CARIM SELF EVALUATION

2019 → 2024

PART C

Case studies

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CARIM

Cardiovascular Research Institute Maastricht

PART C

Case studies

CONTENTS

1 Maastricht Cardiomyopathy Registry

Prof. Stephane Heymans, Department of Cardiology
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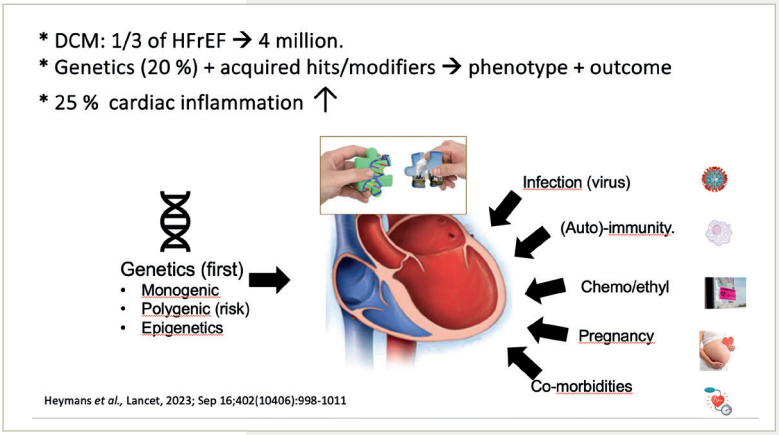
What is the Maastricht Cardiomyopathy Registry?

Since 2004, the Maastricht Cardiomyopathy Registry [1] has evolved into one of Europe's most comprehensive and long-standing prospective clinical and translational research platforms in cardiology. Under the leadership of Prof. Stephane Heymans, Dr Vanessa van Empel, Prof. Hans-Peter Brunner-La Rocca and Dr Job Verdonschot, this registry includes over 3,200 patients and integrates longitudinal clinical data with advanced imaging, biobanking, genomics, and immunologic profiling. With follow-up data spanning up to 20 years, it represents a cornerstone of the CARIM's output and impact in the field of heart failure and non-ischemic cardiomyopathies.



The registry focusses on patients with non-ischemic, non-valvular, non-congenital dilated cardiomyopathy (DCM) or hypokinetic non-dilated cardiomyopathy (since 2003); and patients with heart failure and preserved ejection fraction (HFPEF, since 2015). In 2023, we started including asymptomatic family members carrying genetic variants, hypertrophic cardiomyopathy and amyloid cardiomyopathy patients. Approximately 20% of included patients carry a genetic diagnosis and 25% show inflammatory phenotypes. The cohort is characterised by:

- Echocardiography and cardiac MRI (CMR) in 80%, with strain and fibrosis quantification;
- Cardiac biopsies in 81% for viral PCR, transcriptomics, and histologic inflammation and fibrosis;
- Genetics in 90% (47-gene panel and WES in >470 cases);
- Serial biomarker measurements, including proteomics and cytokines;
- Biobank materials: serum, plasma, PBMCs, DNA, fresh-frozen biopsy tissue.

Who is involved?

The registry is spearheaded by Prof. Stephane Heymans, together with Prof. Hans-Peter Brunner-La Rocca, Dr Job Verdonschot, Dr Vanessa van Empel, and Dr Christian Knackstedt. Prof. Stephane Heymans is recognised expert in inflammation and genetics of heart failure, and Dr Job Verdonschot, whose work in translational data science and genomics has led to key publications in the field. The Maastricht team works in close collaboration with academic and industrial partners, contributing to multi-center studies such as DCM-Next, DCM-Share (11 EU/US centres), and translational pipelines with AstraZeneca and CSL Behring. Dr Michiel Henkens, now coordinating the National Heart Tissue Bank is the person who professionalised our registry to Castor environment.

In 2023, a national effort started, which aims to translate the concept of the cardiomyopathy in Maastricht to a national level. This will further strengthen the position of the registry on an international scale.

Scientific Quality

The aim of the registry is to improve the early recognition and risk stratification of patients with a cardiomyopathy. With a median follow-up of seven years and 52% of patients showing significant LV reverse remodeling (LVRR), this registry supports outcome studies on mortality, transplantation, arrhythmias, and long-term remodelling. Notable contributions include:

- Phenoclustering of DCM patients along transcriptomic profiles distinguishing genetic DCM etiologies (PhD/postdoc of Job Verdonschot) [2-6];
- Discovery of gene-environment interactions and inflammatory signatures [7-11];
- IVIg trial in virus-positive DCM with short [12] and long-term follow-up (unpublished);
- Imaging studies on prediction of outcome in DCM [6, 12-16];
- Numerous HFPEF studies [17-19].

These studies have shaped the concept of gene-environmental interactions in non-ischemic cardiomyopathies and HFPEF, and have been integrated into ongoing EU funded consortia (DCM Next, ID-Preserved) and national consortia (Early HFPEF, Double Dosis, Metacor). The unique content and impact of the registry makes it also a very attractive partner for pharmaceutical collaborations, such as Astra Zeneca and CSL Behring, thereby making a real effort to valorization of research results. Also, young talent got the Eindhoven Dissertation award, young investigator awards at the HFA/ESC congresses and selected for oral presentations at international meetings.

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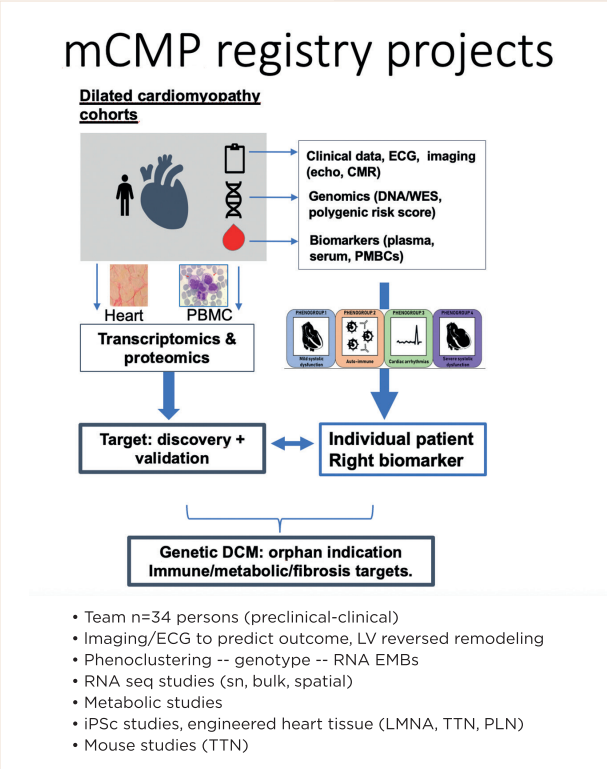
Users and collaborations

The Maastricht CMP Registry demonstrates CARIM's strength in multidisciplinary, high-impact translational cardiovascular research. Its infrastructure, depth, and output position it as a central hub in European cardiomyopathy research, fostering ongoing innovation in diagnostics, therapeutics, and personalised medicine.



The content of the registry formed the basis for the thesis of over 20 PhD candidates. Students/doctors from abroad (e.g., Trieste, Milan, Firenze, Berlin, Zurich) visit CARIM in order to perform research and learn from the registry. This highlights the registry as a valuable instrument for talent acquisition and development. Almost all PhD candidates remain involved in research within the registry, and (successfully) apply for personal research grants further developing and contributing to the registry. Global recognition of the registry and scientific contribution to the field is reflected in the participation of CARIM in the DCM SHaRe registry, an American-European registry including DCM patients from the largest DCM centres. Prof. Stephane Heymans is one of the four leaders of this global initiative.

Societal impact

Most cardiomyopathies are rare diseases, especially the genetic forms. Awareness and education of other health professionals as well as patients is therefore essential for early recognition of disease, and the coping with disease. For this reason we collaborate to multiple initiatives to increase awareness:

- Participation and presenting on multiple patient congresses organised by the Double Dose consortium, the ERN Guard-HEART, and the RESCAR organisation;
- Multiple interviews with local and national media platforms (e.g., L1, DOQ, Dutch Heart Foundation, Nu.nl) to translate our research findings to the broader audience;
- Invited speaker at multiple national and regional symposia;
- Participation in national and international guideline and consensus statement committee from the leading professional societies (ESC, NVVC);
- Open availability of research data for other researchers (e.g., generated transcriptomics data).

2 The MR CLEAN story continues: endovascular treatment of acute ischemic stroke

Prof. Robert van Oostenbrugge, Department of Neurology
Prof. Julie Staals, Department of Neurology
Prof. Wim van Zwam, Department of Radiology & Nuclear medicine

What is acute ischemic stroke and endovascular treatment?

Stroke is a leading cause of death and disability worldwide. In the Netherlands, each year over 40,000 patients are admitted to hospital with a stroke. Most strokes are caused by an intracranial vessel occlusion leading to ischemia of brain tissue. The mainstay of acute ischemic stroke treatment is to re-open the occluded vessel as fast as possible to limit irreversible damage to brain tissue, thereby improving the chances of recovery for the patient. *Time is brain*!

Two treatment options are available to achieve vessel recanalisation, which may be applied in parallel: Intravenous thrombolysis and endovascular treatment (EVT). Intravenous thrombolysis is the intravenous administration of a fibrinolytic agent which dissolves blood clots. This treatment was proven beneficial and is applied since the 90s. EVT involves placing a catheter into the occluded brain artery and removing the clot. This treatment was proven beneficial in the Dutch MR CLEAN trial, which is regarded as a game-changer trial in the acute treatment of ischemic stroke, in 2015. EVT has become standard of care for large vessel occlusions since then. The yearly number of patients treated by EVT in the Netherlands has grown from 600 in 2015 to over 3,000 in 2024.

After the success of MR CLEAN trial, we continued to perform studies to improve the endovascular treatment of acute ischemic stroke with large vessel occlusion. From 2017 to 2022, we had a leading role in the Dutch CONTRAST consortium. Several important and guideline changing studies have been conducted by the CONTRAST consortium, such as MR CLEAN NOIV, MR CLEAN MED and MR CLEAN LATE. MR CLEAN LATE was led by our team (Prof. Wim van Zwam and Prof. Robert van Oostenbrugge) and proved that EVT can be performed safe and effective even after 6h of stroke onset, based on selection of patients with presence of collateral blood flow on CT-angiography. Still, there is much to be gained and the continuation of the consortium from 2023 onwards, called CONTRAST-2 in which we once more have a leading role, aims to further increase the likelihood of a good recovery for acute stroke patients.

The continued story

One important question is whether EVT is safe and effective for more distal occlusions in smaller vessels which are more difficult to treat. We joined the international clinical DISTAL trial and coordinated the Dutch participation in this trial. The results were published in NEJM in 2025: unfortunately the trial could not demonstrate clinical benefit of EVT for stroke caused by occlusion of distal vessels. These results are important for clinical practice: despite high expectations, EVT for distal occlusions cannot be considered the standard treatment yet. The trial results raise additional questions. Currently, we are working on a more in-depth analysis of the trial results to explore e.g. radiological factors, such as CT perfusion and collateral flow parameters, that may determine the effect of treatment.

Another important topic is the improvement of prehospital triage. If an ischemic stroke with large vessel occlusion could be identified pre-hospital, the patient can be transported directly to an intervention center. This would shorten time-to-treatment and improve the clinical outcome of patients. We are developing

and studying the implementation of an automated transcranial Doppler investigation in the ambulance.

Who is involved?

Our research is a joined effort of the department of radiology and nuclear medicine (Prof. Wim van Zwam, Dr Linda Jacobi) and department of vascular neurology (Prof. Robert van Oostenbrugge, Prof. Julie Staals, Dr Inger de Ridder). Several PhD candidates successfully finished their PhD thesis or have work in progress.

Our research is strongly clinically oriented. The studies are embedded in and supported by the clinical teams of the departments of radiology and neurology in Maastricht UMC+. This research line takes a rather unique position within CARIM as not HVC but the Brain and Nerve Center and Center for Acute Care together are responsible for the care paths of these patients.

Collaborations

The CONTRAST-2 consortium started in 2023 and is a partnership of all Dutch university medical centres. It is funded by the Dutch Heart Foundation and The Brain Foundation Netherlands, and supported by the Dutch CardioVascular Alliance. In addition, industry funding is involved. We were involved in the preparation of the overall CONTRAST 2 programme, and we actively participate in several clinical studies of the consortium, such as CASES, DIST and DIVINE. Prof. Julie Staals is WP co-leader of the studies on EVT in distal vessels. In this WP we entered into an ongoing collaboration with Prof. Urs Fischer and Prof. Marios Psychogios from the University Hospital Basel in Switzerland. In this collaboration we work together on finding improvements for the treatment of distal vessel occlusions.

Scientific quality

Over the past decade the MR CLEAN study (2015) and its continuation in MR

CONTRAST
Collaboration for New Treatments of Acute Stroke

CLEAN registry (2015-2018), and the MR CLEAN MED, NOIV and LATE studies which were embedded in the CONTRAST 1.0 consortium (2018-2022) resulted in numerous high impact and open access papers, and new results have been shared at multiple international conferences. To be mentioned from the past 3 years are the publications on the primary results of the MR CLEAN LATE trial (Lancet 2023) and its 2-year follow-up results (Lancet Neurology 2024), and the results of the DISTAL trial (NEJM 2025).

In 2020, Wim van Zwam and Robert van Oostenbrugge, as part of the MR CLEAN group, were awarded the Winkler medal of the Dutch Society of Neurology for the most meritorious contribution to clinical neuroscience in the past five years. It was awarded for the clinical impact of their research on the acute treatment of acute stroke in general and for the publication of the results of the MR CLEAN trial that changed acute stroke treatment worldwide.

We coached several talented PhD candidates. In 2022 Floor Pinckaers (PhD candidate) received the Pélerìn award for her research on dual-energy CT after EVT, and Bob Knapen (PhD candidate) received a HS-BAFTA grant for a research period abroad. In 2023, Quirien Robbe (PhD candidate) received the Harry Crijns Research Grant for a project on the prognostic value of choroid artery occlusion in acute stroke with large vessel occlusion. In 2024, Susan Olthuis (PhD candidate) received the neurovascular research price from the Dutch neurovascular society for her work on the MR CLEAN LATE trial.

In 2024, Julie Staals was appointed as Professor of Neurovascular Diseases'. One of her tasks is to continue the successful research work into the treatment of acute stroke.

Societal impact

The positive result of the first MR CLEAN trial has led to an enormous growth of EVT in the Netherlands and worldwide. The MR CLEAN LATE trial results gave a further boost by extending the time window for treatment up to 24h after stroke onset. Guidelines have been adjusted accordingly: not only the Dutch and international stroke treatment guidelines, but also the ambulance and GP triage guidelines. Currently, more than 3,000 patients are treated by EVT annually in the Netherlands. For the Limburg region, Maastricht UMC+ is the EVT referral center, performing almost 250 EVTs yearly. In 2024 we were awarded a diamond ESO Angel award, an acknowledgement by the European Stroke Organisation for the high quality of our stroke patient care (https://www.mumc.nl/actueel/nieuws/regionale-beroertezorg-voldoet-aan-hoogste-europese-standaard).

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3 Prediction of clinical disease severity and therapeutic response in aortic wall disease using patient-derived induced pluripotent stem cells – AORTiC

Prof. Leon Schurgers, Department of Biochemistry
Prof. Elham Bidar, Department of Cardiothoracic Surgery

The clinical problem: aortic wall disease and thoracic and abdominal aneurysm

Aortic wall disease, including thoracic aortic aneurysms and dissections (TAA/D) and abdominal aortic aneurysms and rupture (AAA/R), pose a significant clinical burden with high morbidity and mortality. Up to 60% of patients who develop acute aortic dissection have no aortic aneurysm or other known causes of disease. While rare monogenic syndromes like Marfan or Loeys-Dietz have improved our understanding of heritable aortic disorders, most patients present with idiopathic or complex multifactorial pathology.

Next to genetics, TAA and AAA share some histopathological and molecular characteristics, as well as pathophysiological mechanisms [1,2]. Emerging evidence points towards a role for vascular smooth muscle cells (SMC), with inflammation, oxidative stress, metabolism, and matrix metalloproteinase (MMP) activity in the pathogenesis of aortic wall disease [3,4,5]. However, a comprehensive understanding of these common pathways and their contribution to aneurysm pathogenesis is lacking. Similarly, therapeutic targets for aneurysms remain elusive. Current treatment strategies primarily focus on managing risk factors and preventing complications, lacking the ability to directly address the underlying mechanisms that drive aneurysm development and progression. Surgical intervention is based on aortic diameter, yet this approach lacks accuracy. Of all aortic wall disease patients, most patients undergoing surgery fall below this threshold, as dissection occurs annually in only 2-4% [6]. Given the heterogeneity within aortic wall disease patients, identifying at-risk individuals remains challenging, leading to a high number of unnecessary open-heart aortic replacement surgeries. Understanding aortic wall disease heterogeneity is crucial for risk prediction and prognosis, ultimately to reduce unnecessary health care costs and personalised treatment.

Biochemical and molecular research: the cell-based solution?

Vascular smooth muscle cells (SMCs) play a central role in aortic wall disease. One of the greatest drawbacks to SMC biology is the lack of consistency in cell material. Primary SMCs are inherently heterogenous, with batch-to-batch differences frequently observed. In our collaboration, we use human induced pluripotent stem cell (hiPSC) models to study aortic wall disease. In the 2021, CARIM initiated and steered core-facility SCRUM (Stem Cell Research University Maastricht) we generate patient specific hiPSC. Our hiPSC models enable an infinite supply SMCs with the same genomic origin as the SMCs in the patient's aortic wall. Within SCRUM, we can differentiate hiPSC in SMCs sub-populations via an intermediate differentiation step towards neural crest, lateral plate or paraxial mesoderm (Aortic arch, aortic root and descending aorta/ peripheral arteries, respectively; Figure 1).

