CARIM MIDTERM REVIEW

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REVIEW

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Case studies

Cardiovascular Research Institute Maastricht

Maastricht UMC+

Maastricht University

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1 MR CLEAN The endovascular treatment of acute ischemic stroke

Prof. Robert van Oostenbrugge and Dr Julie Staals, Department of Neurology
Prof. Wim van Zwam, Department of Radiology

What is acute ischemic stroke and endovascular treatment?

Stroke is one of the major causes of vascular death, and the main cause of dependency in elderly in the western world. For ischemic stroke, caused by vessel occlusion, opening the occluded vessel as fast as possible is of utmost importance to limit irreversible damage to brain tissue, thereby improving the chances of recovery for the patient. *Time is brain*! Two beneficial treatment options are available to achieve vessel recanalisation: Intravenous thrombolysis and endovascular treatment (EVT). Intravenous thrombolysis is the intravenous administration of alteplase which dissolves blood clots. EVT is relatively new and involves placing a catheter into the occluded brain artery and removing the clot. It induced a fast developing clinical research area in which CARIM researchers are playing an active and pioneering role.

MR CLEAN

Up to 2015, it remained unproven whether EVT was beneficial for patients with acute ischemic stroke. MR CLEAN was a multicentre randomised clinical trial of EVT for acute ischemic stroke of the anterior brain circulation in the Netherlands, coordinated by Maastricht UMC+, Erasmus Medical Center (Rotterdam) and the Academic Medical Center (Amsterdam). The results were published in NEJM in 2015: it demonstrated significantly improved clinical outcome for endovascular treated patients. The results were confirmed by five other international trials. After that, EVT was established in the Dutch healthcare system very fast. To monitor the implementation, effect and safety of EVT in daily practice in the Netherlands, all EVT treated patients were included in the national MR CLEAN Registry from 2015 to 2018.

Who is involved?

The success of MR CLEAN and its spin-offs is a joined effort of the Department of Radiology (Prof. Wim van Zwam) and Department of Vascular Neurology (Prof. Robert van Oostenbrugge and Dr Julie Staals). Several PhD candidates successfully finished their PhD thesis and several new PhD candidates have work in progress. Furthermore, blood and thrombus are collected during the EVT procedure for the CONTRAST biobank (Prof. Hugo ten Cate).

Collaborations

CONTRAST consortium

Despite the success of the first MR CLEAN trial, major challenges in the treatment of acute stroke remain. Only few patients with acute ischemic stroke are eligible for EVT and even after successful treatment, a large proportion of patients still have a poor outcome. The CONTRAST consortium (Collaboration for New Treatments of Acute Stroke) was set up with the aim to improve the effectiveness and safety of acute treatment for stroke and to increase the number of eligible patients by expanding indications for treatment. CONTRAST is supported by Netherlands Cardiovascular Research Initiative (CVON, an initiative of the Dutch Heart Foundation), by the Brain Foundation Netherlands, and by several industry partners. Within the framework of CONTRAST, several parallel clinical RCTs started in 2017, i.e. MR CLEAN NOIV, MED and LATE.

The Maastricht UMC+ investigators were heavily involved in the preparation of the overall CONTRAST programme, participated in the executive committees of MR CLEAN NOIV and MR CLEAN MED, and are principal coordinating investigators of MR CLEAN LATE.

Scientific quality

MR CLEAN trial and MRCLEAN Registry resulted in over 100 publications. It increased our knowledge about factors influencing and predicting the clinical result and risk of EVT, imaging- and other biomarkers, stroke outcome, and was a source of inspiration for new research questions. The following three '2nd generation' MR CLEAN trials that started in 2017 have all been finished now, and two were published recently in high impact journals: MRCLEAN NOIV showed that leaving out intravenous thrombolysis before EVT was neither superior nor noninferior to thrombolysis treatment before EVT, and these results were published in NEJM 2021. MRCLEAN MED was published in 2022 in the Lancet and added important information to the safety of EVT: it showed that periprocedural administration of aspirin or heparin is not safe nor has beneficial effect on clinical outcome. The third trial, MRCLEAN LATE aims to assess whether EVT is safe and effective for patients in the 'late' time window (more than 6 hours after symptom onset) in a subset of patients selected on imaging criteria. Last patient was recruited in February 2022 and results are expected in second half of 2022. The CARIM team also participated in BASICS trial, a trial of EVT in the posterior circulation, which was published in NEJM 2021.

This successful collaboration over the past years asks for continuation, and a CONTRAST-2 consortium is now in set-up. The baton is passed to the next generation of researchers who are working on ideas for '3rd generation' MR CLEAN trials that will start in 2022/2023.

Societal impact

The positive result of MR CLEAN has led to an enormous growth of EVT in the Netherlands and worldwide. EVT has become standard stroke treatment and guidelines have been adjusted worldwide. Currently, more than 1,500 patients are treated yearly in the Netherlands. Maastricht UMC+ is the intervention centre performing EVT for stroke patients in the Limburg region. (*https://www.doq.nl/intra-arteriele-trombectomie-steeds-beter-door-samenwerking-en-onderzoek/*) We grew from 20 EVTs per year when MR CLEAN was published, to over 175 EVTs in 2021 in Maastricht UMC+. In March 2022, Maastricht UMC+ performed their 1000st EVT. (*https://www.mumc.nl/actueel/nieuws/succesvolle-limburgse-samenwerking-behandeling-beroerte*) Several initiatives to improve the speed and quality of treatment in our regional network are ongoing, such as the Angels audit initiative which is supported by the European Stroke Organisation. (*https://www.angels-initiative.com/angels-community/stories/excellence-duty-optimising-stroke-care-maastricht*)

2 A tale of the RACE trials

Prof. Harry Crijns, Department of Cardiology
Prof. Uli Schotten, Department of Physiology

What are the RACE trails?

The RACE trials is a series of mostly randomised atrial fibrillation (AF) studies, almost exclusively carried out in The Netherlands. These trials have significantly contributed to the progress in health care of patients with AF and resulted in changes the official guidelines. As an example of an ongoing investigation this case study highlights particularly the RACE 9 Observe-AF trial.

RACE 9

The RACE 9 Observe-AF project aims to investigate the effectiveness of a watchful waiting approach compared to routine care for patients with recent-onset symptomatic atrial fibrillation. Until recently, the standard of care for patients with recent-onset AF was early cardioversion. In the latest ESC AF guidelines (as a result of RACE 7), a delayed cardioversion approach within 48 hours has been added to the recommendations. However, considering the often self-terminating and frequently recurrent nature of AF, cardioversion might not be needed at all and rate control medication might be sufficient to bridge the time until spontaneous conversion to sinus rhythm. The RACE 9 Observe-AF trial is a multicenter, prospective, randomised, open label non-inferiority trial comparing a watchful waiting approach (intervention) to routine care (control). The watchful waiting approach consists of symptom reduction through rate control medication and monitoring for 4 weeks until possible spontaneous conversion, whereas routine care consists of either early or delayed cardioversion within 48h. The primary endpoint of this non-inferiority study is the presence of sinus rhythm on the ECG after four weeks. Figure 1 summarizes the design of RACE 9 Observe-AF. Figure 2 shows the participating centres. RACE 9 Observe-AF is supported by a EUR 800k grant from NWO, ZonMW and the Dutch Heart Foundation (*Hart voor Duurzame Zorg,* grant number 104021005).

