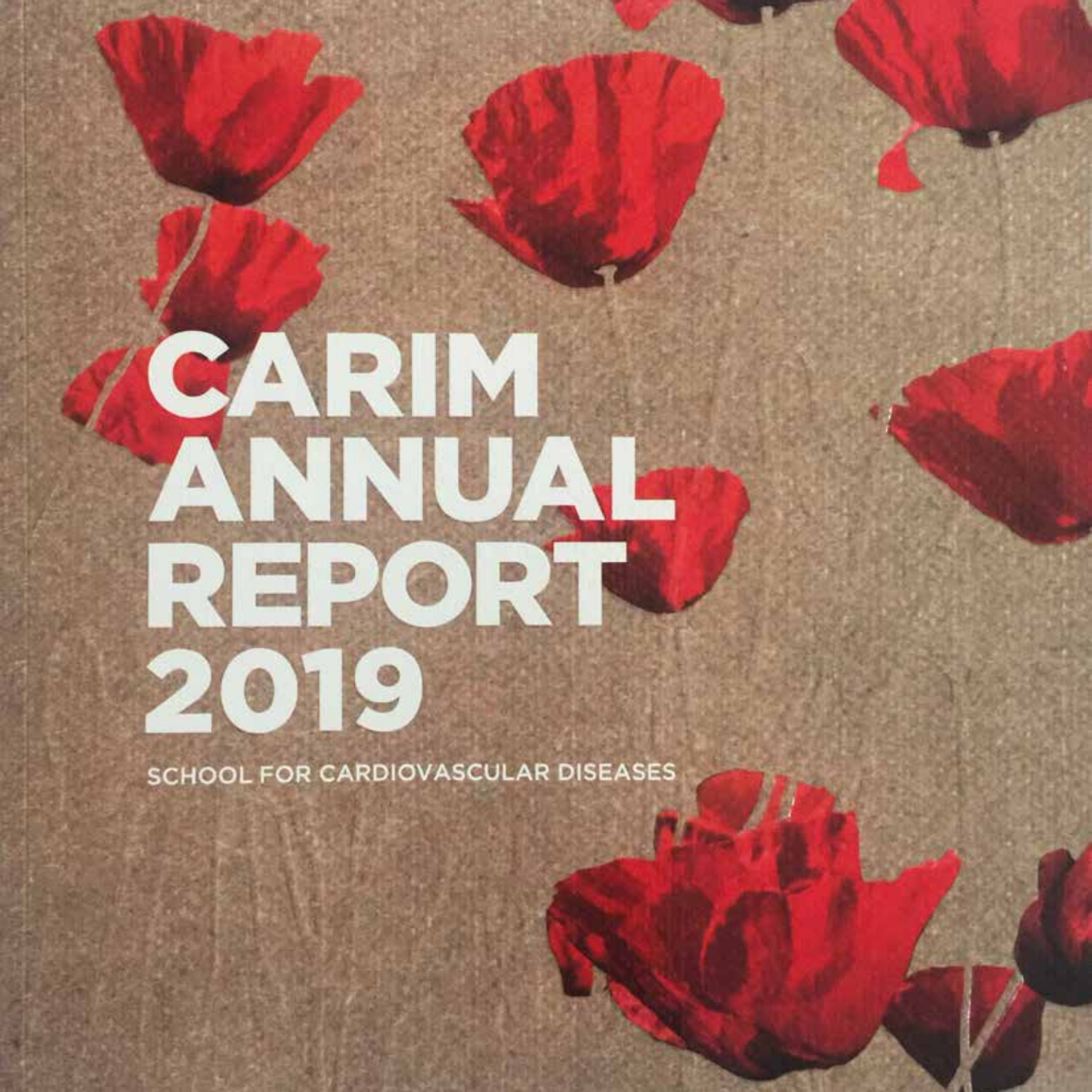


CARIM ANNUAL REPORT 2019

SCHOOL FOR CARDIOVASCULAR DISEASES

CARIM ANNUAL REPORT 2019

SCHOOL FOR CARDIOVASCULAR DISEASES

CONTENTS

PREFACE

...THOUGH POPPIES GROW...

It is with modest pride that I present to you our Annual Report 2019. It's a special report, as CARIM has become better and more productive than the year before, and we are increasingly engaging in societal responsibilities and impact.

CARIM is grateful to 2019. We had a very successful external evaluation, with a final top-score of very good to excellent. I thank all CARIM members for their motivated participation in the presentations and interviews in the intense three-day evaluation process. The highest gratitude and appreciation befalls our CARIM bureau for compiling our massive and impressive Standard Evaluation Protocol, as well as for creating a completely novel website, among the other regular work that comes with running an institute.

Our scientific output increased in quality, with our 521 SCI/SSCI publications surpassing an unprecedented average impact factor of 6. Our young academic professionals continue to thrive on our unique HS-BAFTA talent programme, and our visiting professors have worked with our young researchers on stimulating scientific and cultural exchange, paving roads for future postdoc appointments and securing academic careers.

Yet, one might ask, what does this mean today? All progress achieved in 2019 might seem irrelevant when reflecting on the current state of affairs of our society. The arrival of COVID-19 in our Western Society early 2020 disrupted both life and science as we know it. COVID-19 has fundamentally changed our views on the scientific dogmas behind peer review and evidence-based medicine. Never in the history of science were so many papers on a single topic accepted, and so many rapidly retracted due to publication eagerness and self-inflicted time constraints, in a race to find inhibitors and vaccines. Currently, needs for RCTs of obvious and undisputable beneficial measures are being challenged.

But we should take pride in that a face of society presented itself. Human flexibility and unity brought about almost the impossible, in dealing with the first outbreaks from scratch within months. How our clinicians and health professionals were able to perform within the time and health constraints has been nothing short of amazing. Such an example should be predominant in one's mind, especially by those who think lightly of our governmental regulations concerning COVID-19 prevention. Then the impossible became possible, the all-consuming and dreaded red tape was bypassed. Lastly to nature, COVID-19 has solved air pollution in our metropoles, which was repeatedly and unsuccessfully attempted by all of our governments.

From a scientific point of view it has become clear that all pathological mechanisms leading to COVID-19 fit well in the three divisions of CARIM; Blood, Vessels, and Heart, so quite rightly SARS-CoV-2 might stick around with CARIM as a research topic for years to come.

I am certain that current conditions will take a temporal toll on research progress, but I am also certain that we, as a community, can make the best out of it and will learn from it. We should take the time and opportunity to reflect on where we and our world are progressing. We should rethink what we eat, how we trade, and how our environmental footprints will affect our future. As we work from home - if possible - we could perhaps maintain this routine, to a certain degree in the future. Limiting public and private transport, its personal stress and burden on infrastructure, and find a new sustainable equilibrium into this new millennium.

Finally one might ask why the poppy? Not only is the poppy a beautiful and charming flower. It carries tremendous symbolism, and if ever the poppy was appropriate for the cover of our CARIM annual report, it is today.

Most well-known is the poppy for its symbolic representation of the immense sacrifices made on the battlefields of Belgium and Northern France during the Great War. It became a lasting memorial to all who died then, and in conflicts thereafter. With that the poppy also applies to the lost from the second world war, for which 2019 ushered in our 75th liberation year. Might it therefore not be fair if the poppy would, in the slightest way, be dedicated to the lost from the war against COVID-19, and the consistent sacrifices that have been made by our clinicians and health professionals? I think it does. The poppy reflects growth, hope, spring, and summer, during which it can only flourish if left alone, untouched, in the lap of Mother Earth. Respect nature, do not pick a poppy, it will not survive in a vase.

CARIM's annual report is dedicated to all our clinicians and health professionals of Maastricht UMC+ and beyond, may their commitment and struggle never be forgotten.

This is CARIM 2019.

I hope you enjoy your reading.

Professor Tilman Hackeng
Scientific Director CARIM
School for Cardiovascular Diseases

PROFILE

01

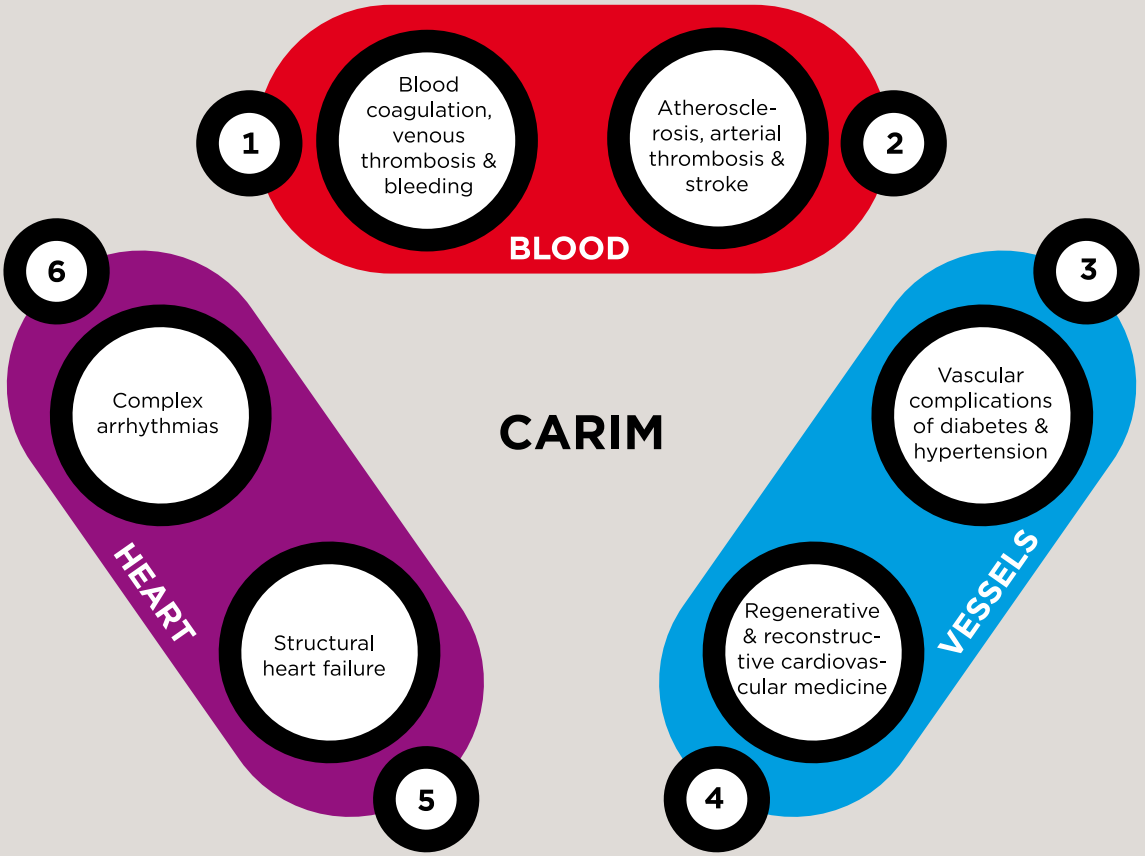
PROFILE

Founded in 1988, the Cardiovascular Research Institute Maastricht (CARIM), School for Cardiovascular Diseases, has established itself over the last three decades as a leading research institute in the field of cardiovascular disease. At CARIM, basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular disease are studied, allowing faster translation of new research concepts to clinical practice. New findings, products and techniques which can be applied in healthcare are evaluated, often in collaboration with private partners, and the results of scientific research are published in high-ranking international journals. Masters students, PhD candidates and MD students are trained to become independent researchers, and postdocs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three research Divisions, 'Blood', 'Vessels' and 'Heart', comprising six programmes: 1. Blood coagulation, venous thrombosis & bleeding; 2. Atherosclerosis, arterial thrombosis & stroke; 3. Vascular complications of diabetes & hypertension; 4. Regenerative & reconstructive cardiovascular medicine; 5. Structural heart failure and 6. Complex arrhythmias. These six programmes together host 22 Principal Investigator (PI) groups, which represent independent research, infrastructural and financial units within CARIM. CARIM addresses key scientific questions through optimal combinations of CARIM programmes, PIs, researchers, and infrastructure in an optimal team science setting combining track record, expertise, and innovative content and to disseminate results to scientific communities and to society as a whole.

All three Divisions involve basic as well as clinical programmes, and are led according to a shared governance principle, executed by the Division leader together with basic and clinical scientists from the Division. This shared governance system enables shared responsibility for the scientific progress of programmes, for linking activities and seeking collaborations between PIs and Divisions and for mentoring of PhD candidates, postdocs and tenure tracks. The individual PIs are responsible for the financial management of their groups.

Cardiovascular scientists from around the world join CARIM because it values open communication, close cooperation, stiff ambitions, good facilities and a critical learning environment. CARIM is one of the six research schools of the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University and is embedded within the Maastricht University Medical Centre+ (Maastricht UMC+). CARIM is appointed as research school by the Royal Netherlands Academy of Arts and Sciences (KNAW) and recognised as an international training site for Early Stage Researchers by the European Union. CARIM researchers have been very active in EU networking activities and the establishment of (inter) national alliances. In total, CARIM is currently involved in about 30 European projects; including nine ITN programmes with a total number of 28 Early Stage Researchers allocated to CARIM.


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

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

KEY FIGURES 2019

ANNUAL BUDGET: **22.6** M€

NEW CONTRACTS AND GRANTS: **9.1** M€

RESEARCHERS: **148.5** FTE (89 INTERNAL PHD CANDIDATES)

TECHNICAL AND SUPPORTING STAFF: **48.3** FTE

DEPARTMENTS/DISCIPLINES: **17**

SCIENTIFIC ARTICLES: **665** (SCI/SSCI: 521)

PHD THESES: **44**

EXTERNAL REVIEW COMMITTEE VERY POSITIVE ABOUT CARIM

One of the main events within CARIM in 2019 was the external evaluation of our institute. After months of preparation – a self-evaluation report was written, the committee was selected and invited, and even a new website was developed – the site visit took place from 23-25 October 2019.

All CARIM members were gathered to present CARIM to the seven-headed committee of internationally recognised experts on cardiovascular research that was led by Prof. Reitsma, but more importantly to discuss science, organisation, the PhD programme, infrastructure and other topics that came up during the presentations and closed sessions. The members were impressed by the enthusiastic and inspiring presentations given by a broad and diverse selection of CARIM researchers and PIs. In particular, the long-term visions of the project leaders were clearly highlighted during the presentations and highly valued by the ERC. The self-evaluation report was received as comprehensive, descriptive, including good narratives, and of an exceptional quality. According to the committee, it was very helpful in preparing for the ERC site visit.

In general, based both on the CARIM self-evaluation report and the impression during the three-day site visit, CARIM was judged to be a well-structured organisation with a clear governance structure, robust leadership skills of the management at all levels, a sound financial position and a state-of-the art infrastructure. The ERC was very positive on the well-structured and high quality organisation of the PhD programme. CARIM received the following scores on a four-point scale from 4 (poorest) to 1 (best):

CARIM SCORE EXTERNAL EVALUATION

	QUALITY	RELEVANCE TO SOCIETY	VIABILITY
SCHOOL OF CARIM	2	1	2
DIVISION BLOOD	2	1	1
DIVISION VESSELS	2	1	1
DIVISION HEART	2	1	1

CARIM scored very well to excellent. CARIMs contribution and relevance to society was judged to be outstanding (1), both on school level and Division. The research quality of CARIM is very good and internationally recognised (2) and CARIM is very well (2) to excellently (1) equipped for the future (“viability”). The full report is available on our website.

But of course, there is always room for improvement. Recommendations from the committee focussed mainly on organisational and cultural issues. One of the main recommendations of the ERC committee was to improve gender and diversity aspects within CARIM. In addition, the committee advised on transparency in appointing new leaders and in career paths.

Furthermore, structural evaluation of financial investments in relation to strategic plans had to be implemented. Another advice was about senior authorships, because independent authorships of junior staff is very important for future positioning in a competitive (European) research environment. It would bring more empowerment and transparency for early career professionals to openly discuss this and set rules.

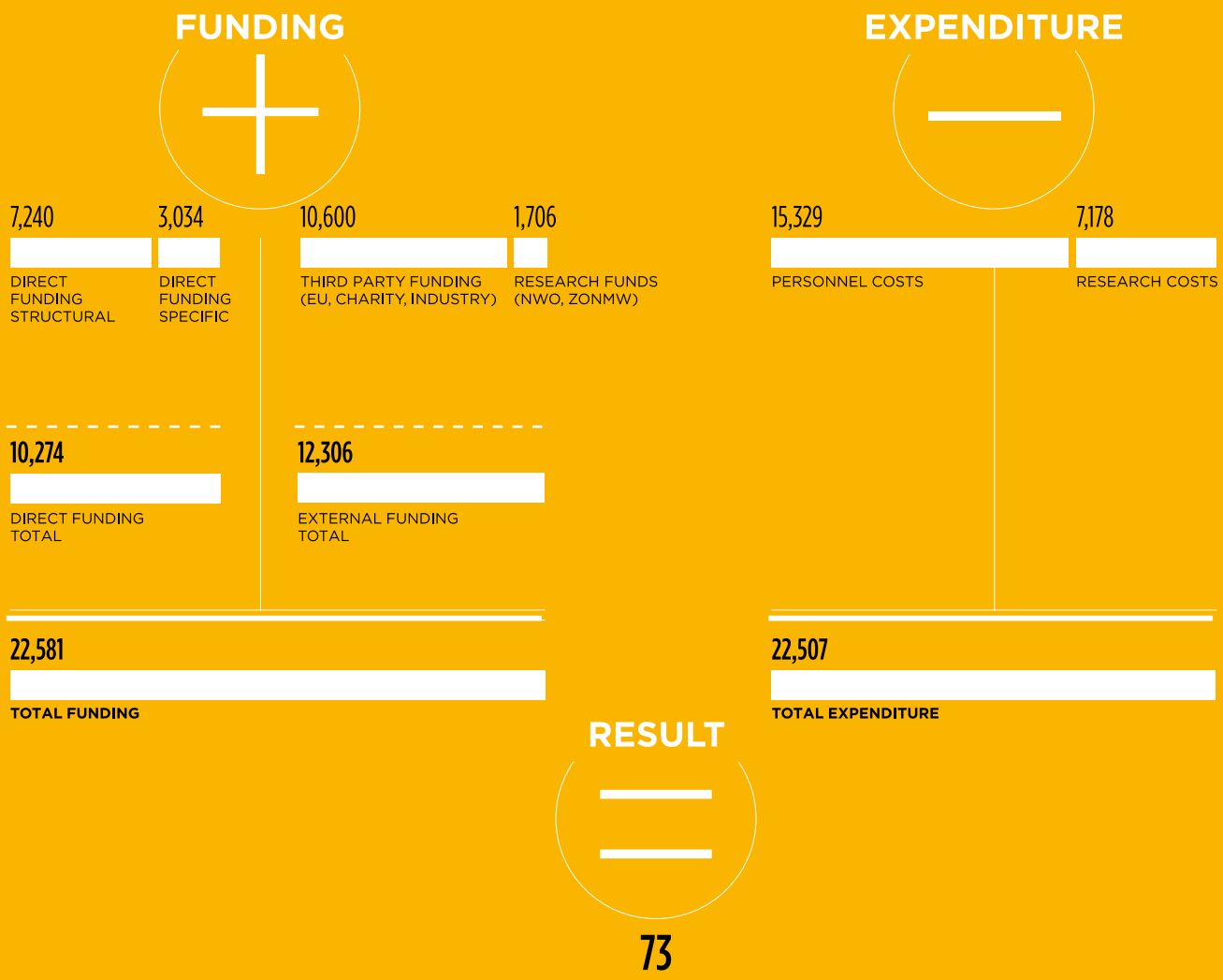
Plans on how to tackle these (and other) recommendations will be presented to the Board of the University in Q3 2020 and will be further developed and implemented in the upcoming years.

From left to right: Drs Carolina Touw (PhD member), Dr Chantal Boulanger, Prof. Ingrid Pabinger, Prof. Alan Flyvbjerg, Prof. Pieter Reitsma (chair), Prof. Eike Nagel, Prof. Thomas Eschenhagen and Dr Roelinka Broekhuizen (secretary).

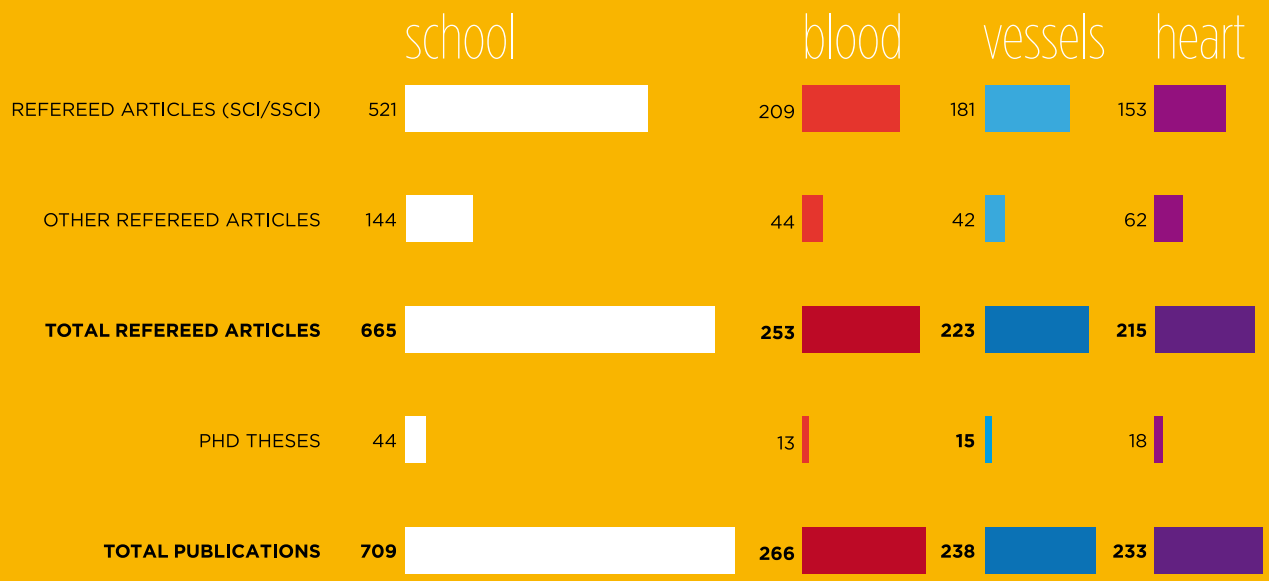
FACTS AND FIGURES

02

FUNDING AND EXPENDITURE (K€) AT INSTITUTIONAL LEVEL 2019



RESEARCH OUTPUT (K€) IN 2019

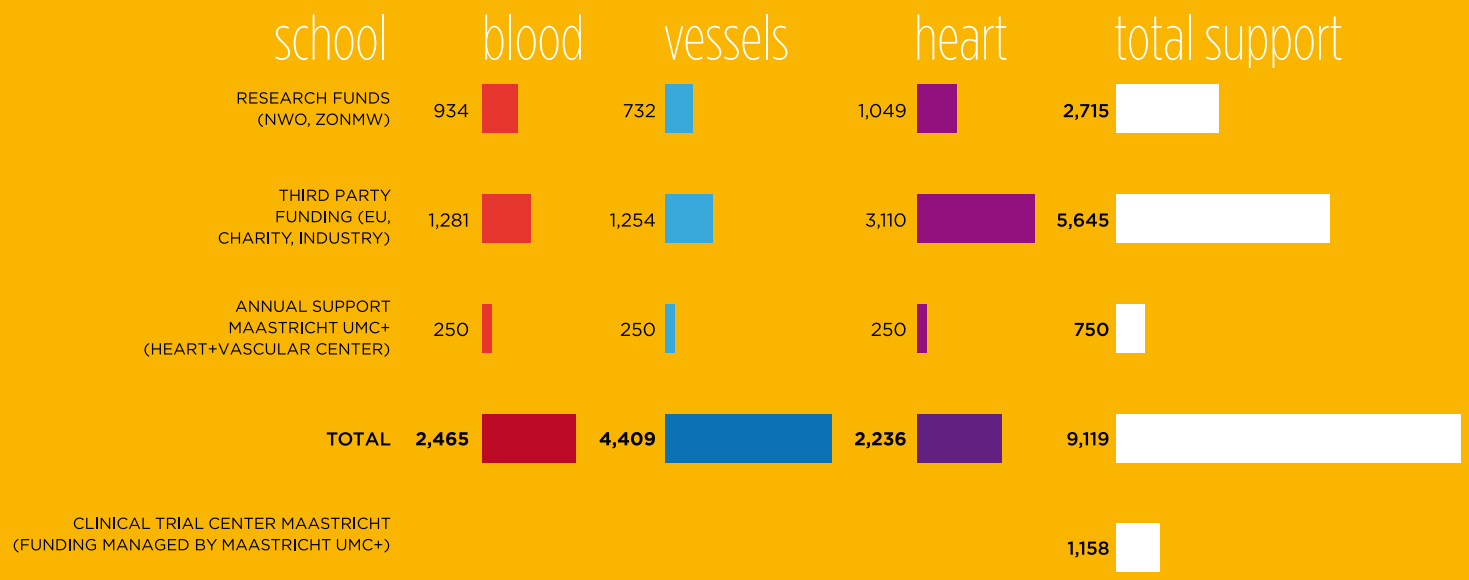


ACADEMIC STAFF **26**

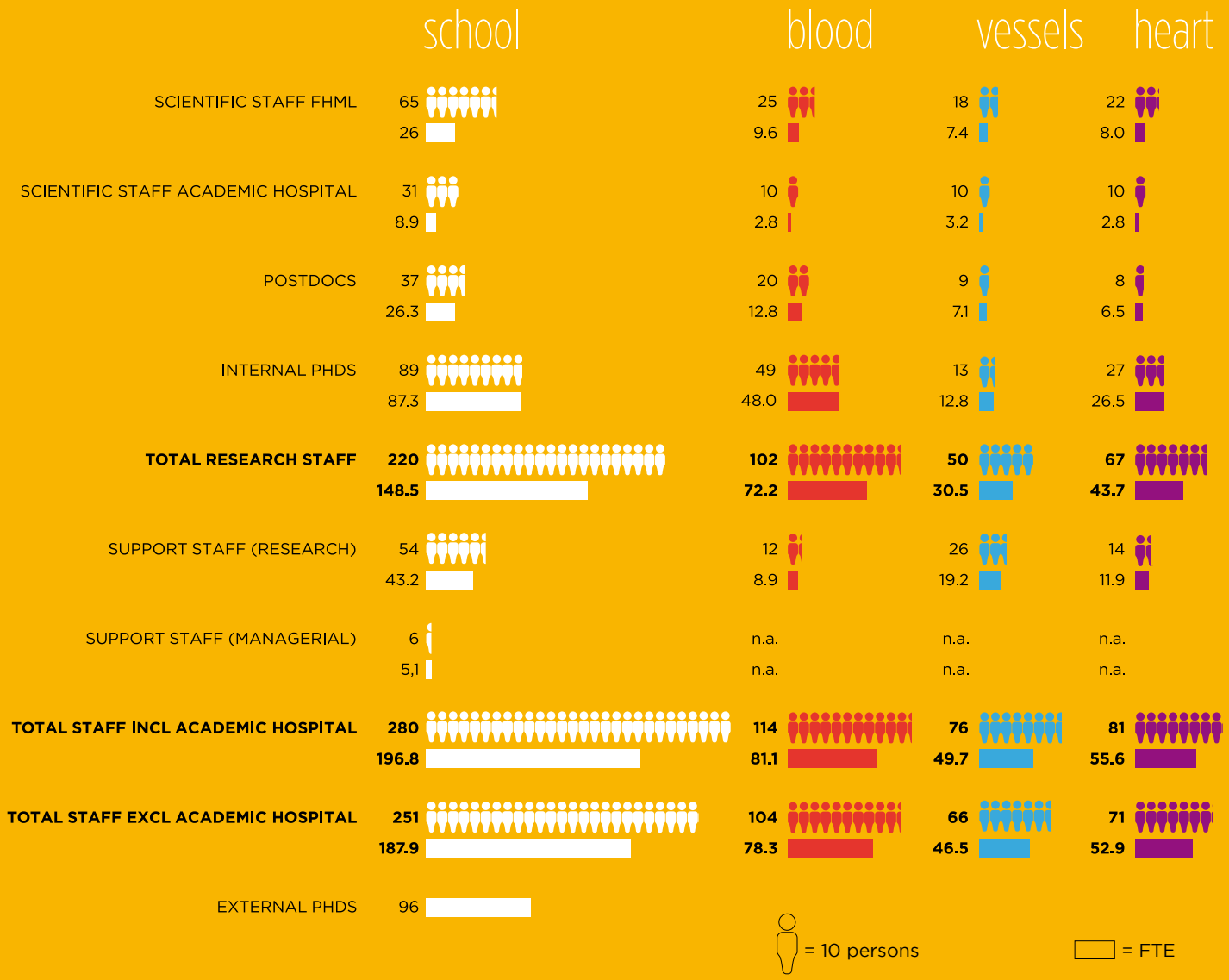
RATIO REFEREED ARTICLES PER FTE ACADEMIC STAFF **20**

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

NEW CONTRACTS AND GRANTS (K€) IN 2019



SUMMARY OF SCIENTIFIC AND TECHNICAL STAFF CARIM AT THE END OF 2019




Can We
Trust
Scientists?


