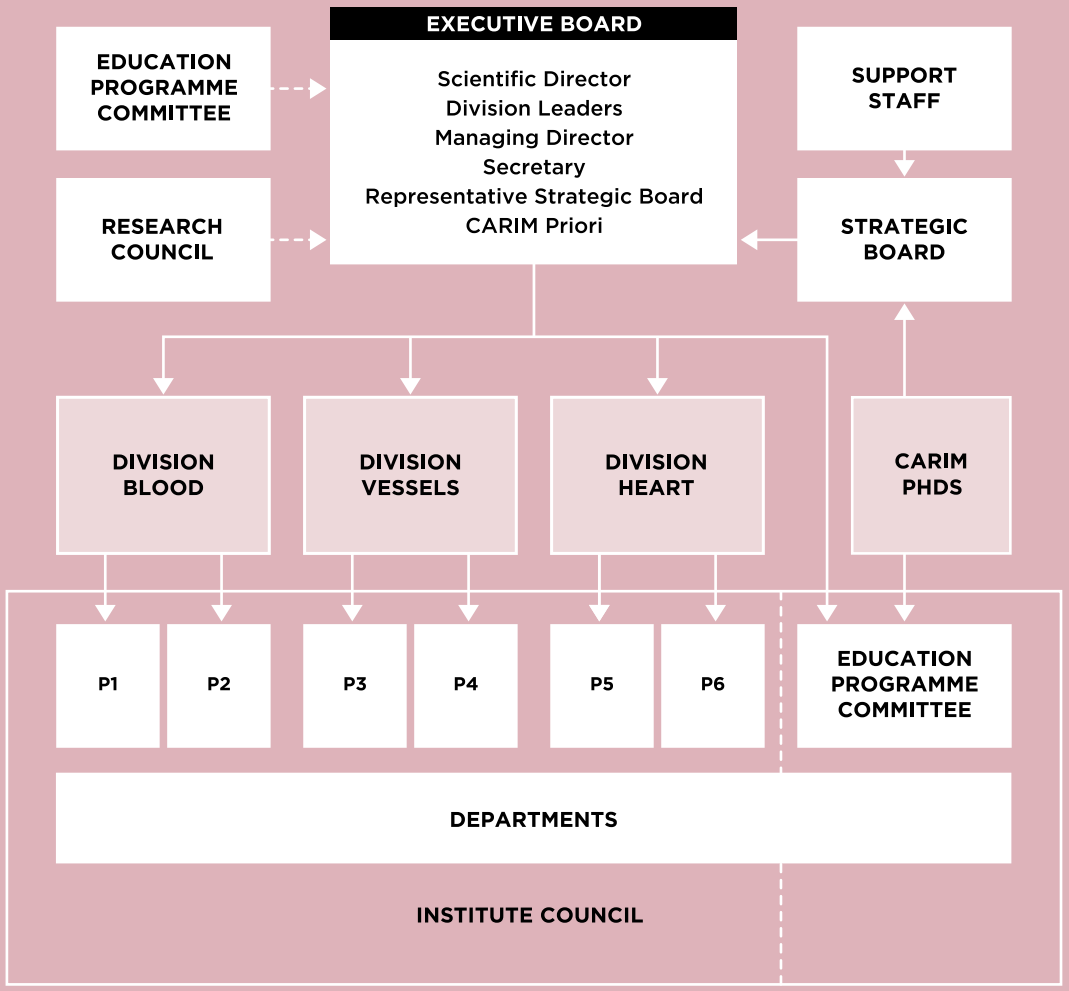
ORGANISATION

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 Bachelor and Master students, PhD candidates and postdocs, 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 by the secretary to the Board, whom together represent the Management Team (MT). The MT meets weekly to discuss daily matters. Together with the three leaders of the divisions, a representative from the Strategic Board and the CARIM priori Board members, the MT constitutes the Executive Board (EB) of the institute. The DB meets monthly to discuss and decide upon issues at strategic and operational level. The EB 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 developing long-term policy. The SB is a discussion forum and generates written visions of the future of CARIM and its survival in an increasingly competitive international scientific environment. The SB meets monthly 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 EB on all issues regarding these educational programmes. The chairperson is also CARIM's PhD Coordinator and advises the EB on all issues regarding the PhD programme. Within CARIM, the PhD Coordinator works closely with the CARIM Office and Scientific Director.

The Research Council advises the PIs, researchers and EB on the quality of research proposals and meets regularly to discuss and guide grant applications. In 2019, the CARIM Grants & Incentives Team was established to boost grant acquisition by activating researchers and research teams, keeping track of submitted, granted and rejected applications and discussing calls and opportunities. The Institute Council consists of all PIs and Department Heads and meets four times a year. The Institute Council is informed by the EB on ongoing matters and advises the Scientific Director on research within the institute and the related education programmes.