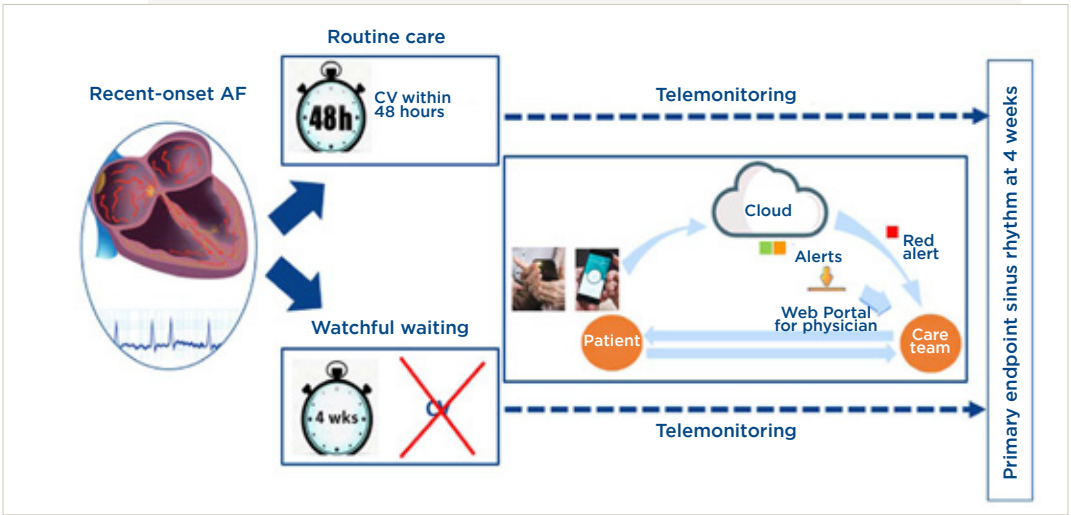

FIGURE 1 An overview of the RACE 9 Observe-AF study

Funding: ZonMw

UMC Groningen
Prof. dr. Isabelle van Gelder (PI)
Prof. dr. Michiel Rienstra (co-PI)
Drs. Colinda van Deutekom (CI)

Zuyderland MC
Dr. Timo Lenderink (PI)
Dr. Pamela Kleikers (CI)
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VieCuri MC
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Dr. Brigitte Essers

Independent expert
Dr. S. (Bas) Bekkers

Data safety monitoring board
Prof. dr. Lucas Boersma
Dr. Sander van Kuijk
Prof. dr. em. Joep Smeets

FIGURE 2 Participating centres in NL in RACE 9

The RACE 9 study involves a patient advisory group to fine-tune the execution and the goals of the study. Furthermore, publications by Maastricht UMC+, the Limburger, NWO/ZonMW and several other institutions focussed on the study, making the study concepts and goals known to the public and other stakeholders.

FIGURE 3 Radcliffe interview: Prof. H. Crijns Dr E. Dudink Drs N. Pluymaekers

Dutch contribution to the field

- The revolutionary notion of 'electrical remodelling' inspired many investigators to develop new clinical concepts including 'the second factor' to complement electrical remodelling, AF progression as an endpoint in clinical trials, and early AF management and early comprehensive upstream therapy to improve prognosis.
- Several significant paradigm shifts in AF treatment happened: rhythm control was offset by rate control in persistent AF, aggressive by lenient rate control in permanent AF, and acute restoration of sinus rhythm by the wait-and-see approach in recent-onset AF. Lately the concept that electrical cardioversion should be considered a diagnostic rather than a therapeutic procedure emerged. The RACE studies also fed the notion that besides stroke, AF patients are even more threatened by heart failure and cardiovascular death.
- Cardiovascular risk scores to steer AF management were developed and swept the world, among which CHA_2DS_2-VASc, HAS-BLED and HATCH scores.
- The RACE consortium strongly advocated nurse-led integrated chronic care for atrial fibrillation and demonstrated its overall effectiveness; nurses steering integrated care perform better than stand-alone doctors.

FIGURE 4 Dutch contribution to the clinical field

Scientific tradition and impact of the RACE trials

The RACE consortium, led from 1998 onward by Prof. Isabelle van Gelder (UMCG) and Prof. Harry Crijns (CARIM, Maastricht UMC+) is now headed by the clinicians Prof. Kevin Vernooy (CARIM, Maastricht UMC+) and Prof. Michiel Rienstra (UMCG), strongly supported by Prof. Uli Schotten (Physiology, CARIM). The Dutch contribution to the clinical field was not only through the RACE trials, but in particular also by the ESC-based EuroHeartSurvey of atrial fibrillation (the 'mother of all AF surveys' around the world), led by Prof. Harry Crijns. [1] The RACE trials challenged several existing clinical concepts and hypotheses. The RACE studies are funded by CVON (Cardiovasculair Nederland), the Dutch Heart Foundation, ZonMw and/or NWO. The RACE studies have led to numerous scientific publication, such as a NEJM paper in 2019, two PhD theses, an award of the Netherlands Society of Cardiology award to Nikki Pluymaekers, the incorporation in ESC Guidelines for AF (Guidelines changing study), and a NEJM editorial by Healey and McIntyre: The RACE to Treat Atrial Fibrillation in the Emergency Department.

Societal impact of the RACE trials

One of the most important impacts of the RACE trials is the major decrease in major adverse cardiovascular and cerebrovascular events and bleeding rates in patients with atrial fibrillation between 2002 and 2010, Figure below, from ref [2], which related to the ground shaking concept consistently propagated by the RACE consortium that AF should be considered a vascular disease rather than an arrhythmia. [2] Over 2.3 years follow-up, RACE (published 2002) [3] had significantly more endpoint events than RACE-II (published 2010) [4], despite baseline cardiovascular risk being comparable and with an even higher intrinsic risk in permanent AF in RACE-II. This time-dependent change was likely due to the more widespread use of anticoagulants in RACE-II with far fewer thromboembolic complications but coming at the cost of (unchanged) bleeding. In addition, the more extensive prescription of renin-angiotensin system blockers in RACE-II also contributed. An overview of the trials' results and subsequent changes is shown in Table 1 on the next page.

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	CONCEPT/HYPOTHESIS	RESULT/CHANGE
RACE	Sinus rhythm better than AF	Rate control not inferior to rhythm control
	Mending the rhythm improves prognosis	No change
	Rhythm control affects sudden death?	No impact
	Sex differences may exist in rate and rhythm control outcomes	Females suffer excess cardiovascular events under rhythm control
	Rhythm controls gives better QoL	No difference with with RC
	Costs lower with RC	Costs proven lower with RC
	RC may be deleterious in patients with CHF	In patients with ild to moderate CHF, RC is not inferior to rhythm control
	Clinical lone AF is not associated with cardiovascular events	Clinical lone is associated with bleeding and thromboembolism
	Underlying comorbidities may affect outcome differently between rate and rhythm control	In hypertensives, pharmacological rhythm control is associated with cardiovascular morbidity/mortality; consider default RC
	Anticoagulation should be bridged around surgery	Extremely low perioperative thromboembolism risk;interruption of warfarin less dangerous than previously thought
	Strict RC is standard of care (comparison of RC in RACE (lenient) and AFFIRM (strict)	Strict RC causes CV events, including excess artificial pacemaker implantations
RACE-II	Strict rate control with resting heart rate in AF recommended as <80bpm	Lenient RC not inferior to strict RC
	Strict RC in AF and HF improves symptoms, CV prognosis and QoL	No beneficial effect of strict RC in permanent AF patients
	Strict RC improves QoL	Stringency of RC does not affect QoL; symptoms, sex, age, underlying disease affect QoL
	Strict RC may fail, wich predisposes to events	Strict RC fails in 33% of patients but is not associated with events; lenient RC is preferred
	Digoxin affects morbidity and mortality	The use of digoxin was not associated with increased morbidity and mortality
RACE3	Targeted 'upstream therapy' for secondary AF prevention unproven	First study to show improved rhythm outcome with upstream therapy
RACE4	Doctors manage AF better than nurses	(Experienced) nurses manage better
RACE-V	AF progression is driven by hypercoagulation	Expected change; anticoagulation prevents AF progressions, not only stroke
	Uncertain role for ILR	EXPECTED: ILR detects temporal types of AF
RACE6CV@H	Electrical cardioversion must be done in-hospital	Expected change:cardioversion can be safely performed at home
RACE7-ACWAS	Early cardioversion better than delayed cardioversion for recent-onset Af	Delayed cardioversion not inferior to early to early cardioversion
RACE8-HF	Cryoballoon PVI improves prognosis in persistent AF and heart failure	Expected change: uncertain, remains to be seen
RACE9	Cardioversion (early or delayed) remains a key procedure in recent-onset AF	Expected change: interventional rhuthm control has no significant role in stable recent-onset AF
	Telemonitoring in management of recent-onset AF has–as yet–no place!	Expected change: telemonitoring prevents needless interventions and keeps patients safely out-of-hospital

3 INTRICARE

Prof. Tilman Hackeng and Prof. Leon Schurgers, Dept. of Biochemistry

What is INTRICARE?