Maastricht UMC+

HIGHLIGHT
DIVISION BLOOD

ARINA TEN CATE-HOEK

Department of Vascular Surgery

Each year over 25,000 new cases of deep venous thrombosis (DVT) are diagnosed in the Netherlands alone. Overall, our country is doing quite well as regards diagnosing and treating these patients, especially in the acute phase of the disease. We have streamlined the diagnostic work-up in such a manner that the use of a clinical decision rule (CDR) and a simple blood test (d-dimer test) enables us to effectively and efficiently decide who needs further imaging to confirm the diagnosis and who does not [1,2]. An algorithm based on a CDR and a blood test can rule out DVT in about 30-50% of patients without the need of imaging [3]. If patients are diagnosed with DVT, anticoagulant treatment is very effective, with on-treatment recurrence or propagation rates <1% [4,5]. Moreover, although the risk of treatment-associated bleeding is twice as high as the rate of recurrence, these risks are still manageable. Bleeding rates are low even in patients over 75 years of age [4]. In addition, we have a range of drugs at our disposal: four types of direct oral anticoagulants: apixaban, rivaroxaban, edoxaban and dabigatran (all Xa inhibitors except for dabigatran, a IIa inhibitor); two types of vitamin k antagonists: acenocoumarol and fenprocoumon; and several low molecular weight heparins (LMWH) [5]. This allows treatment to be tailored to individual patients' needs, and it may be even further improved when safer anticoagulants come available as result of the ongoing search for the "holy grail", that of an effective anticoagulant without the risk of bleeding. In addition, factor XIa inhibitors may represent the next step towards safer anticoagulation.

At the same time, it is disconcerting that at least one in three patients suffers from chronic post-thrombotic complaints. So far, however, this has not been prioritised in clinical research.

Post-thrombotic syndrome (PTS) is defined as a combination of patient-reported symptoms, including tiredness of the leg, pain and oedema, and irreversible skin changes such as hyperpigmentation, venous ectasia and, in more severe cases, lipodermatosclerosis and venous ulceration [6] PTS has a detrimental effect on patients' quality of life and is associated with increased healthcare as well as societal costs [7,8].

Within the Division Blood, we are currently trying to get a better understanding of the pathophysiology that underlies PTS, with the aim of improving management options for

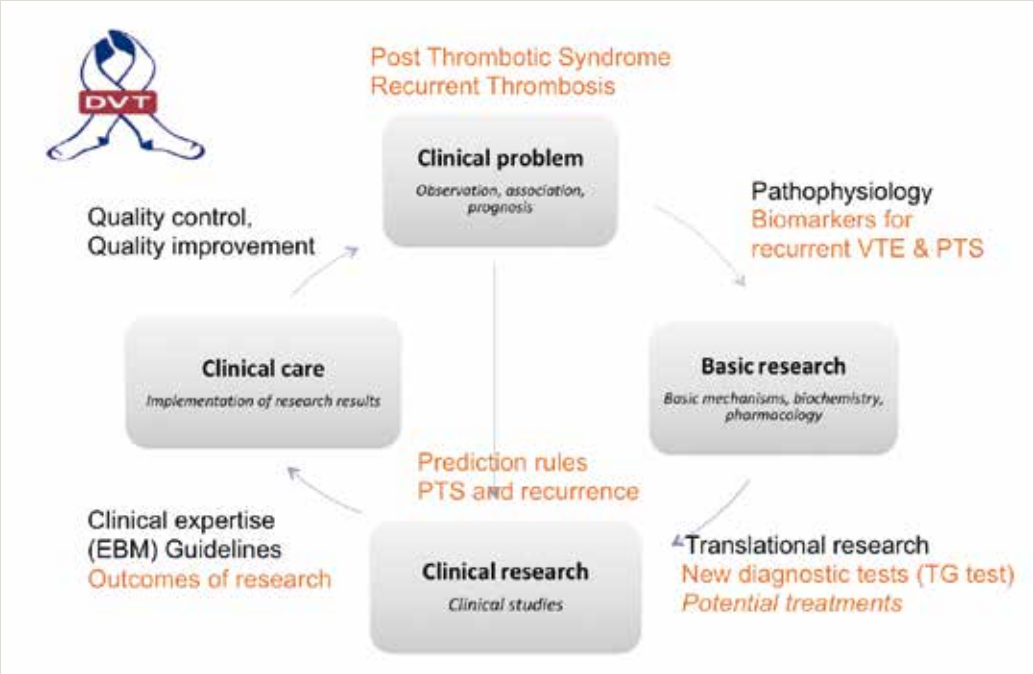


FIGURE 1 Clinical Care Pathway for Deep Venous Thrombosis.

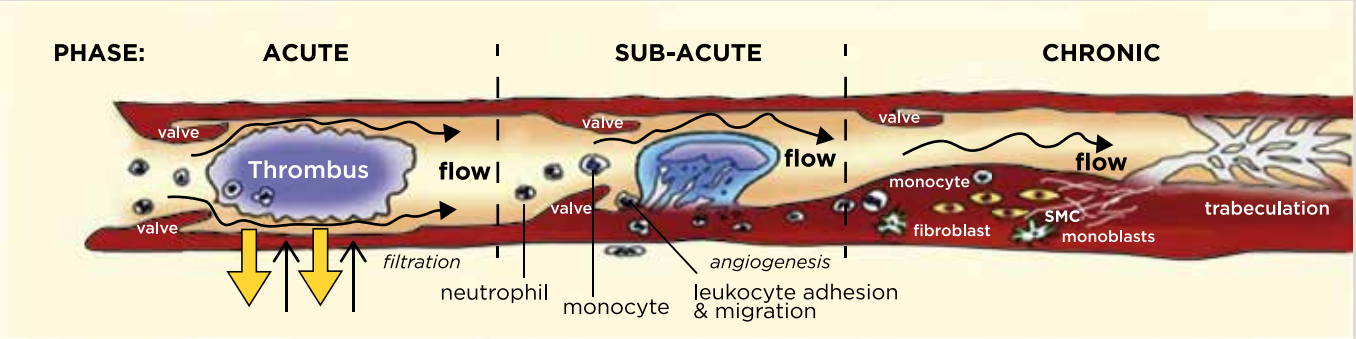
these patients. Patients are followed in the context of a clinical care pathway (CCP). This enables us to capture clinical problems in research questions (at an early point in time) and translate findings from basic research into clinical practice, optimizing treatment as a result. Suitable prevention and treatment are important because DVT patients are relatively young (mean age 57 years) and mostly active within the workforce. The problem of PTS prevention is therefore clearly relevant to patients, doctors as well as policy makers.

One of the important challenges is to select those patients who will benefit the most from treatment. The diagnostic strategy for PTS is currently limited to a clinical scoring system [9]. The critical question is whether biomarkers can be of added value and if so, how this may influence future therapy.

Following acute DVT, recanalisation is enabled by a combination of fibrinolysis, thrombus organisation, and neovascularisation. Complete lysis of the thrombus is associated with fewer PTS manifestations. [10]. Our current understanding of the origin of PTS is that if thrombus resolution is hampered, resulting in a combination of valvular reflux and impaired venous outflow, this will cause ambulatory venous hypertension, which results in complaints such as pain, oedema and skin changes.

The development of PTS can be roughly divided into three phases: the acute thrombotic phase, characterised by active coagulation and inflammatory responses; the subacute phase, where resolution of the thrombus is associated with pronounced inflammatory reactions, driven by reduced flow and reduced oxygenation; and the chronic phase, in which inadequate revascularisation and impaired fibrinolysis result in ongoing venous outflow restriction. It has been shown that both the thrombus and the vein wall play a role in the development of PTS (**Figure 1**) [10,11].

Another major challenge is that of developing suitable treatment modalities for PTS. To achieve this, more attention should be directed towards acquiring knowledge about its pathophysiology, as a basis for the development of treatment options such as thrombolysis (with or without stenting) and pharmaco-therapeutic drugs. PTS is characterised by thrombo-inflammation with vascular remodelling upon impaired thrombus resolution. These features are influenced by flow, and therefore the concept of the “open vein hypothesis” with early thrombus removal by thrombolysis seems reasonable. However, this treatment modality has so far produced conflicting results, and has yielded only limited benefits [12-14]. This makes thrombolytic therapy an unlikely candidate for first-line preventive treatment for PTS. It might, however, offer potential for appropriately selected patients. We intend to investigate this in an individual patient data analysis, together with the investigators of the CaVenT and ATTRACT trials, using their data as well as our own CAVA trial data. While appropriate patient selection might be the answer to PTS prevention at a mechanical-functional level, this does not conclude our quest for suitable preventive treatment for the majority of patients. This will require a more fundamental approach. We previously studied properties of clot structure in patients with PTS and found that the clot structure of these patients was different from those without PTS, with denser fibres, making them more resistant to fibrinolysis. [15]The association between biomarkers and thrombo-inflammation in PTS was only found in the acute phase [16]. We did not find indications of higher levels of inflammatory markers after longer follow-up (median of 63 months) in



patients with PTS, while markers of endothelial damage were still increased at this late point in time. [17] More recently we started to look into gene expression profiles in patients with PTS. This study identified differences in leukocyte gene expression between patients with PTS and patients with a history of DVT without PTS, offering new avenues for further research. An important further objective is to use this knowledge about mechanisms and to be able to apply pharmacological preventive therapies preferably in the acute phase of DVT.

As a proof of principle, we aim to start with a pilot study exploring the use of currently available drugs such as the venoactive O-β-hydroxyethylrutoside, with potential vascular-protective and anti-thrombo-inflammatory properties, as an adjunct to standard anticoagulant therapy. We intend to study the mode of action of this agent in order to answer the critical question whether this drug can re-direct leukocytes to the thrombus rather than the venous wall, which may offer some vascular-protective benefit, potentially by increasing endogenous clot lysis.

REFERENCES

[1] ten Cate-Hoek AJ, Prins MH. Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism: a systematic review. J Thromb Haemost 2005; 3(11): 2465-70.

[2] ten Cate-Hoek AJ, Toll DB, Büller HR et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. J Thromb Haemost. 2009 Dec;7(12):2042-9.

[3] Büller HR, ten Cate-Hoek AJ, Hoes AW et al. Safely ruling out deep venous thrombosis in primary care. Ann Intern Med 2009; 150(4): 229-35.

[4] Cohen AT, Gitt AK, Bauersachs R, et al. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. Thromb Haemost 2017; 117(7): 1326-1337.

[5] Iñurrieta A, Pedrajas JM, Núñez MJ, et al. Outcomes beyond the Third Month of Anticoagulation in Patients Aged >75 Years with a First Episode of Unprovoked Venous Thromboembolism. TH Open 2018; 2(4): e428-e436.

[6] Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009; 145: 286–95.

[7] Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. J Thromb Thrombolysis 2009; 28(4): 465–76.

[8] Kahn SR, Solymoss S, Lamping DL, et al. Long-term outcomes after deep vein thrombosis: postphlebitic syndrome and quality of life. J Gen Intern Med 2000; 15(6): 425–9.

[9] Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009; 7: 879–83.

[10] Meissner MH, Wakefield TW, Ascher E, et al. Acute venous disease: venous thrombosis and venous trauma. J Vasc Surg 2007; 46: 25S–53S Suppl. S.

[11] ten Cate-Hoek AJ, Henke PK, Wakefield TW. The post thrombotic syndrome: Ignore it and it will come back to bite you. Blood Rev 2016; 30(2): 131-7.

[12] Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012; 379: 31–38.

[13] Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med 2017; 377: 2240–52.

[14] Notten P, ten Cate-Hoek AJ, Arnoldussen CWKP, et al. Ultrasound-accelerated catheter-directed thrombolysis versus anticoagulation for the prevention of post-thrombotic syndrome (CAVA): a single-blind, multicentre, randomised trial. Lancet Haematol 2020; 7(1): e40-e49.

[15] Bouman AC, McPherson H, ten Cate-Hoek AJ. Clot structure and fibrinolytic potential in patients with post thrombotic syndrome. Thromb Res 2016; 137: 85-91.

[16] Rabinovich A, Cohen JM, Kahn SR. Predictive value of markers of inflammation in the postthrombotic syndrome: a systematic review: inflammatory biomarkers and PTS. Thromb Res 2015; 136(2): 289-97.

[17] Bouman AC, Cheung YW, ten Cate-Hoek AJ. Biomarkers for post thrombotic syndrome: a case-control study. Thromb Res 2014; 134(2): 369-75.

INTERVIEW

HARRY CRIJNS AND NIKKI PLUYMAEKERS

“Wait and see”: an excellent policy for atrial fibrillation

When the statistical reviewer at the New England Journal of Medicine (NEJM) says there is nothing wrong with your numbers, you feel a strong relief as a cardiovascular researcher. When that same person adds a note saying he is more concerned about the “wait and see” approach for atrial fibrillation advocated in the paper, you suspect that he may be affected by this condition himself! Professor Harry Crijns grins as he tells the anecdote. His name concludes the list of authors of a 2019 NEJM paper, which is headed by PhD candidate Nikki Pluymaekers. He also had a second paper published in the same issue. And at the end of 2019, Pluymaekers and Crijns jointly secured an €800,000 grant for further research into their “wait and see” approach to atrial fibrillation.

Atrial fibrillation resolves spontaneously in 70% of cases, without infusions of medication or electric shock therapy. Hence, a policy of "sitting on your hands" for 48 hours, as Prof. Harry Crijns also calls it, proves just as effective as acute treatment of this cardiac arrhythmia at the emergency department. Not only does a wait and see approach relieve the pressure on the emergency department, it also boosts patients' confidence in their own heart, as it is able to normalize the rhythm itself without any intervention (which always carries risk of complications).

INSPIRATION FROM HEALTHCARE PRACTICE

The notion that a "wait and see" policy could be a promising approach arose in healthcare practice, where the heart rhythm was often seen to recover even before the treatment with medication or defibrillation could be administered. Clinical research physician Nikki Pluymaekers is the second PhD candidate in this project, supervised by Crijns. In a Zoom call, she explains: "The symptoms a patient with atrial fibrillation reports include chest pain, shortness of breath or palpitations. Reducing the heart rate with medication relieves those symptoms. If we then give the body some time to see whether the heart rhythm recovers spontaneously, this actually happens in 70% of cases."

OBSTACLES IN THE STUDY PROCESS

Although the idea of researching this phenomenon in-depth might seem obvious, Crijns, speaking from a second Zoom window, recalls that it was not immediately possible to secure a research grant for it. "After all, nothing is as resistant as routine in a conservative organisation, and the medical profession is as conservative as it gets. Because if you deviate from the standards, things might go wrong." And once the research grant had finally been obtained, another problem arose. The nurses at the cardiac emergency department hardly allowed patients with atrial fibrillation to come to the hospital anymore, as waiting at home to see how things went might be just as effective. "The study initially didn't make as much progress as we had hoped", says Crijns. By having fourteen other centres on-board of the study, they managed to include almost 450 patients, and were able to prove that "wait and see" is just as effective as the standard treatment.

RESEARCH CONTINUES

As the professor knows, this type of "disruptive" research, which results in changes to care practice, can be of interest to the prestigious New England Journal of Medicine (NEJM). The PhD candidate is beaming when the conversation turns to the upcoming formalisation of the new policy for atrial fibrillation in the next guidelines of the European Society of Cardiology. Meanwhile, however, research continues. Pluymaekers: "After 48 hours, we still treated the remaining 30% of patients. But perhaps they just needed a bit more time to spontaneously recover. Therefore, we're going to monitor the same patient group at home, using a RACE-9 grant that we got at the end of 2019." The team received €800,000 from the joint funding programme called "Hart voor duurzame zorg" (sustainable cardiac care) of the Dutch CardioVascular Alliance (DCVA) and the Innovative Medical Devices Initiative (IMDI).

WAITING LONGER THAN 48 HOURS

Patients who present at the emergency department with atrial fibrillation are checked and sent home with a monitoring system. The heart rhythm is measured three times a day plus whenever symptoms arise, and medication can be adjusted by remote management. "In this study

ATRIAL FIBRILLATION RESOLVES SPONTANEOUSLY IN 70% OF CASES, WITHOUT INFUSIONS OF MEDICATION OR ELECTRIC SHOCK THERAPY

we will monitor patients for four weeks, to see if they too recover spontaneously. We think that in the end only 10% will need infused medication or an electric shock", says Pluymaekers. Of course the system includes an alarm function in case the heart rate increases faster or if dangerous rhythms arise. This way, only those patients who really need care have to come to the hospital. The project was originally due to start on 1 May 2020, but because of the coronavirus crisis (which is also the reason why the interview is conducted through Zoom) all patient-based research has been delayed.

MORE ATTENTION TO RISK FACTORS

Most people get atrial fibrillation more than once. A third of the patients in the study reported in NEJM had one or more new episodes within four weeks. Pluymaekers: "Such an episode can also be a sign of insufficiently treated high blood pressure or overweight. Those risk factors should also be treated." Crijns adds: "This study has also contributed greatly to doctors' awareness that what you see (the aberrant ECG) is not the real issue. You have to look at a wider picture than just the heart rhythm, and include underlying cardiovascular problems. Once you've had an arrhythmia, you're at increased risk of premature death; that risk is twice as high without treatment. And the risk of heart failure increases four-fold, etc. You can treat the rhythm primarily to relieve the symptoms, but what's much more important is to correctly gauge the cardiovascular risks and look for underlying abnormalities."

STARTING FROM THE DIAGNOSIS

Crijns' educational self now briefly comes to the fore. "Now that it's possible to visualise many things in the heart, and you have lots of therapeutic options to cure people, it's very important to start from a diagnosis, and work from there. You have to know what's going on. The diagnosis is not: the patient has atrial fibrillation, as that's what I see on the ECG. More than anything, it's a sign of an underlying disorder. Of course what you want to do first of all is treat the rhythm, which is what the patient is complaining of. He doesn't complain about his high blood pressure, and that's something you can't just cure with a shock."

In the same issue of NEJM, Crijns also published a second study, concerning patients with cardiac arrest. The research question was whether such patients still need acute coronary angtioplasty. "That study also found that it's a good idea to wait a while after you've stabilised the patient. And then you can catheterise only those patients who really need it. So the message from this study was also 'There's still time'. So yeah, Maastricht did rather well in NEJM that day."

Prof. Harry Crijns has worked as a cardiologist since 1987, and has specialised in cardiac arrhythmias. He heads the cardiology department at Maastricht UMC+ and is president of the scientific advisory council of the Dutch Heart Foundation, and a member of the scientific advisory council of the Netherlands Heart Institute (previously called ICIN).

Nikki Pluymaekers MD graduated in medicine at Maastricht University in 2016, and has since been engaged in a PhD research project focussing on the treatment and underlying causes of atrial fibrillation. She hopes to obtain her PhD degree in 2020, after which she can start training as a cardiologist.

THEY WERE ABLE TO PROVE THAT "WAIT AND SEE" IS JUST AS EFFECTIVE AS THE STANDARD TREATMENT

INTERVIEW
PIETER REITSMA

ERC chairman looks back on external review

"A fascinating process"

The quality of research at CARIM is "very good to excellent". That was the conclusion of the External Review Committee (ERC) that visited the research school in October 2019. CARIM's PhD programme and the school's social relevance were also highly praised. In the end, however, the purpose of such a review is to improve the school even further. In this respect, it must be said that the gender balance in CARIM's top management, well..., it's basically non-existent. "Simply a matter of taking action", says the committee's chairman, Prof. Pieter Reitsma.

Pieter Reitsma, emeritus professor at Leiden University, has pleasant memories of their visit to Maastricht last year. During the previous external review, he was a member of the committee, while this time he was chairing it. “To some extent, such a committee is something for the elderly”, he says drily. “Each member is an expert in part of the CARIM disciplines, and is reasonably ‘seasoned’, but the chair is usually the oldest member”, he grins. After the committee has ploughed through huge wads of information about the research school, they visit it for a three-day jam-packed programme, which also includes the evenings. “It’s a lot, and it’s intense, but above all it’s really a very pleasant experience. You learn a lot about scientific research, meet interesting people, you get to dine at Chateau Neercanne; the whole process is just fascinating. I can wholeheartedly recommend it.”

NOT THE BIG STICK

Reitsma emphasises that the main purpose of such a review is to further the school’s development. It is guided by the Standard Evaluation Protocol drawn up by the Royal Netherlands Academy of Arts and Sciences (KNAW), which defines all themes to be assessed. “In many cases, the institute itself will indicate targets for improvement, and it may be useful for the management if we offer suggestions. They can serve as incentives to implement changes, as in most organisations such changes do not occur spontaneously. We’re there to help, not to wield the big stick.”

TARGET FOR IMPROVEMENT: GENDER BALANCE

One of the targets for improvement at CARIM was immediately obvious at the first plenary presentation during the review visit. “By the way, it was very nice that all presentations were open to the entire CARIM community, and were not held behind closed doors. Anyway, we entered the room, and behind the table at the front of the room there was the CARIM management, with nametags on the table in front of them. All men! So we really drove the point home that that was not on these days, especially at a university with a female Rector. Of course they are aware of this too, but getting to grips with it is a different matter.”

“IT’S A LOT, AND IT’S INTENSE, BUT ABOVE ALL IT’S REALLY A VERY PLEASANT EXPERIENCE”

The committee did not get the impression that there was a carefully worked out plan in place to redress the balance. “That doesn’t change of its own accord, of course. You have to take action.”

A TIP: “TRANSPARENT COMMUNICATION”

The committee also highlighted the balance between staff trained at CARIM itself and fresh blood coming in from other institutes. At CARIM, this balance has a tendency to tip towards the homegrown talents, whereas the committee feels it is also a good thing if people move out and outsiders come in. “We also noticed that young researchers often didn’t have a clear idea of their future in Maastricht. You have to communicate that in a transparent way, not leave it unclear whether there will be a place for them in the long run. It’s always difficult to say no, which in itself is very human and which you find everywhere.” Finally, the committee sees room for improvement regarding strengthening the strategic basis of investment decisions. “On the whole, however, they’ve passed with flying colours,” concludes Reitsma, “and CARIM can use our report to improve itself even further in the future.”

Prof. Pieter Reitsma retired as Professor of Thrombosis and Haemostasis at Leiden University in 2016. At Leiden, he co-founded the Einthoven Laboratory for Experimental Vascular Medicine. In the course of his scientific career he discovered “Factor V Leiden”, the most common hereditary risk factor for thrombosis. Since his retirement he has worked as Chief Scientific Officer for the spin-off company VarmX.

GRANTS, PRIZES AND HIGHLIGHTS

03

SCIENTIFIC HIGHLIGHTS

In 2019, the successful work of our researchers was reflected in **665** scientific publications in peer refereed journals (**521** refereed articles with Impact Factor, excluding abstracts and **30** letters to the editor), **44** PhD theses, **one** patent, one spin-off company and **2,7** million Euros funding received in competition from national science foundations and **5,6** million Euros funding from third money parties, charities, EU framework programmes and industry. In 2019, the overall average Impact Factor is **6.0**.