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- Dr Gwynned de Looijer (from December 2022)
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- Prof. Judith Sluimer
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- Prof. Chris Reutelingsperger

CARIM OFFICE

The CARIM Office consists of specialists that support the institute and its researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Esther Willigers and Barbara Przybylski are responsible for administrative issues, including supporting the EB. The controllers of CARIM are Lynn Lemeer and Hans Slenter. The Finance Department of Maastricht University provides support on accounting the CARIM research projects with Henny Kerckhoffs, Johan Noordijk and Jacqueline Roufs-Scheepers. Petra Suurmond 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. Gwynned de Looijer is the Faculty support for funding acquisition. Managing Director Danny Luciana is the head of the CARIM office as of 1 September 2022.

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
- Clinical Pharmacy
- Internal Medicine
- Intensive Care
- Neurology
- Pathology
- Radiology & Nuclear Medicine
- Vascular Surgery

INTERVIEW

LEON SCHURGERS AND HAN VAN 'T KLOOSTER

Towards large-scale automated cell culturing

Call them romantics, but Leon Schurgers and Han van 't Klooster are convinced that one day, perhaps within 15 years from now, if you have had a cardiac infarction, you will be treated with cultured stem cells, whether or not derived from your own cells. The heart is reconditioned (or partly so) and you'll be good to go again. "It's a bit like having the engine in a car reconditioned", says Schurgers. "You have to set yourself a target if you want to make progress", says Van 't Klooster. Together they talk about ReGEN Biomedical, a subsidiary of Maastricht University, where science and business meet.

For a number of years now, regenerative medicine has been high on the agenda, including that of the Dutch government. For instance, the RegMed XB initiative was started in 2017, with the aim of making progress in the Netherlands and Belgium towards new forms of treatment for kidney diseases, diabetes, heart failure and osteoarthritis. Marianne van der Steen, Professor of Entrepreneurship in Healthcare is the co-founder CEO of the Maastricht pilot plant called ReGEN Biomedical, which started in September 2021. Together with Clemens van Blitterswijk, she was the driving force behind the impulse given by the National Growth Fund (NGF) for starting up the National RG pilot plant RegMed XB, which made it possible to develop ReGEN Biomedical. The new facilities in the various regions together constitute the pilot plant. They cover the entire chain from development to production of stem cells, tissues, mini-organs, macro-tissues and smart (bio)materials.

AFFORDABLE

ReGEN Biomedical explicitly aims at automated tissue culture, making upscaling possible and affordable. The tissues they want to culture will meet the highest standards with the strictest regulations, i.e. Good Manufacturing Practices (GMP). This will allow them to eventually be applied in humans. But they have not got that far yet, as the two explain during the interview. Han van 't Klooster is the Chief Operating Officer, and Leon Schurgers is researcher at CARIM, and one of the members of the Strategic Advisory Board. They share their enthusiasm for the subject, the will to improve patient care, and they know from experience that it starts with ambition, after which you absolutely depend on each other to make progress. Schurgers: "Scientists mostly want to investigate specific things, at a small scale, as we want to understand molecular mechanisms in great detail. Collaborating with business enables you to speed things up." Van 't Klooster: "Realising ambitions in this new field cannot be achieved in 'splendid isolation'. We need CARIM particularly for the culturing of heart cells."

BIO-INCUBATORS

The aim is thus to culture cells on a larger scale, for scientific and commercial research, for instance at pharmaceutical companies or companies producing organoids like the 'heart-on-a-chip'. Schurgers and his colleagues are trying to work towards mimicking the heart's physiology ever more accurately in culture. "We are now able to take a blood sample from a patient, isolate the white blood cells and reverse their development. This causes them to return to the stage of stem cells, which can subsequently develop into any type of body cell, including heart cells. What we cannot yet do is to upscale this process. For that we need an industrial plant, where cells can be cultured on a large scale in bio-incubators." Van 't Klooster "Such large-scale cell cultures can be used for things like testing medicines. But we also intend to achieve automated and accelerated culturing for individual patients. Scale, pricing and quality are essential at ReGEN Biomedical."

PRECISION

The advantage of automated cell culture is not just that the technology becomes more accessible to a wide range of patients, but also that variations due to human activity can be avoided. Van 't Klooster: "Tissue culture is a high-precision process. And although humans can work with great precision too, there's always a considerable risk of infection when working with living cells. Automation reduces the risk of infection and enables you to offer the tissues to patients affordably and at high quality." One of the major challenges for the coming years is the 'vascularisation' of cell cultures. Schurgers: "When you're culturing heart cells and

the size of the culture exceeds some 300 microns, its centre will no longer receive enough oxygen and nutrients to survive. Cells will then become apoptotic; they die. Making blood vessels grow into a culture allows it to expand further." He adds: "CARIM has extensive knowledge about this process, making the collaboration very useful and obvious for both parties."

CONCRETE

Professor Chris Hughes of the University of California Irvine was among the first to make a 'vascularised micro-organ on a chip', and he is a visiting professor at Maastricht University. One of the staff members of ReGEN Biomedical will shortly be leaving for the US for a few months to learn from Hughes. Van 't Klooster: "This shows that the collaboration is very concrete, and indeed it has to be, as it's a very practical discipline. We actually make products, which I regard as one of the attractive aspects of my job."