To educate the new leaders in science, a PhD programme from a single academic research group will not suffice anymore. To educate these new leaders in the field of science, education, and impact, dedicated teaching and learning across Europe, with strategic support from high-quality academic and instructional assessments is key.

To achieve this goal, the consortium 'International Network for Training on Risks of vascular Intimal Calcification And roads to Regression of cardiovascular disease' (INTRICARE) was founded as an interdisciplinary and international European consortium involving four leading academic institutions and nine SMEs from five different countries. Within INTRICARE, 15 Early-Stage Researchers (ESRs; PhD candidates) have been trained in a joint/double PhD programme to obtain the skills and knowledge to contribute to the understanding of initiation and progression of the number one cause of death in Europe, cardiovascular disease. In this, the goal was detection, understanding, and translation of novel insights into meaningful clinical interventions for this multi-faceted disease. The INTRICARE training programme has provided the ESRs with multidisciplinary scientific, technical, and commercial skills, while exploiting the specific research expertise and infrastructure of INTRICARE beneficiaries and industrial partners.

INTRICARE is shaped to address the urgent, unmet medical needs concerning cardiovascular disease and the high burden of morbidity and mortality. INTRICARE is guided by academic and industrial demand for a new generation of entrepreneurial scientists that have the skills, expertise, and know-how to expedite our understanding of early cardiovascular disease and translation thereof into concrete clinical interventions for prevention and therapy. Organised around three pillars, notably initiation of cardiovascular disease, associated microcalcification induced vascular remodelling and imaging of microcalcification and vulnerable plaque formation, three front-running research institutes in the field of vascular biology address these needs through training and research. Each of the three themes incorporated both basic and translational science and education, supported by a strong network of academic and non-academic partner organisations.

Who is involved?

INTRICARE is a joint doctorate programme between CARIM (Coordinator), RWTH Aachen and Karolinska Institute and has received funding from the European Union's Horizon 2020 research and innovation programme. In addition, nine partner organisations have been involved providing secondments, training, and guidance of ESRs. The joint doctoral programme has awarded collaborative PhDs by two universities. These joint and double PhD degrees offer talented students the opportunity to spend their time at more than one university, benefiting from parallels between different research specialisms at each institution. The joint PhD candidate is supervised by a primary supervisor of the host university while a secondary supervisor at the secondment university. Within INTRICARE, all ESRs where exposed to industrial training secondments.

FIGURE 1 INTRICARE host institutes

FIGURE 2 INTRICARE partner organisations

This joint doctorate programme requires ESRs to be fully registered at two universities, having to comply with admission requirements and assessment regulations at both universities. Within INTRICARE, we have closely collaborated with the education, legal, and ethics departments to pave the way for joint doctoral PhD theses of our ESRs. At the end of their PhD trajectory, PhD candidates receive a double or joint degree.

INTRICARE was shaped by an international consortium of principal investigators that together with a programme manager and a financial officer paved the way for recruitment of 15 ESRs.

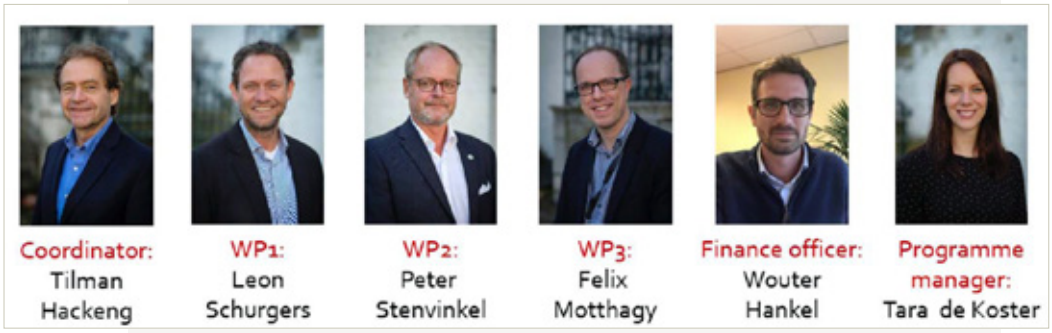


FIGURE 3 INTRICARE coordination team

After a careful recruitment and selection procedure 15 ESR were hired from 12 countries, of which one was enrolled in the European partner programme allowing families to accompany our ESRs to the site of their host institution.

Training

The network-wide training activities consisted of a spectrum of obligatory and optional courses and training opportunities at basic and advanced levels that are organised both around VC pathophysiology, experimental techniques

and general and transferrable skills. This was complemented by local courses organised by the involved institutes. Additionally, the basis of the network-wide training were the secondments at both a partner academic institute (for obtaining the joint PhD), as well as at an industrial site to gain knowledge on transferable skills, valorisation, and market value.

European Joint Doctorate

The European Joint Doctorate was INTRICAREs start up vibe and at the same time a firm challenge to align diverse academic criteria for defending a PhD. INTRICARE paved the way for smoothing inter-academic routing and optimal regulatory designs to accommodate joint and double degrees, which were laid down in several bi-academic formats serving double PhD tracks in the future. INTRICARE leaders served on the evaluation panel of the REA-MSCA-JD networking event in which Maastricht University was among the top rank of successful ITN projects of the Europe.

Scientific quality

At the date of our final annual meeting on 11 November 2021, 44 out of 45 deliverables had been met, the missing 45th being the special issue in the international peer reviewed scientific journal Thrombosis and Haemostasis (special issue) that is currently being realised. In addition, all 21 milestones were reached, with all four annual meetings organised, notwithstanding the challenges of COVID-19 pandemics. We carried out all six planned scientific network wide workshops, but only 28 out of 39 secondments were performed on site because of traveling limitations during the pandemic. However, most of these deficits were sufficiently and satisfactorily countered and solved by flexible and skilled organisation by active participation in online scientific meetings and progress reporting.

More than 30 SCI high impact and open access publications have been published by our ESRs and in total INTRICARE funding has been acknowledged in more than 60 publications. All publications have been published in either Gold or Green Open Access. Six ESRs have successfully defended their PhD theses at two institutes, others are planned or will follow in the upcoming year. Within Maastricht University CARIM has initiated the latest core-facility 'Stem Cell Research University Maastricht' (SCRUM), as a direct spin-off of the academic achievements within INTRICARE.

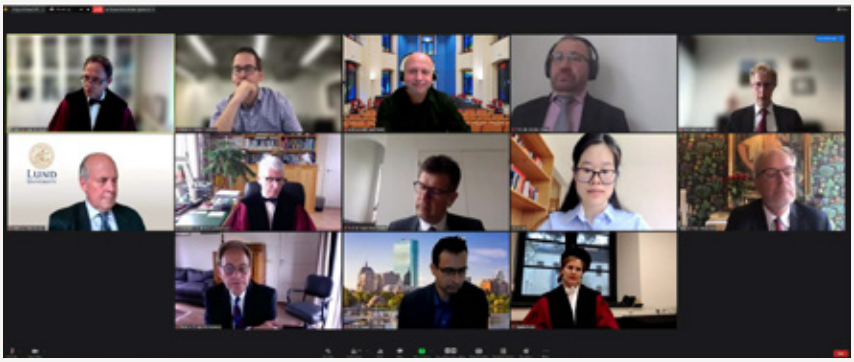
Societal impact

The direct impact of the dissemination activities of INTRICARE include increased awareness of the role of VC in human health and AMI, the roles of CKD and DMT2 in VC and the importance of microcalcification in the development of vascular disease. Dissemination is also critical towards the implementation of actual preventive, diagnostic and/or therapeutic tools based on the INTRICARE research outcomes as to create awareness amongst critical stakeholders and to motivate them further (co-)develop and implement proposed solutions.

In current academics, coaching and guiding are key activities of interdisciplinary research teams and principal investigators to prepare their ESRs for academic or alternative professional careers, and no better medium for that is offered by social gatherings. INTRICARE has provided these occasions in many ways, and often has combined these with the annual courses and meetings. By doing so, a strong bond was created between ESR themselves and with their supervisors, gaining mutual trust and inspiration for follow-up activities and careers.