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as first and/or last author)

Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, Van Opstal JM, Alings M, Oomen, A, Kirchhof CJ, Van Dijk VF, Ramanna H, Liem A, Dekker LR, Essers BAB, Tijssen JGP, Van Gelder IC, **Crijns HJGM,** RACE 7 ACWAS Investigators
Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation.
New England Journal of Medicine 2019; 380(16): 1499-1508. IF 70.670

Lutgens E, Atzler D, Doering Y, Duchene J, Steffens S, **Weber C**
Immunotherapy for cardiovascular disease.
European Heart Journal 2019; 40(48): 3937-3946. IF 23.239

Goossens P, Rodriguez-Vita J, Etzerodt A, Masse M, Rastoin O, Gouirand V, Ulas T, Papantonopoulou O, Van Eck M, Auphan-Anezin N, Bebien M, Verthuy C, Thien Phong Vu Manh, Turner M, Dalod M, Schultze JL, Lawrence T
Membrane Cholesterol Efflux Drives Tumor-Associated Macrophage Reprogramming and Tumor Progression.
Cell Metabolism 2019; 29(6): 1376-1389. IF 22.415

Smulders MW, Kietselaer BLJH, Wildberger JE, Dagnelie PC, Brunner-La Rocca H-P, Mingels AMA, van Cauteren YJM, Theunissen RALJ, Post MJ, Schalla S, van Kuijk SMJ, **Das M,** Kim RJ, **Crijns HJGM, Bekkers SCAM**
Initial Imaging-Guided Strategy Versus Routine Care in Patients With Non-ST-Segment Elevation Myocardial Infarction.
Journal of the American College of Cardiology 2019; 74(20): 2466-2477. IF 18.639

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as first and/or last author)

van der Meijden PEJ, Heemskerk JWM
Platelet biology and functions: new concepts and clinical perspectives.
Nature Reviews Cardiology 2019; 16(3): 166-179. IF 17.420

Mahmoud AD, Ballantyne MD, Miscianinov V, Pinel K, Hung J, Scanlon JP, Iyinikkel J, Kaczynski J, Tavares AS, Bradshaw AC, Mills NL, Newby DE, Caporali A, Gould GW, George SJ, Ulitsky I, **Sluimer JC,** Rodor J, **Baker AH**
The Human-Specific and Smooth Muscle Cell-Enriched LncRNA SMILR Promotes Proliferation by Regulating Mitotic CENPF mRNA and Drives Cell-Cycle Progression Which Can Be Targeted to Limit Vascular Remodeling.
Circulation Research 2019; 125(5): 535-551. IF 15.862

Kario K, Thijs L**, Staessen JA**
Blood Pressure Measurement and Treatment Decisions Masked and White-Coat Hypertension.
Circulation Research 2019; 124(7): 990-1008. IF 15.862

de Boer RA, De Keulenaer G, Bauersachs J, Brutsaert D, Cleland JG, Diez J, Du X-J, Ford P, Heinzel FR, Lipson KE, McDonagh T, Lopez-Andres N, Lunde IG, Lyon AR, Pollesello P, Prasad SK, Tocchetti CG, Mayr M, Sluijter JPG, Thum T, Tschoepe C, Zannad F, Zimmermann W-H, Ruschitzka F, Filippatos G, Lindsey ML, Maack C, **Heymans S**
Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology.
European journal of heart failure 2019; 21(3): 272-285. IF 13.965

Hahn RT, Waxman AB, Denti P, **Delhaas T**
Anatomic Relationship of the Complex Tricuspid Valve, Right Ventricle, and Pulmonary Vasculature A Review.
JAMA Cardiology 2019; 4(5): 478-487. IF 11.866

van Sloten TT, Boutouyrie P, Tafflet M, Offredo L, Thomas F, Guibout C, Climie RE, Lemogne C, Pannier B, Laurent S, Jouven X, Empana J-P
Carotid Artery Stiffness and Incident Depressive Symptoms: The Paris Prospective Study III.
Biological Psychiatry 2019; 85(6): 498-505. IF 11.501

Gorcsan J, Anderson CP, Tayal B, Sugahara M, Walmsley J, Starling RC, **Lumens J**
Systolic Stretch Characterizes the Electromechanical Substrate Responsive to Cardiac Resynchronization Therapy.
JACC-Cardiovascular Imaging 2019; 12(9): 1741-1752. IF 10.975

Bianchini M, Duchene J, Santovito D, Schloss MJ, Evrard M, Winkels H, Aslani M, Mohanta SK, Horckmans M, Blanchet X, Lacy M, von Hundelshausen P, Atzler D, Habenicht A, Gerdes N, Pelisek J, Ng LG, Steffens S, **Weber C, Megens RTA**
PD-L1 expression on nonclassical monocytes reveals their origin and immunoregulatory function.
Science Immunology 2019; 4(36): Article 3054. IF 10.551

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as as co-author)

Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA., Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GH, Eikemans BJW, van der Harst P, **van der Horst IIC,** Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, Van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans TACM, de Ruijter W, Delnoij TSR, **Crijns HJGM,** Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Van de Ven PM, Oudemans-van Straaten HM, van Royen N
Coronary Angiography after Cardiac Arrest without ST-Segment Elevation.
New England Journal of Medicine 2019; 380(15), 1397-1407. IF 70.670

Claassens DMF, Vos GJA, **Bergmeijer TO,** Hermanides RS, **van 't Hof AWJ,** van der Harst P, Barbato E, Morisco C, Gin RMTJ, Asselbergs FW, Mosterd A, Herrman J-PR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A, Boersma C, Deneer VHM, ten Berg JM
A Genotype-Guided Strategy for Oral P2Y(12) Inhibitors in Primary PCI.
New England Journal of Medicine 2019; 381(17): 1621-1631. IF 70.670

Piccolo R, Bonaa KH, Efthimiou O, Varenne O, Oliva B, Urban P, Kaiser C, Remkes W, Raber L, de Belder A, **van 't Hof A**, Stankovic G, Lemos PA, Wilsgaard T, Reifart J, Rodriguez AE, Ribeiro EE, Serruys PW, Abizaid A, Sabate M, Byrne RA, de la Torre Hernandez JM, Wijns W, Juni P, Windecker S, Valgimigli M.
Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials.
Lancet 2019; 393(10190): 2503-2510. IF 59.102

Yang W-Y, Melgarejo JD, Thijs L, Zhang Z-Y, Boggia J, Wei F-F, Hansen TW, Asayama K, Ohkubo T, Jeppesen J, Dolan E, Stolarz-Skrzypek K, Malyutina S, Casiglia E, Lind L, Filipovsky J, Maestre G, Li Y, Wang J-G, Imai Y, Kawecka-Jaszcz K, Sandoya E, Narkiewicz K, O'Brien E, Verhamme P, **Staessen JA**, Mujaj B, Cauwenberghs N, Kuznetsova T, Thijs L, Wei F-F, Yang W-Y, Yu C-G, Zhang Z-Y, Li Y, Sheng C-S, Huang Q-F, Wang J-G, Filipovsky J, Seidlerova J, Ticha M, Hansen TW, Ibsen H, Jeppesen J, Rasmussen S, Torp-Pedersen C, Dolan E, O'Brien E, Casiglia E, Int Database Ambulatory Blood.
Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes.
JAMA 2019; 322(5): 409-420. IF 51.273

Silvestre-Roig C, Braster Q, **Wichapong K,** Lee EY, Marie Teulon J, Berrebeh N, Winter J, Adrover JM, Santos GS, Froese A, Lemnitzer P, Ortega-Gomez A, Chevre R, Marschner J, Schumski A, Winter C, Perez-Olivares L, Pan C, Paulin N, Schoufour T, Hartwig H, Gonzalez-Ramos S, Kamp F, **Megens RTA,** Mowen KA, Gunzer M, Maegdefessel L, **Hackeng T,** Lutgens E, Daemen M, von Blume J, Anders H-J, Nikolaev VO, Pellequer J-L, **Weber C,** Hidalgo A, **Nicolaes GAF,** Wong GCL, Soehnlein O
Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death.
Nature 2019; 569(7755): 236-240. IF 43.070

Yin C, Ackermann S, Ma Z, Mohanta SK, Zhang C, Li Y, Nietzsche S, Westermann M, Peng L, Hu D, Bontha SV, Srikakulapu P, Beer M, **Megens RTA,** Steffens S, Hildner M, Halder LD, Eckstein H-H, Pelisek J, Herms J, Roeber S, Arzberger T, Borodovsky A, Habenicht L, Binder CJ, **Weber C,** Zipfel PF, Skerka C, Habenicht AJR
ApoE attenuates unresolvable inflammation by complex formation with activated C1q.
Nature Medicine 2019; 25(3): 496-506. IF 30.641

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as co-author)

Campbell BCV, Majoie CBLM, Albers GW, Menon BK, Yassi N, Sharma G, **van Zwam WH, van Oostenbrugge** RJ, Demchuk AM, Guillemin F, White P, Davalos A, van der Lugt A, Butcher KS, Cherifi A, Marquering HA, Cloud G, Macho Fernandez JM, Madigan J, Oppenheim C, Donnan GA, Roos YBWEM, Shankar J, Lingsma H, Bonafe A, Raoult H, Hernandez-Perez M, Bharatha A, Jahan R, Jansen O, Richard S, Levy EI, Berkhemer OA, Soudant M, Aja L, Davis SM, Krings T, Tisserand M, San Roman L, Tomasello A, **Beumer D,** Brown S, Liebeskind DS, Bracard S, Muir KW, Dippel DWJ, Goyal M, Saver JL, Jovin TG, Hill MD, HERMES Collaborators
Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data.
Lancet Neurology 2019; 18(1): 46-55. IF 28.755

Wilson D, Ambler G, Lee K-J, Lim J-S, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, Wong YK, Mak HKF, Prats-Sanchez L, Martinez-Domeno A, Inamura S, Yoshifuji K, Arsava EM, Horstmann S, Purrucker J, Lam BYK, Wong A, Kim YD, Song T-J, Schrooten M, Lemmens R, Eppinger S, Gattringer T, Uysal E, Tanriverdi Z, Bornstein NM, Ben Assayag E, Hallevi H, Tanaka J, Hara H, Coutts SB, Hert L, Polymeris A, Seiffge DJ, Lyrer P, Algra A, Kappelle J, Salman RA-S, Jager HR, Lip GYH, Mattle HP, Panos LD, Mas J-L, **Kooi ME, van Oostenbrugge R, Staals J,** Microbleeds Int Collaborative Net.
Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies.
Lancet Neurology 2019; 18(7): 653-665. IF 28.755

Smith-Bindman R, Wang Y, Chu P, Chung R, Einstein AJ, Balcombe J, Cocker M, Das M, Delman BN, Flynn M, Gould R, Lee RK, Yellen-Nelson T, Schindera S, Seibert A, Starkey J, Suntharalingam S, Wetter A, **Wildberger JE,** Miglioretti DL
International variation in radiation dose for computed tomography examinations: prospective cohort study.
BMJ (e) 2019; 364: 1-12. IF 27.604

Linner RK, Biroli P, Kong E, Meddens FW, Wedow R, Fontana MA, Lebreton M, Tino SP, Abdellaoui A, Hammerschlag AR, Nivard MG, Okbay A, Rietveld CA, Timshel PN, Trzaskowski M, de Vlaming R, Zund CL, Bao Y, Buzdugan L, Caplin AH, Chen C-Y, Eibich P, Fontanillas P, Gonzalez JR, Joshi PK, Karhunen V, Kleinman A, Levin RZ, Lill CM, Meddens GA, Muntane G, Sanchez-Roige S, van Rooij FJ, Taskesen E, Wu Y, Zhang F, Agee M, Alipanahi B, Bell RK, Bryc K, Elson SL, Furlotte NA, Huber KE, Litterman NK, McCreight JC, McIntyre MH, Mountain JL, Zhao W, **Staessen JA,** Bultmann U, 23and Me Res Team, eQTLGen Consortium, Int Cannabis Consortium, Soc Sci Genetic Association Con.
Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences.
Nature Genetics 2019; 51(2): 245-256. IF 25.455

Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhoff D, Bonow RO, Chopra VK, de Boer RA, **de Windt L,** Hamdani N, Hasenfuss G, **Heymans S,** Hulot J-S, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR**,** Maack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T, Rosano G, Rouleau J, Seferovic PM, Shah AM, Starling RC, Tocchetti CG, Trochu J-N, Thum T, Zannad F, Brutsaert DL, Segers VF, De Keulenaer G
The continuous heart failure spectrum: moving beyond an ejection fraction classification.
European Heart Journal 2019; 40(26): 2155-2163. IF 23.239

Seijkens TTP, Poels K, Meiler S, van Tiel CM, Kusters PJH, Reiche M, Atzler D, Winkels H, Tjwa M, **Poelman H,** Slutter B, Kuiper J, **Gijbels M,** Kuivenhoven JA, Matic LP, Paulsson-Berne G, Hedin U, Hansson GK, **Nicolaes GAF,** Daemen MJAP, **Weber C,** Gerdes N, de Winther MPJ, Lutgens E
Deficiency of the T cell regulator Casitas B-cell lymphoma-B aggravates atherosclerosis by inducing CD8(+) T cell-mediated macrophage death.
European Heart Journal 2019; 40(4): 372-382. IF 23.239

Maack C, Eschenhagen T, Hamdani N, Heinzel FR, Lyon AR, Manstein DJ, Metzger J, Papp Z, Tocchetti CG, Yilmaz MB, Anker SD, Balligand J-L, Bauersachs J, Brutsaert D, Carrier L, Chlopicki S, Cleland JG, de Boer RA, Dietl A, Fischmeister R, Harjola V-P, **Heymans S,** Hilfiker-Kleiner D, Holzmeister J, de Keulenaer G, Limongelli G, Linke WA, Lund LH, Masip J, Metra M, Mueller C, Pieske B, Ponikowski P, Ristic A, Ruschitzka F, Seferovic PM, Skouri H, Zimmermann WH, Mebazaa A
Treatments targeting inotropy.
European Heart Journal 2019; 40(44): 3626-3640. IF 23.239

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as as co-author)

Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, Popescu BA, Prendergast B, Tornos P, Sadeghpour A, Oliver L, Vaskelyte J-J, Sow R, Axler O, Maggioni AP, Lancellotti P, Granada, Mahia M, Ressi S, Nacinovich F, Iribarren A, Fernandez Oses P, Avegliano G, Filipini E, Obregon R, Bangher M, Dho J, Cartasegna L, Plastino ML, Novas, Shigel C, Reyes G, Schneider M, Ahmed M, Ali M, Landry G, Wild C, Papadopoulos C, **Crijns HJ, Bekkers SC, Cheriex EC, Gilbers M, Kietselaer BL, Knackstedt C, Lorusso R, Schalla S,** Streukens SA, van Dongen E, Ahmed B, Ahmed A, EURO-ENDO Investigators
Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study.
European Heart Journal 2019; 40(39): 3222-3232. IF 23.239

Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, Brandes A, Bustamante A, Casadei B, **Crijns HJGM,** Doehner W, Engstrom G, Fauchier L, Friberg L, Gladstone DJ, Glotzer TV, Goto S, Hankey GJ, Harbison JA, Hobbs FDR, Johnson LSB, Kamel H, Kirchhof P, Korompoki E, Krieger DW, Lip GYH, Lochen M-L, Mairesse GH, Montaner J, Neubeck L, Ntaios G, Piccini JP, Potpara TS, Quinn TJ, Reiffel JA, Ribeiro ALP, Rienstra M, Rosenqvist M, Sakis T, Sinner MF, Svendsen JH, Van Gelder IC, Wachter R, Wijeratne T, Yan B
Searching for Atrial Fibrillation Poststroke A White Paper of the AF-SCREEN International Collaboration.
Circulation 2019; 140(22): 1834-1850. IF 23.054

Gurbel PA, Fox KAA, Tantry US, **ten Cate H,** Weitz J
Combination Antiplatelet and Oral Anticoagulant Therapy in Patients With Coronary and Peripheral Artery Disease Focus on the COMPASS Trial.
Circulation 2019; 139(18): 2170-2185. IF 23.054

Cremer S, Michalik KM, Fischer A, Pfisterer L, Jae N, Winter C, Boon RA, Muhly-Reinholz M, John D, Uchida S, **Weber C,** Poller W, Guenther S, Braun T, Li DY, Maegdefessel L, Matic LP, Hedin U, Soehnlein O, Zeiher A, Dimmeler S
Hematopoietic Deficiency of the Long Noncoding RNA MALAT1 Promotes Atherosclerosis and Plaque Inflammation.
Circulation 2019; 139(10): 1320-1334. IF 23.054

Adrover JM, del Fresno C, Crainiciuc G, Isabel Cuartero M, Casanova-Acebes M, Weiss LA, Huerga-Encabo H, Silvestre-Roig C, Rossaint J, Cossio I, Lechuga-Vieco AV, Garcia-Prieto J, Gomez-Parrizas M, Quintana JA, Ballesteros I, Martin-Salamanca S, Aroca-Crevillen A, Chong SZ, Evrard M, Balabanian K, Lopez J, Bidzhekov K, Bachelerie F, Abad-Santos F, Munoz-Calleja C, Zarbock A, Soehnlein O, **Weber C,** Ng LG, Lopez-Rodriguez C, Sancho D, Moro MA, Ibanez B, Hidalgo A
A Neutrophil Timer Coordinates Immune Defense and Vascular Protection.
Immunity 2019; 50(2): 390-402. IF 21.522

Mossanen JC, Kohlhepp M, Wehr A, Krenkel O, Liepelt A, Roeth AA, Moeckel D, Heymann F, Lammers T, Gassler N, Hermann J, **Jankowski J,** Neumann UP, Luedde T, Trautwein C, Tacke F
CXCR6 Inhibits Hepatocarcinogenesis by Promoting Natural Killer T- and CD4(+) T-Cell-Dependent Control of Senescence.
Gastroenterology 2019; 156(6): 1877-1889.e4. IF 19.233

Paumelle R, Haas JT, Hennuyer N, Bauge E, Deleye Y, Mesotten D, Langouche L, Vanhoutte J, Cudejko C, **Wouters K,** Hannou SA, Legry V, Lancel S, Lalloyer F, Polizzi A, Smati S, Gourdy P, Vallez E, Bouchaert E, Derudas B, Dehondt H, Gheeraert C, Fleury S, Tailleux A, Montagner A, Wahli W, Van den Berghe G, Guillou H, Dombrowicz D, Staels B
Hepatic PPAR alpha is critical in the metabolic adaptation to sepsis.
Journal of Hepatology 2019; 70(5): 963-973. IF 18.946

Lee KK, Ferry AV, Anand A, Strachan FE, Chapman AR, **Kimenai DM, Meex SJR,** Berry C, Findlay I, Reid A, Cruickshank A, Gray A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Keerie C, Weir CJ, Shah ASV, Mills NL, High-STEACS Investigators
Sex-Specific Thresholds of High-Sensitivity Troponin in Patients With Suspected Acute Coronary Syndrome.
Journal of the American College of Cardiology 2019; 74(16): 2032-2043. IF 18.639

Ferraro B, Leoni G, Hinkel R, Ormanns S, Paulin N, Ortega-Gomez A, Viola JR, de Jong R, Bongiovanni D, Bozoglu T, Maas SL, D'Amico M, Kessler T, Zeller T, Hristov M, **Reutelingsperger C,** Sager HB, Doering Y, Nahrendorf M, Kupatt C, Soehnlein O
Pro-Angiogenic Macrophage Phenotype to Promote Myocardial Repair.
Journal of the American College of Cardiology 2019; 73(23): 2990-3002. IF 18.639

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as co-author)

Dobrev D, Aguilar M, **Heijman J,** Guichard J-B, Nattel S
Postoperative atrial fibrillation: mechanisms, manifestations and management.
Nature Reviews Cardiology 2019; 16(7): 417-436. IF 17.420

Niederer SA, **Lumens J,** Trayanova NA
Computational models in cardiology.
Nature Reviews Cardiology 2019; 16(2): 100-111. IF 17.420

Klotz L, Eschborn M, Lindner M, Liebmann M, Herold M, Janoschka C, Garrido BT, Schulte-Mecklenbeck A, Gross CC, Breuer J, Hundehege P, Posevitz V, Pignolet B, Nebel G, Glander S, Freise N, Austermann J, Wirth T, Campbell GR, Schneider-Hohendorf T, Eveslage M, Brassat D, Schwab N, Loser K, Roth J, Busch KB, **Stoll M,** Mahad DJ, Meuth SG, Turner T, Bar-Or A, Wiendl H
Teriflunomide treatment for multiple sclerosis modulates T cell mitochondrial respiration with affinity-dependent effects.
Science Translational Medicine 2019; 11(490): Article 5563. IF 17.161

Heestermans M, Salloum-Asfar S, Streef T, Laghmani EH, Salvatori D, Luken BM, Zeerleder SS, **Spronk HMH,** Korporaal SJ, Kirchhofer D, Wagenaar GTM, Versteeg HH, Reitsma PH, Renne T, van Vlijmen BJM
Mouse venous thrombosis upon silencing of anticoagulants depends on tissue factor and platelets, not FXII or neutrophils.
Blood 2019; 133(19): 2090-2099. IF 16.562

Downes K, Megy K, Duarte D, **Vries M,** Gebhart J, Hofer S, Shamardina O, Deevi SVV, Stephens J, Mapeta R, Tuna S, Al Hasso N, Besser MW, Cooper N, Daugherty L, Gleadall N, Greene D, Haimel M, Martin H, Papadia S, Revel-Vilk S, Sivapalaratnam S, Symington E, Thomas W, Thys C, Tolios A, Penkett CJ, Ouwehand WH, Abbs S, Laffan MA, Turro E, Simeoni I, Mumford AD, **Henskens YMC,** Pabinger I, Gomez K, Freson K, NIHR BioResource
Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders.
Blood 2019; 134(23): 2082-2091. IF 16.562

Brandsma E, Kloosterhuis NJ, Koster M, Dekker DC, **Gijbels MJJ,** van der Velden S, Rios-Morales M, van Faassen MJR, Loreti MG, de Bruin A, Fu J, Kuipers F, Bakker BM, Westerterp M, de Winther MPJ, Hofker MH, van de Sluis B, Koonen DPY
A Proinflammatory Gut Microbiota Increases Systemic Inflammation and Accelerates Atherosclerosis.
Circulation Research 2019; 124(1): 94-100. IF 15.862

Climie RE, **van Sloten TT,** Perier M-C, Tafflet M, Fayosse A, Dugravot A, Singh-Manoux A, Empana J-P
Change in Cardiovascular Health and Incident Type 2 Diabetes and Impaired Fasting Glucose: The Whitehall II Study.
Diabetes Care 2019; 42(10): 1981-1987. IF 15.270

Heerkens M, Dedden S, Scheepers H, **Van Paassen P,** Masclee A, de Die-Smulders C, Olde Damink SWM, Schaap FG, Jansen P, Koek G, Beuers U, Verbeek J
Effect of Plasmapheresis on Cholestatic Pruritus and Autotaxin Activity During Pregnancy.
Hepatology 2019; 69(6): 2707-2710. IF 14.971

Mullens W, Damman K, Harjola V-P, Mebazaa A, **Brunner-La Rocca H-P,** Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ
The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology.
European journal of heart failure 2019; 21(2): 137-155. IF 13.965

Bauersachs J, Koenig T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, Hamdan R, Jackson AM, Forsyth P, de Boer RA, Mueller C, Lyon AR, Lund LH, Piepoli MF, **Heymans S,** Chioncel O, Anker SD, Ponikowski P, Seferovic PM, Johnson MR, Mebazaa A, Sliwa K
Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy.
European journal of heart failure 2019; 21(7): 827-843. IF 13.965

Beldman TJ, Malinova TS, Desclos E, Grootemaat AE, Misiak ALS, van der Velden S, van Roomen CPAA, Beckers L, van Veen HA, Krawczyk PM, Hoebe RA, **Sluimer JC,** Neele AE, de Winther MPJ, van der Wel NN, Lutgens E, Mulder WJM, Huveneers S, Kluza E
Nanoparticle-Aided Characterization of Arterial Endothelial Architecture during Atherosclerosis Progression and Metabolic Therapy.
ACS Nano 2019; 13(12): 13759-13774. IF 13.903

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as as co-author)

Plat J, Baumgartner S, Vanmierlo T, Luetjohann D, Calkins KL, Burrin DG, Guthrie G, Thijs C, Te Velde AA, Vreugdenhil ACE, Sverdlov R, Garssen J, **Wouters K,** Trautwein EA, Wolfs TG, van Gorp C, Mulder MT, Riksen NP, Groen AK, Mensink RP
Plant-based sterols and stanols in health & disease: "Consequences of human development in a plant-based environment?".
Progress in Lipid Research 2019; 74: 87-102. IF 12.540

Marini S, Crawford K, Morotti A, Lee MJ, Pezzini A, Moomaw CJ, Flaherty ML, Montaner J, Roquer J, Jimenez-Conde J, Giralt-Steinhauer E, Elosua R, Cuadrado-Godia E, Soriano-Tarraga C, Slowik A, Jagiella JM, Pera J, Urbanik A, Pichler A, Hansen BM, McCauley JL, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Testai FD, Kittner SJ, Schmidt H, Enzinger C, Deary LJ, Rannikmae K, Samarasekera N, Salman RA-S, Sudlow CL, Klijn CJM, van Nieuwenhuizen KM, Fernandez-Cadenas I, Delgado P, Nonving B, Lindgren A, Goldstein JN, Viswanathan A, Greenberg SM, Falcone GJ, Biffi A, Langefeld CD, **Staals J**, Int Genetics Consortium
Association of Apolipoprotein E With Intracerebral Hemorrhage Risk by Race/Ethnicity A Meta-analysis.
JAMA Neurology 2019; 76(4): 480-491. IF 12.321

Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, San Roman L, Heo J-H, Ribo M, Almekhlafi MA, Liebeskind DS, Teitelbaum J, Cuadras P, de Rochemont RDM, Beaumont M, Brown MM, Yoo AJ, Donnan GA, Mas JL, Oppenheim C, Dowling RJ, Moulin T, Agrinier N, Lopes DK, Aja Rodriguez L, Compagne KCJ, Al-Ajlan FS, Madigan J, Albers GW, Soize S, Blasco J, Davis SM, Nogueira RG, Davalos A, Menon BK, van der Lugt A, Muir KW, Roos YBWEM, White P, Mitchell PJ, Demchuk AM, **van Zwam WH,** Jovin TG, **van Oostenbrugge RJ,** Dippel DWJ, Campbell BCV, Guillemin F, Bracard S, Hill MD, Goyal M, Marquering HA, Majoie CBLM
Mediation of the Relationship Between Endovascular Therapy and Functional Outcome by Follow-up Infarct Volume in Patients With Acute Ischemic Stroke.
JAMA Neurology 2019; 76(2): 194-202. IF 12.321