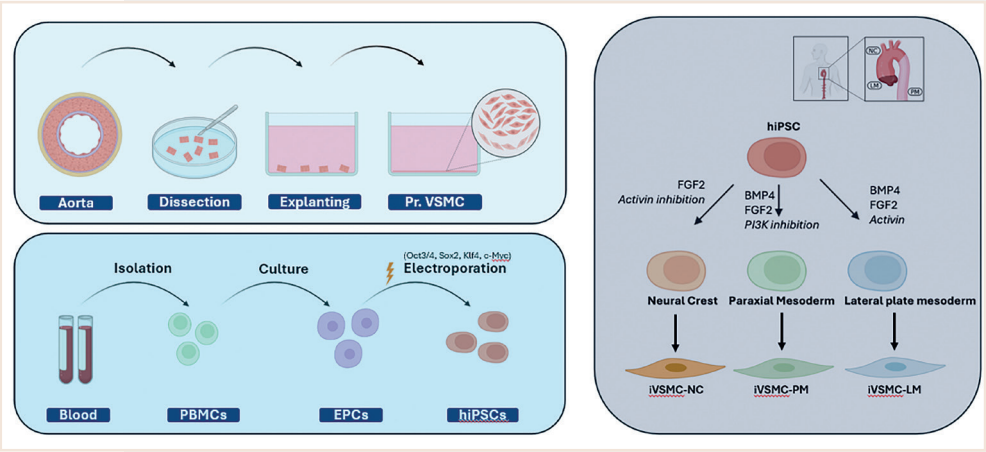

FIGURE 1 Heterogeneity of vascular smooth muscle cells in the aorta.

Our primary aim is to decypher underlying mechanisms of SMCs contributing to cardiovascular disease, in a non-invasive manner. We propose to use *in vitro* modelling to predict patient-specific disease severities and identify distinct patient therapeutic drug responses. We pioneered an induced pluripotent stem cell (iPSC)-based model, which recapitulates key features of the aortic wall disease phenotype. Using Marfan syndrome (MFS) iPSC lines we aim to develop an *in vitro* severity scoring, using generic criteria such as apoptosis, proteolysis and proliferation, that may predict patient-specific disease severity.

The HVC+CARIM collaboration builds on the principle that the aortic wall is not a passive structure, but a dynamic tissue influenced by both mechanical forces and cell-intrinsic programs. SMCs are central in maintaining vessel integrity, and their dysfunction is a key driver in aortic wall degeneration, a hallmark of aortic wall failure. Traditional models fail to capture the molecular heterogeneity and patient-specific disease course. We therefore embarked on a translational approach that combines patient-specific biology, systems-level insights, and functional validation, with the ultimate role of our infrastructure to further understanding the pathophysiology of aortic wall failure.

Who is involved?

The success of AORTiC is a joined effort of the Department of Biochemistry (Prof. Leon Schurgers), the Department of Vascular Surgery (Prof. Barend Mees), the Department of Biomedical Engineering (Dr Koen Reesink) and the department of Cardiothoracic Surgery (Prof. Elham Bidar). Several PhD candidates successfully finished their PhD thesis and several new PhD candidates have work in progress. Furthermore, blood, tissue and iPSCs are collected and generated during the surgical procedure for the MAPEX biobank (Figure 3; [7]). This collaboration overarching multiple departments within HVC and CARIM ensures a full integration ultimately to aid understanding aortic wall disease from macro (patient) to micro (cell) level.

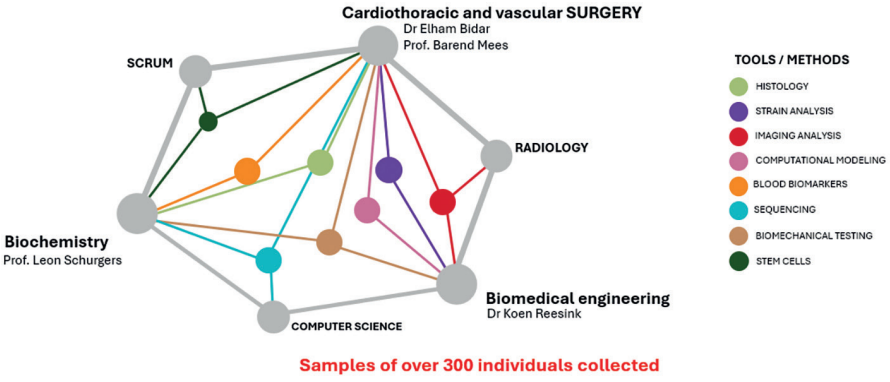

FIGURE 2 Multidisciplinary research as the solution: Biobanking.

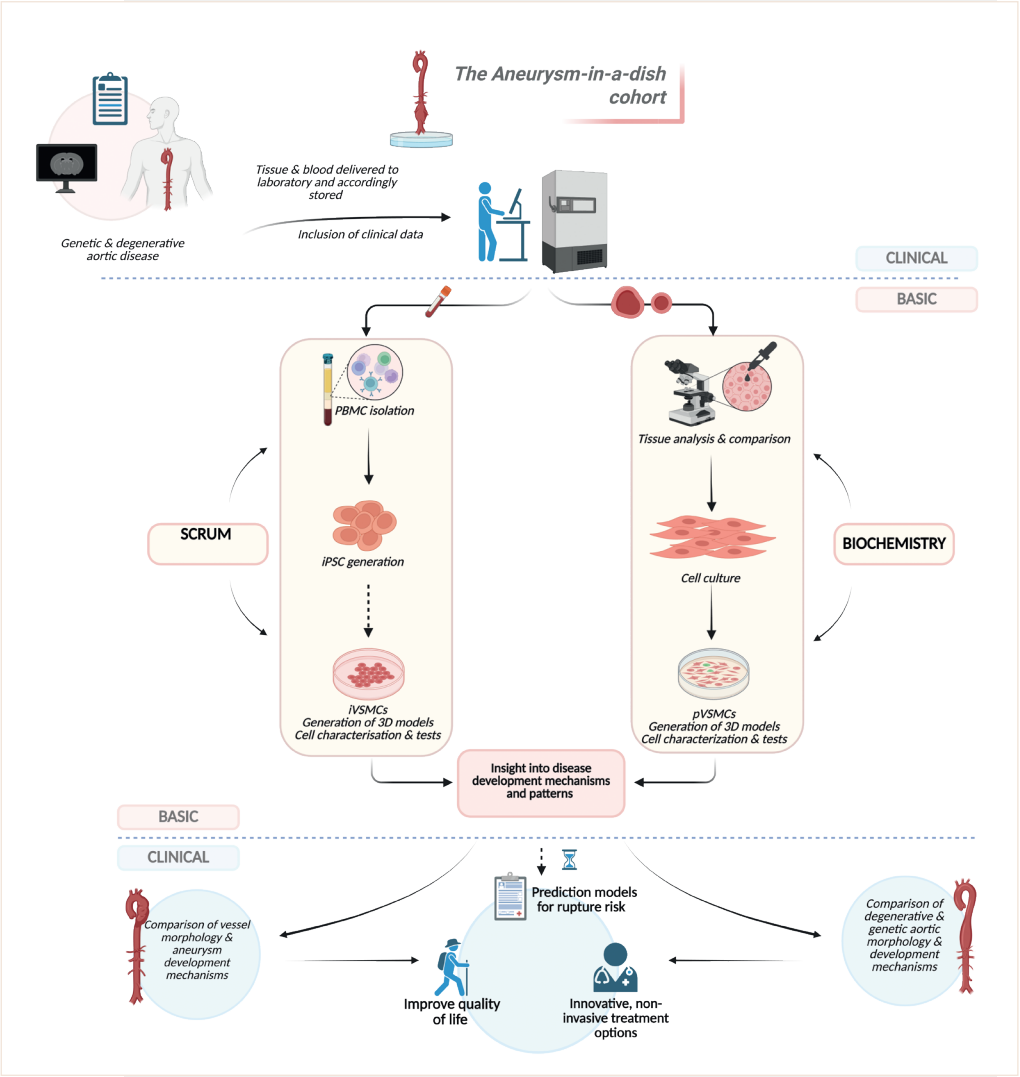

FIGURE 3 The HVC+CARIM biobank – Aneurysm-in-a-dish cohort. Primary vascular smooth muscle cells (pSMCs) will be isolated from tissue obtained during surgery. Further, human induced pluripotent stem cells (hiPSC) will be generated from the same patient to differentiate to hiSMCs. These cells will be used for insight into disease development, risk prediction models and for non-invasive treatment options.

Scientific quality

To improve the understanding of aTAA pathophysiology, AORTiC has established a multi-disciplinary research infrastructure. The scientific and clinical focus of the platform is on the dynamic interactions between SMCs and extracellular matrix (i.e., cell-matrix cross talk), which play an essential role in aortic wall mechanical homeostasis. Accordingly, we consider pathophysiological influences of wall shear stress, wall stress, and SMC phenotypic diversity and modulation. Co-registrations of hemodynamics and deep phenotyping at histological and cell-biology level are a key innovation of our platform and are critical for understanding aneurysm formation and dissection at a fundamental level. Our platform has included over 300 patients with aortic wall disease, which are clinically and phenotypically fully characterised. Isolation of primary SMCs from left-over vascular tissue and generation of hiPSC derived iSMCs will enable us to compare primary and induced SMC behaviour. In this was we establish a patient-specific, stem cell-based platform for dissecting the molecular mechanisms of aortic wall disease. Using CRISPR/Cas-edited and patient-derived iPSCs to model SMC function across genetic and non-genetic backgrounds, generating insights that enable stratification, drug testing, and ultimately, tailored care. For this 2D cell-culture models and 3D engineered vascular tissue will be generated using a SMC-collagen or fibrin mix using the Cuore system. This 3D contraction force platform provides a precise functional readout for engineered vascular muscle

tissue offering precise cell-matrix and cell-cell interactions during prolonged duration, closely mimicking pathological *in vivo* conditions.

Our enhanced, cell-cell and cell-matrix phenotyping will be integrated using both multiple regression methods as well as machine learning to accurately predict age of aortic dissection or surgery. Pilot data show also that, as in clinical trials, different patient iPSC-SMCs respond differently to therapeutics. We will therefore collaborate with systems biology and carry out a machine learning analysis of patient derived aortic tissues to predict potentially therapeutic drugs and test these on patient specific primary aortic SMCs as well as iPSC-SMCs from the same patient. Correlating *in vitro* and clinical severities with distinct drug responses will be vital in guiding future research and, with clinical support, prognosis and treatment of patients.

Societal impact of AORTiC

AORTiC has generated outstanding outreach, including leading roles in CELLSYSTEMICS (ZonMw-SGF-LSH *Humane Meet modellen*), ANEURYSM-NL (national consortium funded by the Dutch Heart Foundation), and WISER (Eurostars, EU funded). Further, we collaborate with Prof. Sanjay Sinha on MFS.

Additionally, SCRUM generated the largest biobank on LMNA patients, which resulted in participation in the Leducq consortium PRIORITY. This work on hiPSC cardiomyocytes has also led to outreach via crowdfunding resulting in private donations supporting two additional PhD projects.

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4 Heart Failure with Preserved Ejection Fraction (HFfEF)

Dr Vanessa van Empel, Department of Cardiology

What is HFpEF?

HFpEF is the greatest clinical unmet need within the field of cardiology. With increasing incidence leading to a health care problem of epidemic proportion for which limited treatment exist to improve quality of life. Consequently, an urge exists to better understand the HFpEF pathophysiology. HFpEF is a disease that seems driven by its comorbidities. Emerging evidence suggests a key pathophysiological role for coronary microvascular dysfunction (MVD), with an underlying mechanism of a systemic, low-grade pro-inflammatory state caused by comorbidities.

Unique cohort

After a postdoctoral fellowship at the Alfred Hospital in Melbourne, Australia, I returned to the Department of Cardiology at Maastricht UMC+ in 2013, and started the Maastricht HFpEF clinic where we phenotype all HFpEF patients in detail. Not only cardiac aspects but also pulmonary function, exercise tolerance, quality of life and sleep apnea screening are included. Additionally, we collect blood and urine samples in our biobank. This has resulted in a unique HFpEF cohort.

Effect of empagliflozin on microvascular function

Empagliflozin is an effective treatment for heart failure with preserve ejecti-on fraction(HFpEF), but its definite mechanism of action is unclear. Systemic microvascular dysfunction (MVD) strongly relates to HFpEF aetiology, and we investigated whether empagliflozin improves microvascular function. MVD assessment using laser speckle contrast analysis of the dorsal forearm during iontophoresis of vasoactive stimuli (acetylcholine, insulin, sodium nitroprusside) was performed at baseline and after three months of empagliflozin treatment. This study shows that three months treatment with empagliflozin changed pe-ripheral microvascular function in patients with HFpEF, specifically via vascular actions of insulin, rather than a general effect on endothelial vasoregulation or smooth muscle cell function. As such, systemic microvascular dysfunction can be a modifiable factor in patients with HFpEF.

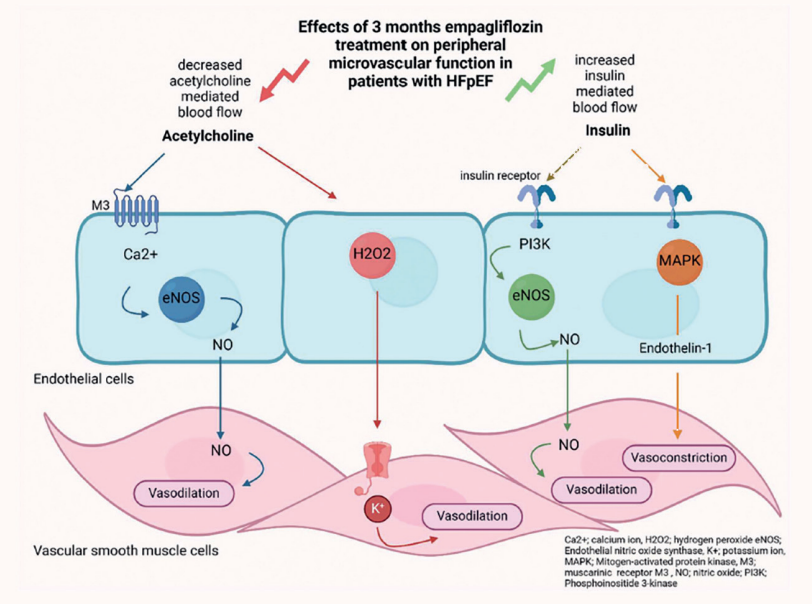


FIGURE 1 Graphical abstract (Mourmans et al Cardiovas Diabetol. 2025).

Improving HFpEF diagnosis

The LA/NP approach includes elevated natriuretic peptides (NP) or enlarged left atrial (LA) volume indexed by height^2, using different cut-off values depending on atrial fibrillation. The approach was developed in a large real-world cohort suspected of HFpEF (n=443) and externally validated in Chicago, USA (n=503) and Amsterdam, the Netherlands (n=123). Patients suspected for HFpEF can be ruled-in for HFpEF diagnosis in most cases based on enlarged LA or elevated NPs (respectively 60%, 59%, and 39%). We demonstrated that our novel approach identifies most HFpEF patients with high specificity as 1st step before other existing algorithms, it reduced the need for additional diagnostics. The LA/NP approach facilitate recognition and simplifies diagnosis of HFpEF in many patients in everyday clinical practice. (Weerts et al, EJHF, doi 10.1002/ejhf.3651)

Accelerated pacing in HFpEF

For a long time it was believed that pharmalogical heart rate lowering proved clinical benefits in HFpEF through an increase in diastolic filling time. However we hypothesised the opposite to be true. We hypothesised accelerated atrial pacing to offer potential benefits compared with standard lower-rate pacing. Together with Prof. Kevin Vernooy and Prof. Joost Lumens, we investigated the relationship between atrial pacing rate and left-heart filling pressure and demonstrated that accelerated pacing acutely reduced left-heart filling pressure in patients undergoing AF catheter ablation. Computer simulations with HFpEF features, suggesting it as a potential therapeutic strategy to alleviate congestion symptoms. Virtual HFpEF patient cohorts hypothesise that AV sequential pacing may further optimise this therapy's beneficial effects. We will further test these findings and evaluate the effect continuous accelerated AV sequential pacing as a treatment in HFpEF.

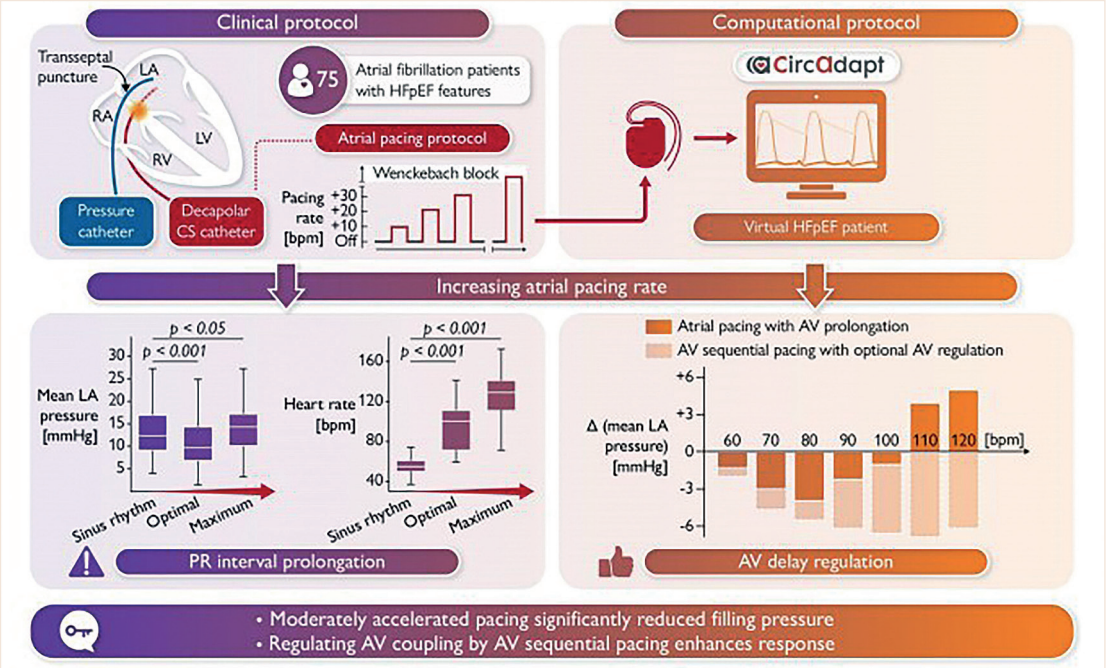


FIGURE 2 Graphical abstract.