From our 15 ESRs, six have successfully defended their PhD, six have achieved an academic position, and six have found a position in governmental or private sector. Nine are still preparing for their final defence. One of our highlights was the double PhD defence of Lu Dai, taking place in Maastricht/Stockholm on 6 and 18 May 2021.

Additionally, it is becoming increasingly clear, that in order to tackle global challenges in a targeted manner, a strong network with international partners is required. Building on two successful ITN consortia INTRICARE and CaReSyAn, coordinated from Maastricht and Aachen, respectively, we have recently established a bi-national research institute on Cardiorenal research and named it 'AMICARE; the Aachen-Maastricht Institute for CArdio-REnal disease' as a first European institute focussed on innovation and dedication to the field of cardiovascular and kidney diseases. AMICARE represents a novel joint institute initiated by RWTH Aachen and Maastricht University and is a direct product of a close and successful European ITN cooperation, aiming at expanding ongoing collaboration between researchers, clinicians as well as private partners to accelerate patient-relevant research, education and translation into clinical applications. In this way, we will sustain the generous investment from Europe in this crucial research area and to seed and cultivate this initiative.



4 Heart Failure with preserved Ejection Fraction (HFpEF)

Dr Vanessa van Empel, Dept. 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 no curative treatments exist to date. 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, and contributed to the current diagnostic criteria (doi 10.1002/ejhf.1614 and 10.1002/ejhf.2019).

Microvascular dysfunction

An important aspect of the pathophysiology of HFpEF was attributed to microvascular dysfunction (MVD). Together with Dr Boy Houben (and The Maastricht Study) we are investigating peripheral microvascular function in HFpEF. As part of the CVON SHE predicts we included the analyses of sex differences in these assessments. Also, we are investigating whether coronary and peripheral microvascular function correlate, this is a collaboration with Dr Ed Eringa, and Amsterdam MC.

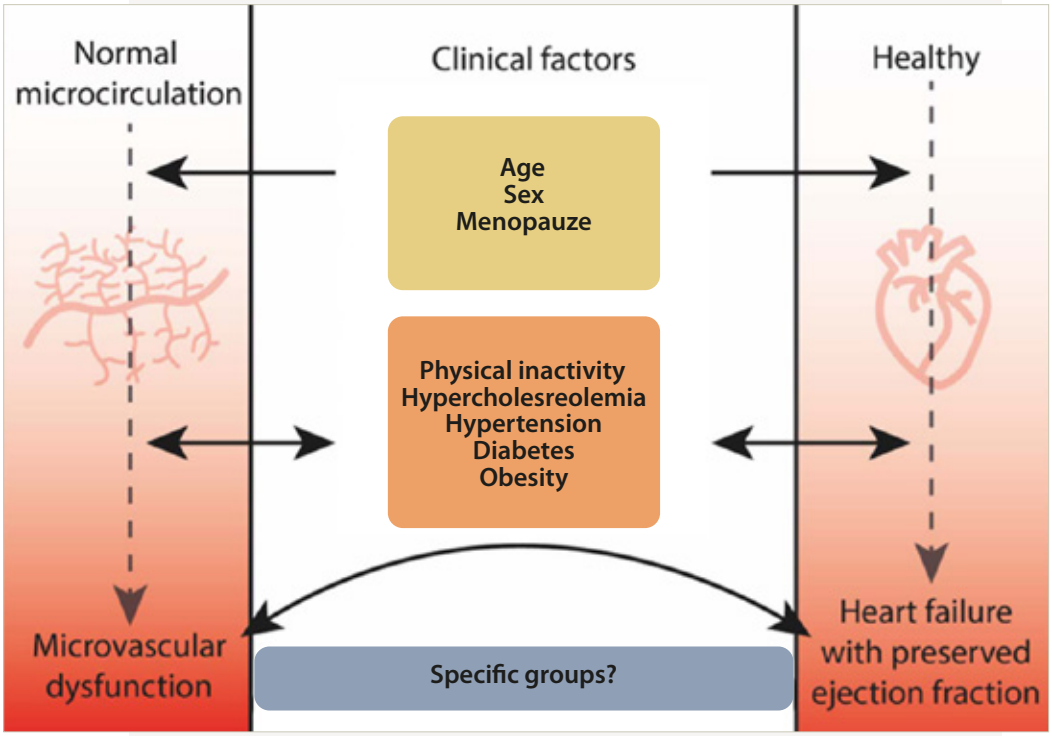


FIGURE 1 MVD in HFpEF, from Weerts et al (doi 10.1016/j.yjmcc.2022.04.001)

Sex differences
Since HFpEF is a disease predominantly present in female, the focus on sex differences is imperative. Microvascular dysfunction has been proposed to be present more often in women, and linked to both MINOCA (myocardial infarction with non-obstructive coronary) and HFpEF. Innovative technology has made assessment of coronary MVD (using invasive catheterisation) more accessible, and with the increase in assessment more insights into the prevalence of this diseases. As part of the DCVA consortium IMPRESS, I collaborate on building a knowledge platform with special focus on microvascular dysfunction and arteries (MINOCA) and HFpEF.

Atrial dysfunction: link between AF and HF?
HFpEF and AF are closely interlinked with shared risk factors, the high AF occurrence in the natural history of HFpEF and the independent contribution of each condition to poor outcomes. Atrial dysfunction seems to be an important shared denominator. Together with Prof. Kevin Vernooy and Prof. Joost Lumens we will evaluate electrical and mechanical atrial dysfunction to assess its role in diagnosis and risk-stratification.

Who is involved?

My group currently counts three PhD candidates, one postdoc and several master students.

FIGURE 2 HFpEF research team at ESC HFA 2022. From left to right Anouk Achten, Jeremy Weerts, Sanne Mourmans, Vanessa van Empel, Arantxa Barandiaran.

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. Carolyn Lam (National Heart Centre Singapore), Prof. Sanjiv Shah (Northwestern, Chicago), Prof. Carsten Tschoepe (Charité, Berlin) and Prof. Anthoni Bayés-Genís (Barcelona, Spain).
We also collaborate with various research groups within Maastricht UMC+. The Maastricht Study (Prof. Coen Stehouwer, Dr Boy Houben) collaborates with regard to microvascular dysfunction. With Prof. Blanche Schroen and Dr Judith Cosemans we evaluate platelet function in HFpEF patients. Together with AF researchers (Prof. Kevin Vernooy and Dr Dominik Linz) and imaging cardiologist (Dr Christian Knackstedt) we analyse atrial dysfunction and strain in HFpEF. The use of circadapt models HFpEF and aids in personalised medicine, an innovative collaboration with Prof. Joost Lumens and Dr Tim van Loon.

Naturally we collaborate nationally, some of the national collaborations are:

- Prof. Walter Paulus, Prof. Bert van Rossum, Dr Joline Beulens, Dr Louis Handoko, Dr Yolande Appelman Cardiology/ Epidemiology&Biostatistics, VU Medical Centre, Amsterdam (Early detection of HFpEF, CVON consortium, impact on sex- and gender sensitive cardiovascular medicine, DCVA consortium IMPRESS);
- Prof. de Boer, UMCG, Groningen (sex differences in HF, CVON consortium);
- Prof. Hester de Ruiter, UMC Utrecht (impact on sex- and gender sensitive cardiovascular medicine, DCVA IMPRESS);
- Prof. Michiel Rienstra, Prof. Dirk Jan van Veldhuisen, Cardiology, UMCG, Groningen (VIP HF study).

Scientific quality

In the last eight years (2014-2022), my group has published numerous papers in high impact journals. I was awarded a CVON grant, as PI of the CVON SHE-PREDICT, and a personal Aspasia grant, both investigating various aspects of sex differences in HFpEF. Furthermore, I am work package leader of the DCVA consortium IMPRESS, which investigates sex differences in microvascular disease, and am national coordinator of the international H2020 consortium CARDIATEAM, which focusses on characterisation of diabetic cardiomyopathy and HFpEF. I have been an invited speaker at several international conferences, including the ESC congress and ESC HFA congress. I am a member of the ESC working group on coronary pathophysiology and microcirculation.