Bourcier R, Goyal M, Liebeskind DS, Muir KW, Desal H, Siddiqui AH, Dippel DWJ, Majoie CB, van Zwam WH, Jovin TG, Levy EI, Mitchell PJ, Berkhemer OA, Davis SM, Derraz L, Donnan GA, Demchuk AM, **van Oostenbrugge RJ,** Kelly M, Roos YB, Jahan R, van der Lugt A, Sprengers M, Velasco S, Nijeholt GJLA, Ben Hassen W, Burns P, Brown S, Chabert E, Krings T, Chloe H, Weimar C, Campbell BCV, Ford GA, Ribo M, White P, Cloud GC, San Roman L, Davalos A, Naggara O, Hill MD, Bracard S, HERMES Trialists Collaboration
Association of Time From Stroke Onset to Groin Puncture With Quality of Reperfusion After Mechanical Thrombectomy A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials.
JAMA Neurology 2019; 76(4):405-411. IF 12.321

Porcu E, Rueger S, Lepik K, Agbessi M, Ahsan H, Alves I, Andiappan A, Arindrarto W, Awadalla P, Battle A, Beutner F, Bonder MJ, Boomsma D, Christiansen M, Claringbould A, Deelen P, Esko T, Fave M-J, Franke L, Frayling T, Gharib SA, Gibson G, Heijmans BT, Hemani G, Jansen R, Kahonen M, Kalnapenkis A, Kasela S, Kettunen J, Kim Y, Kirsten H, Kovacs P, Krohn K, Kronberg-Guzman J, Kukushkina V, Lee B, Lehtimaki T, Loeffler M, Marigorta UM, Mei H, Milani L, Montgomery GW, Mueler-Nurasyid M, Nauck M, **Stehouwer CDA, Isaacs A, Schalkwijk CG, van der Kallen CJH, van Greevenbroek MMJ,** eQTLGen Consortium, BIOS Consortium
Mendelian randomization integrating GWAS and eQTL data reveals genetic determinants of complex and clinical traits.
Nature Communications 2019; 10:Article 3300. IF 11.878

Liu J, Carnero-Montoro E, van Dongen J, Lent S, Nedeljkovic I, Ligthart S, Tsai P-C, Martin TC, Mandaviya PR, Jansen R, Peters MJ, Duijts L, Jaddoe VWV, Tiemeier H, Felix JF, Willemsen G, de Geus EJC, Chu AY, Levy D, Hwang S-J, Bressler J, Gondalia R, Salfati EL, Herder C, Hidalgo BA, Tanaka T, Moore AZ, Lemaitre RN, Jhun MA, Smith JA, Sotoodehnia N, Bandinelli S, Ferrucci L, Arnett DK, Grallert H, Assimes TL, Hou L, Baccarelli A, Whitsel EA, van Dijk KW, Amin N, Uitterlinden AG, Sijbrands EJG, Franco OH, Dehghan A, Spector TD, Dupuis J, Hivert M-F, Rotter J, Meigs JB, Pankow JS, van Meurs JBJ, **Isaacs A,** Boomsma D, Bell JT, Demirkan A, van Duijn CM
An integrative cross-omics analysis of DNA methylation sites of glucose and insulin homeostasis.
Nature Communications 2019; 10: Article 2581. IF 11.878

TOP PUBLICATIONS

WITH THE HIGHEST IMPACT FACTOR IN 2019 (with CARIM researcher as co-author)

Noordegraaf AV, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, Kawut SM, Langleben D, **Lumens J,** Naeije R
Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update.
European Respiratory Journal 2019: 53(1): Article 1801900. IF 11.807

Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, **Lorusso R,** Mazzolai L, Meneveau N, Áinle FN, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL, The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC).
European Respiratory Journal 2019; 54(3): Article 1901647. IF 11.807

van Dongen J, Zilhao NR, Sugden K, Hannon EJ, Mill J, Caspi A, Agnew-Blais J, Arseneault L, Corcoran DL, Moffitt TE, Poulton R, Franke B, Boomsma D, Heijmans BT, t'Hoen PAG, van Meurs J, **Isaacs A,** Jansen R, Franke L, Pool R, Hottenga JJ, **van Greevenbroek MMJ, Stehouwer CDA, van der Kallen CJH, Schalkwijk CG,** Wijmenga C, Zhernakova S, Tigchelaar EF, Slagboom PE, Beekman M, Deelen J, van Heemst D, Veldink JH, van den Berg LH, van Duijn CM, Hofman BA, Uitterlinden AG, Jhamai PM, Verbiest M, Suchiman HED, Verkerk M, van der Breggen R, van Rooij J, Lakenberg N, Mei H, van Iterson M, van Galen M, Bot J, Zhernakova D, van t' Hof P, BIOS Consortium
Epigenome-wide Association Study of Attention-Deficit/ Hyperactivity Disorder Symptoms in Adults.
Biological Psychiatry 2019; 86(8): 599-607. IF 11.501

Benedikter BJ, Bouwman FG, **Heinzmann ACA, Vajen T,** Mariman EC, Wouters EFM, Savelkoul PHM, **Koenen RR,** Rohde GGU, **van Oerle R, Spronk HM,** Stassen FRM
Proteomic analysis reveals procoagulant properties of cigarette smoke-induced extracellular vesicles.
Journal of Extracellular Vesicles 2019; 8(1): Article 1585163. IF 11.000

Mast TP, Taha K, Cramer MJ, **Lumens J,** van der Heijden JF, Bouma BJ, van den Berg MP, Asselbergs FW, Doevendans PA, Teske AJ
The Prognostic Value of Right Ventricular Deformation Imaging in Early Arrhythmogenic Right Ventricular Cardiomyopathy.
JACC-Cardiovascular Imaging 2019; 12(3): 446-455. IF 10.975

Mentrup T, **Theodorou K,** Cabrera-Cabrera F, Hethig AO, Happ K, **Gijbels M,** Gradtke A-C, Rabe B, Fukumori A, Steiner H, Tholey A, Fluhrer R, **Donners M,** Schroeder B
Atherogenic LOX-1 signaling is controlled by SPPL2-mediated intramembrane proteolysis.
Journal of Experimental Medicine 2019; 216(4): 807-830. IF 10.892

Arts P, Simons A, AlZahrani MS, Yilmaz E, Alldrissi E, van Aerde KJ, Alenezi N, AlGhamdi HA, AlJubab HA, Al-Hussaini AA, AlManjomi F, Alsaad AB, Alsaleem B, Andijani AA, Asery A, Ballourah W, Bleeker-Rovers CP, van Deuren M, van der Flier M, Gerkes EH, Gilissen C, Habazi MK, Hehir-Kwa JY, Henriet SS, Hoppenreijs EP, Hortillosa S, Kerkhofs CH, Keski-Filppula R, Lelieveld SH, Lone K, MacKenzie MA, Mensenkamp AR, Moilanen J, Nelen M, ten Oever J, Potjewijd J, **van Paassen P,** Schuurs-Hoeijmakers JHM, Simon A, Stokowy T, van de Vorst M, Vreeburg M, Wagner A, van Well GTJ, Zafeiropoulou D, Zonneveld-Huijssoon E, Veltman JA, van Zelst-Stams WAG, Faqeih EA, van de Veerdonk FL, Netea MG, Hoischen A
Exome sequencing in routine diagnostics: a generic test for 254 patients with primary immunodeficiencies.
Genome Medicine 2019; 11: 1-15. IF 10.886

Zhong H, Penders J, Shi Z, Ren H, Cai K, Fang C, Ding Q, Thijs C, Blaak EE, **Stehouwer CDA,** Xu X, Yang H, Wang J, Wang J, Jonkers DMAE, Masclee AAM, Brix S, Li J, **Arts ICW,** Kristiansen K
Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children.
Microbiome 2019; 7: Article 2. IF 10.465

RESEARCH GRANTS AWARDED TO INDIVIDUALS

NWO TALENT SCHEME

Dr **Rachel ter Bekke** (Dept. of Cardiology) and Dr **Alma Mingels** (Dept. of Clinical Chemistry, Central Diagnostic Laboratory) both received one of the 24 Veni grants awarded in the field of Medicine by the Netherlands Organisation for Scientific Research (NWO). Rachel ter Bekke received the grant for her research project "Mechanics matter: high-resolution electromechanical mapping to unravel ventricular tachyarrhythmias". The goal of this project is to establish high spatiotemporal resolution (non)invasive electromechanical mapping in long-QT syndrome patients at baseline and during smart pharmacological provocation in order to improve sudden death risk stratification. Also, the mechano-electric coupling preceding ventricular tachyarrhythmias will be assessed by using a novel intracardiac electromechanical mapping catheter in a drug-induced long-QT animal model. This research will highlight the importance of mechanics on the occurrence of ventricular ectopy and tachyarrhythmias in the long-QT syndrome. Insights obtained from these analyses may facilitate sudden cardiac death risk stratification for patients with the long-QT syndrome and, ultimately, other patients at risk for ventricular arrhythmias.

Alma Mingels received the grant for her proposal "First aid for a heart attack: towards a specific diagnostic tool in the blood circulation". A heart attack or myocardial infarction is diagnosed by the detection of elevated cardiac troponins in the blood together with typical clinical and/or imaging findings. Unfortunately, the recent introduction of high-

sensitivity assays in the clinic has come at the cost of their specificity. The goal of this project is to investigate new tools to specifically detect the acute phase of myocardial infarction that are based on the sub forms of cardiac troponins. Also, to clarify minimum troponin release, the whole lifecycle of cardiac troponins, from the exact mechanism of troponin release by cardiomyocytes up to their clearance from the blood circulation will be analysed.

NWO ASPASIA JUDITH SLUIMER

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

NHS DR E DEKKER PROGRAMME

Within the framework of the Dr E. Dekker programme of the Dutch Heart Foundation, Dr **Stijn Agten** (Dept. of Biochemistry) and Dr **Miranda Nabben** (Dept. of Genetics and Cell Biology) both received a grant from the Dutch Heart Foundation. Stijn received a postdoc grant for his project "Chemical protein synthesis of Matrix Gla-protein: decoding the molecular structure that governs vascular health". This grant will allow Stijn to continue his research activities within the Department of Biochemistry which focus on using chemical techniques to address important cardiovascular problems. Vascular calcification is implicated in severe pathologies such

as atherosclerosis and chronic kidney disease. However, much is unclear regarding initiation and inhibition of calcification while detection can only be achieved at a late stage, hampering intervention. The key player in calcification is matrix Gla-protein (MGP) which plays a crucial role in the prevention of vascular calcification by an unknown mechanism of action. Previous research into MGP is hampered by its inability to be produced by conventional methods such expression or isolation. To provide access to multiple variants of MGP chemical protein synthesis will be employed. In collaboration with colleagues at the Department of Biochemistry MGP's structure will subsequently be elucidated and its function will be evaluated in in vitro and in vivo assays. This will lead to the development of imaging agents for early detection and preventative medicine of vascular calcification.

Miranda received a senior scientist grant for her project entitled "Are men bigger sweethearts? Molecular metabolic differences at the basis of gender-specific cardiac pressure overload disorders". The grant enables Miranda to foster and expand her research activities that focus around designing therapies against cardiovascular diseases via metabolic modulation, within the Department of Genetics and Cell Biology and Cardiology. There exists no cure for pressure overload-induced heart failure, a life-threatening condition affecting millions worldwide. Hypertension and aortic stenosis are leading risk factors of pressure overload-induced heart failure. Nonetheless, our current molecular understanding of what triggers heart failure and determines its progression remains incomplete. In collaboration with colleagues at the Departments of Genetics and Cell biology, Cardiology, and Nuclear Medicine, Miranda aims to determine the early regulatory events connecting altered cardiac substrate metabolism and protein synthesis, in the context of developing pressure overload-induced heart failure. This regulatory link will form the basis for novel diagnostics and therapeutics to rescue the heart from hypertrophic dysfunction. A special focus will be put on gender related differences. See pages 72-75 for the scientific highlight of Miranda.

EFSD SANOFI GRANTS

Dr **Marleen van Greevenbroek** and Dr **Kristiaan Wouters** (Dept. of Internal Medicine) both received a grant within the EFSD/Sanofi European Diabetes Research Programme in Macrovascular Complications of Diabetes. The programme is intended to stimulate and accelerate European research on macrovascular complications.

Kristiaan received the grant for his project "A unique blood immune cell signature for macrovascular complications of diabetes". Inflammation is a risk factor for the macrovascular complications of diabetes, such as atherosclerosis. However, knowledge about the specific immune cells that contribute to this increased risk in order to specifically target the immune system as a treatment for macrovascular complications of diabetes is currently lacking. Circulating immune cells are important drivers of atherosclerosis. In this proposal, the contribution of these cells to macrovascular risk in diabetes is investigated using novel techniques that are beyond the state of the art. A unique 'immune cell signature' in the blood to predict diabetes-related risk for macrovascular complications will be identified. Furthermore, new immune cell types that are important for vascular complications will be identified and characterised.

Marleen received the grant for her project "An alternative path towards macrovascular complications in type 2 diabetes". The complement system contributes to cardiovascular diseases (CVD). People with prediabetes or type 2 diabetes (T2DM) may be particularly vulnerable

to the effects of complement activation on macrovascular disease because they have a high potential for alternative pathway activation. Firstly, because T2DM patients have high plasma concentrations of complement. This may be, at least partly, due to adiposity. Secondly because hyperglycaemia compromises the function of complement inhibitors.

It is hypothesised that the high risk of macrovascular disease in prediabetes and T2DM is, at least in part, due to increased expression and activation of the alternative complement pathway. Concurrent hyperglycaemia and obesity modulate this relationship. Future perspective: Understanding the processes that underlie the development of macrovascular disease in T2DM will help to improve focused and personalized treatment targets. These may include modulation of complement activation, e.g. via targeted drugs and/or modulation of carbonyl stress. See pages 56-63 for the scientific highlight of Marleen.

KOOTSTRA FELLOWSHIPS

In 2019, two Kootstra Talent Fellowships were awarded to CARIM researchers. During the first round, **Dorien Kimenai** (Dept. of Clinical Chemistry) was awarded a fellowship for the project: "Cardiac troponins — the shift from diagnosis to prognosis". In the second round, a fellowship was granted to **Stepan Denisov** (Dept. of Biochemistry) for his proposed study entitled "Catching Evaders: Structure Elucidation and Molecular Mechanisms of Tick Salivary Proteins".

The Kootstra Talent Fellowships are granted to young scientific talents by the Board of Maastricht UMC+ with the aim to support developing their scientific careers. The fellowship aims to facilitate talented researchers to develop their own research ideas and CV, and subsequently help increase their chances of obtaining personal grants at external funding agencies.

CARIM PHD CALL

In 2019, CARIM launched a call for proposals to fund three PhD candidates in order to reduce financial reserves and to invest in strategic opportunities. The following projects were awarded:

1) "Platelets as an accomplice in microvascular dysfunction" from Dr **Judith Cosemans,** Prof. **Blanch Schroen,** Dr **Sander Verheule,** Dr **Rory Koenen,** Dr **Vanessa van Empel:** Microvascular dysfunction has recently emerged as a potentially pivotal underlying disease mechanism in various forms of cardiac disease. Since platelets are in close contact with microvascular endothelium, and are known to initiate and propagate endothelial inflammation, it is hypothesised that platelets could have an unrecognised importance in the pathophysiology of microvascular dysfunction. In this multidisciplinary PhD project, the association of platelet function with microvasculature status, severity and progression of atrial fibrillation and heart failure with preserved ejection fraction will be investigated. Mechanistic insight whether targeting platelets will reduce endothelial- and microvascular dysfunction in vitro will be obtained using advanced vessel-on-a-chip models.

2) "AGE-ing of the brain microvessels: the road to vascular cognitive impairment" from Prof. **Casper Schalkwijk,** Prof. **Robert van Oostenbrugge,** Dr **Sébastien Foulquier.** Diabetes is associated with a two-fold risk of cognitive impairment. Due to the increasing prevalence of diabetes, it becomes urgent to decipher the mechanisms coupling diabetes to cognitive impairment. High blood glucose levels lead to an increased production of the highly reactive methylglyoxal (MGO). MGO levels can also be increased by a defect of the glyoxalase system involved in its detoxification. MGO exposure was previously linked to microvascular dysfunction.

Since a major increase of MGO in the brain of diabetic mice was identified, it is hypothesised that MGO induces dysfunction of the brain microcirculation, leading to an increased permeability of the Blood Brain Barrier (BBB). The impact of the MGO-glyoxalase balance on BBB will be studied, using brain imaging, and consequences for cognitive function using different animal models.

3) "Microvascular Fingerprinting using Radiomics-based interpretable A.I" from Prof. **Coen Stehouwer,** Prof. Philippe Lambin, Dr **Boy Houben,** Dr Henry Woodruff: Microvascular dysfunction (MVD) is considered a crucial pathway in the development and progression of cardiometabolic and renal disease (e.g. CKD, heart failure, depression, diabetes) and is associated with increased cardiovascular mortality. The Maastricht Study currently has functional microvascular data of both retina and skin. However, there is yet no data on the architecture of the microvascular network (e.g. capillary density and distribution, tortuosity, fractal dimensions). Combining both functional and structural data allows designing an individual Microvascular Fingerprint, which can be related to both determinants (e.g. diabetes, BP) and outcomes (e.g. depression, CKD, cardiac function). A collaborative project with the Departments of Internal Medicine and Precision Medicine (The D-Lab) is proposed to develop and validate microvascular architecture biomarkers using interpretable Artificial Intelligence (AI). Next, a Microvascular Fingerprint will be determined, combining both architecture and functional measures. The AI approach that is used will use innovative pre-processing standardisation methods, deep learning algorithms, and handcrafted radiomics features. The long-term vision is that this new, non-invasive, Microvascular Fingerprint will be used to screen, diagnose, and follow patients with chronic diseases.

OTHER AWARDS, PRIZES AND GRANTS

In 2019, many CARIM researchers were awarded with other grants, prizes and awards. Below, some of them are highlighted.

'HEART FOR SUSTAINABLE CARE' GRANT RACE 9

The project "Device-based rate versus rhythm control treatment in patients with symptomatic recent-onset atrial fibrillation in the emergency department (RACE 9)" of the group of Drs. **Nikki Pluymaekers,** Prof. **Harry Crijns** and Dr **Dominik Linz** (Dept. of Cardiology) was awarded by a 'Heart for sustainable care' grant of 800 k€. Six research projects have been awarded funding from the joint open call from the Innovative Medical Devices Initiative (IMDI) and the Dutch Cardio Vascular Alliance (DCVA): Heart for sustainable care. These research projects are aimed at the development of medical technology for the earlier detection and better treatment of cardiovascular diseases. The projects also contribute to the sustainability of health care in the Netherlands by reducing the demand for care and/or solving the shortage of care personnel while maintaining accessibility. See pages 26-31 for a full interview with Nikki and Harry.

CVON RECONNECT TALENT PROGRAM GRANT

Dr **Emma Louise Robinson** (Dept. of Cardiology) has been awarded a CVON RECONNECT Talent Program grant. Emma will join this new consortium (CVON2017) and work together with other major Dutch academic medical centres, in particular with teams from Erasmus MC Rotterdam and UMC Utrecht. Her research will reveal the functional epigenetic changes in the different cell types of the heart and vasculature that underlie the pathophysiology of heart

failure with preserved ejection fraction. In addition, she will conduct a multi-centre study on a novel candidate gene that shows potential as a biomarker for HFpEF in women in clinical samples. Her aim is to identify new biomarkers for early diagnosis and targets for effective therapies for this poorly understood and heterogeneous condition, all the while tailoring her research to account for the sex differences in prevalence, disease pathology and response to treatment and environmental triggers.

METADIS

Dr **Marleen van Greevenbroek** and Prof. **Casper Schalkwijk** (Dept. of Internal Medicine) both received an INTIMIC grant in the framework of the Joint Programming Initiative "a Healthy Diet for a Healthy Life" (JPI HDHL). The aim of this call is to support transnational, collaborative research projects that address important research questions regarding the effects of food (components) or diets and/or food processing on overweight and related metabolic diseases. An additional objective is to support early career scientists in the area of food, nutrition and health.

Marleen received funding for the project "Sulfur amino acids, energy metabolism and obesity (STAY)", which is a collaborative project between researchers from Norway, The Netherlands, Czech Republic, and Great Britain investigates the effects of sulfur amino-acids on obesity. Sulfur amino-acids (SAA), are present in high amounts in animal-derived proteins and much less in plant-derived proteins. Within the Dutch part of the project, The Maastricht Study is used to investigate if people who consume a high amount of SAA, e.g. who normally consume substantial amounts of animal–derived foods, generally have a higher body weight and/or more fat. Other project partners will investigate whether a plant-based diet that is low in SAA induces weight-loss in overweight or obese persons. To understand the mechanism by which SAA regulate energy metabolism and obesity, SAA, their derived-products and several indicators of metabolism in blood and/or urine of the study participants is measured. This project will enhance understanding of the mechanisms by which a primarily plant-based diet low in SAA content can benefit human metabolic health. By integrating all findings generated in the project, the consortium will seek to identify risk groups likely to benefit from a diet restricted in SAA. The expected results will aid in risk stratification, prevention and treatment of obesity and related metabolic diseases.

Casper received the grant for the project "The physiological impact of dietary methylglyoxal (ePIDEMic)". The ePIDEMIC project is a collaboration between researchers from The Netherlands, Germany and France and ePIDEMIC explores the consequences of dietary methylglyoxal (MGO) on the intestinal microbiota and on the development of metabolic diseases and cardiovascular disease (CVD). Bioactive compounds produced during food processing can have strong pro-inflammatory properties with potential health implications. Modulation of chronic inflammation may be the mechanism linking diet to risk of chronic diseases such as diabetes and CVD. Advanced glycation endproducts (AGEs) are a heterogeneous group of pro-inflammatory bioactive compounds produced via Maillard reactions during cooking and processing. It is now well established that AGEs are mainly formed from several dicarbonyl compounds, including MGO. We have recently found high levels of MGO in many different foods. There is increasing evidence that elevated levels of MGO are involved in weight gain and the development of diabetes and other chronic inflammatory diseases including cardiovascular disease. However, bioavailability and physiological consequences

of dietary MGO are largely unknown. The effect of dietary MGO on the gastrointestinal tract and microbiota and on the onset of diabetes, vascular diseases and cognitive function in mice will be determined. A detailed database of dietary MGO exposures will be developed and the association of dietary MGO with overweight, weight gain, obesity and risk of associated metabolic diseases (type 2 diabetes, CVD) will be assessed, as well as cognitive function using existing data from three large and deep-phenotyping prospective cohort studies. Tthe role of inflammation, endothelial function and micro- and macrovascular function and microbiota composition as potential underlying mechanisms of dietary MGO action will also be investigated. This comprehensive project will elucidate the role of food-derived MGO as a possible risk factor for overweight and overweight-related metabolic diseases and CVD.

EU HORIZON 2020

Five projects in which CARIM participates as beneficiary were granted in 2019:

- Restoring cardiac mechanical function by polymeric artificial muscular tissue (REPAIR) – Uli Schotten (Dept. of Physiology). FETPROACT-EIC-05-2019 (RIA)
- Integrated silicon photonics for Cardiovascular Disease monitoring (InSiDe) – Frits Prinzen (Dept. of Physiology). ICT-05-2019 (IA)
- Personalized Therapies for Atrial Fibrillation. A Translational Approach (PersonalizeAF) – Uli Schotten (Dept. of Physiology). MSCA-ITN-2019 (MSCA-ITN-ETN)
- MARie Curie Intelligent UltraSound (MARCIUS) – Joost Lumens (Dept. of BME). MSCA-ITN-2019 (MSCA-ITN-EID)
- INnovation in Safety Pharmacology for Integrated cardiovascular safety assessment to REduce adverse events and late stage drug attrition (INSPIRE) – Paul Volders (Dept. of Cardiology). MSCA-ITN-2019 (MSCA-ITN-ETN)

PHILIPS AWARD MATTHIJS CLUITMANS

Dr **Matthijs Cluitmans** (Dept. of Cardiology) received the 2018 Philips Research Outstanding Achievement Award. The award was presented by Paul Put, vice-president of Philips Research: “The worldwide Outstanding Achievement Awards honour those who have achieved exceptional results contributing to the business, while role modelling the Philips behaviours.” Matthijs is part-time postdoc at CARIM and part-time senior scientist at Philips Research. In his dual position, he aims to bridge from novel scientific insights in ventricular arrhythmogenesis to clinical application, using advanced clinical imaging and personalised computational modelling.

DR. SAAL VAN ZWANENBERG EREPRIJS HARRY STRUIJKER-BOUDIER

Emeritus Prof. **Harry Struijker-Boudier** has won the Dr. Saal van Zwanenberg Honorary Prize. This biennial prize of 25 k€ is awarded by the Koninklijke Hollandsche Maatschappij der Wetenschappen (KHMW). The prize is a tribute to scientists who have contributed to research that has led to the development of new drugs. Professor Harry Struijker-Boudier has made important discoveries in the field of blood pressure lowering medicines. The prize was awarded by Louise Gunning-Schepers, president of the KHMW.

ELSO CENTRE OF EXCELLENCE AWARD ROBERTO LORUSSO

Prof. **Roberto Lorusso** (Dept. of CTC) received the Centre of Excellence (Gold) Award from the Extracorporeal Life Support Organisation (ELSO). The ELSO is an international non-profit consortium of health care institutions who are dedicated to the development and evaluation of novel therapies for support of failing organ systems. The ELSO Award for Excellence in Life Support recognises ECLS programmes worldwide that distinguish themselves by having processes, procedures and systems in place that promote excellence and exceptional care in extracorporeal membrane oxygenation.

OTHER HIGHLIGHTS

CARIM COMMITMENT AWARD

Dr **Kristiaan Wouters** (Dept. of Internal Medicine) and **Tara de Koster** (CARIM Office) received the CARIM Commitment Award, intented for any CARIM member who has devoted his/her heart and soul to CARIM in an exceptional way, be it on an academic, managerial, service or community level. The award consists of a bronze coin of the sculptor Marina van der Kooi.

DVCA LEADERSHIP PROGRAMME

Dr **Joost Lumens** (Dept. of BME), Dr **Matthijs Cluitmans** (Dept. of Cardiology) and Dr **Barend Mees** (Dept. Vascular Surgery) have been selected as the future leaders in the cardiovascular arena. They are laureates of the first edition of the DCVA Leadership Program, which will officially start in 2020. Out of 59 applicants, fifteen talents were selected, who will work on five relevant and present topics the DCVA partners encounter; evaluation of healthcare, implementation of research results, how to deal with data and registries, patient perspectives, and how to successfully make use of already existing technologies. The fifteen selected talents represent different aspects of the cardiovascular field; fundamental researchers, clinicians, engineers, policy makers, and patients. Each topic will be assigned to the talents, who will work in groups of three on the topic of their preference during the two-year program. During the programme they are guided by established professionals in the cardiovascular field and trained by a professional trainer, after which they will be prepared to be a leader in the cardiovascular arena. See pages 102-107 for a full interview with Joost, Matthijs and Barend.