International and national collaborations

A crucial phase for my research has been my postdoctoral fellowship in at the Alfred Hospital with Prof. David Kaye. His enthusiasm and knowledge strengthened my plan to start the Maastricht HFpEF cohort. It took some years before the time and energy to build this cohort was rewarded. Now we have an unprecedented cohort and this allows us to collaborate with other key leaders in the field of HFpEF, such as Prof. Sanjiv Shah (Northwestern, Chicago), Prof. Carsten Tschöpe (Charite, Berlin), Prof. Julio Chirinos (UPenn, Philadelphia) and Prof. Anthoni Bayés-Genís (Barcelona, Spain). We have expanded our international collaborations to translational research, and collaborate with Prof. Ebba Brakenhielm (INSERM, Rouen, France), Prof. Arantxa Gonzales Miqueo (Pamplona, Spain) and Prof. Elizabeth Jones (KU Leuven, Belgium). Additionally we have innovative collaborations with pharmaceutical companies such as Jean-Christophe Rain (Hybergenics), and Owkin.

We also collaborate with various research groups within Maastricht UMC+, for instance with the Maastricht study (topic microvascular dysfunction), with Prof. Blanche Schroen and Prof. Judith Cosemans (evaluation of platelet function), with Prof. Kevin Vernooy, Prof. Dominik Linz and Prof. Joost Lumens (atrial dyfunction, pacing in HFpEF). Additionally various collaboration with other Dutch centers exist (Amsterdam, Groningen, Leiden, Nijmegen and Rotterdam).

Who is involved?

FIGURE 3 HFpEF research team. My group currently counts two cardiologist, three PhD candidates, two postdocs and several master students.

Scientific quality

In the last ten years, my group has published numerous papers in high impact journals. I was awarded a CVON grant, as PI of the CVON SHE predicts, and a personal Aspasia grant, both investigating various aspects of sex differences in HFpEF. Recently, I was granted the European ERA-CVD grant: the HFpEF-DIVA consortium focusses on the role of inflammation in HFpEF, and whether specific interleukins can be inhibited. I have been an invited speaker at several international conferences, including the ESC congress and ESC HFA congress. I am the president of the Dutch NVVC HF working group and a member of the ESC HFA working group on HFmrEF & HFpEF.

Societal impact

Since HFpEF is a relatively new disease, not easily diagnosed and difficult to treat, creating more awareness for HFpEF and sex differences in cardiovascular disease is essential. I therefore contributed to various initiatives to increase awareness:

- Various educational events on improving diagnotics in HFpEF for GPs and cardiologistInterview in magazine Programma1: monthly magazine of daily regional paper, interview on sex differences in cardiovascular disease, 2022;
- Night of Science: '*Is hartfalen of een hartinfarct bij vrouwen anders dan bij mannen'*, 5 april 2022;
- Documentary '*De langste adem*' (www.langsteadem.nl): background story of patients and the doctors involved in the care of pulmonary hypertension, Jun 2018;
- Interview in magazine Programma1: monthly magazine of daily regional paper, interview on;the Maastricht HFpEF clinic, Sept 2017;
- Women awareness meeting, November 2016, Maastricht, NL;
- Fundraiser '*Loop met je dokter*': team captain of fundraiser organised by the Health Foundation Limburg, yearly event;
- Interview in magazine Chapeau: national magazine, interview on the Maastricht HFpEF clinic and our HF research, July 2016;
- Invited speaker at various regional symposia and RESCAR patient congress.

FIGURE 4 *Loop met je dokter.* Vanessa van Empel with her team at the annual fund raiser organised by the Health Foundation Limburg (Sept 2024).

5 The Netherlands Heart Tissue Bank (NLHI-HTB): Accelerating Cardiovascular Research Through an Open-Access Human Heart Tissue biobank

Dr Michiel Henkens, Department of Cardiology
Dr Rogier Veltrop, Department of Biochemistry

What is the Netherlands Heart Tissue Bank (NLHI-HTB)?

The NLHI-HTB (www.hearttissuebank.nl) is an open-access, non-profit biobank established in 2020 by the Netherlands Heart Institute (NLHI), with the aim of advancing cardiovascular research by providing researchers access to high-quality human heart tissue and associated clinical data. Inspired by the model of the Netherlands Brain Bank (NBB), the NLHI-HTB provides a centralised infrastructure for the collection, storage, and distribution of human heart tissue from individuals with or without cardiovascular disease.

The biobank addresses a critical bottleneck in cardiovascular research: limited access to human heart tissue and related clinical data. The NLHI-HTB enables research that would otherwise rely on less representative models and thereby facilitates deeper mechanistic understanding of cardiomyopathies, heart failure, and arrhythmias.

The NLHI-HTB recently expanded its scope to also include cardiovascular residual tissue from routine clinical care (e.g. residual tissue from procedures such as heart transplantations). This extension increases tissue diversity and availability, further enhancing the translational relevance of research findings. It also promotes a more efficient and inclusive use of valuable clinical materials that would otherwise remain unused.

Who is involved?

The NLHI-HTB is coordinated by Dr Michiel Henkens (Head of NLHI-HTB; pathology resident at the Department of Pathology, Maastricht UMC+) and Dr Rogier Veltrop (Scientific Coordinator), both postdoctoral researchers at CARIM. The biobank operates under the Netherlands Heart Institute (NLHI), which represents the cardiology departments of all Dutch university medical centres. Key partners include the Dutch Heart Foundation, the Dutch Cardiovascular Alliance (DCVA), and the Netherlands Brain Bank.

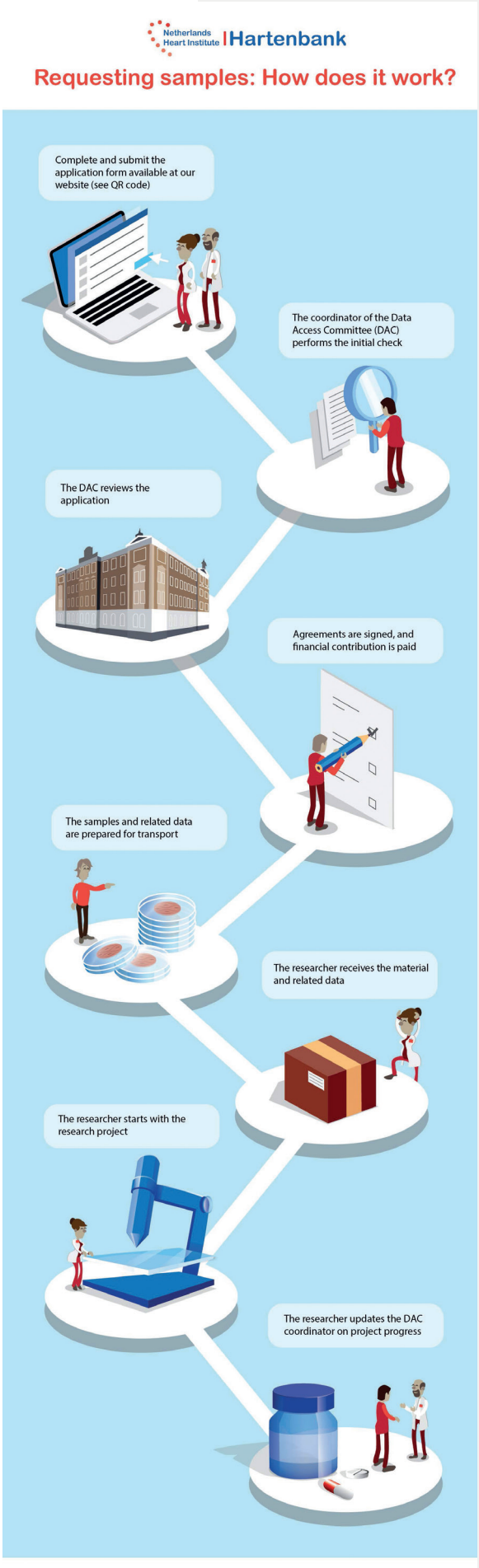
Users and collaborations

The NLHI-HTB collaborates nationally with Amsterdam UMC, Erasmus MC, Leiden UMC, Maastricht UMC+, Radboud UMC, UMC Groningen, and UMC Utrecht. It is embedded within national and international research consortia such as CURE-PLaN and PSIDER-Heart and works with partners including PALGA and the Dutch National Tissue Portal to expand decentralised access to cardiovascular residual tissue. Multiple (inter) national researchers have already submitted requests to the NLHI-HTB, and the first researchers currently make use of the heart tissue from the NLHI-HTB.

Scientific quality

Key indicators of scientific quality include:

Peer-reviewed publications: First scientific article on the infrastructure and objectives of the NLHI-HTB published in the Netherlands Heart Journal (2023; doi: 10.1007/s12471-022-01713-8).
Grants and funding: Recently awarded follow-up funding from the Dutch Heart Foundation (EUR 700.000) for the period 2024–2028 (additionally in kind contribution of the NLHI: k€ 700), following a successful start-up phase (2020–2024).



Conference contributions: Regular presence at national and international conferences (e.g. DCVA/NLHI congress, AECVP congresses, ESC congresses). In Q4 2025, the NLHI-HTB will organise a dedicated workshop on the application of human tissue in early diagnosis, treatment, and prevention of cardiovascular diseases, supported by the Wiek van Gilst Collaboration Prize k€ 10).
Scientific governance: Transparent review of tissue requests via an independent Data Access Committee (DAC). The application process is clearly outlined on the NLHI-HTB website (www.hartenbank.nl) and visualised in the illustration on the right.

Societal impact

The societal impact of the NLHI-HTB is reflected through several indicators:
Open access infrastructure: A national open-acces biobank serving both academic and non-academic partners, aiming to accelerate the detection, treatment, and prevention of cardiovascular diseases.
Stakeholder engagement: Public registration campaigns for post-mortem donation, and in the future, post-operative residual tissue. The NLHI-HTB is supported by advisory structures, such as patient-focused groups and the Scientific Advisory Board (SAB), which provide essential feedback to guide the bank's strategy. As a formal unit within the NLHI, it maintains direct ties with the heads of cardiology departments from all Dutch academic centers.
Public outreach: Ongoing engagement through public events (e.g., the NLHI spinning marathon), social media, and collaboration with the Dutch Heart Foundation.
Ethical innovation: Promotes the replacement of animal models by offering ethically sourced human tissue, aligning with national policy to reduce animal testing.
Educational value: The first educational workshop focusing on human tissue for cardiovascular research is scheduled for Q4 2025.

6 Cardiac Magnetic Resonance-guided electrophysiological intervention (iCMR)

Dr. ir. Rob Holtackers, Department of Radiology & Nuclear Medicine
Dr Miranda Bijvoet, Department of Cardiology

What is a cardiac magnetic resonance-guided electrophysiological intervention?

Catheter ablation is an important treatment strategy for patients with symptomatic cardiac arrhythmias. Historically, catheter navigation during ablation treatments is guided by fluoroscopy, which contributes to a possibly harmful radiation dose. Recently, 'zero fluoroscopy' electrophysiological (EP) procedures are gaining popularity, with magnetic resonance imaging (MRI) as an important imaging tool to possibly replace fluoroscopy. Although an MRI scan is normally only used for diagnostics, it can now also be used for the actual treatment of the patient while inside the scanner. This innovation, better known as interventional cardiac MRI (iCMR), brings important benefits to both patients and staff members.

A limited number of centres worldwide have already performed ablation treatments in MRI scanners, but Maastricht UMC+ has gone one step further. The combination of advanced software and special catheters allows the electrical signals from the catheters to be directly displayed on the MRI images of the heart itself. These images can then be viewed in any desired cross-section, unlike fluoroscopy. A 3D model of the anatomy of the heart can also be made, in which the current position and orientation of the catheters can be viewed in real-time. Until recently, no system was available that could integrate the electrical information and anatomy of the heart by displaying it directly on the heart. As a result, the anatomy of the heart can now be visualised in such detail that the optimal route for the catheter can be determined (Bijvoet et al., Eur Heart J Cardiovasc Imaging 2024). This will not only make the treatment more efficient but also significantly reduces the risk of complications.

In addition, MRI is the reference standard for the visualisation of various tissue structures in the heart as well as neighbouring (extra)cardiac structures. This allows for the ability to perform additional imaging directly before and after the treatment, providing an improved insight and better understanding of the effect of the treatment on the cardiac tissue. Furthermore, imaging during treatment allows real-time tracking and visualisation of the location and orientation of the catheters in the heart itself. Therefore, iCMR not only allows for real-time ablation through detailed visualisation of the catheter and the anatomy of the heart but can also map tissue changes during and directly after ablation. Due to this more detailed pre-, peri-, and post-procedural visualisation, treatments can potentially be performed faster, better, and safer.

The growing availability of MR compatible EP equipment has accelerated the clinical implementation of iCMR procedures, currently enabling the clinical treatment of right-atrial flutter. Most centres have therefore built dedicated suites with both X-ray and MRI systems installed in adjacent rooms to facilitate a hybrid approach. At Maastricht UMC+, however, we can temporarily transform one of our pre-existing MRI environments into an interventional cardiac MRI suite, where we have been performing safe and successful procedures since early 2021.

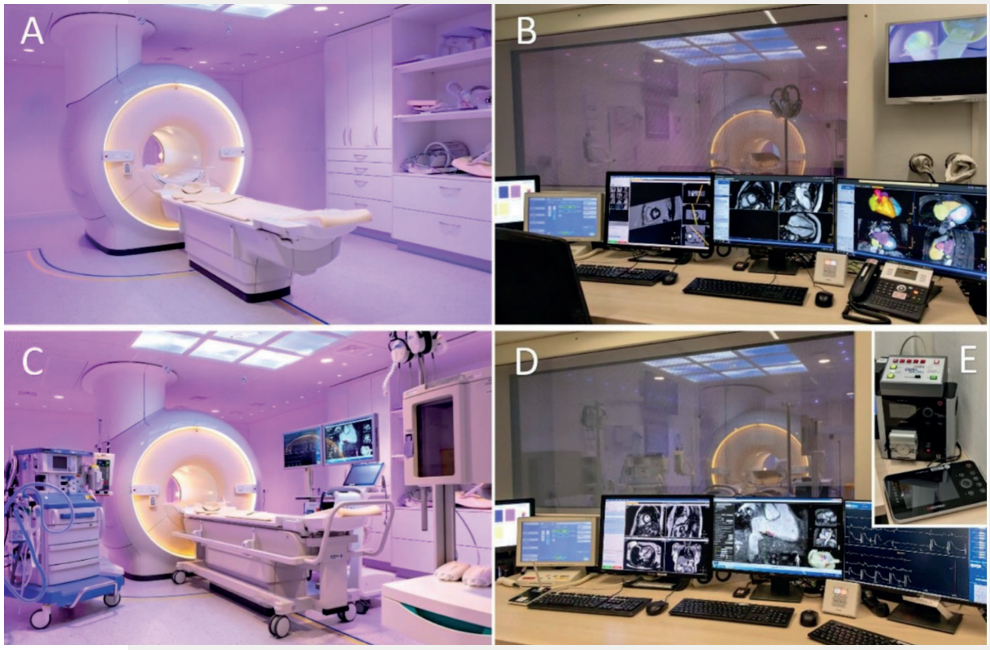


FIGURE 1 Full transformation of the pre-existing MRI environment (A,B) into an interventional cardiac MRI suite (C,D,E).

Multidisciplinary iCMR team - who is involved?

The various technical, clinical and practical challenges in the setup, implementation and execution could only have been overcome by combining the individual expertise of all team members in their respective fields. Our multidisciplinary iCMR team consists of electrophysiologists, cardiovascular radiologists, imaging cardiologists, anaesthesiologists, (MRI) physicists, biomedical engineers, medical instrumentation technologists, electrophysiology, MRI technicians, and financial controllers/strategists. Diversity in our team lies in all aspects, including gender (almost 50/50), experience (PhD candidates, junior researchers/clinicians/technicians, senior staff members), affiliations (5 departments/centres), and a large variety of complementary technical and clinical skills and expertise (a mix of clinicians, engineers, technicians, visionaries, and finance).

Within our iCMR team, we are committed to specific tasks and roles, both at the time of the technical and procedural implementation of this innovative technique as well as during the procedure itself. We constructed and documented an iCMR procedural workflow where each involved member has their own task. A dedicated and well-trained multidisciplinary iCMR team proved to be a prerequisite for a safe and feasible implementation of iCMR, subsequently bridging the gap between the pre-existing workflows of both radiological teams and interventional electrophysiology teams.

As pioneers in the field, we closely collaborate with industry partners, including Philips Healthcare, Imricor Medical Systems, Osypka Medical, and Optoacoustics, to accelerate technological developments and further advance patient care. The input and feedback of our multidisciplinary team members to solve encountered problems, address shortcomings, and propose new functionality, in every aspect of the procedure, are crucial here. These are discussed with our industry partners after each clinical case, as well as on a regular basis apart from the procedures. The ongoing development of new MRI-conditional ablation equipment through this collaboration with the industry is likely to enable the application of CMR-guided ablations for more complex cardiac arrhythmias soon (e.g., atrial fibrillation and ventricular arrhythmias). The current position of Maastricht UMC+ in the field of cardiac arrhythmias and the available expertise in the field of advanced techniques play a key role in these developments. Our team has been invited multiple times to present the development and implementation of this novel innovative technique in the field of both cardiology and radiology.