FIGURE 3 Loopt met je dokter. Vanessa van Empel with her team at the annual fund raiser organised by the Health Foundation Limburg

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 diagnostics in HFpEF for GPs and cardiologist, a.o. with CVGK: https://cvgk.nl/2021/04/07/diagnostiek-van-hfpef/
- 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: congress I organized in Maastricht, on sex and gender differences in cardiovascular medicine for >150 participants. November 2016, Maastricht, NL.
- Fundraiser *'Loop met je dokter'*: team captain of fundraiser organised by the Limburg Health Organization. September 2017-2021, yearly event
- Interview in magazine Chapeau: national magazine, interview on the Maastricht HFpEF clinic and our HF research, July 2016.
- Invited speaker at RESCAR patient congress: presentation of the unique Maastricht HFpEF clinic and the data of our HFpEF research, June 2016.
- Invited speaker at various regional symposia.

5 Queen of Hearts

Dr Chahinda Ghossein-Doha, Dept. of Cardiology

Health care problem

As a cardiologist in training, embedded in both the departments of Cardiology and Gynaecology, I aim to position pregnancy as a sex-specific cardiovascular stress test that will, if valued appropriately, change the remote cardiovascular health prognosis of women in the future. My PhD thesis (2015) focussed on cardiac physiological and pathophysiological adaptations during and after preeclamptic pregnancy. In my thesis, I showed that 25% of women have subclinical heart failure after preeclampsia. This finding resulted in a better recognition of subclinical cardiovascular disease after preeclampsia and provided scientific arguments to the National Queen of Hearts consortium on early detection of heart failure after complicated pregnancy.

In 10% of all pregnancies, women develop serious vascular complications which affect both mother and child. These complications include pregnancy induced hypertension, preeclampsia (PE) and peripartum cardiomyopathy. PE is clinically defined as de novo hypertension along with end-organ disease after 20 weeks of gestation and is characterized by endothelial dysfunction with superimposed circulatory, metabolic and inflammatory abnormalities. In the short term, PE is associated with serious fetal (poor growth, preterm birth and fetal death) and maternal complications (pulmonary edema, stroke, acute respiratory distress syndrome, acute renal failure, seizures and death). Unfortunately, the impact of pregnancy complications does not resolve after delivery. In the long term, PE is associated with increased cardiovascular risk including ischemic heart disease, cerebrovascular accidents, arrhythmias and heart failure. Moreover, about 25% of women suffer from psychological difficulties. Clinicians, society and employers are often unaware of the long-term impact.

Scientific studies

In the last year of my PhD, Prof. Marc Spaanderman and I initiated with our team the Queen of Hearts study to investigate the physical, physiological and cognitive impact of pregnancy complications on women's health. The first patient was included in December 2015 and now we included already 1700 women. A follow up to these women now seven years later is being prepared and this cross sectional cohort study will continue as a prospective cohort study to identify early markers for subclinical cardiac, vascular and cerebral disease. Beside the core cohort, several studies, linked to Queen of Hearts, are also initiated.

The **DECONNECT (DEcreased Cognitive functiON, NEurovascular CorrelaTes)** study investigates the link between cognitive problems after preeclampsia on the one hand and cardiac and cerebral microvessel disease on the other hand. This study is a collaboration between Cardiology, Gynaecology, Scannexus and the Department of Radiology and Nuclear Medicine. I received the `Kootstra Talent Fellowship` for postdocs and the `pioneer and stimuleringsfund` from FHML and SWOL. In a subset of women from the Queen of Hearts cohort, we perform cognitive tests, cardiac MRI and cerebral 7 tesla MRI scans to assess the blood brain barrier and connectome. Last year, one of our PhD candidates, Lisanne Canjels, defended her thesis showing that women after preeclampsia have blood brain disruption and inefficient connectome function. In the coming `LINDA` edition, this study is being covered. I was also interviewed for a podcast for BNR radio due to this study.

The **PEARLS study** (PlacEntal Acute atherosis RefLecting Subclincal atherosclerosis) investigates whether atheroma in the spiral arteries of the placenta reflects systemic atherosclerosis. To this end, I collected placentas from women through the Netherlands and invited them to undergo a cardiovascular screening including CT angiography one year after birth. For this study I received the 'Innovation Fund' from the Dutch Heart Foundation where my crowdfunding journey started. This study has gained the most media attention and is largely funded by crowdfunding (see list at the end of this document).

With the **EVA** (Early Vascular Adjustment) trial we showed that tailored early blood pressure treatment in high risk women decreases the risk for a recurrent preeclampsia with 50% (REF). One of our PhD candidates, Eva Mulders, defended her thesis last year with an international defence committee.

With the **CROWN study**, we collaborate with the '*bevolkingsonderzoek*' and Biomedical Engineering Department of Radboud Nijmegen and Zuyderland Medical Center. We investigate whether vascular calcification, seen on mammograms, performed for breast cancer screening, can be used as an early screening for coronary calcification. I received from Bayer over EUR 70k to perform this study. Currently, 1,000 mammograms have been investigated and we are developing a method based on artificial intelligence to.

The **TREASURE** trial aims at investigating whether early blood pressure treatment with angiotensine converting enzyme (ACE) inhibitors reverse abnormal left ventricular remodelling after preeclampsia. For this study, one of my PhD candidates, Zenab Mohseni, has been awarded the Mosaic fund from ZonMw this year.

Who is involved?

Queen of Hearts is embedded in the specialised '*Transmuraal Vrouwen Dagcentrum*', an infrastructure combining women specific clinical care, research and education and is capable in efficiently running predefined study protocols on study as well as clinical cohorts. The inclusion rate for the QoH study is 576 women each year and keeps on increasing. My research line builds upon a strong collaboration of a multidisciplinary and translational team across the different FHML schools (CARIM, GROW, CAPRHI, MHeNS) with experts on obstetric care (Prof. Marc Spaanderman), cardiology (Prof. Arnoud van 't Hof, Prof. Hans-Peter Brunner-La Rocca, Dr Christian Knackstedt), experimental cardiology (Prof. Leon de Windt), radiology and nuclear medicine (Dr S. Gerritsen, Prof. Eline Kooi, Dr Casper Mihl), cerebral imaging (Prof. Walter Backes), epidemiology (Dr S. van Kuijk), and neuropsychology (Dr V. van de Ven and Dr P. Hurks).

Users and collaborations

We interact closely with the 'the patient panel' of the Queen of Hearts Foundation. They participate in our meetings and by evaluating our information documents in order to make them understandable. This group consists of women with a complicated pregnancy in the history. Many of these women participated already in the Queen of hearts program and are aware of the measurements and the setting in which this study will be performed. In the following link a report of that day written by the patient organization can be found http://hartvoorhellp.nl/samenvatting-lotgenotendag-maastricht-18-februari-2017/. We provided all women with a platform on social media with over 1,000 followers to share with us their needs so that we can adapt our research to their priorities. Moreover, we shared our ongoing research and gave them the possibility to provide us with feedback. Only mentioning the plans to enrol the study led to overwhelming responses of women that wanted to be included in the study. Our profiles are being featured by influencers and bloggers (Mamma Lotje, Katja Schuurman/Return to sender and Eva Jinek).

Scientific quality

After my PhD, I continued my research with a joined appointment at the departments of Gynaecology and Cardiology to continue building bridges between both fields to improve women's cardiovascular health. I believe that an interdisciplinary approach is essential to reduce the burden of cardiovascular disease in women. I successfully obtained several personal grants to facilitate my research positions from the start of my PhD trajectory until now, including two times a Kootstra Talent Fellowship (2014 and 2017) and the Mosaic NWO grant (2016). For the Queen of Hearts study we received almost one million euros from the DHF in 2014.

My scientific output and active participation in international conferences gained international standing and in 2016, I was appointed Guest Editor of a special issue on maternal hemodynamics for the 'Journal of Ultrasound in Obstetrics' (ranked third in Maternal Health Journals). Currently, I am Editor of a special issue in 'Frontiers in Cardiovascular Medicine'. Moreover, in 2021, I was appointed as a visiting professor at the Brescia University, Italy. I was also invited to join as the youngest member the `International society for maternal hemodynamics`, a '*denktank*' group consisting of leading researchers on maternal cardiovascular physiology. As a member, I have been invited to lecture and represent our working group several times in Toronto (Sinai University), London (Sint Georges, Kings College) Cambridge and next month in Oxford University. This year, I organised with my team in Maastricht UMC+ the 4th International Congress on Maternal Hemodynamics from 23 to 25 June, which has been visited by over 200 international experts.