FACULTY AWARD ROB VAN DER ZANDER

Rob van der Zander was distinguished with the 'Faculty Award' for his great achievements for the faculty and CARIM in particular. From the foundation of CARIM in May 1988 until February 2019, Rob was the Managing Director of our school. During his career he has served with seven scientific directors and in those many years he played a pivotal role in shaping our school from infancy into the mature, world renowned institute it is today.

The 'Faculty Award' was introduced in 1997. Employees who have had a great significance for the faculty, or who have performed special services outside their own field, receive this award as a tangible souvenir of the Faculty of Health, Medicine and Life Sciences from the dean or his deputy.

WOUTER HANKEL MANAGING DIRECTOR CARIM

As from 1 February 2019, **Wouter Hankel** successes Rob van der Zander as CARIM's Managing Director. Since 2015, he has been working at Maastricht University, most recently in the role of deputy director of the Aachen-Maastricht Institute

for Biobased Materials (AMIBM). AMIBM is a joint institute of Maastricht University, RWTH Aachen University and Fraunhofer IME and is located at the Brightlands Chemelot Campus in Geleen. Before Maastricht University, he worked as a managing consultant at PNO Consultants, a grants consultancy firm. He was the account manager for several Dutch universities. He studied Political Science and Public Administration at Leiden University.

SITE VISIT ERC

From 23 until 25 October, CARIM was assessed by an External Review Committee that consisted of the following members: Pieter Reitsma (chair), Chantal Boulanger, Thomas Eschenhagen, Allan Flyvbjerg, Eike Nagel, Ingrid Pabinger, Carolina Touw and Roelinka Broekhuizen (secretary).
See pages 32-35 for a full interview with Pieter Reitsma and pages 12-13 for an article about the assessment.

TANS MEDAL COEN HEMKER

Prof. **Coen Hemker** (Dept. of Biochemistry) was awarded the highest distinction at Maastricht University, the Dr. J.G.H. Tans Medal. Prof. Hemker is one of the founding scientists of UM and was rector between 1982 and 1984. In Maastricht University's early stages, he played a crucial role in putting the university on the map as an innovative research university, both nationally and internationally.

Within his field of thrombin generation, he is internationally recognised as a pioneer, as evidenced by the three *Nature* publications he has to his name. See pages 64-71 for a full interview with Coen Hemker.

2 NEJM PUBLICATIONS HARRY CRIJNS

In the April edition of the New England Journal of Medicine, two publications of which Prof. **Harry Crijns** (Dept. of Cardiology) was co-author, were published. The paper 'Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation' was a result of the RACE 7 AWACS trial. Patients with acute atrial fibrillation reporting to the first heart aid are mostly treated with an acute electrical cardioversion under sedation. The RACE 7 ACWAS trial showed that wait-and-see strategy may replace the acute cardioversion since most patients revert to normal heart rhythm within an hour or two.

The same issue of NEJM published a second study concerning patients with cardiac arrest (COACT trial). Patients resuscitated from cardiac arrest may have hidden coronary artery disease as a cause of their arrest. It is uncertain if these patients should undergo immediate angiographic intervention upon presentation. The COACT trial showed that immediate angiography with an intent to revascularize is not superior to delayed angiography.

ILJA ARTS IN BOARD OF NWO DOMAIN SCIENCE

Prof. **Ilja Arts** (Dept. of Epidemiology) was appointed by the NWO Executive Board as new board member for the NWO Domain Science, from 1 May 2019. Ilja is Professor of Molecular Epidemiology of Chronic Diseases at Maastricht University, Scientific Director of the Maastricht Centre for Systems Biology (MaCSBio), and PI at CARIM. She focusses on the integration of omics and complex phenotypic data from epidemiological studies using systems biology approaches in the fields of cardiovascular and metabolic disease.

PROFESSORSHIPS

The following CARIM researchers were appointed to professor in 2019:

Martijn Brouwers (Dept. of Internal Medicine) – Professor of Internal Medicine, specialising in Endrocrinology and Metabolic Diseases

Bastiaan de Galan (Dept. of Internal Medicine) – Professor of Internal Medicine, specialising in Diabetology

Roberto Lorusso (Dept. of CTC) – Professor of Cardiac Surgery and Extra-Corporeal Life Support

Frank de Vries (Dept. of Internal Medicine) – Professor of Clinical Pharmacy & Epidemiology

Wim van Zwam (Dept. of Radiology) – Professor of Radiology, particularly interventional Neuroradiobiology

HIGHLIGHT
DIVISION VESSELS

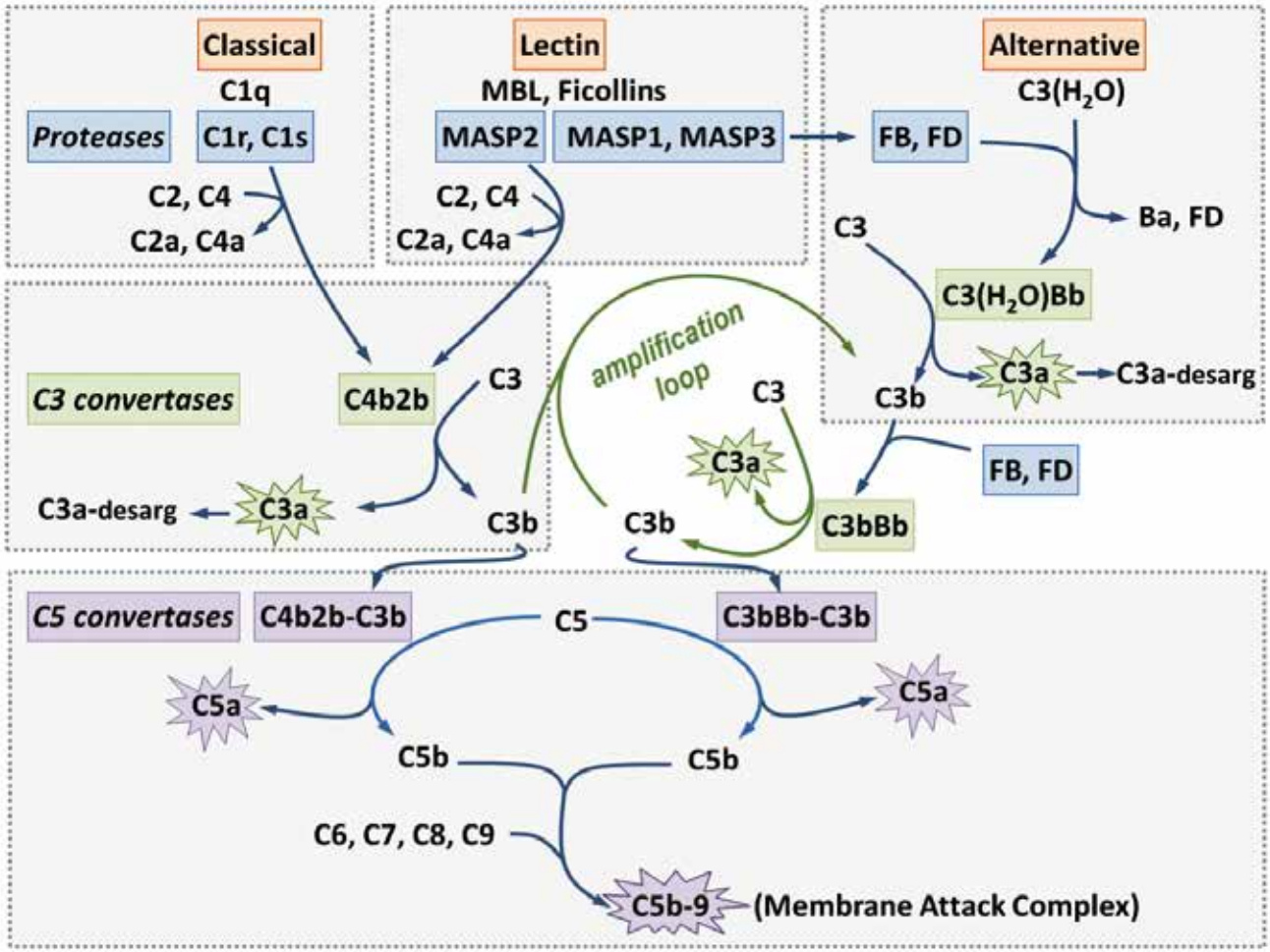
MARLEEN VAN GREEVENBROEK

Department of Internal Medicine

Setting

The complement system is one of the oldest components of the immune system and is part of the innate immune system. Canonically, the complement system is implicated in the defence against pathogens and environmental or self-derived antigens.

Activating receptors of the complement system include pattern recognition receptors (PRRs), which sense pathogen- or danger-associated molecular patterns (PAMPs or DAMPs). Complement activation leads to a self-enhancing cascade of activation steps that triggers a strong inflammatory response.


Classical
C1q
Proteases
C1r, C1s
C2, C4
C2a, C4a
Lectin
MBL, Ficollins
MASP2
MASP1, MASP3
C2, C4
C2a, C4a
Alternative
C3(H2O)
FB, FD
Ba, FD
C3
C3(H2O)Bb
C3a
C3a-desarg
C3b
FB, FD
C3bBb
C3 convertases
C4b2b
C3
C3a-desarg
C3a
C3b
amplification loop
C3
C3a
C3b
C5 convertases
C4b2b-C3b
C5
C3bBb-C3b
C5a
C5a
C5b
C5b
C6, C7, C8, C9
C5b-9
(Membrane Attack Complex)

F**IGURE 1** The complement system consists of soluble and membrane-bound proteins functioning in cascades of stepwise protease activation. Activation of any of the three pathways (the classical, the lectin or the alternative pathway) of the complement system can lead to the cleavage of the C3, the central complement component, and subsequent activation of C5, C6, C7, C8 and C9 of the terminal pathway. C1q, MBL and ficollins are pattern recognition molecules of the classical and lectin pathways. C1s, C1r, MBL-associated serine proteases (MASP), C2 and C4 further participate in the activation of C3 via the classical and lectin pathways. While MASP2 is the key enzyme for the cleavage of C4 and C2, MASPs 1 and 3 have also been implicated in the activation of the alternative pathway. The alternative pathway can be initiated via two routes: activation can start either through spontaneous hydrolysis of C3, which generates C3(H_2O), or through C3b, which is generated by the cleavage of C3 by convertases derived from all complement pathways. C3b and C3(H_2O) render factor B available for cleavage by factor D. This yields Bb, which combines with C3b or C3(H_2O) to generate the alternative pathway C3 convertase (C3bBb or C3(H_2O)Bb). The alternative pathway thus functions as an amplification loop for all activation pathways. Activation of the terminal pathway leads to the formation of membrane-bound and soluble C5b-9 complexes (C5b-9, also known as membrane-attack complex, and sC5b-9, respectively). During complement activation, the proinflammatory anaphylatoxins C3a and C5a are released, as well as multiple other protein fragments such as C4d, Bb, C3c and C3d. Activated complement can trigger responses by signalling the anaphylatoxins through their respective receptors, but also via surface-bound fragments that are recognised by other complement receptors. Protein complexes of the terminal pathway insert into cell membranes and thereby induce intracellular signals or disturb the membrane integrity, eventually promoting cell lysis. Not indicated are many additional complement inhibitors and a proposed fourth pathway for complement activation in which C3 and C5 are activated via proteases of the coagulation, fibrinolysis and kinin systems.

Uncontrolled complement activation can lead to dysregulation of coagulation/fibrinolysis, systemic inflammation and shock and is implicated in severe clinical pathologies such as atypical haemolytic uraemic syndrome (aHUS) or paroxysmal nocturnal haemoglobinuria. The extent of complement activation is therefore under rigid control of various circulating and cell-bound complement regulators and inhibitors.

Novel discoveries on the widespread roles and functions of the complement system have inspired new views, which include that, apart from its role in defence against pathogens, complement is also involved in tissue development, remodelling and homeostasis, as well as in metabolism [1]. A clear point of interplay between the immune and metabolic roles of complement is at the level of C3 and C5 activation (**Figure 1**). Their activation generates the highly active, proinflammatory anaphylatoxins C3a and C5a, which are rapidly desarginated by carboxypeptidases. While this desargination inactivates the proinflammatory properties of the anaphylatoxins, the resulting C3a-desarg and possibly also C5a-desarg are increasingly recognised as metabolically active compounds with distinct metabolic effects. In particular, C3a-desarg (also known as acylation stimulating protein, ASP) has been implicated in adipose tissue metabolism through effects on triglyceride storage and glucose uptake [2]. Moreover, in mouse models of diet-induced diabetes, the deletion of the G-coupled protein receptors for C3a (C3AR1) [3] and C5a (C5AR) [4] suggests that their activation induces insulin resistance, while deletion of the proposed receptor for C3a-desarg (C5AR2) may be protective [3]. Additionally, whereas complement was classically perceived to be produced primarily by the liver and in immune cells, it is becoming increasingly clear that

other tissues, particularly adipose tissue, are an additional relevant source of complement.

The relevance of the growing range of immunometabolic and metabolic roles of complement is emphasised by the ongoing obesity pandemic and its related diseases. These include type 2 diabetes, cardiovascular disease and their comorbidities, which are central to the research that is done in the Department of Internal Medicine (in the programme 'Vascular complications of diabetes & hypertension' within the Division Vessels). The research in our department revolves around the interrelationships among disturbances to the normal functioning of large and small vessels and metabolism. Part of my work within this research line focuses on the role of the complement system in cardiometabolic diseases.

CURRENT WORK

A unifying underlying cause of many obesity-associated and other cardiometabolic diseases is an ongoing state of low-grade inflammation and related insulin resistance. Inflammation is a major effector mechanism of complement activation, and a state of mildly enhanced complement activation (or the potential for such activation) in obese individuals may be a relevant inductor of chronic low-grade inflammation. In recent years we have measured a range of complement factors in the plasma of participants of the prospective, observational Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) study, and have indeed shown positive relationships between circulating concentrations of complement factors, including activated complement products, and markers of low-grade inflammation, endothelial dysfunction and cardiovascular disease (see also **Figure 2**).

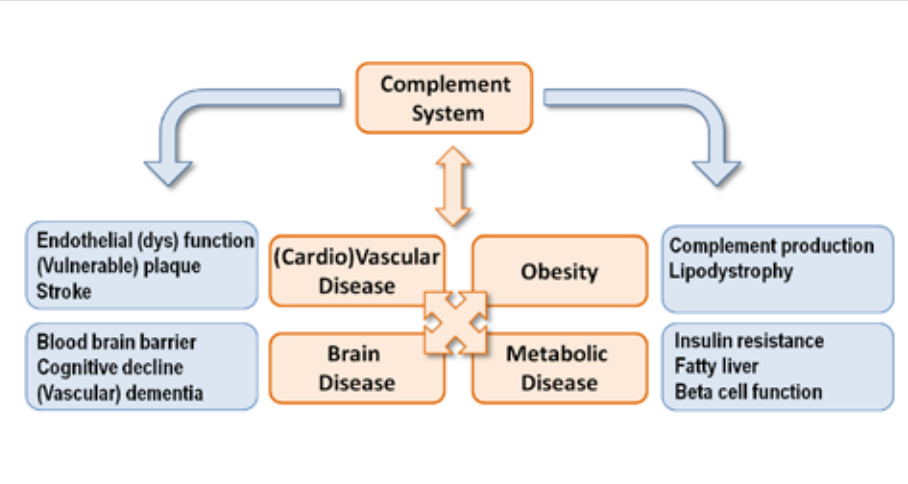


FIGURE 2 The complement system in cardiometabolic diseases. In the past 10-15 years we and others have shown that components of the complement system and complement activation are positively associated with endothelial dysfunction [5], with cardiovascular events [6-9], with vascular and other types of brain diseases [10] and with obesity and related metabolic disease, including type 2 diabetes [11-13]. The references included here are examples and not intended as a complete list. These human data are corroborated by data from animal models, but functional human data are limited.

It remains to be investigated to what extent these effects are related to (i) activation of circulating complement, e.g. on the endothelial lining of the macro- and microvasculature; (ii) local production and activation of complement, e.g. in perivascular and/or pericardiac fat depots; or (iii) local production at sites of "injury", such as the atherosclerotic plaque. Current data suggest that these processes may all contribute. In addition, currently less explored contributors can be envisioned, such as an interplay between the gut microbiome, dietary factors and complement activation, with a possible effect on insulin resistance and metabolism. Recently, some components of the complement system that had previously been implicated in the development of insulin resistance have been proposed to be involved in the preservation of beta cell function and insulin production (**Figure 3**). It remains to be seen if this is a primary effect or rather a compensatory feedback mechanism to overcome complement-induced insulin resistance. Supported by a grant from the Dutch Diabetes Foundation, we are currently evaluating the hypothesis that modification of the intracellular complement component CD59 (an inhibitor of the terminal complement pathway) by methylglyoxal can hamper its reported stimulatory role in insulin secretion.

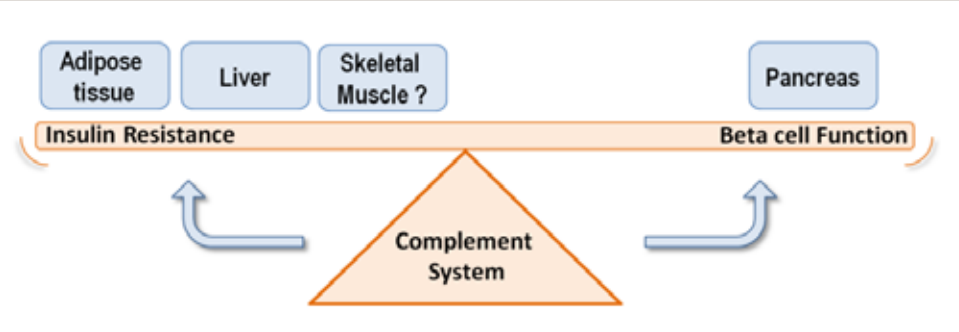


FIGURE 3 Contribution of the complement system to glucose homeostasis. A striking example of the emerging role of complement and complement activation in tissue and whole body metabolic homeostasis relates to the regulation of glucose metabolism. Currently this appears to be primarily, although not exclusively [14], related to the alternative and terminal pathways of complement activation. Human and mouse data support the view that activation of the alternative complement pathway is related to more insulin resistance. This was shown to be, at least partly, mediated via activation of the C3a-C3a receptor axis, resulting in accumulation of proinflammatory cells in adipose tissue and in the liver [3]. At the same time, more recent publications suggest that the proinflammatory anaphylatoxin C3a stimulates insulin secretion by β-cells and supports β-cell preservation, and thereby contributes to maintaining glucose balance [15]). Treatment of diabetes-prone db/db mice with factor D (adipsin) resulted in better glucose homeostasis. However, in db/db mice, plasma factor D/adipsin concentrations are almost absent, in sharp contrast with human obese and/or diabetic individuals, who have high factor D concentrations. Thus, there are indications that, in humans, some components of the alternative pathway, particularly C3, are associated with a higher risk of type 2 diabetes [11], while others, particularly factor D, may be associated with a lower risk of type 2 diabetes [16]. Notably, both these effects were reported to be mechanistically mediated via C3a signalling, although these functional data were primarily derived from animal studies [3, 15, 16].

PROSPECTS

Supported by a grant from the European Foundation for the Study of Diabetes, we are currently measuring several complement components (at least C3, C3a, factor D and C1q) in The Maastricht Study, to investigate their relations with macro- as well as micro-vascular diseases. The large number of participants and the deep level of phenotyping that is available in The Maastricht Study will allow us to also perform detailed investigations of the role of the complement system in human metabolism and disease in a wider context. For instance, we can evaluate the contribution of different fat depots to complement-mediated inflammation and insulin resistance, to evaluate if the above-mentioned seemingly beneficial effect on insulin production differs between men and women, and hence to explore if this might contribute to the known difference in obesity-associated risk of type 2 diabetes between the sexes. In addition, the detailed information on brain structural and functional changes will allow us to evaluate the potential contributions of complement to these processes. And it may even turn out that persons who have a higher basal state of low-grade inflammation and greater complement activation or the (potential for such activation), such as those with obesity, T2D and CVD, as illustrated by their higher concentrations of e.g. C3 and C3a, are more prone to develop severe lung disease after infection with SARS-CoV-2, the causative agent of COVID-19, which kept us all at home in the period when this CARIM progress report was being written [17]. This is a topic that may also be evaluated in The Maastricht Study.

These epidemiological evaluations will subsequently be extended to analyses on incident disease that are being obtained in follow-up measurements in The Maastricht Study. In these investigations we aim to corroborate the data we obtain from human observational studies with additional experimental analyses.

REFERENCES

[1] Hajishengallis G, Reis ES, Mastellos DC, Ricklin D, Lambris JD. Novel mechanisms and functions of complement. Nat Immunol 2017; 18: 1288-1298.

[2] Fisette A, Munkonda MN, Oikonomopoulou K, Paglialunga S, Lambris JD, Cianflone K. C5L2 receptor disruption enhances the development of diet-induced insulin resistance in mice. Immunobiology 2013; 218: 127-33.

[3] Mamane Y, Chung Chan C, Lavallee G, Morin N, Xu LJ, Huang J, Gordon R, Thomas W, Lamb J, Schadt EE, Kennedy BP, Mancini JA. The C3a anaphylatoxin receptor is a key mediator of insulin resistance and functions by modulating adipose tissue macrophage infiltration and activation. Diabetes 2009; 58: 2006-17.

[4] Phieler J, Chung KJ, Chatzigeorgiou A, Klotzsche-von Ameln A, Garcia-Martin R, Sprott D, Moisidou M, Tzanavari T, Ludwig B, Baraban E, Ehrhart-Bornstein M, Bornstein SR, Mziaut H, Solimena M, Karalis KP, Economopoulou M, Lambris JD, Chavakis T. The complement anaphylatoxin C5a receptor contributes to obese adipose tissue inflammation and insulin resistance. J Immunol 2013; 191: 4367-74.

[5] Hertle E, van Greevenbroek MM, Arts IC, van der Kallen CJ, Feskens EJ, Schalkwijk CG, Stehouwer CD. Complement activation products C5a and sC5b-9 are associated with low-grade inflammation and endothelial dysfunction, but not with atherosclerosis in a cross-sectional analysis: the CODAM study. Int J Cardiol 2014; 174: 400-3.

[6] Hertle E, Arts ICW, van der Kallen CJH, Feskens EJM, Schalkwijk CG, Stehouwer CDA, van Greevenbroek MMJ. Classical Pathway of Complement Activation: Longitudinal Associations of C1q

and C1-INH With Cardiovascular Outcomes: The CODAM Study (Cohort on Diabetes and Atherosclerosis Maastricht)-Brief Report. Arterioscler Thromb Vasc Biol 2018; 38: 1242-1244.

[7] Hertle E, Arts IC, van der Kallen CJ, Feskens EJ, Schalkwijk CG, Stehouwer CD, van Greevenbroek MM. The alternative complement pathway is longitudinally associated with adverse cardiovascular outcomes. The CODAM study. Thromb Haemost 2016; 115: 446-57.

[8] Gravastrand CS, Steinkjer B, Halvorsen B, Landsem A, Skjelland M, Jacobsen EA, Woodruff TM, Lambris JD, Mollnes TE, Brekke OL, Espevik T, Rokstad AMA. Cholesterol Crystals Induce Coagulation Activation through Complement-Dependent Expression of Monocytic Tissue Factor. J Immunol 2019; 203: 853-863.

[9] Prugger C, Luc G, Haas B, Arveiler D, Machez E, Ferrieres J, Ruidavets JB, Bingham A, Montaye M, Amouyel P, Yarnell J, Kee F, Ducimetiere P, Empana JP; PRIME Study Group. Adipocytokines and the risk of ischemic stroke: the PRIME Study. Ann Neurol 2012; 71: 478-86.

[10] Orsini F, De Blasio D, Zangari R, Zanier ER, De Simoni MG. Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis. Front Cell Neurosci 2014; 8: 380.

[11] Wlazlo N, van Greevenbroek MM, Ferreira I, Feskens EJ, van der Kallen CJ, Schalkwijk CG, Bravenboer B, Stehouwer CD. Complement factor 3 is associated with insulin resistance and with incident type 2 diabetes over a 7-year follow-up period: the CODAM Study. Diabetes Care 2014; 37: 1900-9.

[12] Xin Y, Hertle E, van der Kallen CJH, Schalkwijk CG, Stehouwer CDA, van Greevenbroek MMJ. Longitudinal associations of the alternative and terminal pathways of complement activation with adiposity: The CODAM study. Obes Res Clin Pract 2018; 12: 286-292.

[13] Xin Y, Hertle E, van der Kallen CJH, Schalkwijk CG, Stehouwer CDA, van Greevenbroek MMJ. Complement C3 and C4, but not their regulators or activated products, are associated with incident metabolic syndrome: the CODAM study. Endocrine 2018; 62: 617-627.

[14] Hillian AD, McMullen MR, Sebastian BM, Roychowdhury S, Kashyap SR, Schauer PR, Kirwan JP, Feldstein AE, Nagy LE. Mice lacking C1q are protected from high fat diet-induced hepatic insulin resistance and impaired glucose homeostasis J Biol Chem 2013; 288: 22565-75.

[15] Lo JC, Ljubicic S, Leibiger B, Kern M, Leibiger IB, Moede T, Kelly ME, Chatterjee Bhowmick D, Murano I, Cohen P, Banks AS, Khandekar MJ, Dietrich A, Flier JS, Cinti S, Blüher M, Danial NN, Berggren PO, Spiegelman BM. Adipsin is an adipokine that improves β cell function in diabetes. Cell 2014; 158: 41-53.

[16] Gómez-Banoy N, Guseh JS, Li G, Rubio-Navarro A, Chen T, Poirier B, Putzel G, Rosselot C, Pabón MA, Camporez JP, Bhambhani V, Hwang SJ, Yao C, Perry RJ, Mukherjee S, Larson MG, Levy D, Dow LE, Shulman GI, Dephoure N, Garcia-Ocana A, Hao M, Spiegelman BM, Ho JE, Lo JC. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. Nat Med 2019; 25: 1739-1747.

[17] Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, Lambris JD. Complement as a target in COVID-19? Nat Rev Immunol 2020 Apr 23. doi: 10.1038/s41577-020-0320-7.