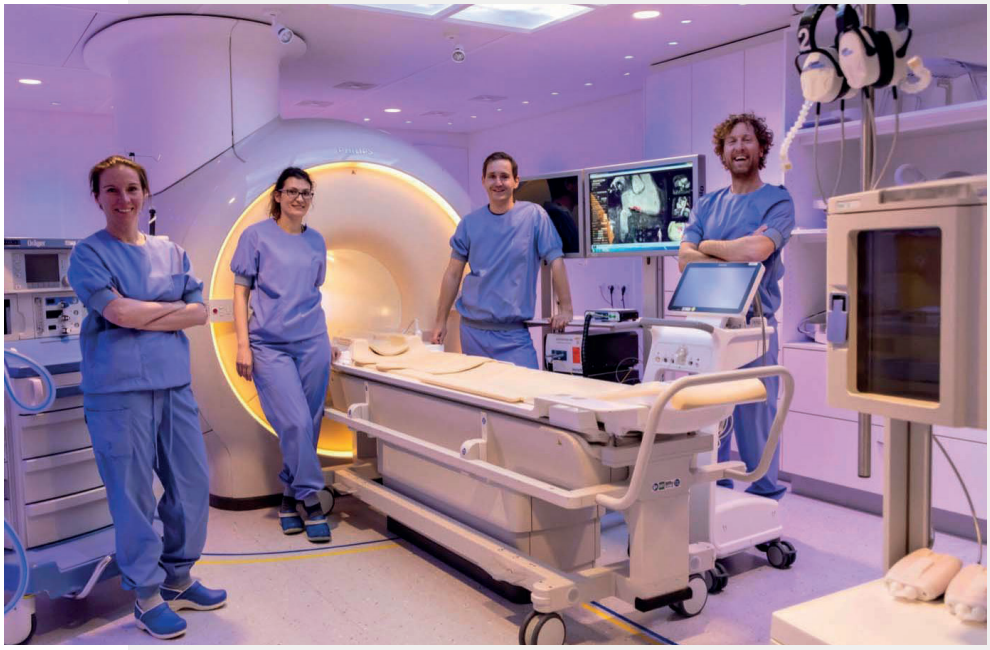


FIGURE 2 Part of the multidisciplinary iCMR team at the transformed MRI scanner. From left to right: Dr Miranda Bijvoet (imaging cardiologist), Dr Marisevi Chaldoupi (electrophysiologist), Dr. ir. Rob Holtackers (MRI physicist), and Dr Casper Mihl (cardiovascular radiologist).

Scientific achievements and societal impact

The implementation of CMR-guided electrophysiological procedures in our centre may not only improve clinical care but also contributes to scientific achievements as well as has a significant societal impact.

Two complementary PhD trajectories have been successfully completed to harvest the full potential of iCMR by timely researching the opportunities and addressing potentially upcoming challenges. These ambitious and intensely collaborating PhD candidates, one from the Department of Cardiology and one from the Department of Radiology & Nuclear Medicine, have been employed to further strengthen the multidisciplinary aspect of our team. On 11 April 2024, Miranda Bijvoet successfully defended her PhD thesis on the topic of iCMR entitled 'The role of cardiac MRI in the treatment of patients with atrial arrhythmia'. On 25 June 2025, Hedwig Nies will defend her PhD thesis entitled 'Advances in cardiac magnetic resonance imaging: A paradigm shift from diagnostics to therapy'.

The efficient and close collaboration within the iCMR team has led to twelve publications in peer-reviewed scientific journals (see overview below) and various invited presentations at international conferences in the field of both electrophysiology and MRI. Among these: the HRS congress in Boston (2021, Dr Marisevi Chaldoupi), the SCMR congress in San Diego (2023, Dr Miranda Bijvoet and Dr.ir Rob Holtackers were invited to cover multiple lectures of iCMR) and recurrent invitations to present at the iMRI symposium in Leipzig and Boston (2022, 2024, Bijvoet). Our iCMR project was nominated for the very first 'Marja van Dieijen Award' in 2021 and became runner-up. In 2022, our multidisciplinary iCMR team received the NWO team science award, for combining team expertise, fundamental science, engineering and patient care. In 2023, Dr. ir. Rob Holtackers obtained a personal NWO Veni grant for his research project on studying long-term follow-up MRI imaging characteristics after CMR-guided electrophysiological procedures to improve long-term procedural success. A new PhD candidate, Lara van der Meulen, started under Rob's supervision in May 2024 to coordinate and execute this project.

Apart from research, our iCMR team at Maastricht UMC+ plays a large role in education as well. Maastricht UMC+ has been recognised and assigned as 'iCMR education centre' for other hospitals and their staff. Other start-up centres

can therefore visit Maastricht UMC+ to gain knowledge and experience with these new innovative procedures. To further standardise the procedures and ensure safety for both patients and staff, our iCMR team developed procedural workflow and general safety protocols. Additionally, a bail-out procedure was documented and tested in several dry runs with the entire team. These protocols and workflow documents have been made publicly available (Bijvoet et al., J Cardiovasc Electrophysiol 2021) as guidance for centres interesting in starting iCMR procedures.

Also, for students from Maastricht University the iCMR innovation is already an interesting project that offers unique learning opportunities during clinical and scientific rotation. Various semi-doctors have registered on their own initiative to be present with this innovative technique during their internship in cardiology and radiology. iCMR is therefore a breeding ground for future GEZP and WESP students. Besides education on a professional level, our iCMR team also contributed to educating the general public and discussing this new innovative procedure. Our iCMR team contributed twice to an article in the Hartpatiënten Nederland magazine. Finally, we cherish the recognition from our industrial partners. This is reflected by our close developmental collaboration with industry and qualification as 'IMRICOR educational iCMR centre', trusted to educate fellow physicians in the field.

Our future goal as a multidisciplinary iCMR team is clear: to offer the best possible treatment for every patient, that is tailored to the individual, which does therefore not necessarily need to be this new iCMR innovation. Due to the unique team effort, we were able to combine an innovative, high-standard patient treatment, scientific research, and education to move this innovative technique further in direct collaboration with our industry partners.

Publications in the general press:

- '*Unieke techniek: behandeling hartritmestoornissen in MRI*', article in magazine 'Hartpatiënten Nederland' (https://www.hartpatienten.nl/nieuws/unieke-techniek-behandeling-hartritmestoornissen-in-mri/)
- '*Dit is wat mijn vak zo mooi maakt*', article in magazine 'Hartpatiënten Nederland' (https://www.hartpatienten.nl/nieuws/dit-is-wat-mijn-vak-zo-mooi-maakt/)

Scientific publications:

- Nies HMJM, Linz D, Bijvoet GP, et al. Local atrial bipolar electrogram voltage drops during cardiac magnetic resonance guided catheter ablation of typical atrial flutter: Associations with delivered radiofrequency energy and peri-procedural imaging. Heart Rhythm O2. 2024;5(11):778-787. Published 2024 Sep 6. doi:10.1016/j.hroo.2024.08.015
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- Nies HMJM, Bijvoet GP, Smink J, et al. A comprehensive guide on real-time catheter localization techniques in magnetic resonance imaging-guided ablation therapy for cardiac arrhythmias. Eur Heart J Cardiovasc Imaging. 2024;25(2):149-151. doi:10.1093/ehjci/jead325
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cardiac imaging and electro-anatomical mapping. Int J Cardiol Heart Vasc. 2023;49:101276. Published 2023 Oct 11. doi:10.1016/j.ijcha.2023.101276
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- Bijvoet GP, Holtackers RJ, Nies HMJM, Mihl C, Chaldoupi SM. The role of interventional cardiac magnetic resonance (iCMR) in a typical atrial flutter ablation: The shortest path may not always be the fastest. Int J Cardiol Heart Vasc. 2022;41:101078. Published 2022 Jun 28. doi:10.1016/j.ijcha.2022.101078
- Nies HMJM, Gommers S, Bijvoet GP, et al. Histopathological validation of semi-automated myocardial scar quantification techniques for dark-blood late gadolinium enhancement magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2023;24(3):364-372. doi:10.1093/ehjci/jeac107
- Bijvoet GP, Chaldoupi SM, Bidar E, Holtackers RJ, Luermans JGLM, Maesen B. Epicardial box lesion using bipolar biparietal radiofrequency and multimodality scar evaluation-a case series. Eur Heart J Case Rep. 2021;6(1):ytab530. Published 2021 Dec 27. doi:10.1093/ehjcr/ytab530
- Bijvoet GP, Holtackers RJ, Smink J, et al. Transforming a pre-existing MRI environment into an interventional cardiac MRI suite. J Cardiovasc Electrophysiol. 2021;32(8):2090-2096. doi:10.1111/jce.15128

7 Silencing clot and flame: synthetic proteins inspired by blood-feeding parasites

Prof. Ingrid Dijkgraaf, Department of Biochemistry

What is the benefit of proteins derived from blood-sucking parasites for our health?

My research mainly focusses on proteins derived from blood-feeding parasites, such as ticks, which have evolved highly effective strategies to interfere with the human immune system and hemostasis. These organisms secrete proteins in their saliva that block inflammation and prevent blood clotting, enabling them to feed for extended periods without detection. Understanding how these proteins work not only reveals fascinating aspects of host–parasite interactions but also provides valuable starting points for developing novel diagnostics and therapeutics for cardiovascular and inflammatory diseases. Through chemical synthesis, recombinant production, and functional analysis of these parasite-derived proteins, we aim to uncover their potential as innovative tools in biomedicine. Although the focus is on cardiovascular diseases, adjacent projects are occasionally carried out as well, such as work on tick cement proteins that may one day be used as biomaterials, or our work on synthetic anti-tick vaccines to prevent tick-borne diseases in humans and animals, such as Lyme borreliosis, anaplasmosis, babesiosis, Crim-Congo hemorrhagic fever, and heartwater. The insights we gain from this research will hopefully also be applicable in the long term to the prophylaxis of cardiovascular diseases.

Major breakthroughs

To unravel the right disulfide bond connectivity of tick salivary protein evasin-3 unambiguously, we established an alternative approach for disulfide mapping in cysteine-rich peptides and proteins. This method is based on NMR chemical shift perturbations caused through S–Se bonds by a single Cys to Sec substitution (Figure 1, [1]).

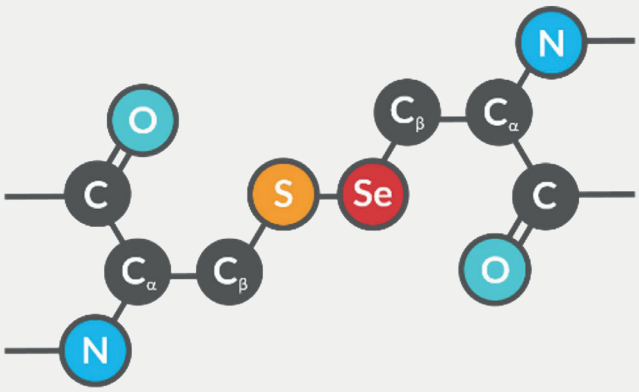

FIGURE 1 Schematic representation of the mixed Cys-Sec bond indicating Cα/Cβ carbons.

Subsequently, we could solve the 3D structure of evasin-3 and identify how it binds to chemokines CXCL1- and -8 by NMR [2,3]. In a fellow-up project, we showed that fluorescently labeled evasin-3 can visualise inflamed endothelium, a hallmark of progressive atherosclerosis [3].

The structure of evasin-4 was elucidated with X-ray crystallography and the molecular determinants of evasin-4 and chemokine CCL5 interactions were investigated with NMR [4]. It appeared that mainly the N-terminus of evasin-4 binds to CCL5.

We further investigated the therapeutic potential of both evasins and it appeared that they reduce the number of immune cells (monocytes, neutrophils) that migrate towards a chemotactic gradient of chemokines. Evasin-3 could even reduce the adhesion of neutrophils and monocytes to LPA-activated endothelial cells (ECs, Figure 2A-B).

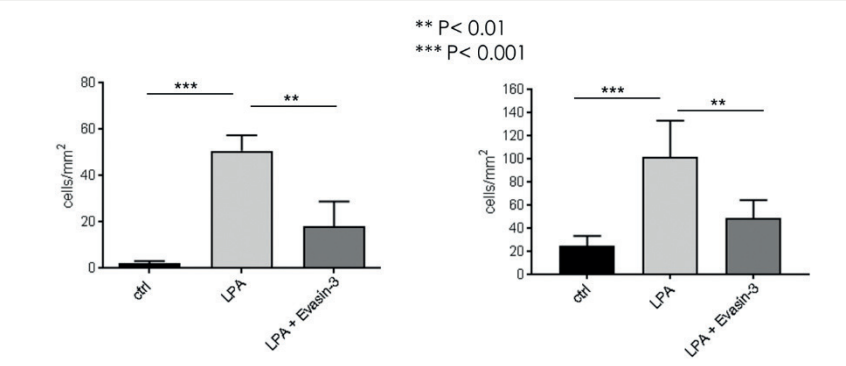

FIGURE 2 Evasin-3 reduces the number of neutrophils (left) and monocytes (right) that adhere to human endothelial cells after activation with 10 μM lysophosphatidic acid. ** P< 0.01; *** P< 0.001.

In another study, we identified $BaSO_4$-adsorbing protein 1 (BSAP1) isolated from the soft tick *Ornithodoros savignyi* as a distant homolog of tick salivary lectin pathway inhibitor (TSPLI)/Salp14 proteins found in hard *Ixodes scapularis* ticks and showed that it inhibits the lectin complement pathway but not coagulation [5]. We recently started to unravel the hardening process of tick cement [6].

Users and collaborators

Over the years, I have established a broad network of local (Maastricht UMC+), national, and international collaborations to support our multidisciplinary research. In the field of chemokine biology, we work closely with Dr Rory Koenen, Prof. Oliver Soehlein (University of Münster, Germany), Prof. Paul Proost and Prof. Pedro Elias Marques Weber (Catholic University Leuven, Belgium). For structural elucidation, we collaborate with Dr Hans Ippel (Department of Biochemistry, Maastricht University), Prof. Bert Janssen (Utrecht University), and Prof. Kevin Mayo (University of Minnesota, USA). In the design and development of chemokine-binding proteins, our partners include Dr. Peter Timmerman (Biosynth) and Dr Stepan Denisov (University of Vienna, Austria), Prof. Shoumo Bhattacharya (University of Oxford, UK), Prof. Akane Kawamura (Newcastle University, UK), and Prof. Ram Bhusal (Monash University, Australia). For nuclear imaging of cancer and cardiovascular disease, we collaborate with Prof. Felix Mottaghy, Dr Matthias Bauwens, and Dr Ludwig Dubois (all Maastricht UMC+) [7], and Prof. Susanne Lütje (RTWH Aachen, Germany). In the field of hemostasis, we work with Dr Elisabetta Castoldi and Prof. Henri Spronk (both Maastricht UMC+). For Lyme disease prophylaxis, key partners include Prof. Joppe Hovius (Amsterdam UMC) and Prof. Tina Vermonden (Utrecht University). To prevent other tick-borne infections, we collaborate with Dr. Hein Sprong (RIVM), Prof. Michalis Kotsyfakis (Institute of Molecular Biology and Biotechnology, Greece), Prof. Anabella Gaspar (University of Pretoria, South Africa), Dr Ben Mans (University of South Africa), Dr Esther Kanduma (University of Nairobi, Kenya), and Prof. Julie Champion (Georgia Tech, USA). A few years ago, we started a collaboration in the field of tick cement proteins with Siddharth Deshpande (Wageningen University, the Netherlands). In the field of radiochemistry, I collaborate with Chondropeptix.

Scientific quality

Research on tick-derived proteins has led to two completed PhD projects (Denisov, 2019; Van den Kerkhof, 2021), multiple internships, and nine publications in journals like *Bioconjugate Chemistry*, *JBC*, and *Chemical Communications*. Two joint PhD projects with KU Leuven and Hasselt University on tick salivary proteins are ongoing. I also (co-)supervised PhD candidates Annemiek Dickhout (2022) and Yuandi Zhao (2025) and currently mentor another PhD candidate.

The work has attracted several grants: an NWO ECHO grant (2018) for BSAP1 research, and prestigious fellowships for Stepan Denisov (CARIM Kootstra,

NWO Rubicon, Marie Curie). Visiting postdoc Amine Jmel received an EMBO grant and is now an assistant professor at the University of Nancy.

Societal impact

To engage and inform the public about our research, I have voluntarily given talks to Dutch secondary school students since 2012. In 2014, I received an Outreach Lecturing Fund Award (U.S. Department of State) to lecture at Mississippi Valley State University, where I also participated in campus life and student discussions.

Our tick protein research has received wide public attention. In 2019, it was featured in a KNCV 'Eye Opener' video and nominated for the Klokhuis Science Prize. Media coverage followed, including features in *C&EN News* and *C2W* (2020), *Research Features* (2021), and interviews with *BNR Nieuwsradio* and *Financieel Dagblad*. In 2025, our work on tick cement proteins was highlighted in *C2W*, *Chemistry World* (RSC), and in a *Nature Communications* editorial.

Since March 2025, I have served as chair of the KNCV section Medical Chemistry and Chemical Biology, representing professionals in the field and coordinating public outreach efforts.

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8 The Digital Twin

Dr Uyên Châu Nguyên, Department of Cardiology
Dr Matthijs Cluitmans, Department of Cardiology
Prof. Jordi Heijman, Department of Cardiology
Prof. Joost Lumens, Department of Biomedical engineering

What is a Digital Twin and why do we need it?

Digital Twin initiatives aim to provide an integrative personalised modeling and data analysis platform capturing an individual patient's cardiovascular disease substrates. Personalised heart models enable mechanistic patient-stratification strategies and facilitate *in silico* evaluation of therapeutic strategies, enabling an informed assessment of treatment efficacy based on the individual patient's disease spectrum. Thereby, the Digital Twin technology will lay a strong foundation for personalised medicine approaches superior to the current standard-of-care (Figure 1).