The past two years I supervised as a co-promotor successfully three PhD candidates who defended their thesis on Queen of Hearts topics. Currently, I am supervising eight more PhD candidates. With the team, we have been publishing in high impact cardiovascular journals (JACC, Hypertension, Lancet e-clinical medicine) and top three journals in Maternal health (AJOG and BJOG and UOG). Besides, as an expert on women's health, I was invited to participate in a COVID-19 consortium and to investigate the role of sex in the heterogeneity in the disease course of COVID-19. I initiated a study on the 'Sex-gap in COVID-19 trials' as part of a European collaboration which also resulted in a granted INTERREG application. I particularly provided expertise in the potential biological mechanisms that underlie the gender differences in outcome in COVID-19 patients and. This has led to several scientific publications in (e.clinical medicine, BMJ open). As a work package leader, I also received with a National Consortium a ZonMW grant to study myocardial damage in COVID (DEFENCE study, EUR 800k and as a consortium leader a ZonMw grant to study Long COVID (CORFU study, EUR 586,586). Last year I have also been selected for the Dutch Cardiovascular Alliance Leadership trajectory. Together with two laureates, we work defining the new 'Recognition and Rewards' in cardiovascular research.

Societal impact

In 2020, I initiated the Queen of Hearts Foundation. Our mission is on the one hand to organise crowdfunding activities to support related studies and on the other hand to create awareness on the impact of pregnancy complications on women. As a chair, I want to translate with the foundation board the results of our research back to the people, to get the message across to people. One of the ways of doing that is through music, art and sports. The scientific language is not readily transparent to everyone, so we have to look for other forms of communication. That's how we gain the trust of the people. Because of our scientific activities as well as our societal engagement, we have received widespread media awareness for our research and findings.

- Eva: 'Droom groot is het boek dat ik zelf wil lezen' | Eva Jinek
- Podcast van VPRO en Slow Pony: Geen kleine man - VPRO
- Podcast BNR radio: Het lichaam | Zware bevalling veel meer impact op vrouwenlichaam dan gedacht | BNR Nieuwsradio

- Interview: VrouwenHart interview met Dr. Chahinda Ghossein-Doha: "Mijn ambitie is de vrouwspecifieke cardiovasculaire gezondheid zorg te transformeren van reactief naar proactief" - Vrouwenhart
- Interview Eva Jinek website https://www.evajinek.nl/onderwerpen/artikel/5117346/zwangerschap-complicaties-chahinda-ghossein
- Interview https://l1.nl/avondgasten-22-mei-2017-129143/
- Interview https://l1.nl/de-stemming-16-juni-2019-150326/
- Article: http://www.lindanieuws.nl/nieuws/grotere-kans-op-hartfalen-na-zwangerschapsvergiftiging/
- Article: "http://www.nu.nl/gezondheid/4034888/zwangerschapsvergiftiging-belangrijke-voorspeller-van-hartfalen.html
- Interview: '*Mijn ontdekking*'; in *Gezond Idee Magazine* 3, January 2015
- http://www.randalesser.nl/mkw_upload/gezond%20idee/6870_GezondIdee_herfst_2015_H.pdf
- Interview: '*Pak van mijn Hart*'; in *Dagblad de Limburger* http://www.queen-of-hearts.eu/wp-content/uploads/2014/11/DDL-artikel.pdf

Together with the foundation board, I organise concerts, charity gala and last year a vernissage during the Dutch Design week about pregnancy complications. Moreover, I regularly co-organise patient information days and develop information brochures and information posters. I am particularly proud of the publication of my book 'Queen of Hearts: *De Kracht van Kwetsbaarheid*'. I initiated this book to raise awareness on the impact of pregnancy complications on women and I was invited to launch its publication in the talkshow 'Jinek-RTL'. In this book, stories of women's personal experiences are presented.

With each activity, many new people join Queen of Hearts. They recognise themselves in the stories we publish, from their own experience and/or from their professional practice, and so they try to contribute to our mission. Many of them say that for the first time in years they understand wat has happened to them, and they no longer feel alone. They realise how many women are confronted with this, and want to dedicate themselves to the cause. And so it's become more of a movement rather than just a research programme. I'm at least as proud of that as of the funds we raise. Maybe even more so, as it means something permanent for a whole generation of women.

This is also how artist Kiki van Eijk got involved in the foundation, after having seen my performance in Eva Jinek's popular talkshow on Dutch TV. Through her own expertise, art and design, Kiki van Eijk felt a personal necessity to collaborate with the campaign in order to improve the availability of information about pregnancy complications and to increase awareness about Queen of Hearts. Like Jinek, Van Eijk had had preeclampsia herself, and during the 2021 Dutch Design Week she created a large art installation centring on a formalin-preserved placenta and the stories of women who had experienced complications of pregnancy. During the Dutch Design Week, visitors experienced an interactive exhibition showcasing the sensitivity of pregnancy complications in a poetic manner. She presents three stages of the impact of pregnancy complications in three subsequent rooms, whereby the placenta of a woman who recently gave birth was a central feature. In addition, she produced a silk-screen print called 'Fragile' in an edition of 200 copies which are for sale, with part of the revenues going to the foundation. Eva Jinek was presented with the first copy last year. Besides, `Fragile` has been selected as an artwork to be presented at `HeaRT` gallery of the European society of cardiology (ESC) conference in august 2022'.

Besides music and art, sport is a very effective method to motivate people and develops a team spirit. In 2021 and 2022, we raised money for research by entering with several teams in the Iron Man sports event and next year we aim at doubling our teams. For the above mentioned research, translation to the public and societal participation, I am very honoured to have been nominated for *Topvrouwen Limburg* 2022. *Topvrouwen Limburg* is a foundation that honours and stimulated female leadership.

Clinical guidelines and policy reports
I am regularly invited to provide a state of the art update on this matter for high impact journals (JACC 2017, UOG 2017, Hypertension 2022).

- ***Ghossein-Doha C,*** M. Hooijschuur, Spaanderman M. Preeclampsia: A twilight zone between health and cardiovascular disease? JACC 2018 jul3;72(1):12-16

- ***Ghossein-Doha C,*** Khalil A, Lees C; Title: Maternal Hemodynamics: a 2017 update; Ultrasound in Obstet Gynecol 2017;49:10-14.

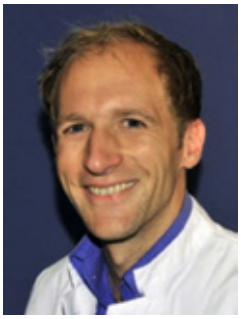
- Veronica Giorgione, Gwyneth Jansen, Jamie Kitt, ***Chahinda Ghossein-Doha,*** Paul Leeson, Basky Thilagalathan. Peripartum and Long-Term Maternal Cardiovascular Health After Preeclampsia; Hypertension; DOI: 10.1161/HYPERTENSIONAHA.122.18730

My active participation in COVID research, showing the gender gap, has lead to being cited by name and reference in a debate in the 'Tweede Kamer'. After this debate, the minister promised to provide extra money for research in women specific subjects. Moreover, I co-worked and co-wrote the national Post COVID clinical guideline and the cardiac health care pathway for the nederlandse vereniging voor cardiologie (NVVC). My participation in this field has also gained widespread media attention and has been features in the scientific magazine `Science`.