INTERVIEW

COEN HEMKER

A born researcher

In 2019, the year in which Coen Hemker turned 85, he finally decided to present his formal farewell address at Maastricht University.
On that occasion, he was awarded the highest honour the UM can bestow: the Dr J.G.H. Tans medal. That was the one thing still missing under the heading “Main Distinctions and Awards” on his impressive CV. Although he has received plenty of personal recognition, the professor emeritus is still baffled by the lack of recognition for thrombosis as the “main cause of death”. And by extension the fact that “his” thrombin generation test is still not widely used in health care. “I’m a lousy lobbyist.”

No, he certainly does not feel 85, and he definitely does not feel living to such a ripe old age is his personal merit. “For instance, I’ve never engaged in sports. When I turned sixty, I started to do morning exercises for a quarter of an hour a day. When I turned 80, I extended that to half an hour. For the rest, it’s a matter of chance whether you have a long life. Cancer is a lottery you’d best not win, just like corona, but you shouldn’t be afraid of it.” It therefore went without saying that this interview should be held simply at his own home in Maastricht, despite corona. “This place is big enough to keep a two metre distance.” And so we got together. At that distance, the professor looked back upon his long career, at first in his library, then in the “computer room” and finally during a short tour of the attic, where he restores clarinets in a professional looking workshop.

RESEARCH WITHOUT PRESSURE

There is much to look back upon with satisfaction. Over five hundred publications, including four in *Nature,* more than seventy PhD candidates (among whom his own father), over ten of whom became professors, and many distinctions. Hemker was one of the “founding fathers” of Maastricht University, and dedicated himself particularly to scientific research from the moment he came south in 1974. “Tans had no idea there was such a thing as research. But research is crucial to university education. All forms of teaching revolve around passing on existing knowledge. But it’s only at a university that something extra comes in: It is only there that you can be taught how you can contribute to the acquisition of new knowledge, only at the university you can be trained to do research.”

The fact that there was little interest in, and recognition for, research in the early years at Maastricht, which was somewhat unsatisfactory on the one hand but rather pleasant at the other. “We could just do things our own way, without snooping administrators looking over our shoulders. A common interest in cardiovascular problems among people from different groups brought the idea of organising research in projects rather than along the lines of disciplines. That laid the foundation for CARIM, but Rob Reneman contributed much more to that than I did.”

FROM PHYSICIAN TO RESEARCHER

Although Hemker has done other things in his working life, research proves to be the core of his personality and his greatest strength. He started his career as a medical doctor. “My parents were poor but very intelligent, and felt that I should to go to university. If you didn’t want to become a clergyman, doctor was the obvious alternative. Moreover

WE COULD JUST DO THINGS OUR OWN WAY, WITHOUT SNOOPING ADMINISTRATORS LOOKING OVER OUR SHOULDERS

my father was extremely interested in medical research, Koch and Pasteur were his heroes. Once an MD, I aimed at becoming a paediatrician, but I soon found out I was far more fascinated in the scientific problems posed by diseases than by sick people. I felt that I was not patient-oriented enough to become a good doctor. Moreover, I was terrified by the idea that a child in my charge would die. So maybe I was too sentimental as well."

Later, at Maastricht, he was the "rector magnificus" for three years, with as a main aim to promote the scientific nature of the teaching, and to boost research. "So for a while I couldn't do much interesting work", he says drily, showing that only one type of work is interesting to Coen Hemker. "I'm a born researcher."

What part of your career do you look back on with the greatest satisfaction?

"Two things: the first is that I was able to turn blood coagulation into sound chemistry. When I started to work on the subject, in 1962, it was a purely medical topic. My labs at Leiden and Maastricht, together with a few American labs, have changed that. We were able to start publishing in the major biochemical journals, like the Journal of Biological Chemistry and so on. The second is that, after my rectorship, I managed to use biochemistry for the benefit of patients, by developing the thrombin generation method."

And what is you greatest frustration, in retrospect?

"I guess the fact that thrombosis has always remained the poor relation among medical interests. The total number of people who die as a result of an obstructed blood vessel – like cardiac infarction, stroke or pulmonary embolism – exceeds those who die from malignant cell growth. And still nobody sees this as a major medical problem. A few years ago, 'Discovery' presented 'the most important unanswered questions in medicine,' but thrombosis wasn't one of them. When the national Dutch research agenda was being established: not a single question about thrombosis. The members of the Royal Netherlands Academy of Arts and Sciences with an interest in thrombosis research – there are five of them – then submitted the question: 'How can we influence the haemostasis and thrombosis mechanism in such a way that, at any age and under all circumstances, adequate haemostasis is associated with a minimal thrombotic tendency?' Of course it didn't get included. It's not a sexy subject, because people aren't afraid of it. When you say the word 'cancer', everyone starts to tremble, and rightly so, but when you mention thrombosis, they ask 'What was that again?' Dutch coagulation research is of very high quality, but the whole subject is not being taken sufficiently serious, worldwide."

The spin-off company Synapse, which you set up, developed a thrombin generation test that enables a safer use of anticoagulants.

"After my rectorship, in 1985, I shifted my interest from pure biochemistry to more patient-oriented research. I started that work in Paris and continued it here after 1988. It was mainly aimed at the development of a test to detect a tendency of thrombosis and to supervise the effect of anticoagulant treatments.

The breakthrough that enabled us to produce a clinically usable test came in 1998, one year before my retirement as professor. In order not to drop the subject at that interesting stage, we created a spin-off company which, in fact, was just a continuation of my research group under a different name.

The essence of that test is that you no longer measure coagulation times, as has been done for over two centuries, but that you determine how much of the coagulation enzyme thrombin is being formed in coagulating blood.
If there's one thing that has emerged over the last twenty years, it is that the amount of thrombin formed is a much better predictor of haemorrhage and thrombosis than clotting times are. This is sustained by scores of publications from all over the world. But the test is still hardly being applied in clinical practice.
For instance, in recent years, anticoagulants have come on the market that according to the manufacturers should be used in standard dosage. Our test would make it possible to adept the dosage of such a drug to the needs of each individual patient, just as happens with insulin for diabetes or with antihypertensives for high blood pressure. We have also shown that such adaptation is likely to significantly improve the results of the treatment because there are large variations in the individual capacity to generate thrombin as well as in the sensitivity to such drugs. But the pharmaceutical industry has strategic reasons to maintain that individualised dosage will do. They spend hundreds of millions each year to settle in tens of thousands of court cases with patients who had developed haemorrhages, haemorrhages which could have been largely prevented if the dosage had been tailored to the individual needs."

Has this test been clinically validated yet?

"It has for the treatment of haemophilia and related diseases, not as a prophylaxis against thrombosis. We don't yet have the patient-based evidence, which should actually be very easy to obtain, however. It's just a matter of collecting blood samples from the patients that developed haemorrhage or thrombosis while using that type of drug. You could then show that those who bled indeed produce little thrombin to start with, and/or react strongly to the drug, while those who developed thrombosis produce too much thrombin and/or react poorly to the drug. Two hundred thousand euros would suffice to complete such a study. But nobody will start it because it's not in the interest of Big Pharma. Not yet, anyway, as the first company to realise this will of course make the biggest profit. But I won't live to see it, unless I live to be 110."

WE ALL HAVE TO FIND OUR OWN WAY TO GET WHERE WE WANT TO BE

It bothers you very much?

"Of course it does, but it doesn't help to get dismayed about it, when you are no longer among the active players. So I try to get used to a place on the side-lines. I have never been very good at selling my ideas anyhow. I can open up a new area; I've done that a few times, and then I hope somebody else will take it up and develop it further. I have been lucky that several of my ideas have been worked out by a marvellous department and I'm hoping the same will happen with the thrombin generation tests. The patent on

the method will expire in three years' time, and then large diagnostics companies can tackle it. That might accelerate things because the current tests are not fundamentally different from what we were doing around the year 2000. By now, I have some ideas about how they can be improved a lot, and I'm writing those up now.

What bothers me more is that the biochemical discipline on which the work of the past fifty year has been based, enzyme kinetics, is now getting almost obsolete. Physiological chemistry is Cinderella in comparison to molecular biology. It's just gone out of fashion, just as shooting marbles can be all the rage one moment and then forgotten again. I guess it will make a comeback someday, but whether I'll live to see that? I won't live to 150. Once again an undeservedly neglected area; it seems to be my specialty..."

What is the best advice you could give a young researcher?

"That's absolutely impossible to say. In giving an advice, you subconsciously assume that this young researcher has a personality comparably to your own, but in fact we all have to find our own way to get where we want to be. It's the same with attracting staff. I have been lucky with the department that I could build here at the university, supposing them to be passionate scientists – and they were. But my successor at Synapse for instance turned out to be much more of an entrepreneur, which caused the company to radically change direction; regretfully, because it means that part of my life's work is lost and I that can no longer actively partake in further development. So basically, you should not assume that all people are like you. But well, that's obviously something I'm not always good at."

The quotation "Science is difficult, people are impossible" was prominently displayed at your office. What sort of people do you regard as impossible?

"It applies to all people, as far as I'm concerned. I once had an altercation with Winand Wijnen, who said that you first had to teach students the easy stuff and then the difficult. So he said: first psychology and then biochemistry. Nonsense. Those molecules are far more predictable than humans. It's just that you can fool yourself into thinking that you understand people much better because it's easy to empathise with them."

What was it like to supervise your father's doctorate?

"That was of course the ultimate sublimated Oedipus complex. Swapping roles by teaching your own father. But I didn't overdo it. I gave him the idea of studying the history of coagulation research, and he tackled the subject energetically and independently. So he wasn't in my lab every day."

ANY GOOD, CREATIVE SCIENTIST ALWAYS HAS MORE IDEAS THAN HE CAN WORK OUT ON HIS OWN


Hemker
NEE
JA

You once said in an interview that you call yourself a soloist, but one who needs a team. Is that not a contradiction?

"No, not at all. Any good, creative scientist always has more ideas than he can work out on his own. About weekly I develop some new ideas about what I would still like to investigate, and that's probably never going to stop. For instance, as I said, I see clearly how to fundamentally improve this thrombin generation method. But I no longer have a team to work it out. That's pretty difficult to accept."

How do you deal with that?

"I just go and restore another clarinet, or go about one of my other hobbies: cooking, brushing up my Spanish, translating poetry, reading... Look, this is the second clarinet I've ever owned. I'm now restoring it. I used it when I was playing in the national students' orchestra."

Prof. Coen Hemker has built up an impressive career in haemostasis and thrombosis research since 1962. He held professorships at Leiden, Brussels Paris and New York and is a member of several national scientific academies. He moved to Maastricht in 1974, where he was one of the founders of Maastricht University. For many years, he led the Biochemistry Department, and he was the university's rector from 1982 to 1985. His research group showed, among other things, that the amount of thrombin is a better measure of blood coagulation than the coagulation time, and discovered the association between thrombosis and the contraceptive pill.

INTERVIEW
MIRANDA NABBEN

Miranda Nabben was awarded a Dekker grant

Gender differences and the thickening of the heart muscle

Miranda Nabben has some idea what aspects have had a positive effect on her 2019 application for a Dekker grant from the Dutch Heart Foundation. Her experience of various research technologies and research models combined beautifully in her grant application. She had gained this experience by working in various labs, including two years in the USA. And for the past five years she has been a member of the board of the international Society for Heart and Vascular Metabolism, which enabled her to build up an extensive network. Miranda Nabben studies the role of the v-ATPase protein in the development of heart failure caused by thickening of the heart muscle, focussing specifically on the differences between men and women in this respect.

Miranda Nabben received her PhD from Maastricht University's School of Nutrition and Translational Research in Metabolism (NUTRIM). There she conducted many *ex vivo* studies into a particular protein of the skeletal muscles, and discovered that the same protein played a major role in cardiac metabolism. She continued this research at the University of Washington in Seattle, where *in vivo* cardiac metabolism in hypertrophy and heart failure was her main research topic. She then worked for 3.5 years at Eindhoven University of Technology, where she examined developmental changes in the cardiac function and metabolism in animal models of heart failure using advanced *in vivo* imaging techniques. Since her return to Maastricht in 2015, her research in the Department of Genetics and Cell Biology has been concentrating more on *in vitro* studies. So she can now describe herself as reasonably all-round with regard to various research techniques. "I will use the Dekker grant to become more involved in clinical work. I collaborate with the Department of Clinical Genetics in the area of functional cardiogenetics, and with the Department of Cardiology I plan to study biopsies from the hearts of patients with heart failure. In addition, I will be working with the Department of Nuclear Medicine to map the metabolism in a non-invasive way."

VICIOUS CIRCLE

Her research revolves around the protein v-ATPase, for which important metabolic roles were discovered by the cardiac metabolism research group a few years ago. This protein functions as an endosomal proton pump, and has been found to disintegrate in diabetes, when cells are subjected to high fat. As a consequence, more fatty acid transporters travel to the cell membrane, causing greater uptake of lipids by heart muscle cells. "It's a kind of vicious circle which you'd rather want to avoid, as those lipids start to accumulate and interfere with all kinds of pathways, which doesn't do the body any good."

CAUSE OR EFFECT?

In simple terms, a heart normally uses more or less equal amounts of fat and sugar. "But if the heart muscle becomes thickened, the heart starts to burn a lot of sugar. Until now, the idea was that thickening is a kind of mechanism to compensate for the fact that the heart's pumping capacity is reduced. But we're not yet sure what is the cause and what the effect. I suspect that this protein, v-ATPase, plays a role in the switch to increased glucose uptake. Thus, the protein doesn't disintegrate, as it does in diabetes, but remains intact and active, causing the fatty acid uptake to be inhibited and the glucose uptake to be increased."

PROMISING PILOT DATA

Nabben has collected promising pilot data that seem to confirm this idea. She also has some ideas about ways to influence this protein to reduce its damaging effects, both

I WILL USE THE DEKKER GRANT TO BECOME MORE INVOLVED IN CLINICAL WORK

by molecular means and with an existing drug. While she can as yet not give any further details, what she can say is that she is going to use her Dekker grant specifically to look at the differences between men and women. “Before the menopause, women appear to be better protected against heart failure caused by thickening of the heart muscle, whereas after the menopause they are at greater risk. I will investigate the differences in substrate metabolism, especially with regard to the uptake of fatty acids and glucose.”

ALL MODELS HAVE ADVANTAGES AND DISADVANTAGES

Her project involves all research methods that she has been using up to now, from animals and HL1 cell cultures of mice to heart cells of adult rats and human stem cells that are differentiated into heart cells. Additionally, she will use the human heart cells collected from biopsies. “Each model has its advantages and disadvantages, which is why we’re using a combination. Heart cells derived from human stem cells are relatively immature in terms of metabolism; their glucose metabolism is much higher than their fatty acid metabolism. In mature cells, it’s the opposite. That’s why I’m pleased to also have human biopsy specimens. The murine cell line is also more glycolytic, but has the advantage that it’s easier to manipulate genetically. The rat heart cells come from adult rats, so in metabolic terms they resemble human cells more closely. In all cases we try to use as few animals as possible.”

THE ROAD TO THE GRANT

Nabben had several colleagues take a critical look at her grant application. She also attended an interview training course, and the research office arranged a practice interview for her with colleagues who “could be expected to ask some critical questions”. The real interview at the Dutch Heart Foundation was actually very pleasant, she remembers. “I now know that I’m sensitive to the atmosphere of a place.” The various places she has worked in so far have also taught her a lot about herself. “Working in different labs gives you a sense of what suits you as a researcher. The atmosphere in Seattle was very competitive, whereas team spirit is more important in Eindhoven and Maastricht.” Her work for the board of the international Society for Heart and Vascular Metabolism (“a very friendly, cooperative group of researchers”) has also taught her that teamwork is what suits her best. “For me, collaboration is the best way forward to make progress.”

FOR ME, COLLABORATION IS THE BEST WAY FORWARD TO MAKE PROGRESS

Miranda Nabben studied pharmaceutical sciences at Utrecht University, after which she did a PhD at Maastricht University. She then worked as a postdoc researcher at the University of Washington, Eindhoven University of Technology, and UM, where she returned in 2015. She was awarded a Veni grant from the Dutch Research Council (NWO) in 2013, and a 400 k€ Dekker grant from the Dutch Heart Foundation in 2019.

EDUCATION AND TALENT DEVELOPMENT

04

INTRODUCTION

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

In addition, CARIM's staff is involved in the design of a contiguous and state-of the-art PhD (doctoral) training programme. The content of the PhD education programme has been developed by CARIM's top researchers, while its framework has been created by senior educators of Maastricht University, who have earned an excellent international reputation for their didactical system that is based on problem-based learning.

RESEARCH MASTER

In the Biomedical Sciences programme, Masters students are informed about CARIM and the programmes of the other FHML schools during the start of the master. Members of the CARIM staff actively participate in the design and execution of the teaching programme in the second and third course. Students can attend school-specific lectures and parallel programmes organised by school researchers. In the second semester, they may become acquainted in more detail with School specific practical research. In this respect, CARIM offers students the opportunity to do a junior research internship in the field of cardiovascular biology at one of CARIM's laboratories. In the second year, the students that are attracted to cardiovascular research can do their senior research internship and master thesis in CARIM. These internships are also accessible for students from other master programmes, provided that they have an adequate background. All too often successful Master students subsequently start 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 Biomedical Masters. At the end of 2019, in total 302 (internal as well as external) PhD candidates candidates attended our PhD programme. In 2019, 53% of our PhD candidates came from abroad, creating an exciting multicultural and international atmosphere. The translational nature of CARIM's research is exemplified by the mix of PhD candidates with a background in medicine or in the basic sciences. The principal goal of the four-year PhD training programme is to support PhD candidates in developing themselves into independent and productive researchers in the cardiovascular field. To ensure high quality PhD training, CARIM offers frequent interaction of PhD candidates with skilled and experienced supervisory teams, thereby providing a stimulating and critical environment to further develop research skills. We also offer our PhD candidates a broad range of possibilities to attend general and school specific courses, to attend seminars and master classes. PhD candidates are stimulated to visit symposia to present their own research on national and international podia. In 2019, 89 new PhD candidates started their trajectory at CARIM, of which 21 were employed at Maastricht University.

POSTGRADUATE PROGRAMME

One of the key needs identified by the European Society of Cardiology is the training of future leaders in arrhythmia management and research. For this purpose, a unique two-year postgraduate educational programme entitled 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM) has been established. DAS-CAM trains the future leaders in cardiac electrophysiology by integrating state-of-the-art knowledge of cardiac arrhythmia management, ranging from fundamental mechanisms to the design of a clinical electrophysiology unit, with leadership skills, biostatistics and health technology assessment.

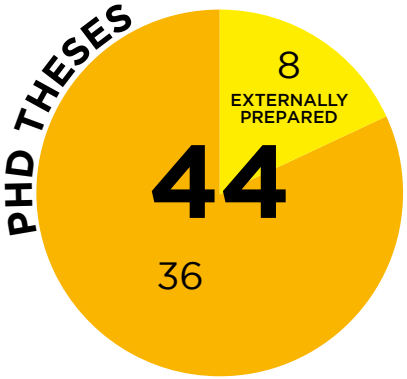
DAS-CAM is a collaboration between Maastricht University, the European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA). It consists of eight modules (six of which take place in Maastricht) each chaired by two expert anchor persons supported by the Scientific Program Committee. The first DAS-CAM cohort consisted of 32 cardiac electrophysiologists from 20 different countries who received their diplomas in October 2018.

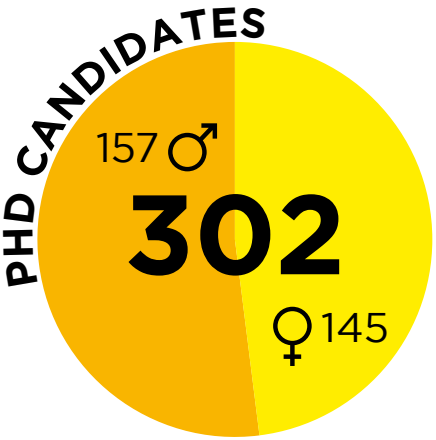
A second cohort has started in January 2019. Researchers from CARIM have a major role in the DAS-CAM programme, with four CARIM Principal Investigators serving as anchor persons and several CARIM researchers involved as

members of the Scientific Program Committee. In addition, a number of participants from the first DAS-CAM cohort will continue to be affiliated with CARIM through a PhD research project.

PHD DELIVERABLES

In 2019, 36 PhD candidates finished their theses within our institute, and eight theses were externally prepared. The table below illustrates the numbers of PhD candidates in the years 2009-2014, related to the period in which they obtained their degree.





CARIM THESES 2019

Van Hunnik A
Title: Dynamics of propagation patterns and anti- arrhythmic mechanisms during atrial fibrillation
Supervisor: Prof. U. Schotten
Co-supervisors: Dr S. Verheule, Dr S. Zeemering
10 January

Van Vuuren T
Title: Deep venous obstruction: towards optimizing treatment strategies
Supervisor: Prof. C. Wittens
Co-supervisor: Dr R. de Graaf
11 January

Kicken C
Title: Extreme blood coagulation; investigating the influence of physiological extremes on thrombin generation and platelet activation
Supervisor: Prof. W. Buhre
Co-supervisors: Dr B. de Laat, Dr M. Lancé, Qatar
17 January

Heuts S
Title: The Potential of Pre-operative Planning in Cardiothoracic Surgery
Supervisor: Prof. J. Maessen
Co-supervisor: Dr P. Sardari Nia
7 February

Amin E
Title: Personalized Management of Post-Thrombotic Syndrome
Supervisors: Prof. H. ten Cate, Prof. M. Joore
Co-supervisor: Dr A.J. ten Cate-Hoek
7 February

Zhang E
Title: Novel insights in the pathophysiology of cerebral small vessel disease – a study using advanced imaging techniques
Supervisors: Prof. R. van Oostenbrugge, Prof. W. Backes
Co-supervisor: Dr J. Staals
8 February

Lozekoot P
Title: Intra-aortic Balloon Pumping; New insights for an old therapy
Supervisors: Prof. S. Gelsomino, Prof. J. Maessen
Co-supervisor: Dr D. Johnson
15 February

Wetzels S
Title: Advanced glycation endproducts in multiple sclerosis
Supervisors: Prof. C. Schalkwijk, Prof. J. Hendriks, UHasselt
Co-supervisors: Dr K. Wouters, Dr T. van Mierlo, UHasselt
21 February

Eijkenboom I
Title: A zebrafish model of small-fiber neuropathy
Supervisors: Prof. H. Smeets, Prof. C. Faber
Co-supervisor: Dr J. Vanoevelen
22 February

Bijnen M
Title: The inflamed liver: RAGE and Gluttony
Supervisor: Prof. C. Schalkwijk
Co-supervisor: Dr K. Wouters
22 February 2019

Ding S
Title: Maintaining the stemness of satellite cells during long-term culture
Supervisors: Prof. M. Post, Prof. G. Zhou
27 March

Zonnebeld N
Title: Enter the Matrix: Computational and mechanistical approaches to improve arteriovenous fistula maturation
Supervisors: Prof. T. Delhaas, Prof. J. Tordoir
Co-supervisor: Dr.ir W. Huberts
29 March

Vroomen M
Title: The evolving landscape in the hybrid treatment of atrial fibrillation
Supervisors: Prof. H. Crijns, Prof. L. Pison
Co-supervisor: Prof. B. Maesen
11 April

CARIM THESES 2019

Peeters F
Title: The snowball effect in aortic valve disease; gaining insight in imaging, circulating and tissue biomarkers towards a halt in disease progression
Supervisors: Prof. H. Crijns, Prof. L. Schurgers
Co-supervisors: Dr S. Meex, Dr B. Kietselaer
18 April

Van Doorn P
Title: Functional interactions between factor V and TFPIa during onset of blood coagulation
Supervisor: Prof. T. Hackeng
Co-supervisor: Dr E. Castoldi
1 May

Raso A
Title: MicroRNAs as therapeutic targets in heart diseases
Supervisor: Prof. L. de Windt
Co-supervisor: Dr P. Da Costa Martins
2 May

Zwaveling S
Title: The impact of oral anticoagulants on haemostasis; A step towards individualized therapy
Supervisor: Prof. H. ten Cate
Co-supervisors: Dr S. Bloemen, Dr A. ten Cate-Hoek
3 May

Knapen L
Title: Insight in disease and drug interactions, with treatment optimisation of patients with cancer
Supervisor: Prof. V. Tjan-Heijnen
Co-Supervisors: Dr S. Croes, Dr F. de Vries, Dr N. van Erp, Radboud
10 May

Kimenai D
Title: Female versus male hearts; battle of the cardiac troponins
Supervisor: Prof. O. Bekers
Co-supervisor: Dr S. Meex
16 May

Moorlag M
Title: Thrombinoscopy Revisited
Supervisors: Prof. T. Hackeng (de jure), Prof. H. Hemker (de facto)
17 May

Sondermeijer H
Title: Bioengineering of novel 3D scaffolds for cell-based therapy in heart failure and diabetes mellitus
Supervisors: Prof. M.J. Post, Prof. A.A. van der Laarse, LUMC Leiden
17 May

Hermans-Beijnsberger S
Title: Emerging roles of small and long non-coding RNAs in Cardiac disease
Supervisor: Prof. B. Schroen
Co-supervisor: Dr M. van Bilsen
22 May

Giamouridis D
Title: Preclinical Development of Gene Therapy; The effects of Urocortin 2 and Urocortin 3 gene transfer in murine models of heart failure and diabetes
Supervisors: Prof. E. Biessen, Prof. H. Hammond
Co-supervisor: Dr M. Blankesteijn
5 June

De Jong R
Title: Type 2 diabetes mellitus and gastrointestinal cancer; Disease, drugs, or distortion?
Supervisors: Prof. A. Masclee, Prof. M. Janssen-Heijnen
Co-supervisor: Dr F. de Vries
5 June

Schütten M
Title: Microvascular effects of aldosterone and salt in Health, obesity and hypertension; consequences for blood pressure and insulin sensitivity
Supervisors: Prof. C. Stehouwer, Prof. P. de Leeuw
Co-supervisor: Dr A. Houben
20 June

Van Stipdonk A
Title: Simplicity is key in CRT: Patient selection and management in cardiac resynchronization therapy
Supervisors: Prof. F. Prinzen, Prof. H. Crijns
Co-supervisor: Dr K. Vernooy
21 June

CARIM THESES 2019

Huntjens P
Title: Pacing the heart: synchronization or orchestration?
Supervisors: Prof. T. Delhaas, Prof. P. Bordachar, Univ. de Bordeaux
Co-supervisors: Dr J. Lumens, Dr S. Ploux, Univ. de Bordeaux
27 June