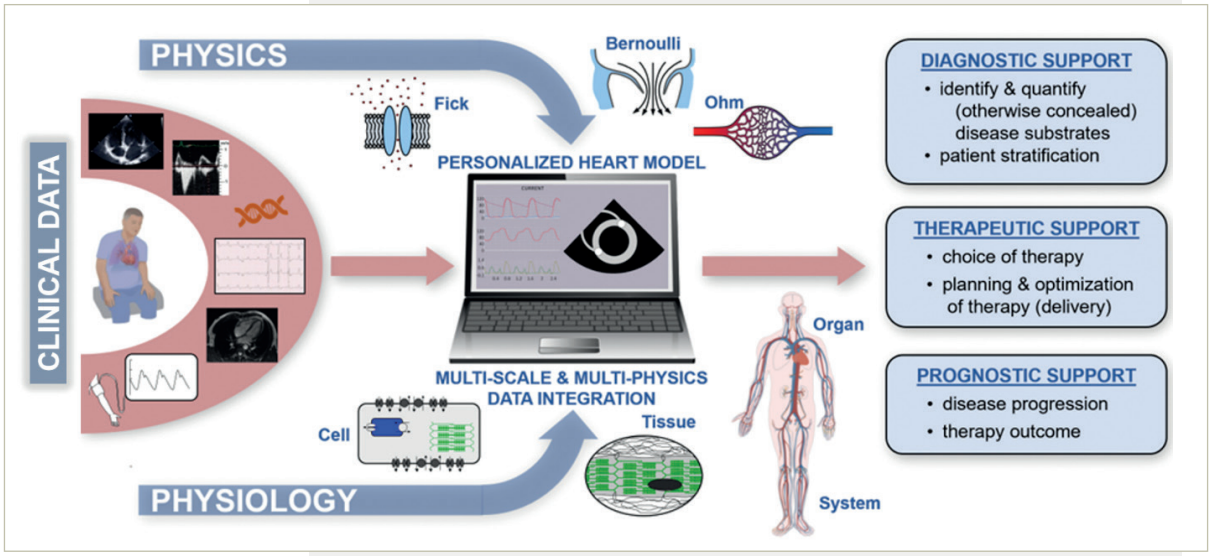

FIGURE 1 The Digital Twin of a patient's heart and circulation adds value to the existing clinical workflow by offering more objective insight in the underlying disease substrates and provides a platform for virtual evaluation and optimisation of a therapy.

Central to the Digital Twin concept are *in silico* simulations of an individual patient's heart, using biophysical models of cardiovascular physiology at multiple scales (from ion channel function to system hemodynamics) obtained by adjusting a well-considered set of relevant parameters in the model to match the clinical phenotype of the individual patient as closely as possible (Figure 1). When biophysical processes are not fully understood, such mechanistic models can alternatively be augmented by artificial intelligence fuelled with population-based data. Digital Twin insights can be leveraged to improve patient stratification and guide disease management. CARIM teams have long pursued Digital Twin development. The following example highlights its academic, clinical, and societal impact. [1-3]

The 'Electrical Twin'

Assessment of the electrical activity of the heart is an essential element of clinical cardiology and plays a major role in the diagnosis and treatment of arrhythmias and heart failure. Electrical activity is typically assessed with the standard 12-lead ECG, which only reflects 'averaged' electrical activity but lacks spatial information about local electrical activity within the heart. The clinical gold standard in this field is electro-anatomic mapping, an invasive procedure involving the measurement of intracardiac signals from multiple points in 3D space by catheters placed in the heart. By combining local electrical measurements derived from electro-anatomic mapping with anatomical and structural

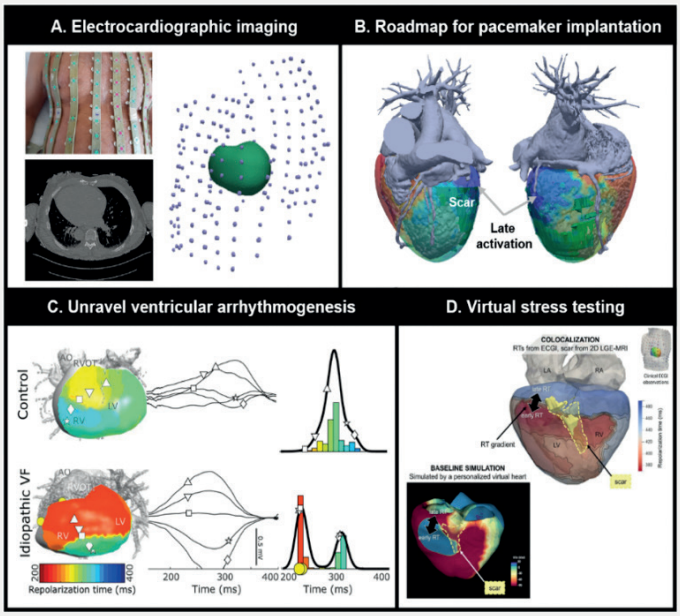

FIGURE 2 ECG-imaging workflow in Maastricht (A) with two representative clinical applications in the electrical treatment of heart failure (B) and assessment of idiopathic ventricular arrhythmias (C). The 'electrical twin' can virtually test the inducibility of arrhythmias (D).

information, one can tailor the treatment of arrhythmias and heart failure. [4] ECG-imaging (ECGI) is a technique that non-invasively reconstructs the electrical activity of the heart using measurements from ~200 chest electrodes and a patient-specific geometry, creating a virtual 'Electrical Twin' of the heart.

We have an in-house developed 'Maastricht' ECGI system (Figure 2A) that was validated in anesthetised animal models [5]. This system has since then been employed to provide patient-specific electrical twins of more than 100 patients, providing guidance for pacing in heart failure (Figure 2B) [6]. It also provided clinically relevant information that could not be seen on the 12-lead ECG in patients with unexplained ventricular fibrillation (Figure 2C), contributing to our understanding of arrhythmogenesis in these patients [7]. In the recently funded Dutch Heart Foundation (DHF) project ELECSUR, CARIM researchers, led by applicant Dr Matthijs Cluitmans, aim to identify optimal treatment strategies for patients at risk of life-threatening arrhythmias. This will be achieved by evaluating the inducibility of arrhythmias and potential treatment options using the Electrical Twin framework, informed by ECGI (Figure 2D). Our work was featured in a public science television show 'Jekels Jacht' for Dutch public television (NPO) by CARIM researchers Dr Matthijs Cluitmans, Dr Job Stoks and Dr Yesim Kaya (Media reference A).

The 'Mechanical Twin'

At CARIM similar Digital Twin approaches have been developed for the mechanical aspects of the heart ('Mechanical Twin') based on non-invasive strain imaging [8]. For example, The CircAdapt modelling framework was used to identify subclinical disease in arrhythmogenic cardiomyopathy patients before conventional criteria detect them. Our patient-specific simulation approach revealed subtle abnormalities and their progression across all age groups, challenging guidelines that recommend reducing follow-up with age. [9] In another study, we demonstrated how personalised heart models can predict therapy response before device implantation in heart failure patients treated with cardiac resynchronisation therapy [10]. This breakthrough received national media attention (Media reference B). Current efforts are focused on integrating both electrical and mechanical components into a combined 'ElectroMechanical Twin' [11]. To advance this concept, CARIM researcher Dr Uyen Chau Nguyen (lead applicant), in collaboration with Dr Roel Meiburg (co-applicant) from Eindhoven University of Technology, has been awarded the first Dekker Team Science grant from the DHF to investigate the ElectroMechanical

Twin in the context of pacing therapy for heart failure as part of the COMPUTE-HF study.

Who is involved?

The work presented encompasses a collaborative effort from multiple disciplines (physiology, cardiology, radiology, biomedical engineering) and research teams (Prof. Frits Prinzen, Prof. Kevin Vernooy, Prof. Joost Lumens, Prof. Tammo Delhaas, Prof. Uli Schotten, Prof. Jordi Heijman, Prof. Paul Volders, Dr Matthijs Cluitmans, Dr Uyên Châu Nguyên). We have diverse training backgrounds (engineering, applied mathematics, clinical technology, physiology, clinical cardiology) and share a common interest in computational cardiology. Importantly, the unique CARIM environment where clinical researchers actively embrace and contribute to digital health innovations, and technology-oriented researchers are well-versed in cardiovascular (patho) physiology, positions Maastricht UMC+ as an ideal breeding ground for the development and implementation of Digital Twin technologies.

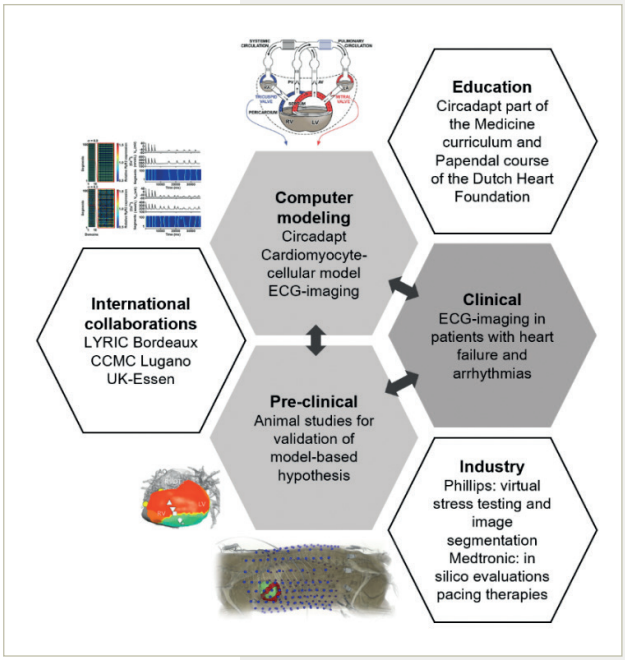

FIGURE 3 Integrative digital twin network within CARIM.

Users and collaborations

Collaborations: There is a strong synergistic environment within CARIM (Figure 3). We organise monthly translational research meetings on pacing and tachyarrhythmias, and cross-faculty cardiac computational research meetings with the Faculty of Science and Engineering. Key national partners include TU Eindhoven and Catharina Hospital; international collaborators include institutes in Bordeaux, Brno, and Barcelona, among others.

Public-private collaborations: Large medical device companies, such as Medtronic, Philips and GE Vingmed, actively invest in and advocate the use of Digital Twin technologies. For example, the group of Prof. Joost Lumens has been contracted by Medtronic to perform *in silico* evaluations of novel pacing therapies and valve implant technologies in the CircAdapt cardiovascular model. [8] The same group is also involved in a European public-private network working on the development of intelligent ultrasound systems (MARCIUS project). Another academia-industry collaborative project with Philips led by Dr Matthijs Cluitmans focusses on the development of a clinically applicable pipeline for personalised electrophysiology modeling. [12] This year, a Public-Private Partnership grant from the DHF was awarded to Dr Uyen Chau Nguyen as lead applicant, supporting a collaborative project between ECG technology startup VDI Technologies and Catharina Ziekenhuis Eindhoven.

Education: An important and rapidly growing group of users of our modelling technologies are academic teachers and students. In particular the CircAdapt Simulator educational tool is used for teaching cardiovascular physiology and pathophysiology at many national and international universities. This unique tool is freely available through our CircAdapt web portal. Since 2013, more than 40,000 users have downloaded the application and many (inter)national universities (e.g., Nijmegen, Utrecht, Hasselt, Copenhagen, Cali, Stellenbosch and several institutes in the USA) are known to structurally employ the educational tool in their medical curriculum. At UM, the tool is implemented in several semesters of the medical curriculum. In addition, the tool is used for teaching during the national Papendal course organised by the DHF and plays a major role in International Training Networks subsidised by the European

Union (Personalized In-silico Cardiology, MARCIUS). Another tool developed by CARIM researchers that is used for cardiac cellular electrophysiology teaching is Myokit. [13]

Scientific quality

The scientific quality is reflected by the numbers and impact of peer-reviewed papers published and prestigious grants awarded. Over the past decade CARIM researchers collectively published over 370 papers within the digital twin/ computational cardiology topic (Pubmed). Additionally, over 60 scientific papers involving the CircAdapt team and model have been published. [14] Dr Uyên Châu Nguyên has been lead applicant on multiple awarded grants, including the Dekker Clinical Scientist Grant (DHF, 2021), the Stipend Scholarship (CARIM, 2024), the Dekker Team Science Grant (DHF, 2024), and the Public-Private Partnership Grant (DHF-Health Holland, 2025). Dr Matthijs Cluitmans was awarded the Dekker Junior Postdoc grant from the DHF and the Veni grant from the Dutch Research Council (NWO; both in 2018) as well as a Dekker senior postdoc grant from the DHF (2024). Prof. Jordi Heijman was awarded a NWO Veni and Vidi grant (2015 and 2020) and a Young Talent grant from the CVON/DHF PREDICT consortium (2017). Prof. Joost Lumens was awarded two personal grants from the DHF (2012 and 2015), a Vidi from NWO (2017) and an NWO Take-Off grant to investigate the commercial valorisation potential of a Digital Twin solution in cardiology. These prestigious grants underscore CARIM's national leadership in Digital Twin technology.

Societal impact

Patient and family involvement is essential for the clinical translation of our study findings and the development of patient-centred study protocols. Prof. Joost Lumens, Dr Matthijs Cluitmans and Dr Uyên Châu Nguyên have presented their work at the patient congress (RESCAR Foundation) and have contributed to the Bordeaux Summer School in Cardiac Electrophysiology and to the PhD training courses from the DHF. Furthermore, the CARIM Digital Twin team was involved in the Dutch Cardiovascular Alliance (DCVA) initiated inventory and policy document on animal-free innovations for cardiovascular research (link) and published in an Consensus document of the ESC Working Group on Myocardial Function and the ESC Working Group on Cellular Biology of the Heart. [15] The team also contributed to unlocking technological innovations for clinical application in a report for the DCVA (Media reference C) as well as contributions to defining a nation-wide Cardiovascular Technological Agenda (Media reference D).

Conclusion

CARIM's Digital Twin initiatives demonstrate clear clinical impact through innovative Electrical and Mechanical Twin technologies that have already benefited patients and educated thousands worldwide. With strong industry partnerships and ongoing integration toward comprehensive ElectroMechanical Twins, CARIM is uniquely positioned to lead the translation of Digital Twin technology into clinical standard-of-care.

CARIM's Digital Twin team media exposure

- Jekels Jacht: NPO tv programme 'Jekels Jacht' 2024, season 2 episode 8 on Willem Einthoven.
- *Digitale Tweeling Uitkomst voor Hartpatiënten*: National news (RTL4 journaal; NPO Radio 1 journaal), link
- Documentary for the DCVA on the role of implementation of technological innovations in healthcare, link
- 'Cardiovascular Technical Agenda' for the DCVA (2023), link
- ESC TV Today on Digital Twins, April 2025, link
- Interview '*Virtueel hart heeft veel voordelen*'. Stichting Hartpatiënten NL (2025), link
- '*Het Digitale Tweelinghart*' video for NFU campaign 'Laat Wetenschap Werken', link

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9 Towards an Integrated Remote Atrial Fibrillation Clinic

Prof. Dominik Linz, Dept. of Cardiology
Dr Astrid Hermans, Dept. of Cardiology

What is TeleCheck-AF?

Atrial fibrillation (AF) is the most common sustained atrial arrhythmia, and is characterised by an irregular and often very rapid heart rhythm. In the Netherlands, AF is affecting approximately 350,000 people, with around 31,000 newly diagnosed AF patients each year. AF patients often experience a reduced quality of life and shorter life expectancy, and in the long term, the irregular and rapid heartbeat can contribute to the development of heart failure and stroke. These complications often lead to increased hospitalisations and higher healthcare costs. Importantly, patients with lower socio-economic status, particularly in regions like Limburg, face greater comorbidities and reduced healthcare access.

Recognising the need for timely AF detection and management, Maastricht UMC+ transitioned traditional face-to-face outpatient AF consultations into teleconsultations using the mHealth platform TeleCheck-AF. This approach empowered patients to perform three daily heart rate and rhythm recordings for one week prior to consultations, with additional measurements during symptoms. Data were securely transmitted in real-time to physicians, enabling personalised care regardless of patients' geographical location.

TeleCheck-AF proved patient-friendly, accurate, feasible, and safe. It also reduced care product claims, facilitating the establishment of a new reimbursement code for this approach by the Dutch healthcare authority.

Moving beyond TeleCheck-AF: Towards an Integrated Remote AF Clinic

While TeleCheck-AF laid the foundation, further optimisation is essential for fully integrated remote AF management. Our vision extends beyond heart rate and rhythm monitoring to include: remote cardiovascular risk management optimisation, lifestyle coaching, patient education and empowerment, medication management and rehabilitation support. By embedding these components into a comprehensive care infrastructure, we aim to improve healthcare access, deliver the right care at the right time and place, and enhance patient outcomes and experience. This integrated approach fosters multidisciplinary collaboration, personalised treatment, and has the potential to reduce socio-economic disparities in AF management.

To achieve a high-impact, top referral AF clinic and become the largest integrated remote AF clinic in the Netherlands, we focus on nurse-led AF care. Traditionally, cardiologists managed AF patients. However, evidence shows that multidisciplinary care coordinated by specialised AF nurses under cardiologist supervision improves guideline adherence, reduces cardiovascular hospitalisations and mortality, and enhances patient quality of life. At Maastricht UMC+, we are currently implementing this nurse-led pathway, combining structured mHealth use with multidisciplinary consultations. Our specialised-AF nurses play a pivotal role in coordinating care and guiding patients through their treatment journey. The nurse-led AF care is organised from the newly established AF Control Room, which has been fully set up in the outpatient clinic in recent months (Figure 1). All telephone consultations and supervision moments with cardiologists take place in this space, enabling efficient, team-based and patient-centred remote care coordination.

Another key element of our Integrated Remote AF Clinic is the development of an online platform (called MetAFib) designed for both patients and physicians, based on and including the current guidelines for AF management. MetAFib will consolidate various digital applications into a unified, transparent dashboard, eliminating the need for multiple apps and cloud systems. It serves as a secure repository for longitudinal self-monitoring data, presenting dynamic patient health trends tailored to individual profiles, including age, education level, and treatment type. This digital solution supports personalised care plans to ensure integrated and personalised AF care from a distance. Currently, this online platform is in the development phase, with ongoing efforts focused on ensuring it meets clinical needs, user-friendliness, security standards, and seamless integration with existing systems. Moreover, the platform is expected to generate a large volume of research data.