The first cell cultures have already been produced at the plant, and the next step will be to design protocols for large-scale automated cell culture. Finding the necessary staff is one of the challenges involved. But they will also need to hold talks with registration authorities like the European Medicines Agency and the Dutch Medicines Evaluation Board. Schurgers: "As soon as you start working with stem cells, there are sensitivities to deal with. People are worried about how far this could go; will it ever be possible to culture an entire human being?" Van 't Klooster has had this experience in previous jobs too. "But we'll manage to solve that, as this is definitely going to happen. It's too valuable for patients."

Their enthusiasm is catching. Schurgers: "Of course we're romantics. If we don't believe in it, who will? But I'm convinced that by working hard and finding the right people we're going to achieve this." Van 't Klooster: "I also really think that we'll make it. The main question is: how soon?"

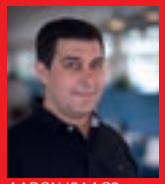
OF COURSE WE'RE ROMANTICS

IF WE DON'T BELIEVE IN IT, WHO WILL?

FACES

BLOOD P1

BLOOD COAGULATION,
VENOUS THROMBOSIS & BLEEDING


AARON ISAACS


ALMA MINGELS


ARINA TEN CATE-HOEK


CONSTANCE BAATEN


DENNIS SUIJLEN


ELISABETTA CASTOLDI


ELKE MAGDELEYNS


ERIK BECKERS


GERRY NICOLAES


HANS IPPEL


HEIDI NOELS


HENRI SPRONK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OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENÉ VAN OERLE


RENSKE OLIE


RORY KOENEN


SIMONE WIELDERS


STELLA THOMASSEN


STEVEN MEEX


STIJN AGTEN


TILMAN HACKENG


YVONNE HENSKENS

FACES

BLOOD P2 ATHEROSCLEROSIS, ARTERIAL THROMBOSIS & STROKE


ANDY BAKER


CASPER MIHL


CHRISTIAN WEBER


CLAIRY DINJENS


DIETBERT NEUMANN


ELINE KOOI


EMIEL VAN DER VORST


ERIK BIESSEN


FELIX MOTTAGHY


GREGORIO FAZZI


JACK CLEUTJENS


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MARJO DONNERS


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PIETER GOOSSENS


REMCO MEGENS


ROB HOLTACKERS


ROBERT VAN OOSTENBRUGGE


SIMON SCHALLA


SYLVIA HEENEMAN


WERNER MESS


WIM VAN ZWAM

FACES

VESSELS P3 VASCULAR COMPLICATIONS OF DIABETES & HYPERTENSION


AMAURY MONARD


ANNEMARIEK DRIESSEN


BASTIAAN DE GALAN


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


ELLEN FRANKORT


JULIE STAALS


KRISTIAAN WOUTERS


MARC HEMMELDER


MARGEE THEUNISSEN


MARLEEN VAN GREEVENBROEK


MARTIJN BROUWERS


MIRANDA SCHRAM


NORDIN HANSSEN


PAUL SCHIFFERS


PETRA NIESSEN


PHILIPPE VANGRIEKEN


RONALD HENRY


SÉBASTIEN FOULQUIER


SIMONE EUSSEN


THOMAS UNGER


THOMAS VAN SLOTEN

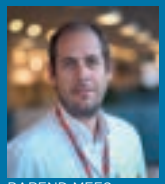

VICKY VERMEULEN


YVETTE DERKS

FACES

VESSELS P4 REGENERATIVE & RECONSTRUCTIVE CARDIOVASCULAR MEDICINE


ARMAND JAMINON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BART MAESEN


CECILE MAASSEN


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ED ERINGA


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JOS MAESSEN


LEON SCHURGERS


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MARK POST


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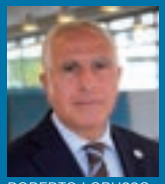
PEYMAN SARDARI NIA


PIETER VAN PAASSEN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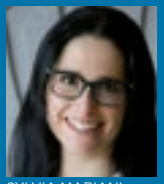
SANDRO GELSOMINO


SUZANNE KATS


SYLVIA MARIANI

FACES

HEART P5 STRUCTURAL HEART FAILURE


BEN JANSSEN


CHRISTIAN KNACKSTEDT


ELLEN WELTJENS


GUIDO HAENEN


HANS-PETER BRUNNER-LA ROCCA


JOB VERDONSCHOT


LEON DE WINDT


LIZ JONES


MARK HAZEBROEK


MARTIJN HOES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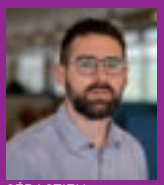
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WOUTER VERHESEN

FACES

HEART P6 COMPLEX ARRHYTHMIAS


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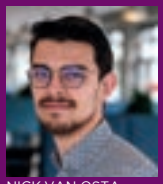
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