Fabris E
Title: Myocardial reperfusion in STEMI and the role of the antithrombotic/antiplatelet therapy Supervisor: Prof. A. van 't Hof
Co-supervisors: Dr E. Kedhi, Dr R. Hermanides
28 June

Opačić D
Title: Metabolic modulators as a treatment of atrial fibrillation
Supervisor: Prof. U. Schotten
Co-supervisors: Dr S. Verheule, Dr S. Zeemering
4 July

Smedema J
Title: Delayed-Enhanced Cardiovascular Magnetic Resonance in the diagnosis and management of Cardiac Sarcoidosis
Supervisor: Prof. H. Crijns
4 July

Brandenburg V
Title: Beyond lipids and smoking - the nephrologist's perspective on cardiovascular disease associated with CKD
Supervisor: Prof. H-P. Brunner-La Rocca
Co-supervisor: Dr C. Knackstedt
6 September

Cetinkaya M
Title: Translational Approach for New Therapeutic Targets in Prevention of Severe Neonatal Morbidities: From Bench to Bedside
Supervisors: Prof. B. Kramer, Prof. T. Delhaas
Co-supervisor: Dr D. Gavilanes
17 September

Xin Y
Title: The complement system and obesity-associated metabolic disorders: The CODAM study
Supervisors: Prof. C. Stehouwer, Prof. C. Schalkwijk
Co-supervisor: Dr M.M.J. van Greevenbroek
25 September

Heusinkveld M
Title: Digital Twin of Analogue Man; Development of a Computational Modelling Platform to Assess Heart-Vessel Interaction in Humans
Supervisor: Prof. T. Delhaas
Co-supervisors: Dr K.D. Reesink, Dr W. Huberts
4 October

Beumer D
Title: Insights in acute endovascular treatment in ischemic stroke
Supervisors: Prof. R.J. van Oostenbrugge, Prof. D.W.J. Dippel, Prof. W.H. van Zwam
10 October

Crombag G
Title: MRI Imaging of carotid intraplaque hemorrhage and microvasculature
Supervisors: Prof. M.E. Kooi, Prof. J.E. Wildberger, Prof. R.J. van Oostenbrugge
11 October

Nagy M
Title: Discovering new pathways in thrombus formation
Supervisors: Prof. J. Heemskerk, Prof. S. Watson, Birmingham
Co-supervisor: Dr J. Cosemans
7 November

Nijssen E
Title: AMACING; A MAastricht contrast-induced nephropathy guideline project; Evaluation of guideline-recommended prophylaxis to prevent contrast-induced nephropathy
Supervisor: Prof. J. Wildberger
Co-supervisors: Dr P. Nelemans, Dr G. van Ommen
27 November

CARIM THESES 2019

Oshagbemi F
Title: Biomarkers in real-life COPD Management
Supervisors: Prof. E.F.M. Wouters, Prof. F. de Vries
Co-supervisor: Dr F.M.E. Franssen, CIRO Horn
2 December

Veugen M
Title: Health burden in (pre)diabetes and the role of cardiovascular Function; Extensive phenotyping in a population-based approach
Supervisors: Prof. H.P. Brunner-La Rocca, Prof. C.D.A. Stehouwer
Co-supervisor: Dr R.M.A. Henry
11 December

Quicken S
Title: GRAFTWERK; A structured approach for optimising dialysis grafts
Supervisor: Prof. T. Delhaas
Co-supervisors: Dr W. Huberts, Dr B.M.E. Mees
12 December

Van der Linde H
Title: The cardiac ElectroMechanici Window & Arrhythmogenesis. Veni-Vidi-Vivo
Supervisor: Prof. P.G.A. Volders
Co-supervisor: Dr D.J. Gallacher, Janssen Research Dev., Beerse, Belgium
13 December

Raffa G
Title: Extracorporeal Membrane Oxygenation Support in Post-Cardiotomy Shock
Supervisors: Prof. R. Lorusso, Prof. J.G. Maessen
Co-supervisor: Dr J.W. Sels
16 December

Denisov S
Title: Catching evaders: structure elucidation and molecular mechanisms of tick salivary proteins
Supervisor: Prof. T.M. Hackeng
Co-supervisor: Dr I. Dijkgraaf
18 December

PATENTS 2019

Prinzen F
Electrocardiographic signal processing
Date: 29-11-2019

DISSERTATION PRIZE 2018

Dr **Rachel ter Bekke** (Dept. of Cardiology) received the CARIM Dissertation Award 2018 for her thesis 'Ventricular arrhythmogenesis in the genetically-susceptible Heart; time to change concepts of mechanisms and management'.

KNOWLEDGE TRANSFER

CARIM COURSES

From 17 until 21 June, the annual CARIM Course Week took place. The week consisted of parallel courses, covering several aspects of CARIM's research, alternated with a combined scientific programme and a social programme organised by I'M CARIM, the organisation of CARIM's PhD candidates. In 2018, two courses were organised by CARIM researchers: 'Drug Development' and 'Vascular Inflammation and Thrombosis'. Almost 40 PhD and Masters students participated. Furthermore, the course 'Advanced Microscopy and Vital Imaging', which is accessible to CARIM PhD candidates, was organised in the same week. Nine CARIM PhD candidates participated in the course.

CARDIOVASCULAR GRAND ROUNDS AND CARIM SYMPOSIUM 2019

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 the framework of the Cardiovascular Grand Rounds Maastricht, three successful lecture series were organised in 2019 by Prof. **Blanche Schroen** and Dr **Jordi Heijman** (Dept. of Cardiology), with cardiovascular lectures given by national and international experts, on a weekly basis. These lectures take place early in the morning, with breakfast provided, and are of very high scientific level, worthy of an early rise. For the current programme please visit our website. CARIM's annual scientific symposium was held in Maastricht on 20 November. During the morning programme, this year's NWO and Dutch Heart Foundation laureates presented their

research, followed by a session on scientific integrity. In the afternoon, some of CARIM's HS-BAFTA recipients presented their research. 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 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.

This year's Robert Reneman lecture was presented by Prof. Vasan S. Ramachandran. Prof. Ramachandran has been Principal Investigator and Director of the Framingham Heart Study and Director of the Framingham Heart Study fellowship programme in cardiovascular epidemiology for the last 25 years. Vasan S. Ramachandran is Professor of Medicine and Epidemiology at Boston University School of Medicine/Boston University School of Public Health, and Chief of Section of Preventive Medicine and Epidemiology, Department of Medicine, BUSM. He is the Jay & Louis Coffman Professor of Vascular Medicine at BUSM. Prof. Ramachandran is a trained cardiologist with subspecialty

training in echocardiography. For the last 20 years, Prof. Ramachandran has focussed his research on the genetic and non-genetic epidemiology of congestive heart failure; on population-based vascular testing and echocardiography; on genetic and non-genetic epidemiology of high blood pressure; and on CVD risk estimation in the short, medium- and long-term, with novel biomarkers including genomic biomarkers.
Finally, the CARIM Award (see page 52), Dissertation prize (see page 84) and the poster prizes were awarded. The following posters were awarded with a prize:

* 'Cardiometabolic consequences of non-alcoholic fatty liver disease' by Brouwers M, Simons N, Buziau A, Simons P, Schalkwijk C, Schaper N, Stehouwer C
* 'The role of Factor Xa in AF-related cardiac remodelling' by d'Alessandro E, Scaf B, Spronk H, Schotten U, ten Cate H
* 'Generation of iPS-CMs as a model for Arrhythmogenic Cardiomyopathy' by Sacchetto C, Rabino M, Mattiotti A, Vitiello L, Condorelli G, Rampazzo A, di Pasquale E, et al

OTHER CARIM LECTURES, SEMINARS AND SYMPOSIA 2019

Complementary to the regular lecture series and CARIM symposium, several lectures, seminars and conferences were organised by our research staff in 2019. Some of them are presented below.

Since 2015, CARIM and the Institute of Cardiovascular Research (IMCAR) of the University Hospital RWTH Aachen (headed by Prof. **Joachim Jankowski**) have been organising joint **Cardiorenal Seminars**. This lecture series, which is alternately held in Aachen and Maastricht, offers a platform for international top scientists in the field of vascular biology and nephrology to present their recent work. In 2019, six keynote lectures were given by Prof. Alberto Ortiz (Autonomous University of Madrid, 27 February), Prof. Patrick D'Haese (University of Antwerp, 11 April), Prof. Neil Henderson (University of Edinburgh, 13 June), Prof. Anton Jan van Zonneveld (Leiden UMC, 22 August), Dr Florian Kahles (Harvard Medical School, 28 November) and Prof. Wilfried Mullens (Hasselt University, 12 December).

The **Maastricht Systems Biology Forum** brings together researchers in the Maastricht area who are interested in the development and application of systems biology approaches. The main aim is to share research, experience and, through this exchange, inspire and initiate new research directions and collaborations. The Forum held a second special 'highlights session' on 2 July in which six PhD candidates from various departments showcased the wide range of Systems Biology topics that are being researched in Maastricht. In 2019, the Forum was organised by Dr **Michiel Adriaens** (MaCSBio), Dr **Pietro Bonizzi** (DKE), Dr **Mike Gerards** (MaCSBio), Dr **Jordi Heijman** (CARDIO),

Dr **Martina Kutmon** (BiGCaT & MaCSBio), Dr **Joost Lumens** (BME), and Dr **Stef Zeemering** (FYS).

The three-monthly **'Maastricht Immunology Seminar Series'** bring together researchers from Maastricht that are interested in immunology and inflammation. These informal meetings are ideal to expand local networks, and to share research techniques and experience. Each seminar, an external speaker is invited and two PhD candidates or postdocs from Maastricht present their research. In 2019, the invited speakers were Bart Everts (LUMC Leiden), Thomas Marichal (University of Liege, Belgium), Jannie Borst (LUMC Leiden), and Bieke Broux (Hasselt University, Belgium). Afterwards, there are drinks to stimulate networking and exchange between researchers of the different research schools. The meetings are organised by Dr **Kristiaan Wouters** (Dept. of Internal Medicine) and Dr Lotte Wieten (Dept. of Transplantation Immunology). The Organisation Committee also contains PhD candidates from different research schools: **Xiaodi Zhang** (Dept. of Internal Medicine), Nicky Beelen (Dept. of Transplantation Immunology), Ines Reis (Dept. of Molecular Genetics), and Marina Damas (Dept. of Psychiatry and Neuropsychology).

On 8 February, Prof. **Sandro Gelsomino** (Dept. of CTC) held his inaugural lecture titled 'Two-voice Inventions: My Life Between Music and Science'.

The third **Maastricht Consensus Conference on Thrombosis** was held from 13 until 15 February and attracted about 200 attendants. The focus of the meeting was 'Thrombo-Inflammation in Cardiovascular Disease' and the document resulting from the 2.5 days of intense presentations, discussions and proceedings, was recently published in Thrombosis and Haemostasis (DOI https://doi.org/ 10.1055/s-0040-1708035). The meeting was, again, perceived as a unique forum for exchanging ideas about the ways that research related to the focus area could be directed. The mixture of basic and translational scientists, clinicians, students and representatives of industry, created a melting pot of ideas and new collaborations; this is the unique and much appreciated formula of this meeting. The LOC consisted of Dr **Henri Spronk**, Dr **Paola van der Meijden**, Dr **Yvonne Henskens**, Dr **Arina ten Cate-Hoek**, Prof. **Harry Crijns** and Prof. **Hugo ten Cate**.

On 20 March, **the 6th annual scientific meeting of The Maastricht Study**, entitled 'From Dee-Phenotyping To Big Data', took place at Maastricht UMC+. The aim of the scientific meeting is to present recent results from the Maastricht Study, in order to facilitate discussions between scientists from a broad range of disciplines and to strengthen collaborations within Maastricht UMC+ and Maastricht University. This year, duos of senior and junior researchers presented. The senior researcher introduced the topic, followed by the junior researcher, who presented a selection of their results within The Maastricht Study. Prof. David Linden, Scientific Director of the School for Mental Health and Neuroscience (MHeNs), opened the meeting where after an update of the study was given by Prof. **Coen Stehouwer. Dr Kristiaan Wouters**, presented his work on immune cells in The Maastricht Study. Furthermore, results of The Maastricht Study showed that; microvascular dysfunction precedes the clinical diagnosis of type-2 diabetes; a greater blood pressure variability was found to be an important risk factor, and may be a potential target for prevention and treatment of cardiovascular and neurodegenerative disease. Preliminary results indicated that fracture incidence differs per fracture location in patients with T2DM as compared to controls; while markers

of microvascular dysfunction in the retina and plasma were associated with the incidence of depressive symptoms over a four-year follow-up period. Keynote speaker Dr Jeroen Lakerveld, threw out a challenge to us to consider how to investigate 'upstream' determinants of chronic disease, and highlighted the importance of investigating these overlooked factors. In addition, he spoke about the Geoscience and Health Cohort Consortium (GECCO) collaboration in which large-scale Dutch cohort studies including The Maastricht Study, share their data.

On 25 April, Prof. **Roberto Lorusso** (Dept. of CTC) held his inaugural lecture titled 'Leonardo da Vinci and the Surgical Investigator: Analogies and Peculiarities of 'Renaissance Men'.

In the context of the yearly meeting of the European Atherosclerosis Society (EAS), that took place in the MECC conference center in Maastricht, a symposium was organised by the European Society of Cardiology Working Group on Atherosclerosis and Vascular Biology (ESC WG on AVB). The symposium focussed on 'Imaging of vulnerable atherosclerotic plaques – biological insights' and was organised by Prof. **Eline Kooi** (Dept. of Radiology), Prof. Esther Lutgens (Amsterdam) and Dr Jolanda Wentzel (Rotterdam) and was dedicated to basic scientists, clinicians and engineers in the field of vascular biology, nuclear imaging, cardiology and radiology.

Another symposium in the context of the EAS congress was the satellite meeting 'Immunometabolism', organised by Prof. **Erik Biessen** and Dr. **Pieter Goossens** (Dept. of Pathology) together with Prof. Danilo Norata (Milan, Italy) and Prof. Laurent Yvan-Charvet (Nice, France) on 25 and 26 May. In this two-day meeting, different angles on the interplay between immunity and metabolism in cardiovascular diseases were explored in exciting presentations by experts in the field that were alternated with discussions, two poster sessions and a speakers' dinner. The programme boosted eleven internationally renowned speakers from The Netherlands, France, Italy, Sweden, USA, Canada and Australia. On top of that, a total of 60 registrations from nine different countries were received. From the submitted abstracts, five were selected for a short oral presentation and fourteen for a poster presentation. At the closing session of the meeting, **Jenny de Bruijn** (The Netherlands) and Mattia Albiero (Italy) received an award for best oral and best poster presentation, respectively.

On 12 and 13 December 2019 the mini-symposium **'Drug-Induced Proarrhythmia'**, organised by the team of Prof. **Paul Volders** (Dept. of Cardiology) took place. During the symposium, that was connected to the PhD defence of **Henk van der Linde** (Dept. of Cardiology), influential speakers in various domains gave state-of-the-art overviews of their fields of expertise and discussed how the assessment of proarrhythmia in drug development, post-marketing surveillance, and clinical management can be further improved. Key-note speaker of the symposium was Dr Norman Stockbridge, Director of the Division of Cardiovascular and Renal Products, at the US Food and Drug Administration, with the lecture 'Contemporary Evaluation of Cardiac Drug Safety at the US FDA: Focus on Drug-Induced Proarrhythmia'.

TALENT PROGRAMME

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

1. HS-BAFTA TALENTED FUTURE PHD CANDIDATES

The fellowship is intended for:

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

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

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

The fellowship amounts to max. € 21,000 (in accordance with scale 7-0) and € 3,000 for exploitation costs and is meant for a period of max. 6 months. For Ba/Ma students the regular curriculum should be interrupted to perform the research fellowship within CARIM. The PI concerned has to match an equal amount of money for the candidate for an equal period of max. 6 months. This brings the max. total annual amount for the HS-BAFTA on € 42,000 for a total of 12 months.

2017 William van Doorn

2018 Jasper Demandt

2019 Mohamed Kassem

2. HS-BAFTA TALENTED PHD CANDIDATES

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

2018 Mueez Aizaz, Jens Posma

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

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

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

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

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

THE H.C. HEMKER CHAIR

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

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

EDMOND HUSTINX CHAIR

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

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

VAN DE LAAR PROFESSORSHIPS ON BIOCHEMISTRY OF HAEMOSTASIS AND THROMBOSIS

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

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

SINT ANNADAL FOUNDATION

2014-2019	J. Hoorntje

HIGHLIGHT
DIVISION VESSELS

PAULA DA COSTA MARTINS

Department of Cardiology

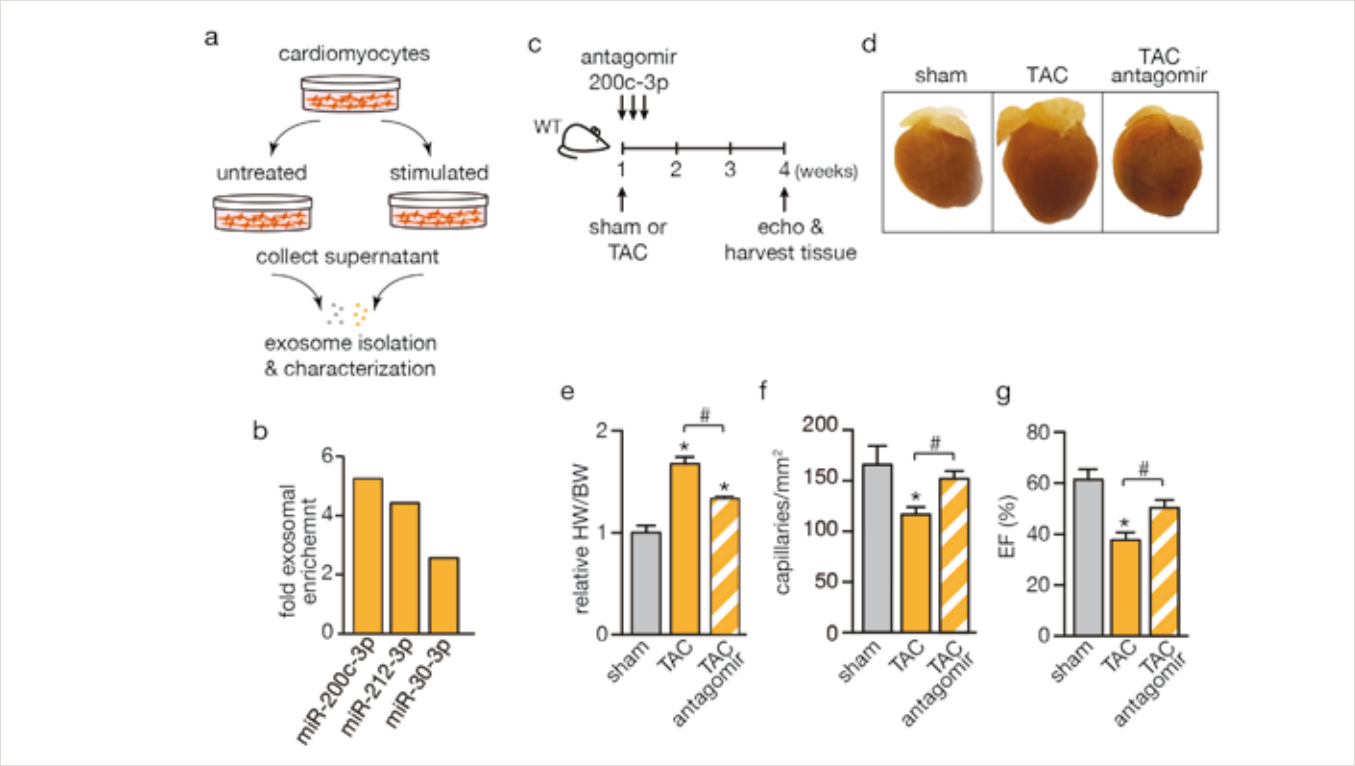
The myocardium is a highly organised complex organ with a multicellular structure. Additional to the contractile cardiomyocytes (CMs), other important non-myocyte cell populations include endothelial cells (ECs), fibroblasts, vascular smooth muscle cells, immune and neuronal cells. While cardiomyocytes have been the focus of most heart failure (HF) research to date, each cellular component has a distinct and critical role in cardiac function, and together they constitute key pathologic determinants in cardiac remodelling in both ventricles and atria. Dynamic interactions among the different cardiac cell populations by mechanical, electrical, chemical and molecular means, as well as their interactions with the extracellular matrix, determine physiology and pathology. CMs mainly contribute to the conduction of electrical impulses and contraction. Non-CMs are responsible for vascularization, secretion of extracellular matrix components and responding to myocardial stress and/or injury caused by pressure increase or oxygen depletion during heart diseases such as aortic stenosis or myocardial infarction [1]. Understanding the multicellular interactions in the myocardial tissue is critically important, not only to provide insight into healthy and diseased cardiac microenvironments, but also to enable the development of engineered tissue culture systems mimicking the myocardial environment for cardiovascular regeneration applications, and to provide potential novel therapeutic targets and more effective therapeutic interventions for the treatment of HF.

In the heart, ECs outnumber CMs at a ratio of nearly 3:1, with virtually every cardiac muscle cell bordering on one or more capillaries. As in most organs, endothelial cells in the heart have complex biological functions, including the control of vascular permeability, vasomotion, regulation of haemostasis, immune responses and angiogenesis. The endothelium also plays an important role in the regulation of heart size, and while an increase in capillary density is important for the development of physiological cardiac hypertrophy, a reduction of the vascular bed size contributes to impairment of cardiac function. CM paracrine signalling plays a key role in the dynamic regulation of the vascular tone and, in the long term, may affect the cardiac vascular bed density. The pathological progression in HF is associated with an imbalance between oxygen supply and demand, as CM hypertrophy is not matched by a corresponding increase in the vasculature [2]. Identification of the mechanisms driving this mismatch between CM and EC growth could lead to the discovery of new approaches to treat HF. At the Department of Cardiology, we are currently investigating

FIGURE 1 MICRORNA-216A IS ESSENTIAL FOR CARDIAC ANGIOGENESIS. (**a**) Representative images of whole hearts and wheat germ agglutinin (WGA)-stained histological sections of wildtype (WT) and miR-216a knockout (KO) hearts. (**b**) Myocardial tissue oxygenation analysis as assessed by combining photoacoustics with high frequency ultrasound. (**c**) Representative images of sequential transversal sections of hearts from WT and KO mice subjected to myocardial infarction (MI). (**d**) Quantification of the infarct areas. (**e**) Ejection fraction as a readout of cardiac function.

the communication routes between CMs and ECs by mainly focusing on the role of non-coding RNAs and their transfer between these two cardiac cell populations via extracellular vesicles.

For the last decade, the contribution of non-coding RNAs, and mainly microRNAs, towards the onset and progression of HF have been the focus of our research. MicroRNAs (miRNAs), which mainly function as guide molecules in RNA silencing, target most protein-coding transcripts and are involved in nearly all developmental, physiological and pathological processes by coordinately targeting functionally related genes. Perturbation of cardiac miRNA biogenesis and/or expression profiles results in HF by affecting critical cellular and molecular functions [3-5], including cardiac angiogenic capacity. A high-content screening to identify regulators of EC function revealed that several miRNAs were anti- or pro-proliferative. Of these, miR-216a, a pro-proliferative miRNA, was shown to be downregulated in mouse models of cardiac pressure overload and myocardial infarction. Extensive expression pattern profiling revealed enrichment of miR-216a in ECs, with the greatest abundance in cardiac ECs. Remarkably, and in contrast to the paucity of lethal phenotypes observed at baseline in most miRNA gene knockout models, gene deletion of miR-216a in mice sufficed to provoke pathological cardiac remodelling, characterised by CM hypertrophy, fibrosis, capillary rarefaction and impairment of cardiac function. In fact, severe impairment of myocardial tissue oxygenation was confirmed using photoacoustics in combination with high-frequency ultrasound (**Figure 1**). The contribution of miR-216a to the maintenance of proper cardiac geometric properties and function becomes more prominent under conditions of cardiac stress as ischemic injury, resulting in larger infarcts and more extensive fibrotic areas, compared to control animals under similar conditions (**Figure 1**). Mechanistically, miR-216a in cardiac ECs interferes with cell proliferation and autophagy by directly targeting genes that are involved in both processes.



To date, perturbed crosstalk between CMs and ECs, defining the pathogenesis of several heart conditions, has been mainly associated with paracrine growth factors from CMs, mainly including secreted proteins and peptides. In addition to paracrine soluble factors, intercellular communication can also occur via extracellular vesicles (EVs). These vesicles shuttle a wide range of functional lipids, proteins, mRNAs and also non-coding RNAs such as miRNAs, long non-coding RNAs and circular RNAs [6].

FIGURE 2 INTERCELLULAR TRANSFER OF MIR-200C-3P IMPAIRS THE ANGIOGENIC CAPACITY OF CARDIAC ENDOTHELIAL CELLS. (**a**) Experimental setup of EV isolation from untreated and stimulated CMs. (**b**) Enrichment of specific microRNAs in EVs derived from stimulated CMs. (**c**) Study design in which WT mice were subjected to pressure overload by transverse aortic constriction (TAC) or sham surgery and subsequently injected with antagomir-200c-3p. (**d**) Representative images of whole hearts. (**e**) Gravimetric analysis of corrected heart weights in sham and TAC animals treated with antagomir-200c-3p. (**f**) Quantification of the total number of capillaries by isolectin B4 staining. (**g**) Assessment of cardiac function by quantification of ejection fraction (EF).

We have recently identified a new mechanism by which, under pathologic conditions, CMs are able to influence the function of the surrounding endothelium by releasing EVs enriched with various miRNAs, such as miR-200c-3p, miR-212-3p and miR-30d-3p. Increased levels of miR-200c-3p and miR-30d in EVs, released by hypertrophic CMs, impair the angiogenic capacity of the cardiac endothelium, suggesting a prominent role for CM-derived EVs in the process of cardiac capillary rarefaction and endothelial dysfunction. The overall result is a drop in capillary density that promotes a poorer cardiac outcome under stress conditions (**Figure 2**). Mechanistically, these anti-angiogenic miRNAs act by perturbing endogenous expression levels of genes that were previously associated with the maintenance of proper cell growth and mobility, cell apoptosis or cell-cell communication, all determinants of proper EC function.