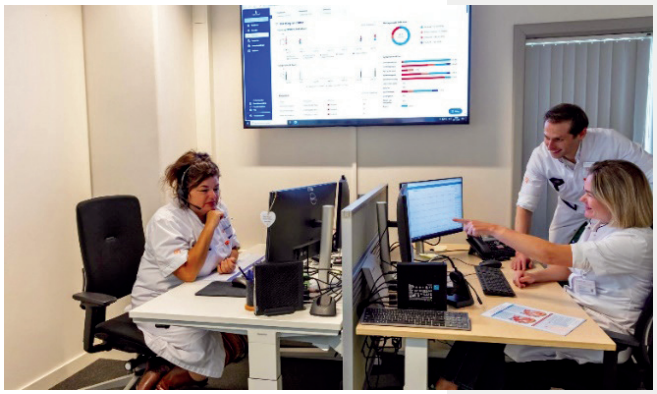

FIGURE 1
AF Control Room.

FIGURE 2 Our project group
(Prof. Domink Linz and Prof. Jeroen Hendriks are missing).

Who is involved?

Our project is driven by a multidisciplinary and highly collaborative team at Maastricht UMC+. Our project group includes: Prof. Dominik Linz, Prof. Jeroen Hendriks, Prof. Kevin Vernooy, Dr Astrid Hermans, Dr Theo Lankveld, Henk Hoogervorst and our specialised AF nurses, Bianca Vorstermans and Mandy Kessels. Our PhD candidates will contribute by analysing large volumes of data which will be collected throughout this project.

Users and collaborations

As we are still in the development and implementation phase of the Integrated Remote AF Clinic, we collaborate closely with a broad interdisciplinary team. This includes electrophysiologists and cardiologists, the Cathlab EP manager and planning staff, the developer of our digital platform, and collaborators from MIT. In addition, we work with security and privacy officers, IT architects, financial experts, and EPIC (EHR) representatives.

Together, this diverse team brings together clinical expertise, technological innovation, and scientific research to co-create a robust, secure, and scalable remote AF care infrastructure. These collaborations ensure that the Integrated Remote AF Clinic is not only medically effective, but also digitally sustainable and future-proof.

Scientific quality

In the last two years (2023-2025), our research group has published multiple peer-reviewed papers stemming from the TeleCheck-AF project, advancing understanding of patient motivation, healthcare utilisation, arrhythmia monitoring and machine learning applications for AF detection (see references).

Societal impact

Our practical expertise and insights contributed to the national publication '*Handreiking: Ondersteunen van patiënten/cliënten bij digitale zorg'* (January 2024), created in collaboration with the *Vliegwiel voor digitale transformatie in*

de zorg. https://vliegwielcoalitie.nl/wp-content/uploads/2024/01/Handreiking-patientondersteuning-2024.pdf

The project has been showcased to key stakeholders, including the Dutch Health and Youth Care Inspectorate (IGJ) and major Dutch health insurers, via poster presentations in 2024.

During Pulse Day at Maastricht UMC+ (1 March 2025), the project was prominently featured as part of a larger campaign to raise awareness about heart rhythm disorders. Pulse Day is an international awareness campaign initiated by the European Heart Rhythm Association (EHRA) to highlight the prevalence of arrhythmias. To mark this occasion, CARIM+HVC organised a series of activities including awareness campaigns in the outpatient clinic, promotional videos featuring well-known Limburgers, and a drive to collect digital pulse measurements via the FibriCheck app. We also shared a series of fun and informative videos with the Pulse Day message across the social media channels of Maastricht UMC+, HVC, UM and CARIM. In addition, we communicated PulseDay widely by using social media (Follow hashtag #PulseDay on Twitter and LinkedIn). The initial goal of collecting 1,000 digital pulses was exceeded within three days, leading to an extended target of 10,000, which was also reached before Pulse Day itself. We were also invited for a number of interviews in the general press, such as:

1. '*Cardioloog Dominik Linz van Maastricht UMC+ daagt mensen uit zelf hartslag te meten voor Pulse Day*' (21-02-2025), De Limburger;
2. '*Het (hart)ritme van gaon nog neet naor hoes'* (06-02-2025), RTV- Maastricht;
3. '*Wat is loos in Mestreech - HELP HET MUMC+ OM 1000 DIGITALE POLSSLAGEN TE VERZAMELEN'* (06-02-2025).

In May 2025, Prof. Dominik Linz and Dr Astrid Hermans were invited for an interview in the upcoming edition of *Praktijk*, the internal Maastricht UMC+ magazine, to share insights into the development, impact, and future ambitions of the Integrated Remote AF Clinic. This article is not yet published.

FIGURE 3 Pulse Day at Maastricht UMC+.

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10 A new chapter in the tale of the RACE trials

Prof. Dominik Linz, Department of Cardiology
Prof. Kevin Vernooy, Department of Cardiology
Prof. Uli Schotten, Department of Physiology
Prof. Harry Crijns, Department of Cardiology

From foundational insights to translational impact

Over the past two decades, the RACE trials have shaped the management of atrial fibrillation (AF) in the Netherlands and beyond. By challenging conventional treatment strategies and influencing international guidelines, these largely Dutch-initiated studies, primarily from Maastricht and Groningen, have played a central role in defining modern AF care. More recently, the RACE 7 and RACE 9 trials informed clinical decisions on cardioversion timing and conservative management, marking a clear shift toward individualised, evidence-based approaches.

RACE 7, published in T*he Lancet*, demonstrated that in patients presenting with recent-onset symptomatic AF, a wait-and-see approach with rate control was non-inferior to immediate cardioversion in achieving sinus rhythm at 4 weeks. This pragmatic strategy emphasised patient safety and minimised unnecessary interventions.

RACE 9 is an ongoing trial designed to test whether an integrated, personalised management approach combining lifestyle modification, risk factor control, and rhythm management improves outcomes in patients with early AF. Its rationale builds on findings from previous RACE studies, aiming to prevent AF progression and improve quality of life through tailored care pathways.

Among the earlier steps in understanding AF progression, the RACE V consortium examined the pathophysiological drivers of atrial remodelling and laid the groundwork for linking AF to broader vascular and structural processes. It introduced the concept that AF progression is not uniform and is deeply influenced by underlying atrial cardiomyopathy (AtCM). Although no longer recent, the scientific insights from RACE V continue to inform current research directions, particularly around risk stratification and mechanisms of AF progression.

RACE X – Early intervention to prevent progression of atrial cardiomyopathy

Building on these insights, the RACE X trial was initiated in 2024 to address a critical clinical question: can early rhythm control with catheter ablation delay the progression of AtCM and improve cardiovascular outcomes? RACE X is a prospective, randomised trial comparing catheter ablation to pharmacological rhythm management in patients with paroxysmal AF and evidence of AtCM, based on elevated left atrial volume.

The trial focusses on hard clinical outcomes, cardiovascular death and hospitalisations (urgent visits), as well as structural and symptomatic changes, aiming to determine whether early intervention can alter the natural course of atrial disease.

Where previous studies such as EAST-AFNET 4 showed the promise of early rhythm control, RACE X takes this a step further by testing the hypothesis specifically in patients with measurable atrial cardiomyopathy, seeking not only to treat AF, but to delay or prevent the progression of atrial cardiomyopathy by keeping patients in SR using catheter ablation. Also, the more recently initiated EASThigh study in which Maastricht researchers are strongly involved follows a comparable idea. EASThigh is a randomised, multicentre trial comparing early AF ablation using cryoballoon pulmonary vein isolation, combined with guideline-based antiarrhythmic drug therapy as needed, versus usual care in

patients with recently diagnosed AF and more advanced comorbidity profile (CHA_2DS_2-VASc ≥ 4).

EmbRACE: Understanding atrial cardiomyopathy beyond rhythm

Whereas the RACE studies test clinical hypotheses, the broader EmbRACE consortium (a recent addition to the RACE study family initiated in 2023) seeks to understand the atrial cardiomyopathy itself. Atrial cardiomyopathy, comprising structural, electrical, and functional changes of the atria, often develops silently and contributes to AF onset, recurrence, and complications such as stroke or heart failure.

EmbRACE is a translational research network that brings together expertise from molecular biology, physiology, cardiology, computational modeling, and digital health to unravel the mechanisms of AtCM. Through analysis of tissue, biomarkers, imaging, and continuous rhythm data, the consortium aims to define subtypes of AtCM, identify markers for early detection, and lay the groundwork for tailored interventions. These mechanistic insights feed directly into trials like RACE X and, in the longer term, into new models of care.

EmbRACE as platform for AF research in the Netherlands

Recognising the urgent need for coordinated efforts in AF research, the Dutch Heart Foundation has entrusted the EmbRACE consortium with a broader mission: to serve as a national platform for future translational and clinical research into AF and atrial cardiomyopathy.

By connecting academic centres, regional hospitals, primary care, and patient organisations, EmbRACE is designed to support long-term innovation in AF care. It provides the infrastructure, expertise, and collaborative spirit needed to translate biological insights into clinical applications, from early detection and risk stratification to personalised therapy and integrated care pathways.

In doing so, EmbRACE ensures that the legacy of the RACE trials continues, not just through past successes, but by laying the foundation for a new era of proactive, mechanism-based AF management in the Netherlands.

11 The Maastricht Study

Dr Carla van der Kallen, Department of Internal Medicine
Dr Miranda Schram, Department of Internal Medicine

What is The Maastricht Study and why do we need it?

The Maastricht Study is a large prospective population-based cohort study, with a specific focus on type 2 diabetes and cardiovascular disease. It was initiated in 2010 and now includes an impressive amount of data on ~9,200 inhabitants of the Maastricht and Heuvelland area between 40 and 75 years of age. The aim is to improve population health in the future, by developing a better understanding of underlying causes and mechanism of common chronic diseases like type 2 diabetes and cardiovascular disease. The study applies a deep phenotyping approach by collecting many biological samples (blood, urine, faeces, hair, DNA, RNA), measuring from (potentially new) early risk markers up to markers of severe clinical disease, using state-of-the-art assessments like cardiac ultrasound, extremeCT and brain and abdominal MRI, and following participants over time by annual questionnaires and linkage to medical registries. In 2020, the first survey was completed and we started the second survey, where all participants were re-invited to undergo all extensive biomedical assessments again. At the end of 2024, 3,750 participants have been included in the second survey.

The power of cohort studies like The Maastricht Study lies in the identification of novel disease risk factors as a basis for effective prevention. The spectacular decline of coronary heart disease mortality over the past decades illustrates this, and was enabled by the identification of the three single risk factors (high serum cholesterol, cigarette smoking, high blood pressure) in first generation population-based cohort studies like the Framingham Heart Study. Recent cohort studies have extended this approach towards more elaborated and sophisticated deep phenotyping including extensive imaging, early risk marker measurement, environmental and genetic approaches. The key features to allow such scientific and societal breakthroughs include repeated and deeply phenotyped data collection from the general population (to allow generalisability), with measurements many years before the clinical expression of a disease (to identify disease mechanisms), and with follow-up of health and disease status over time (to address temporality and potentially causality of associations), just like we apply at The Maastricht Study.

Who is involved?

An initiative like The Maastricht Study is per definition a team effort. First of all, we need commitment from study participants, over 9,000 individuals living in the Maastricht area. Without their voluntary participation we could not exist. The study is supervised by a Management Team consisting of Martijn Brouwers (scientific director), Carla van der Kallen, Miranda Schram, Annemarie Koster, Seb Köhler, Marleen van Greevenbroek, Bastiaan de Galan and Anke Wesselius. Since end 2023, the research centre of The Maastricht Study has been located in the CARIM Clinical Research Unit (CARIM-CRU) at Maastricht UMC+. CARIM-CRU is a new facility at CARIM, available to all CARIM researchers involved in medical studies with participants. The research centre staff is supervised by Dr Carla van der Kallen and includes dedicated study nurses, lab technicians and data managers. But a study like this cannot be performed without the support and input of many scientific experts, so-called domain experts of The Maastricht Study data, that are involved in data collection, data cleaning, data analyses and publication of scientific results. Those scientists reside in four

institutes at Maastricht UMC+ including CARIM (founding institute), MHeNs, CAPHRI and NUTRIM.

Users and collaborations

Having a large scale health data infrastructure like The Maastricht Study is attractive for national and international collaborations. Figure 1 shows our most prominent consortium partners which range from diabetes oriented parties, depression and dementia consortia, risk factor oriented consortia to biobanking and genetic oriented consortia.

FIGURE 1 Overview of most prominent consortium partners of The Maastricht Study.

Scientific quality

Over the past decade The Maastricht Study has resulted in over 190 peer-reviewed scientific publications. Two new professors have been appointed as part of strategic research profiling. Over 36 PhD candidates have successfully defended their PhD thesis. Figure 2 shows an overview of the covers of those 30 PhD theses that were based on The Maastricht Study, which includes a broad area of topics and scientific expertise. In addition, approximately 200 bachelor and master students performed their thesis research at The Maastricht Study.

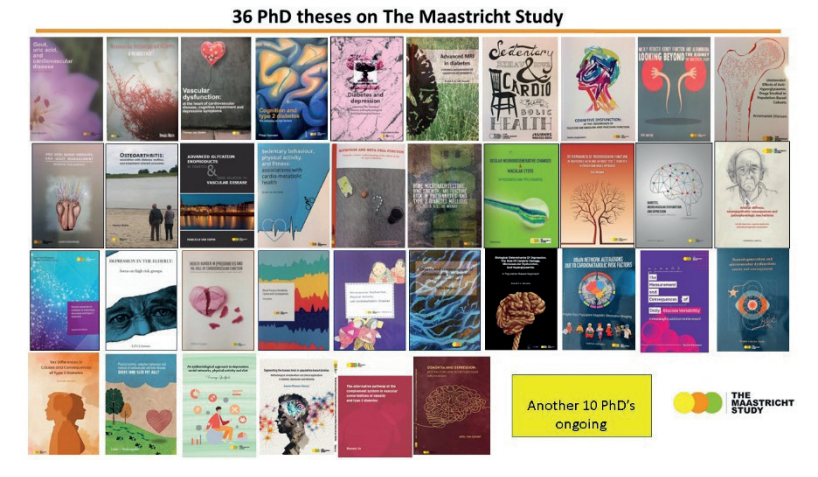

FIGURE 2 Overview of PhD thesis covers based on The Maastricht Study until 2024.

Societal impact

Despite the fact that most results from population-based cohort studies need time to result in clinical impact (like is illustrated by the example of the Framingham Heart Study; initiated in the 1950s, resulting in a decline in coronary heart disease in the 1970s), The Maastricht Study has resulted in societal impact already. As illustrated in Figure 3, we found that one third of our participants either had prediabetes or type 2 diabetes. This sets a major risk for the future, as these individuals are at high risk to develop cardiovascular disease. Many of our investigations have focused on the impact of prediabetes on physical and mental function, and show that damage to the vasculature,

brain and kidneys may already occur in the stage before clinical type 2 diabetes. This finding is of major importance for prevention.

In 2024, The Dutch Diabetes Foundation together with The Maastricht Study launched the campaign called '*Verklein je risico op diabetes type 2*' ('Reduce Your Risk of Type 2 Diabetes'). The aim was to raise awareness of the risks associated with prediabetes and type 2 diabetes, and to promote early prevention. In addition, innovative targets for potential intervention were found, albeit in a cross-sectional setting only, our results indicate that sitting half an hour per day less is associated with less diabetes. Likewise, the social network may prove a promising target for diabetes prevention. We observed that individuals with type 2 diabetes had a smaller social network size.

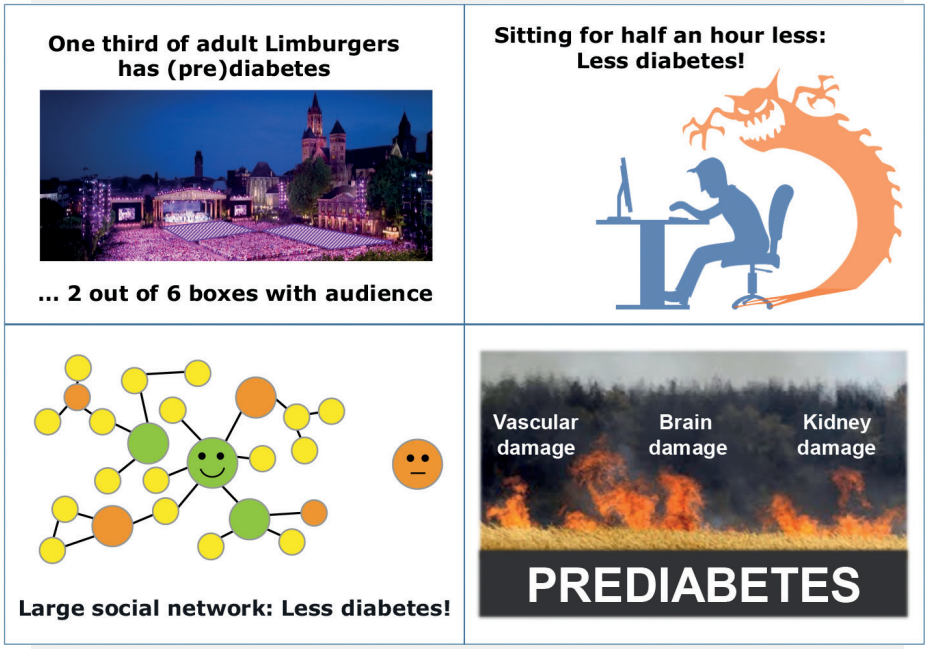

FIGURE 3 Societal impact of results of The Maastricht Study.