Other media attention:
- Interview Kortademigheid, angst en slaapproblemen: uitgebreid onderzoek naar long covid is hard nodig | Nederlands Dagblad
- Interview Dr. Chahinda Ghossein-Doha over onderzoek naar de bijwerkingen na een covid-vaccinatie - Vrouwenhart
- Interview Farmaceuten keken niet naar bijeffecten corona-vaccins op vrouwen - Investico (platform-investico.nl)
- Interview Eén prik voor iedereen? – De Groene Amsterdammer Hoe vrouwen vergeten werden in het Covid-19-onderzoek | Trouw
- Live Interview Radio Starts at 4:55. https://eenvandaag.avrotros.nl/item/eenvandaag-07-04-2021/
- Live interview on Radio 1 Journaal about gender differences in side effects of the COVID-19 vaccines, item start on 5:15. https://www.nporadio1.nl/nos-radio-1-journaal
- Interview Aios Ghossein: 'Houd bij COVID-19-studies rekening met genderverschillen' - DOQ
- *NOS, NPO 2 NOS Radio1 Journaal*, between 7 and 8 AM, starts 0:48:5. https://www.nporadio1.nl/gemist/2020-12-12

6 The TeleCheck-AF project

Dr Dominik Linz and Drs Astrid Hermans, Dept. of Cardiology



Background

Under normal circumstances, patients with atrial fibrillation (AF) receive a face-to-face consultation in the Maastricht UMC+ outpatient clinic and an electrocardiogram (ECG) is taken to make heart rate and rhythm information available for the assessment of our patient [1]. However, during the coronavirus disease 2019 (COVID-19) pandemic face-to-face outpatient appointments were rapidly converted into teleconsultations, to protect our AF patients from being infected with COVID-19. This means that instead of seeing our patients with ECG information, we were calling them without any clinical information about heart rate and rhythm, which made decision making about treatment difficult. We realised, that remote monitoring of heart rate and rhythm by means of novel mobile Health (mHealth) technologies provides an opportunity to bring the best standard of care and expertise to the patient rather than the patient having to visit an outpatient clinic [2, 3]. Particularly the photoplethysmography (PPG) technology, which determines blood volume pulse variation in the local arterioles of the fingertip by measuring the amount of reflected light in the built-in camera of commercially available smart phones, experiences a rapid uptake in current clinical practice.

What is TeleCheck-AF?

We started to contact our AF patients one week prior to a scheduled teleconsultation and instructed them to download a photoplethysmography (PPG) smartphone app called FibriCheck® (Conformité Européenne (CE) marked; www.fibricheck.com). The patients were educated and instructed to perform three heart rate and rhythm recordings a day for one week prior to the teleconsultation, and additional measurements in case of symptoms. All recordings were instantly transmitted to a secure cloud system, which was accessible to the physician at the time of the teleconsultation [4]. We called this on-demand mHealth intervention: TeleCheck-AF. TeleCheck-AF incorporates three important components: (i) a structured teleconsultation ('Tele'); (ii) an app-based on-demand heart rate and rhythm monitoring infrastructure ('Check'); and (iii) comprehensive AF management ('AF') (Figure 1) [5].

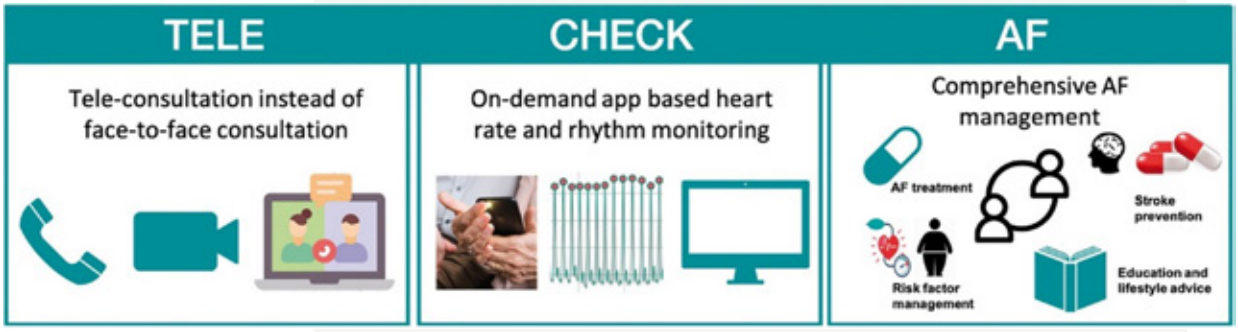


FIGURE 1 TeleCheck-AF steps

Who is involved?

We, Dr Nikki Pluymaekers, Prof. Jeroen Hendriks and Dr Dominik Linz, initially developed the TeleCheck-AF approach and implemented it widely together with our interdisciplinary TeleCheck-AF research team involving physicians, specialised AF-nurses, secretaries who served as case coordinators in the MUMC+ and the developer of the app (FibriCheck, Hasselt). Our PhD candidates, Astrid Hermans, Rachel van der Velden, Dominque Verhaert, Monika Gawalko and Konstanze Betz, are instrumental to analyse the large datasets collected within the TeleCheck-AF project (Figure 2).

National and international collaborations

Currently, the TeleCheck-AF approach is implemented in 41 clinical centres throughout 14 European countries (Figure 2). Important active international collaborations exist with respect to the analysis of TeleCheck-AF with Prof. David Duncker (Hannover, Germany), Dr Martin Manninger (Graz, Austria), Prof. Dhiraj Gupta (Liverpool, UK), Prof. Hein Heidbuchel (Antwerpen, Belgium), Dr Martin Hemels (Arnhem, NL) and Prof. Laurent Pison (Genk, Belgium), which led to several high-profile publications. Additionally, in collaboration with the teams of Prof. Joost Lumens (Biomedical Engineering), Dr Mathias Baumert (The University of Adelaide, Australia) and Dr Jørgen Kanters (The University of Copenhagen, Denmark), we are applying signalling processing and machine learning approaches, to test whether PPG signals incorporate important prognostic features beyond heart rate and rhythm.

FIGURE 2 European centres involved in the TeleCheck-AF project (left). TeleCheck-AF research team members (left) during the European Heart Rhythm Association Conference 2022 in Copenhagen. From left to right: Monika Gawalko, Rachel van der Velden, Astrid Hermans, Konstanze Betz, Dominik Linz, Dominique Verhaert.

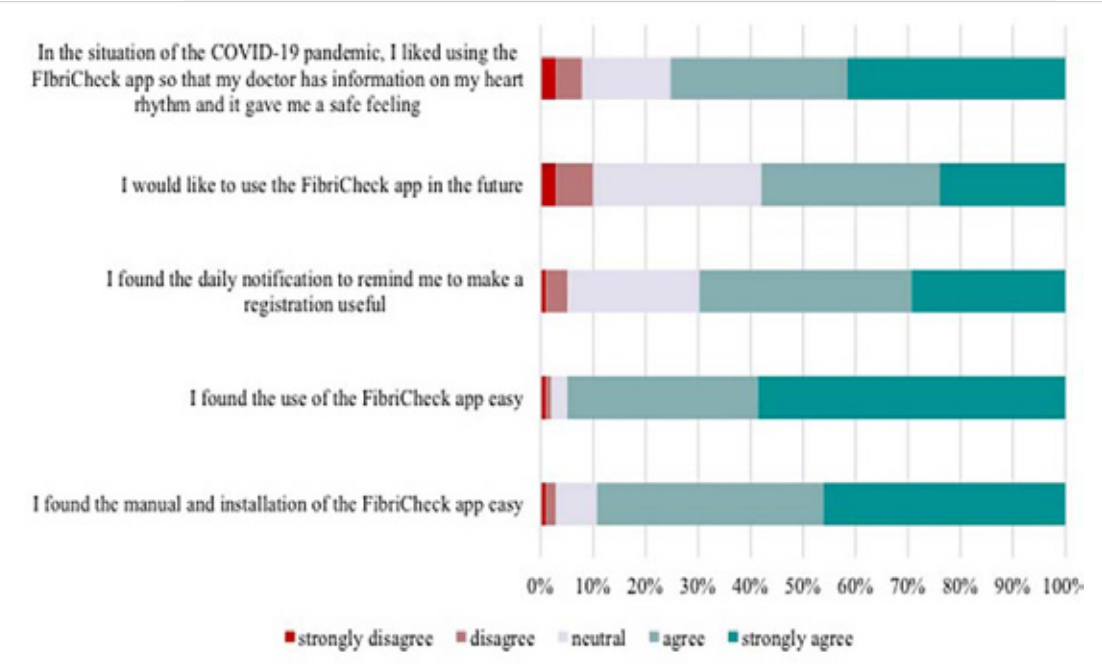
Scientific quality

In the last two years (2020-2022), our research group published several papers as output of the TeleCheck-AF project. Initially, we described the TeleCheck-AF approach in a Standard Operating Procedure manuscript (4) and the TeleCheck-AF project provided new knowledge and awareness about how to use the PPG technology for AF outpatient management, which is now also published in the 'TeleCheck-AF PPG dictionary' [6].