However, it is not only ECs which are able to receive and process these CM-derived non-coding messages. In fact, miR-212-3p in CM-derived EVs can be taken up by cardiac macrophages in the surrounding environment and influence their inflammatory phenotype. Among the different immune cell populations, macrophages have most recently been identified as important regulators of myocardial remodelling and HF. Although cardiac macrophages are known to adopt key functions in inflammation, their specific role in tissue homeostasis, their activating stimuli and their interplay with cardiac cells are barely understood, particularly in disease. *In vivo* loss-of-function studies are currently being performed not only to gain more insight into the precise role of miR-212-3p in pathological cardiac remodelling and, more specifically, in macrophage function, but also to determine its potential as a new therapeutic target in HF.

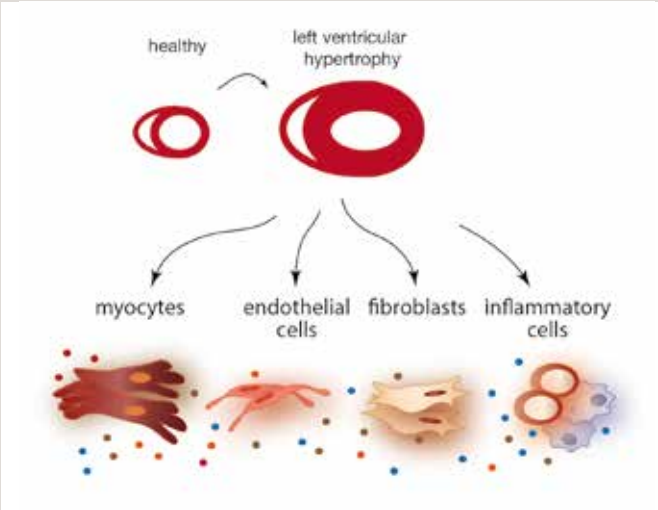


FIGURE 3 INTERCELLULAR COMMUNICATION IN THE HEART. Release of EVs by the different cardiac cell types allows cells to communicate with each other. Transfer of various molecular regulators among the different cardiac cellular components functionally affects the recipient cells and can therefore no longer be ignored when studying the regulatory complexity of cardiac pathological processes.

We recently initiated a collaboration with the University of California at Irvine to further study the therapeutic effect of targeting our miRNAs of interest in a humanized "organ-on-a-chip" model [7], which mimics the human heart environment more accurately than any other 2D/3D model described so far. This is done by integrating organised microvessels, composed of human ECs, smooth muscle cells and pericytes, with human CMs. These functional vessels are able to supply oxygen and nutrients to CMs and respond to vascular modulators and pathological conditions. Despite the many remaining unanswered questions regarding the biology of EVs and their involvement in the onset, development and

regulation of the myocardial response to stress, our research so far supports the existence of communication between CMs and non-CMs via EVs (**Figure 3**), as a critical feature of normal cardiac function. This also reinforces the idea that cardiac heterocellularity needs to be carefully considered in the pathogenesis of HF, particularly when implementing new platforms to screen drug candidates or lead optimization. Furthermore, assessment of EV-mediated intercellular communication in the heart could lead to the identification of additional therapeutic targets to enhance cardiac angiogenesis and/or modulate inflammation in the stressed heart.

REFERENCES

[1] Peters MMC, Sampaio-Pinto V, da Costa Martins PA. Non-coding RNAs in endothelial cell signalling and hypoxia during cardiac regeneration. Biochim Biophys Acta Mol Cell Res 2020; 1867(3): 118515.

[2] Shiojima I, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, Colucci WS, Walsh K. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. J Clin Invest 2005; 115: 2108-2118.

[3] Dirkx E, Gladka MM, Philippen LE, Armand AS, Kinet V, Leptidis S, El Azzouzi H, Salic K, Bourajjaj M, da Silva GJ, Olieslagers S, van der Nagel R, de Weger R, Bitsch N, Kisters N, Seyen S, Morikawa Y, Chanoine C, Heymans S, Volders PG, Thum T, Dimmeler S, Cserjesi P, Eschenhagen T, da Costa Martins PA, De Windt LJ. Nfat and miR-25 cooperate to reactivate the transcription factor Hand2 in heart failure. Nat Cell Biol 2013; 15(11): 1282-93.

[4] da Costa Martins PA, Salic K, Gladka MM, Armand AS, Leptidis S, el Azzouzi H, Hansen A, Coenen-de Roo CJ, Bierhuizen MF, van der Nagel R, van Kuik J, de Weger R, de Bruin A, Condorelli G, Arbones ML, Eschenhagen T, De Windt LJ. MicroRNA-199b targets the nuclear kinase Dyrk1a in an auto-amplification loop promoting calcineurin/NFAT signalling. Nat Cell Biol 2010; 12(12): 1220-7.

[5] da Costa Martins PA, Bourajjaj M, Gladka M, Kortland M, van Oort RJ, Pinto YM, Molkentin JD, De Windt LJ. Conditional dicer gene deletion in the postnatal myocardium provokes spontaneous cardiac remodeling. Circulation 2008; 118(15): 1567-76.

[6] De Abreu RC, Fernandes H, da Costa Martins PA, Sahoo S, Emanueli C, Ferreira L. Native and bioengineered extracellular vesicles for cardiovascular therapeutics. Nat Rev Cardiol 2020; in press.

[7] Phan DTT, Wang X, Craver BM, Sobrino A, Zhao D, Chen JC, Lee LYN, George SC, Lee AP, Hughes CCW. A vascularized and perfused organ-on-a-chip platform for large-scale drug screening applications. Lab Chip 2017; 17(3): 511-520.

INTERVIEW

BAREND MEES, JOOST LUMENS AND MATTHIJS CLUITMANS

Meet the future leaders in the cardiovascular arena

Start the heroic superhero music. In this Zoom session we will subsequently see the figures of Joost Lumens, Matthijs Cluitmans and Barend Mees appear. Their hair – as far as it is still there – blowing in the wind. They are gazing intently at a point on the horizon – which is where the future lies. Trumpets are starting to blare. Right across the screen the title "The future leaders in the cardiovascular arena" appears. Mees looks into the lens and confidently says: "When you are looking at our small group, what you see is in fact a medical industry leader, a research leader and a clinical leader: an ideal combination. What more could you wish for?" A sudden squeaky needle scratch on a record, and the music stops abruptly as Lumens says: "Dream on. We are harnessed to a cart like horses and there is a lot of work to be done in this cardiovascular arena."

Let´s continue on a more serious note now. Because of the corona crisis this interview is organised somewhat differently. We cannot have a live conversation but will conduct the interview via Zoom. Which, by the way, is very convenient for Barend Mees –giving him the opportunity to receive some packages in between things. The leadership programme of the Dutch Cardiovascular Alliance (DCVA), for which these three from Maastricht have been selected, should have started already. But this has been postponed to September 2020 because of corona. So as yet there are few experiences to be shared and a lot is still up in the air. But that doesn't mean that there is nothing to talk about. So they are settling in for an enjoyable interview.

ABOUT THE LEADERSHIP PROGRAM

The new DCVA Leadership Program invests in fifteen talents from the Dutch cardiovascular field for a period of two years. They represent various worlds and are (basic) researchers, doctors, engineers, policy makers or patients. Working in groups of three, they will try to tackle one of the five big challenges identified by the DCVA – from doing research with fewer or no laboratory animals to translating scientific innovations into health care. Apart from this project-based work, the participants will expand their cross-disciplinary network and are being coached by a top person from the cardiovascular world. For the participants, the programme requires a time investment of 0.1 fte on a weekly basis.

Why did you want to participate in this programme?

Joost Lumens: "I have been working mostly with foreign colleagues so far, but am also very interested in cooperation within our country. Maastricht is a bit of a quiet corner in the Netherlands, so this is a wonderful opportunity to come into the picture. Which is also important for the distribution of research funds, I reckon."

Matthijs Cluitmans: "It was the ambition to convert scientific results into optimal care for everybody which appealed to me most. That's my passion and this is why I also have a part-time job with Philips. I want to learn more about the Dutch infrastructure for processes of this type and influence them a bit, wherever possible."

Barend Mees: "My discipline, vascular surgery, originates from general surgery which is a whole different world from the cardiovascular one. So, as vascular surgeons we are relatively new in the Maastricht Heart+ Vascular Centre and I believe it is interesting - not just for me personally but for our entire

IT WAS THE AMBITION TO CONVERT SCIENTIFIC RESULTS INTO OPTIMAL CARE FOR EVERYBODY WHICH APPEALED TO ME MOST

bunch of vascular surgeons - to familiarise ourselves with the cardiovascular field. Also with a view to large research funds which are being granted. Because the patients we see are not merely 'vascular patients', but cardiovascular patients instead."
Lumens: "In summary - I think we all like to do work which is not in our own field of expertise. Interdisciplinary. I will participate in a policy on lab animal use in cardiovascular research. As a basic researcher I am not usually involved in national policy making. It teaches you to take a good, straight-faced look at whatever it is you are doing. Every day I think my work is the most relevant work ever, but when you zoom out, you're in for a rude awakening."
Mees: "In this programme we are all working on a relevant topic, Matthijs and I in the same group by coincidence, but apart from that, it is also a personal leadership programme. For some time now I have been looking for tools for a more personal growth in the leadership area, preferably from someone I am not very familiar with."

So you do see yourselves as the 'future leaders' of the cardiovascular world?

Lumens: "I think that all three of us would answer "no" to that in the first place ..."
Mees: "Definitely would!"
Lumens: "Haha, I was thinking: you can leave out the 'future'. But the DCVA´s objectives are very ambitious, so the approach to this programme should be ambitious, too."
Cluitmans: "There has been no scientifically substantiated selection process to determine if we are truly the future leaders. We have applied for the job and have been selected on a diversity basis."
Lumens: "Which became very clear during our kick-off meeting in Utrecht. Coincidently, the three of us are men, but across the group the gender ratio is very well-balanced. Then again, we three are intrinsically diverse: a doctor, an engineer/basic researcher and a hybrid between industry and academy."
Mees: "Of course it is good for your own PR when you are presented as a 'talent' but one might wonder how many 'future leaders' the cardiovascular world will need in the years to come. And if this programme runs again every year ..."
Lumens, winking: "Yes, but the first batch is of course the best."

What does the project on reducing lab animal use entail?

Lumens: "The government is expecting some kind of estimate how the cardiovascular field will guarantee the use of more lab animal-free technologies. But also: of which areas it is already known that they cannot function without lab animals? We must identify this and implement it in a future plan, let's call it a policy document or advice, which is widely supported by the DCVA. That's a huge challenge which the three of us can never accomplish, but we do have to take the first steps. So that the government can make policies on the basis of facts. The field has every interest in doing it right, because if you don't do it, the government will decide - which may backfire."
Mees: "Do you like the assignment?"
Lumens: "I find it rather thrilling at times, because it is a big responsibility and socially the subject is extremely sensitive. But if there is one single scientific challenge, this is the one. I think I have been selected for this assignment because the computer models that I use for my research can increasingly be used as alternatives for lab animals. On the other hand, I´ll be the last one to claim one can work without test animals. For had there been no lab animals, our model would

never exist and it would be much more difficult to expand and improve our model. This balancing act may have been perceived as useful for this project."

And what does the project on medical technologies consist of?

Cluitmans: "The subject was the actual implementation of existing technologies into cardiovascular care, specifically in home care situations. My daily activities consist mainly of the former part, so this was my favourite project."
Mees: "I also think it is a very interesting topic, especially with the diverse little group that will work it out. I have a great deal to do with new technology and have a clear view as to how new technology should be validated and tested. I have witnessed technology fail in patients. In order to make the step to the clinic easier, people once found out that if a new product looks very much like an existing product, a much smaller number of tests has to be performed in order to get approval from the authorities. This was meant to be an exemption rule, but nowadays 95 out of 100 innovations are marketed using this 'shortcut'. Think stents of new materials, which still look like existing stents. I certainly do not want to stop all innovation, but I think this is an important point of concern."
Cluitmans: "That´s super interesting – being caught between the devil and the deep blue sea – also in this time of corona. Philips has announced the development of a new ventilator, because there is much demand for more production. The parts they are using are all existing components in a new composition, which allows for a much more efficient production. And this is typically a device that can be approved quickly, which of course in these days makes everybody happy. But the value of new technology versus swift and safe marketing is very relevant. Apart from that, we use our assignment to look at the role of health insurance companies as well. Because if new technology is not financed, the health care sector will not use it – even if it's better for both patients and caregivers."

So - plenty of work to be done... starting in September

Lumens: "Absolutely! Apart from this, it was made clear to us during the kick-off meeting that we are expressly seen as lobbyists. We will be ambassadors for DCVA, whose pivotal aim it is to raise a substantial amount of money for the cardiovascular field. They believe that the general public's unawareness of cardiovascular diseases being causes of death is one reason why it is sometimes hard to obtain research funding. We are expected to make a contribution to improving that image."
Cluitmans: "DCVA aims at reducing the cardiovascular disease burden by 25% in 2030. That´s quite an ambition which is inextricably linked with fundraising. And I am happily committed to that goal."
Mees: "Lobbyist is not my favourite word, but we will have to see what happens."
Lumens: "It's a nice little extra that we three are getting to know each better this way."
Mees: "I am looking forward to that as well and I think it will only strengthen the bonds between CARIM and the Maastricht Heart+Vascular Center."
Lumens: "That's right, and what's more: the three of us can make a serious contribution to reducing the gap between fundamental research and application. We are not going to reinforce the bridge, but will finish building it and simply push the whole thing together!"
All three men are nodding at each other in agreement. The future leaders of the cardiovascular arena have great plans.

Matthijs Cluitmans *studied Medicine and Knowledge Engineering and obtained his PhD in 2016 at the Department of Data Science and Knowledge Engineering (DKE) and CARIM, all in Maastricht. After a postdoc period in Bordeaux and Amsterdam he now works at three locations: CARIM, DKE and Philips Research in Eindhoven.*

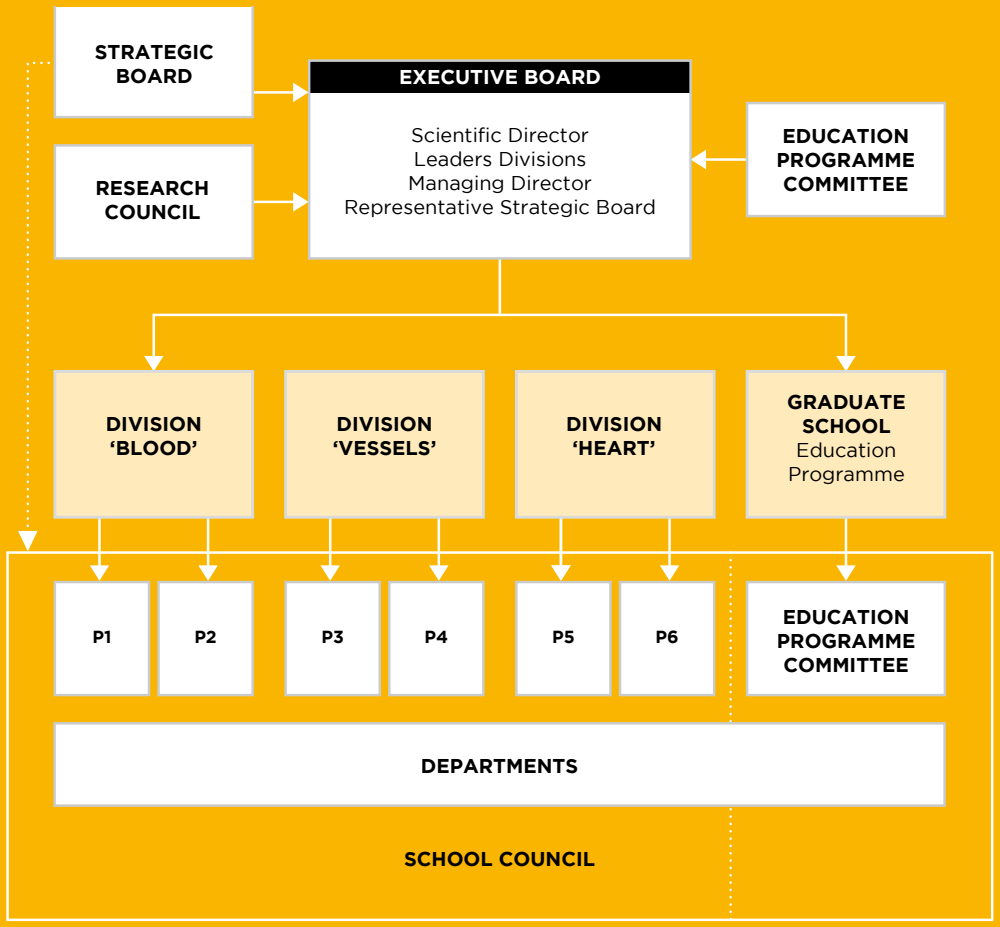
Joost Lumens *studied Biomedical Engineering at the Technical University of Eindhoven (TU/Eindhoven) and is now an Associate Professor at the Department of Biomedical Engineering at Maastricht University. He was awarded several large grants for his research on computer simulation of heart function, in particular the electromechanical properties of the heart.*

Barend Mees *studied medicine at Leiden University and did his PhD at The Max Planck Institute in Bad Nauheim, at INSERM u-689 in Paris and at the Erasmus University in Rotterdam. After having worked as a fellow in vascular surgery in Melbourne for three years, he has been employed as a vascular surgeon at Maastricht UMC+ since 2014.*

ORGANISATION

05

ORGANISATION



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

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

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

EXECUTIVE BOARD

- Prof. Tilman Hackeng, Scientific Director
- Prof. Hugo ten Cate, Leader Division Blood
- Prof. Coen Stehouwer, Leader Division Vessels
- Prof. Harry Crijns, Leader Division Heart
- Wouter Hankel, Managing Director
- Prof. Uli Schotten, Representative Strategic Board

STRATEGIC BOARD

- Prof. Uli Schotten, chair
- Dr Aaron Isaacs
- Dr Martijn Brouwers
- Dr Judith Cosemans
- Dr Jordi Heijman
- Dr Judith Sluimer
- Dr Paola van der Meijden
- Prof. Paul Volders
- Wouter Hankel
- Tara de Koster

PRINCIPAL INVESTIGATORS

- Prof. Ilja Arts, Dept. of Epidemiology
- Prof. Erik Biessen, Dept. of Pathology
- Dr Matthijs Blankesteijn, Dept. of Pharmacology & Toxicology
- Dr Judith Cosemans, Dept. of Biochemistry (from January 2020)
- Prof. Harry Crijns, Dept. of Cardiology
- Prof. Hugo ten Cate, Dept. of Internal Medicine
- Prof. Tammo Delhaas, Dept. of Biomedical Engineering
- Prof. Tilman Hackeng, Dept. of Biochemistry
- Prof. Johan Heemskerk, Dept. of Biochemistry (until January 2020)
- Prof. Stephane Heymans, Dept. of Cardiology
- Prof. Bram Kroon, Dept. of Internal Medicine
- Prof. Jos Maessen, Dept. of Cardiothoracic Surgery
- Prof. Robert van Oostenbrugge, Dept. of Neurology
- Prof. Mark Post, Dept. of Physiology
- Prof. Frits Prinzen, Dept. of Physiology
- Prof. Chris Reutelingsperger, Dept. of Biochemistry
- Prof. Uli Schotten, Dept. of Physiology
- Prof. Coen Stehouwer, Dept. of Internal Medicine
- Prof. Monika Stoll, Dept. of Biochemistry
- Prof. Paul Volders, Dept. of Cardiology
- Prof. Christian Weber, Dept. of Biochemistry
- Prof. Joachim Wildberger, Dept. of Radiology
- Prof. Leon de Windt, Dept. of Cardiology

GRANTS AND INCENTIVES TEAM

- Prof. Frits Prinzen, chair
- Dr Matthijs Blankesteijn
- Dr Marleen van Greevenbroek
- Wouter Hankel
- Dr Mark Hazebroek
- Prof. Johan Heemskerk
- Dr Daniel Molin
- Dr Judith Sluimer
- Willem Wolters

EDUCATION PROGRAMME COMMITTEE

- Dr Marc van Bilsen, chair, PhD Coordinator
- Dr Matthijs Blankesteijn, Coordinator Biomedical Sciences Master
- Prof. Eline Kooi
- Dr Boy Houben
- Margaux Fontaine (until September 2019)
- Kim van Kuijk
- Federica de Majo (until July 2019)
- Tate Chimhanda (until July 2019)
- Kim Maasen
- Renée Tillie (from October 2019)
- Lian Laudy (from October 2019)

CARIM OFFICE

The CARIM Office consists of specialists that support the organisation and its researchers with administrative, financial and legal issues, including HRM and funding. Tara de Koster, Riet Daamen and Esther Willigers are responsible for administrative issues, including supporting the executive management. The controller of CARIM is Lynn Lemeer. The Finance Department of Maastricht University provides support on accounting the CARIM research projects with Henny Kerckhoffs, Esther van Heel and Yves Filot. Mechteld Ostendorf of the Human Resources Department of Maastricht University is dedicated to CARIM. In legal affairs, Suzanne ten Hoeve supports CARIM, and Willem Wolters is responsible for funding acquisition. Managing Director Wouter Hankel is the head of the CARIM office. Former Managing Director Rob van der Zander is a special advisor to the management of CARIM.

The research in CARIM's divisions involved the research activities of employees working in 17 (six basic and eleven clinical) departments of Maastricht UMC+.

6
BASIC DEPARTMENTS

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

11
CLINICAL DEPARTMENTS

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

FACES

BLOOD

P1

BLOOD COAGULATION, VENOUS THROMBOSIS & BLEEDING

P1 ▶


AARON ISAACS


ARINA TEN CATE-HOEK


ELISABETTA CASTOLDI


ERIK BECKERS


FRAUKE SWIERINGA


GERRY NICOLAES


HANS IPPEL


HENRI SPRONK


HUGO TEN CATE


INGRID DIJKGRAAF


JOHAN HEEMSKERK


JUDITH COSEMANS


KANIN WICHAPONG


MARIJKE KUIJPERS


MONIKA STOLL


OTTO BEKERS


PAOLA VAN DER MEIJDEN


RENSKE OLIE


RORY KOENEN


STIJN AGTEN


TILMAN HACKENG


YVONNE HENSKENS

P2 ▶


BAS BEKKERS


CARINE PEUTZ


CASPER MIHL


CHRIS REUTELINGSPERGER


CHRISTIAN WEBER


DIETBERT NEUMANN


ELINE KOOI


EMIEL VAN DER VORST


ERIK BIESSEN


FELIX MOTTAGHY


GOSIA FURMANIK


JACK CLEUTJENS


JOACHIM JANKOWSKI


JOACHIM WILDBERGER


JUDITH SLUIMER


LEON SCHURGERS


MARC VAN ZANDVOORT


MARJO DONNERS

PIETER GOOSSENS

PIETER VAN PAASSEN

REMCO MEGENS

ROBERT VAN OOSTENBRUGGE

SIMON SCHALLA

SUZAN WETZELS

SYLVIA HEENEMAN

WERNER MESS

WIM VAN ZWAM

P2

ATHEROSCLEROSIS, ARTERIAL THROMBOSIS & STROKE

P3 VESSELS

VASCULAR COMPLICATIONS OF DIABETES & HYPERTENSION

P3 ▶


AARON ISAACS


BOY HOUBEN


BRAM KROON


CARLA VAN DER KALLEN


CASPER SCHALKWIJK


COEN STEHOUWER


FRANK DE VRIES


HANS VINK


ILJA ARTS


JULIE STAALS


KAREL LEUNISSEN


KRISTIAAN WOUTERS


MARLEEN VAN GREEVENBROEK


MARTIJN BROUWERS


MIRANDA SCHRAM


NICOLAAS SCHAPER


NORDIN HANSSEN


RONALD HENRY


SEBASTIEN FOULQUIER


SIMONE EUSSEN


THOMAS VAN SLOTEN


WALTER BACKES


BASTIAAN DE GALAN

P4 ▶


BAREND MEES


GEERT WILLEM SCHURINK


JOS MAESSEN


MARK POST


MICHAEL JACOBS


PAUL ROEKAERTS


PEYMAN SARDARI NIA


ROBERTO LORUSSO


SANDRO GELSOMINO

P4

REGENERATIVE & RECONSTRUCTIVE CARDIOVASCULAR MEDICINE

HEART

P5

STRUCTURAL HEART FAILURE

P5 ▶


ALMA MINGELS


BEN JANSSEN


BLANCHE SCHROEN


CHRISTIAN KNACKSTEDT


EMMA ROBINSON


GUIDO HAENEN


HANS PETER BRUNNER-LA ROCCA


LEON DE WINDT


MARC VAN BILSEN


MARK HAZEBROEK


MARTINA CALORE


MATTHIJS BLANKESTEIJN


PAUL SCHIFFERS


PAULA DA COSTA MARTINS


ROBIN VERJANS


SANDRA SANDERS-VAN WIJK


SEBASTIEN FOULQUIER


STEPHANE HEYMANS


STEVEN MEEX


VANESSA VAN EMPEL


WARD HEGGERMONT

P6

COMPLEX ARRHYTHMIAS

P6 ▶


ARNOUD VAN 'T HOF


AURORE LYON


BAS BEKKERS


DOMINIK LINZ


FRANS VAN NIEUWENHOVEN


FRITS PRINZEN


GUDRUN ANTOONS


HARRY CRIJNS


JOOST LUMENS


JORDI HEIJMAN


KEVIN VERNOOY


KOEN REESINK


MATTHIJS CLUITMANS


PAUL VOLDERS


PIM DASSEN


RACHEL TER BEKKE


SANDER VERHEULE


SIMON SCHALLA


STEF ZEEMERING

TAMMO DELHAAS

ULI SCHOTTEN

WOUTER HUBERTS

COLOPHON

EDITOR
Tara de Koster, CARIM

IN COOPERATION WITH
CARIM School Office
CARIM staff members

INTERVIEWS
Femke Kools, FemKools
Jan Klerkx, Bèta Vertalingen
Caroline Vermeulen-Hamerslag, de Tekster

PHOTOGRAPHY
Joey Roberts, Maastricht

GRAPHIC DESIGN
Muis Mücher, Maastricht

PRINT
Drukkerij Hendrix

COPYRIGHT

CARIM SCHOOL FOR CARDIOVASCULAR DISEASES
Maastricht University Medical Centre+
Universiteitssingel 50, 6229 ER Maastricht
P.O. Box 616, 6200 MD Maastricht, the Netherlands

TELEPHONE
+31 (0)43 3881766

E-MAIL
carim-office@maastrichtuniversity.nl

WEBSITE
www.carimmaastricht.nl