Datainfrastructure and FAIRification

Collecting deep phenotyping data at a large scale also resulted in novel digital data infrastructure needed for storage and analysis of The Maastricht Study data. Many advances needed to support scientific data management were accelerated by the progress of data collection in The Maastricht Study, and development of solutions were prioritised. An excellent example of this is the development of the online data dictionary. This dictionary gives an overview of available data and allows the request of data for both internal and external researchers, and is an important step in FAIRification of The Maastricht Study data. This data dictionary can be found at https://demaastrichtstudie.app/data-dictionary.

12 Determinants and cardiometabolic consequences of metabolic dysfunction-associated steatotic liver disease (MASLD)

Prof. Martijn Brouwers, Department of Internal Medicine

Metabolic dysfunction-associated steatotic liver disease: at the heart of cardiometabolic complications

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent disorder that is histologically characterised by intrahepatic lipid accumulation combined with features of the metabolic syndrome. It has been estimated that 30% of the general population is affected by MASLD, which is mainly explained by unhealthy lifestyle habits. MASLD is a risk factor for end-stage liver disease and hepatocellular carcinoma, and has become the principal reason for liver transplantation. The major cause of death, however, is cardiovascular disease. There is an ongoing discussion on whether MASLD per se is causally involved in the pathogenesis of cardiovascular disease, or whether it is an innocent bystander. Furthermore, given the high prevalence of MASLD it is pivotal to better understand its pathogenesis in order to better prevent its sequalae. Some have argued that fructose is the most disadvantageous sugar, which has been disputed by others.

Who is involved?

In the past two decades I have setup a translational research line to unravel the specific role of fructose in the pathogenesis of MASLD, and the role of MASLD in the pathogenesis of cardiovascular disease. I use a variety of methodologies, ranging from animal studies, in-depth phenotyping of rare inborn errors of metabolism (as a so-called human knock-out model), randomised controlled intervention studies, traditional epidemiology (using data from The Maastricht Study) and genetic epidemiology (i.e. Mendelian randomisation).

Users and collaborations

Translational research is team work: it is naïve to assume that all these diverse methodological skills can be possessed by one individual. I have, therefore, carefully invested in local, national and international collaborations, e.g. Prof. Casper Schalkwijk (animal studies, Maastricht University), Prof. Vera Schrauwen (metabolic imaging in in-depth phenotyping and intervention studies), Prof. Edith Feskens (nutritional intervention studies, Wageningen University), Dr Maaike Oosterveer (animal studies, University of Groningen), Dr Stephen Burgess (Mendelian randomisation, University of Cambridge, UK), Dr Dean Tolan (animal studies, University of Boston, USA;), and Prof. David Cassiman (inborn errors of metabolism, University of Leuven, Belgium).

Scientific quality

We used different approaches, including traditional epidemiology, in-depth phenotyping of patients with an inborn error of fructose metabolism, Mendelian randomisation and a randomised controlled trial, to unequivocally show that fructose per se is involved in the pathogenesis of MASLD. We subsequently disentangled the (in)direct pathways by which fructose causes MASLD in animal models. Furthermore, by using summary-level data from publicly available (ultra-) large databases (n=100,00-500,000 participants), we have been able to demonstrate that genetically determined MASLD is associated with coronary artery disease, which is strongly suggestive of a true causal relationship.

Our work has been highly valued as can be appreciated by publications of original data and invited reviews in renowned scientific journals (1-12).

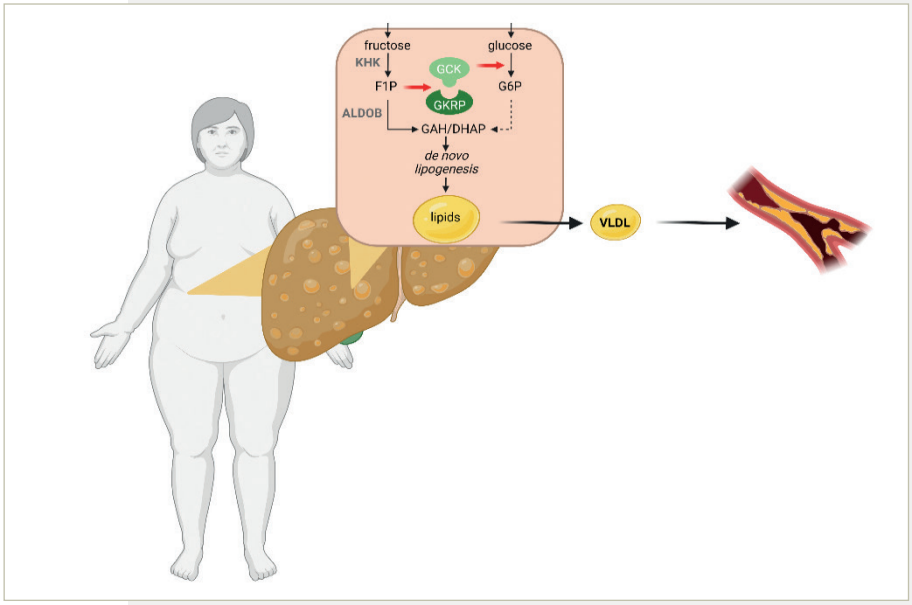

FIGURE 1 Based on my data, I postulate that fructose contributes to MASLD via direct pathways (by serving as a substrate for de novo lipogenesis) and indirect pathways (by stimulating hepatic glucose disposal and subsequent conversion into fat). MASLD drives the overproduction of VLDL particles, which causes coronary artery disease.

Societal quality

Our work contributes to the current concept that we should reduce the intake of simple sugars, particularly fructose, in order to reduce the burden of cardiometabolic disease in Western Society. This could be accomplished by the implementation of a sugar tax on sugar-sweetened beverages. We have contributed to the societal discussion on this topic by publications in national and regional newspapers, public debates, online news sites and webinars (listened > 30,000 times).

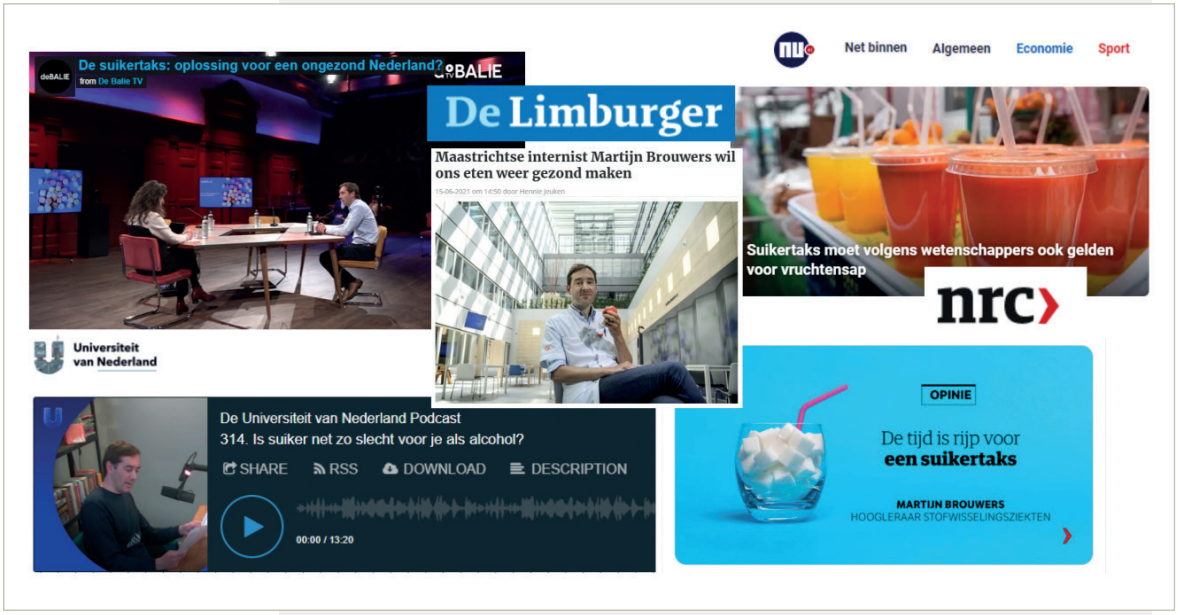

FIGURE 2 Selection of media attention, based on our research.

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13 Green transitions in medication and contrast agent practices

Dr Frank Zijta, Department of Radiology & Nuclear Medicine
Dr Ben Janssen, Pharmacology & Toxicology, Department of Radiology & Nuclear Medicine

Sustainable medication use: where we stand and where we are heading

Healthcare systems progressively depend on pharmacological interventions and diagnostic imaging. Yet, the environmental impact of medication and contrast agent use is becoming an increasing urgent issue. Residues from medications and contrast agents contaminate water and soil (Figure 1), thereby disrupting aquatic ecosystems, accelerating antimicrobial resistance, compromising drinking water supplies, and eventually result in significant public health risks. At the same time, the production, disposal and transportation of both medications and contrast agents enhance healthcare sector's overall carbon (CO_2) footprint.

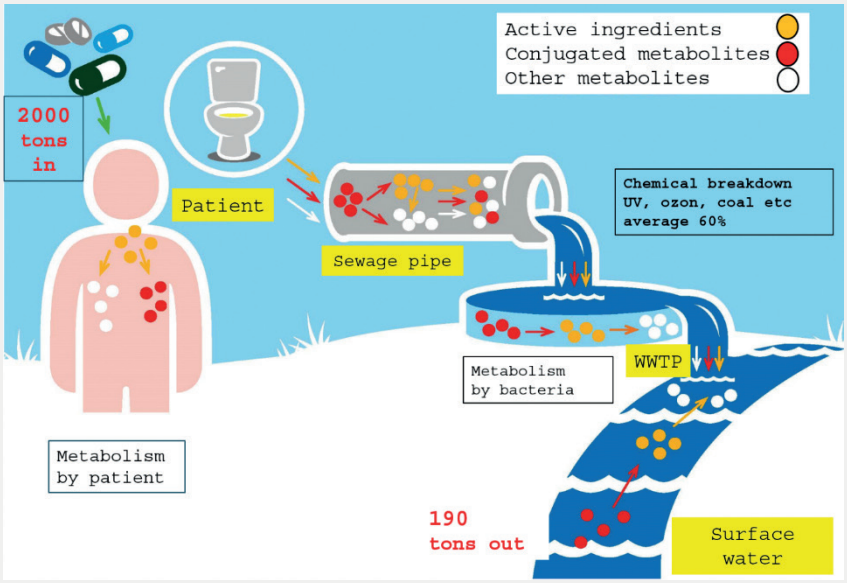

FIGURE 1 Flow of pharmaceutical residues from patient use and metabolism to surface water, highlighting partial removal during wastewater treatment and ultimately contribute to surface water pollution (based on RIVM 2020-088, National Institute for Public Health and the Environment.

In the Netherlands, the healthcare sector is responsible for approximately 7% of national CO_2 emissions, with medication production and use as key contributors. Whereas the urgency to intervene is high, the systematic implementation of mitigation strategies remains limited. Understanding the determinants of unsustainable use of medications and contrast agents is necessary to develop pragmatic and scalable interventions that reduce emissions and environmental release without compromising diagnostic or therapeutic quality or outcome.

At Maastricht UMC+, we aim to establish a translational research line that investigates and mitigates the environmental burden of both medication and contrast agent use. Our approach integrates technological and behavioural perspectives to develop a sustainable medication and imaging cycle that aligns clinical care with environmental responsibility. This research initiative is embedded in the national sustainability framework set forth by the Green Deal Sustainable Healthcare 3.0, a framework signed by, among others, all Dutch university medical centres, committing to a transition toward environmentally responsible care by 2050. The Green Deal outlines five core ambitions: promoting health, raising awareness and knowledge, reducing CO_2 emissions from infrastructure and transport, working circularly with materials, and, most relevant in this context, reducing the environmental impact of medication and contrast agent use.

To support this effort, Maastricht UMC+ has received targeted innovation funding to accelerate the development of organisation wide strategies to reduce these pharmaceutical emissions. Additionally, Maastricht UMC+ is a main partner in the Horizon Europe funded THERESA PCP consortium, a large international collaboration that aims to implement sustainable on-site hospital wastewater treatment solutions. These combined efforts enable us to construct a roadmap for the period 2025-2029, focussed on embedding environmental sustainability at multiple system levels.

Who is involved?

Within Maastricht UMC+, the ambitions of the Green Deal are translated into concrete action through six dedicated project teams. Within the theme focussed on reducing the environmental burden of medication use, we collaborate closely Dr Fatma Karapinar (Department of Clinical Pharmacy) in shaping and executing a comprehensive research and implementation agenda. We are motivated by the belief that sustainability should be a natural part of healthcare, and through the Green Deal we aim to contribute to more environmentally conscious care delivery. Under the coordination of our institutional programme manager for sustainability and environment, Erna Hofs, our project team aims to play a combined position as initiator and advisor. We are responsible for identifying difficulties, proposing solutions, and launching research and practice-based initiatives that align Maastricht UMC+ with the Green Deal's objectives. Our work is strongly linked to the NFU implementation plan, which aims to mitigate the environmental impact of pharmaceutical use through appropriate prescribing, enhanced therapy adherence, waste reduction, improved wastewater treatment and sustainable procurement practices. As a team, we currently mainly focus on reducing medication waste and targeting the final stage of the chain (Figure 2). Specifically, preventing the emission of pharmaceutical and contrast agent residues through smart interventions and source-based filtration. This focus is operationalised through multiple projects that have recently conducted, started or will commence in 2025.

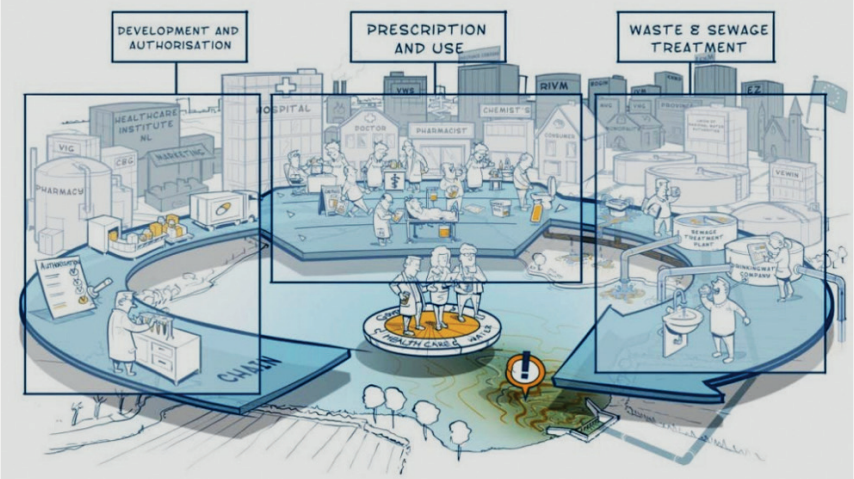

FIGURE 2 Illustration of chain-wide actions proposed in the Green Deal to reduce pharmaceutical residues in water. The figure highlights the roles and responsibilities across the entire chain, from development and authorisation, through prescription and use, to waste and sewage treatment (source: www.medicijnresten.org).

Insights into medication waste in clinical practice

At Maastricht UMC+, we took steps to quantify medication waste by extending measurement activities to more than ten inpatient departments, as well as the Intensive Care Unit and operating rooms. Currently, we are finalising a series of three reproducibility assessments to ensure consistency and validity of medication spillage numbers across departments. These activities are aligned with the national research protocol (NFU) on medication waste and form the foundation for a comprehensive, institution-wide analysis. Our goal is to deliver a full integrated report on medication waste at Maastricht UMC+ by the end of 2025. This will not only inform local strategies for reduction, but also

serve as the basis for scientific publications that contribute to the broader understanding of medication waste and its environmental and operational impact in hospital settings.

Reducing contrast agent emissions through patient-engaged source separation

Maastricht UMC+ recently finalised a prospective multicentre study (2024) investigating the use of urine-collection bags (UCBs) as a low-threshold intervention to reduce the release of contrast agents into (hospital) wastewater. Conducted in collaboration with Laurentius Hospital (Roermond), and *Waterschap Limburg* (Figure 3), this study brought together expertise from clinical radiology and water management. The manuscript has been submitted for publication and provides insights for reducing environmentally persistent contrast agents in hospital effluent. The findings strengthen the evidence base for source-separation measures and may contribute to national discussions on the feasibility and impact of specific hospital-based emission reduction strategies. Based on our research, we believe that in addition to distributing urine bags, on-site collection of post-contrast urine using specialised toilet systems, or other source-based filtration methods, could be a promising approach.

FIGURE 3 Towards a Cleaner Meuse. Within the *Schone Maaswaterketen* initiative, Water Authority Limburg collaborates with partners to improve the Meuse's water quality by reducing pharmaceutical residues and organic micropollutants from wastewater. In cooperation with *Waterschapsbedrijf Limburg*, Maastricht UMC+, and UM, efforts focus on minimising the release of pharmaceuticals and industrial substances into the environment (https://youtu.be/RGNahPAOFmM?si=VnnRf3M1jdY5wBYe).

Innovative treatment strategies for hospital wastewater: *Decentraal en UVectief*

We participate in the national TKI (Top Consortia for Knowledge and Innovation) project *Decentraal en UVectief*, which investigates new technologies for decentralised removal of hospital-specific pharmaceuticals and contrast agents. This project brings together a diverse consortium of stakeholders including KWR Water Research Institute, PureBlue, Royal HaskoningDHV , *Waterschap Limburg* and Maastricht UMC+. In the project two new patented, biologically activated filtration techniques, in combination with and advanced oxidation (UV/H_2O_2) step, are compared in their efficacy to reduce the emission of a set of selected medicines frequently used in the hospital. Maastricht UMC+ provides not only clinical context and (part of the) analytical expertise, but also site-specific wastewater samples and inoculum from hospital sewer systems. Laboratory experiments began in early 2025, followed by a pilot installation at Maastricht UMC+ later this year, to assess real-world effectiveness.

European partnership on sustainable hospital wastewater solutions

Maastricht UMC+ is a key partner in the Horizon Europe-funded THERESA PCP project, a multinational initiative aimed at developing integrated, cost-effective, and environmentally sustainable technologies for on-site treatment of hospital wastewater. The project addresses persistent pharmaceutical pollutants, including antibiotics, cytostatic drugs and contrast agents. The consortium includes 16 organisations from across Europe, ranging from hospitals and universities to NGOs and legal procurement experts. In this context, Maastricht UMC+ uniquely joins a cross-disciplinary team and plays an important role in validating technologies in real clinical settings. The collaboration reflects a multidisciplinary approach to sustainability, connecting healthcare practice with environmental research, technology development, and policy considerations.

Towards 2030: Greening clinical care

Together, we aim to implement effective measures well ahead of 2030, not only to meet policy goals, but to ensure environmentally responsible healthcare. Given the complexity of the issue, close collaboration across the entire water chain, including pharmaceutical manufacturers and organisations responsible for water quality, is essential (*see* medicijnresten.org *for more context*).

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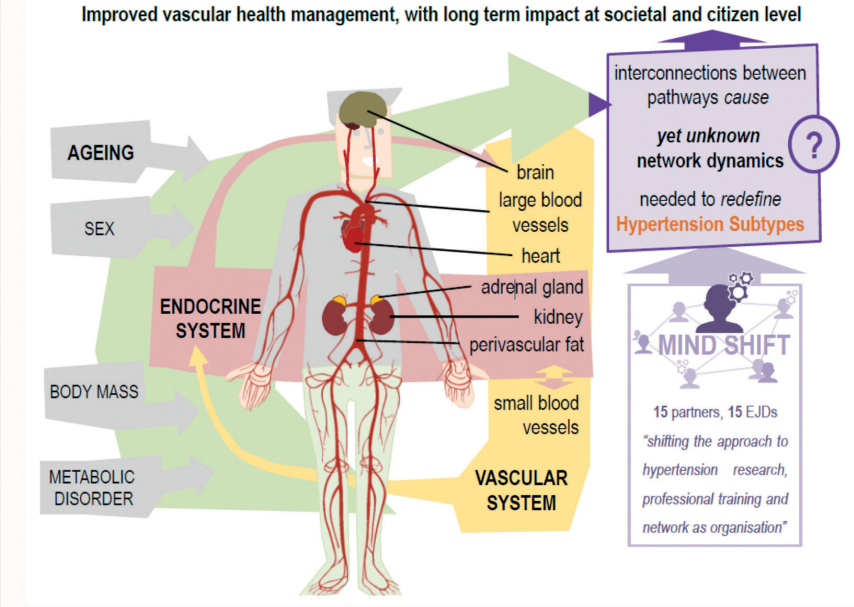
14 Hypertension ... isn't that an issue resolved?

Dr Koen Reesink, Department of Biomedical Engineering

Clearly, the question expresses popular notions around high blood pressure, its treatment, and - most elusively - its underlying mechanisms. This called for a real *shift of mind*!

What is MINDSHIFT?

The MINDSHIFT Innovative Training Network (ITN) is a Marie Skłodowska-Curie European Joint Doctorate (2021-2025) project, commissioned by former CARIM director Em. Prof. Thomas Unger, led by Dr.ir. Koen Reesink (Associate Professor of Biomedical Engineering) and managed by Tara de Koster.



The CARIM-led initiative and network set out to decipher the dynamic crosstalk between vascular and endocrine pathways in hypertension – the leading 'silent killer' behind cardiovascular disease. Recognising hypertension as a systems disorder, MINDSHIFT adopted a network view and approach that blended molecular biology, clinical medicine, bioinformatics, and engineering.

Quoting MINDSHIFT's Executive Coordinator Koen Reesink: "*Hypertension is a networked disease: its parts may not be diseased, but their integrated performance ís. Hence, a network approach to research is essential to develop and integrate (new) knowledge!*"

Fifteen Early-Stage Researchers (ESRs) pursued individual projects while following a seven-phase doctoral framework (see Societal impact below). A dedicated development track, delivered by The Recess College, added action-learning groups, reflective practice and entrepreneurial coaching, ensuring every ESR graduated with both scientific depth and high-level transferable skills. Collaboration ran day-to-day through digital workspaces, themed webinars and twice-yearly residential schools.

Who is involved?

MINDSHIFT is coordinated by CARIM, Maastricht University, and united 15 partners across nine European countries:

- Six host universities – Maastricht University/CARIM (NL), University of Glasgow (UK), Université de Paris Cité, University of Padua (IT), Universidad Autonóma de Madrid and Universidad Complutense de Madrid (ES) – each awarding doctorates and jointly conferring double degrees.
- Nine non-academic organisations – from pharma and med-tech firms to policy and patient-advocacy bodies – provided secondments, industry mentors and applied-research settings.

This academic–industry ecosystem exposed ESRs to basic-science labs, clinical cohorts and commercial innovation pipelines.

Users and collaborations

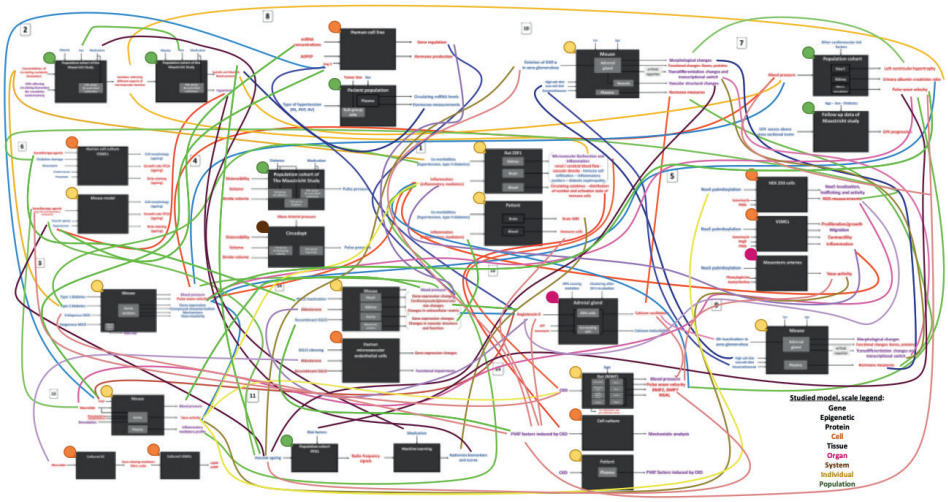
MINDSHIFT functioned as an open node within the wider hypertension community. Notable links included:

- Laboratory collaborations among the six core universities;
- Three EU COST Actions – ENSAT-HT, ADMIRE and VascAgeNet';
- Strategic partnerships with the International Society of Hypertension and the European Society of Hypertension, which helped move findings into guidelines and conference platforms;
- These relationships ensured that discoveries travelled quickly from bench to bedside to policy, including the European Commission (see below).

Scientific quality

By May 2025, the consortium had produced 29 peer-reviewed publications, including field-shaping reviews and guideline contributions, in journals such as Nature Medicine, Nature Communications, Journal of Hypertension and Hypertension. Cross-institution author lists underscored the network's integrative ethos.

MINDSHIFT was particularly dedicated to creating a framework for the mechanistic integration of knowledge, mobilising the collective creative capacity of all project teams – this illustration shows 80+ mechanistic links between projects and studies, and an example of feedback:



"It was a creative activity because it reinforces thinking about possible connections that we did not think about before."

The final EU project report was submitted May 2025, documenting:

- Two doctoral defences completed and the remaining ESRs progressing toward double doctorates in 2025-2026.
- Multiple high-impact conference presentations, patent disclosures under review and invited contributions to European hypertension position statements.

Societal impact

A highly innovative approach in MINDSHIFT was to connect social research on supervision in science networks to the professional development of the PhD candidates and the network as a whole. The social research objective, approach and findings have been summarised in the report 'The relationship dynamics of supervision in science: a social research case study from MINDSHIFT-ITN', with key points:

- Doctoral excellence accelerates when the growth of people is treated as rigorously as the growth of data. Embedding The Recess College-led development track beside the science created a live laboratory for mentoring practice. A codified seven-phase supervision map (recruitment, induction, skill transfer, independence, thesis writing, publication, career planning) helps to surface hidden expectations and shorten mid-term thesis delays. Facilitated action-learning sets and reflection sessions considerably mitigated 'self-reported' overwhelm among the 15 ESRs, while boosting cross-institution authorship.
- Triadic negotiation among ESRs, academic supervisors, and industry mentors, conducted before secondments, aligned objectives and lifted the proportion of placements meeting learning targets substantially. Cross-disciplinary 'lab-pairing' in vascular and endocrine science built a shared vocabulary quickly that joint papers appeared earlier than expected.

- By the final year every ESR chaired at least half of their supervisory meetings, signalling a shift from dependency to strategic self-direction. MINDSHIFT therefore demonstrates that explicit relational design, emotional literacy, and negotiated industry engagement are not 'soft' extras but hard prerequisites for sustainable, high-impact doctoral ecosystems.

Benefits to CARIM already well-credited PhD track support are currently discussed with PhD coordinator and the Director/Management Board. Moreover, the European Commission's Research Executive Agency (Marie Curie funding body) and the Directorate General for Education, Youth, Sport and Culture (EAC) have expressed genuine interest in MINDSHIFT's approach to network development, and development meetings are ongoing.

The world-first development track in MINDSHIFT has led to a formal accreditation process and certification for *'Partnership Working in Science Networks'*:


Recess College

CERTIFICATE
OF ACHIEVEMENT

ESR PERSONAL AND PROFESSIONAL DEVELOPMENT PROGRAMME
WITHIN THE MINDSHIFT ITN ON
PARTNERSHIP WORKING IN SCIENCE NETWORKS

proudly presented to

Your name could be here

DIRECTOR AND FOUNDER
THE RECESS COLLEGE

DIRECTOR,
THE ASSOCIATION OF FACILITATORS

Leadership is who you are ... how you make things happen ... and how you make things happen through others

2024

MINDSHIFT outreach delivered measurable health and educational impact:

- 350+ people screened and counselled across three World Hypertension Day events, advancing WHO prevention goals;
- Quarterly clinics turn research into actionable self-care, boosting adherence and lowering readmission risk;
- Hands-on school demos spark STEM interest and narrow gender-socio-economic enrolment gaps;
- Community seminars demystify PhD pathways, raising application intent among underrepresented groups.
- A curated LinkedIn hub (200 members) sustains dialogue among academics, clinicians, industry, and patients.

Taken together, MINDSHIFT established a premier European hub for systemic, translational hypertension research and demonstrated the enduring value of its interdisciplinary, human-centred training model.

15 MegaCardiocyte -Mapping a blood-bone marrow-heart axis to treat heart failure

Prof. Judith Cosemans, Department of Biochemistry
Prof. Rory Koenen, Department of Biochemistry
Prof. Blanche Schroen, Department of Physiology

What is Heart Failure with preserved Ejection Fraction (HFpEF)?

The pump function of the heart is essential for the supply of blood to the organs of our body. The heart itself has its own blood supply to provide for its energetic needs by the action of its coronary vessels and the intramyocardial microvasculature. Cessation of this blood supply, e.g. due to a myocardial infarction (MI) leads to tissue damage, and ultimately to heart failure. Ischemic muscle damage due to MI or coronary disease is the most common cause of heart failure, characterised by a loss of ejection fraction due to poorer contractility of the heart during systole. Yet a further manifestation is heart failure with preserved ejection fraction (HFpEF), which has a multifactorial etiology for example by diabetes or hypertension and is characterised by a loss of cardiac function due to impaired diastolic function.

Despite impressive advancements in the treatment of ischemic heart failure, HFpEF affects an equally large group of patients and has no available treatment. Instead of the large vessels being affected, a hallmark of myocardial infarction, in HFpEF the smallest vessels are dysfunctional. There are currently no therapies sufficiently improving the functioning of these small vessels, partly because of unknown biological mechanisms causing their dysfunction.

The MegaCardiocyte Consortium - Who is involved?

The tri-national MegaCardiocyte consortium was formed in 2022, when researchers from CARIM teamed up with colleagues from the Centre for Cardiovascular Science, University of Edinburgh, UK (PI Mairi Brittan) and the Ludwig-Maximilians-University of Munich (LMU), Germany (PI Tobias Petzold). Funded by the BHF-DZHK-DHF International Cardiovascular Research Partnership Award, MegaCardiocyte proposes that blood platelets, normally responsible for clotting upon injury, are affected and drive small vessel dysfunction and heart failure. A team of international junior and senior researchers (Figure 1) is currently working to demonstrate that this is indeed the case, and to identify novel targets for therapy.

FIGURE 1 MegaCardiocyte members: Maritte Willems, Aarushi Singhal, Tobias Petzold, Sameera Peri, Mairi Brittan, Claudia Schönichen, Rory Koenen, Blanche Schroen, Judith Cosemans (from left) during a progress meeting in December 2024.

Users and collaborations

Local: A collaboration is ongoing with Dr. Vanessa van Empel, Dept. of Cardiology, concerning the recruitment of patients suffering from HFpEF for biomarker and translational research within MegaCardiocyte. In an associated CSC-project, the technical aspects of platelet-endothelial and blood cell-

endothelial communication are optimised by PhD candidate Xin Xin.
National: MegaCardiocyte is associated with the DCVA Cardiorenal consortium RECONNEXT (PIs Prof. Dirk-Jan Duncker and Prof. Marianne Verhaar). A collaboration exists with RECONNEXT members Dr Lily Jakulj and Micky Karsten on the role of intracellular communication of extracellular vesicles (EV)s in patients without and with HFpEF who undergo peritoneal dialysis.
International: The optimisation of a mouse model for HFpEF is done in collaboration with Dr Gabriele Schiattarella, Max Delbrück Center, Berlin, Germany. The optimisation of megakaryocyte culturing from circulating precursors is done in collaboration with Prof. Kathleen Freson, KU Leuven.

Scientific quality - Exploring a novel blood-bone marrow-heart axis

Recent studies show that platelets play a crucial role in maintaining the health of blood vessels, by monitoring the vessel wall for damage, repairing breaches, and controlling inflammation. Platelets also facilitate the formation of new blood vessels.

During metabolic inflammation platelets have impaired functions, which may ultimately be linked to loss of blood vessel density and contributing to progression of HFpEF. Although platelets are vital for sealing gaps in the vascular endothelium, they can also cause dysfunction of the endothelial cells lining the blood vessels, due to their inflammatory payload.

Platelets are produced by so-called megakaryocytes, primarily in the bone marrow. Research from the group of Prof. Tobias Petzold (PI, DZHK-partner) has shown that during inflammation and MI, neutrophils migrate from the blood to the bone marrow to accelerate platelet production by exerting direct force on the megakaryocytes, thereby 'plucking' the platelets from their parent cells [1]. Platelets that are released by the action of neutrophils may have functions that are skewed towards promoting inflammation rather than towards hemostasis.

Research from the labs of Prof. Judith Cosemans and Prof. Rory Koenen has shown that EVs released by platelets can influence vascular function [2]. Platelets and blood vessel cells are always in close contact and interact in many ways [3,4]. Additionally, platelets act like "information sponges," absorbing and sending messages to and from blood and vessel cells. Therefore, platelets might be more important in the development of blood vessel dysfunction and HFpEF than previously thought [5]. Preliminary research from the lab of Prof. Blanche Schroen has identified candidate noncoding RNAs that may play a role in the platelet-microvessel information exchange. The dynamics of cardiac microvessels during HFpEF and the role of platelets therein will be investigated in genetically modified mice supporting lineage tracing of fluorescent cells (PI, BHF-partner) [6].

The central hypothesis in MegaCardiocyte is that a systemic inflammatory state during metabolic or cardiac disease dynamically influences the production of platelets in the bone marrow, leading to circulating platelets with altered functions. These altered platelets, in turn, affect the functions of the cells lining the small blood vessels, contributing to HFpEF (Figure 2). The project consists of 3 work packages.

- WP1 - Characterise the role of platelets in the function of the cardiac microvasculature during the development of HFpEF.
- WP2 - Determine the influence of systemic inflammation, including neutrophil functions, on platelet production in the bone marrow and on the characteristics and functions of the generated platelets.
- WP3 - Establish a functional connection between altered platelet function and dysfunction of the cells lining the blood vessels during HFpEF, and validate potential therapeutic targets.

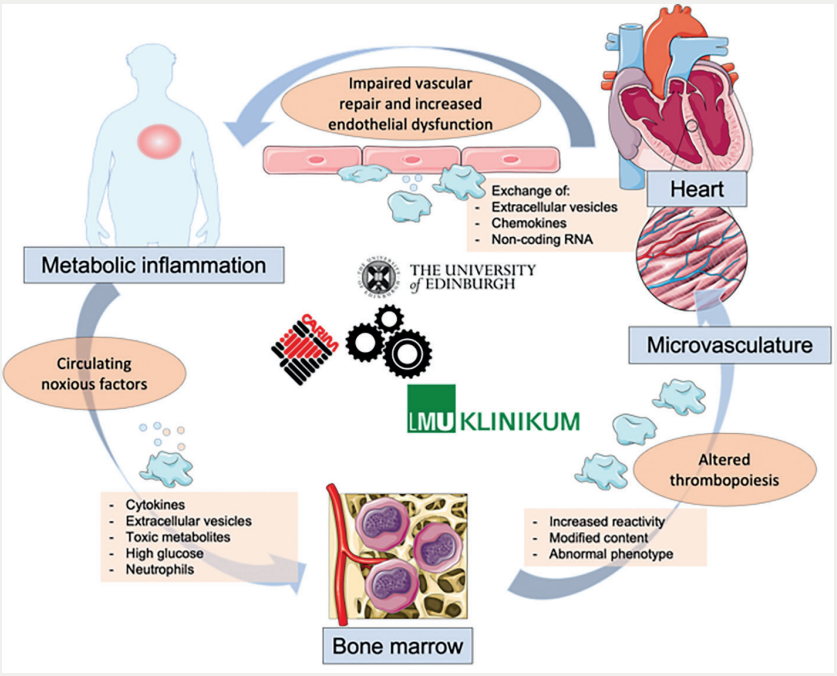


FIGURE 2 Schematic outline of the project hypothesis

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