To evaluate mHealth adherence within the TeleCheck-AF project, data from 990 patients were analysed (median age 64 [57-71] years, the oldest patient being 92 years old, 39% female). Motivation was defined as number of days in which the expected number of measurements (≥three/day) were performed per number of days over the entire prescription period. Adherence was defined as number of performed measurements per number of expected measurements over the entire prescription period. The data suggest, that older age is no contraindication for mHealth use in cardiology [7].

To assess centre and patient experiences within the TeleCheck-AF project, we conducted surveys in the majority of the participating centres [8]. The majority (>80%) of centres reported no problems (concerning cloud access, patient compliance or quality of recordings) during the initial implementation of the TeleCheck-AF approach. Of the 850 patients included in the retrospective patient experience analysis, 94% and 89% agreed that the app was easy to use and easy to install, respectively. The app gave patients a sense of safety (74%). More than half of the patients (58%) agreed or strongly agreed that they would like to use the FibriCheck® app in the future. We presented and discussed the results from the TeleCheck-AF project during several webinars and national and international conferences (European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Nederlandse Vereniging voor Cardiologie (NVVC), German Society of Cardiology (DGK)).

Additionally, the TeleCheck-AF project was instrumental in the development of the recent EHRA consensus manuscript 'How to use digital devices to detect and manage arrhythmias: an EHRA practical guide' [9] and the update of the Nice Guidelines (https://www.nice.org.uk/guidance/mtg64).



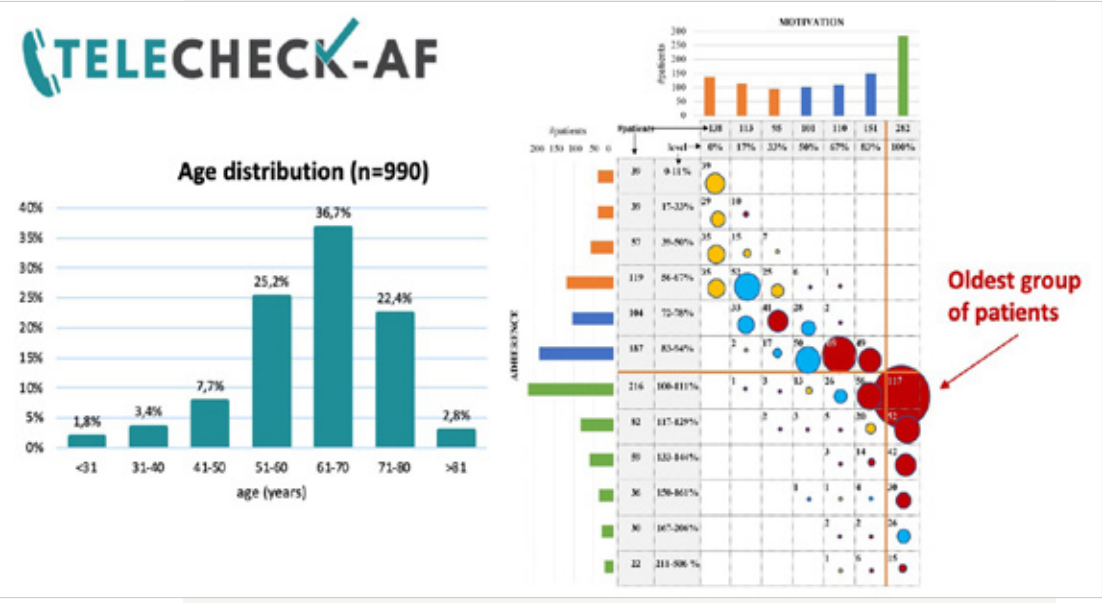


FIGURE 3 Patient experiences, age distribution and and mHealth motivation/adherence.

Societal impact

In close collaboration with the NFU-initiative Citrienfonds e-health, we initiated discussions together with MUMC+ Inkoop (Roger Smeets), the Maastricht UMC+ *Zorg Innovatie Lab* (Dr Herm Martens) and health insurance companies (Nils van Herpen, Innovatie Manager VGZ) to find solutions for reimbursement for the TeleCheck-AF approach. This resulted in the creation of the first reimbursement code for mHealth use in the Netherlands, which is now launched on the website of the Nederlands Zorg autoriteit (NZa) (*Facultatieve prestatie 'Telecheck atriumfibrilleren'* - TB/REG-21679-01). The *facultatieve prestatie 'Telecheck atriumfibrilleren'* is now available for all Dutch hospitals. Together with VGZ, we put together a 'Good Practice' document, which is provided to all Dutch hospitals in the moment.

The TeleCheck-AF approach was recently assessed and is now approved by the *Inspectie Gezondheidszorg en Jeugd* as the representative example how Maastricht UMC+ uses mHealth *('Rapport van het inspectiebezoek in het kader van het toezicht op e-health aan het Maastricht UMC+ te Maastricht op 12 mei 20212; VGR2030998; 2021-2633506; Utrecht, 24 juni 2021*). Finally, the TeleCheck-AF program acts currently as a case model for the *Zorgverzekeraars Nederland (ZN)* and *Nederlandse Vereniging voor Cardiologie* (NVVC) to develop a framework for a national assessment tool for the implementation of new mHealth approaches in the Netherlands. We developed new patient education material on how to use mHealth devices for AF monitoring which is now provided on the Maastricht UMC+ website (https://hartenvaatcentrum.mumc.nl/onderzoeken/fibricheck-app) as well as on the *Vliegwiel* and *Patiëntenfederatie website*.

We also organised a patient webinar for remote instruction and education of patients. On 12 May 2020, the Health Foundation Limburg organised the first '*Online Hart en Vaat Café'* (Heart and Vascular Café in Maastricht to inform patients about the novel TeleCheck-AF infrastructure and their potential role in using the mobile app. We communicated the TeleCheck-AF approach widely by using social media (Follow hashtag #TeleCheck-AF on Twitter and LinkedIn). In addition, we were invited for a number of interviews in the general press. A selection:

- NOS Journal: 10.02.2022, 20:30min.: https://www.npostart.nl/nos-journaal/10-02-2022/POW_05158603
- RTV- Maastricht (*GoodVeurein 71 Veranderende gezondheidszorg*): 19.10.2020: https://vimeo.com/469915196?fbclid=IwAR1B0JWIrKFTCTeXt6-jq0s17ppXSbq67CIE3ZU9WLRjNEenVOpSYkJYJMI
- De Limburger '*Ziekenhuizen bieden zorg op afstand voor patiënten met hartklachten tijdens coronacrisis*' (08.04.2020). https://www.limburger.nl/cnt/dmf20200408_00155506
- '*Afspraak MUMC+ en VGZ: hartpatiënt kan voortaan thuis zelf hartritme meten*' (09.02.2022): https://www.limburger.nl/cnt/dmf20220209_95268468

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7 The Maastricht Study

Dr Carla van der Kallen and 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 reinvited to undergo all extensive biomedical assessments again.

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 Prof. Coen Stehouwer (scientific director), Dr Carla van der Kallen, Dr Miranda Schram, Dr Annemarie Koster, Dr Seb Köhler, Dr Marleen van Greevenbroek, Prof. Pieter Dagnelie, Prof. Bastiaan DeGalan and Dr Anke Wesselius. Data collection and cleaning takes place at The Maastricht Study research center, which is located at Randwycksingel 35 in Maastricht. Research Center 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 co-owners 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 out of six schools of UM/Maastricht UMC+, including CARIM (founding school), 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 like Parelsnoer, Hyporesolve, the European Eye Epidemiology consortium, and the PSAD, to depression and dementia consortia, like NCDC, Enigma and DepressD, to risk factor oriented consortia like Propass, Diogenes and JPI, to biobanking and genetic oriented consortia, like BBMRI and CHARGE. We have recently initiated a national approach to combine Dutch population-based cohort studies for future data collection and analysis. This initiative is named the Netherlands Cohorts Consortium (NCC) and is headed by Dr Miranda Schram.

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 120 peer-reviewed scientific publications, including at least 20 high impact papers (impact factor >10). Over 30 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 170 bachelor and master students performed their thesis research at The Maastricht Study.

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

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 focussed 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. Also 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.

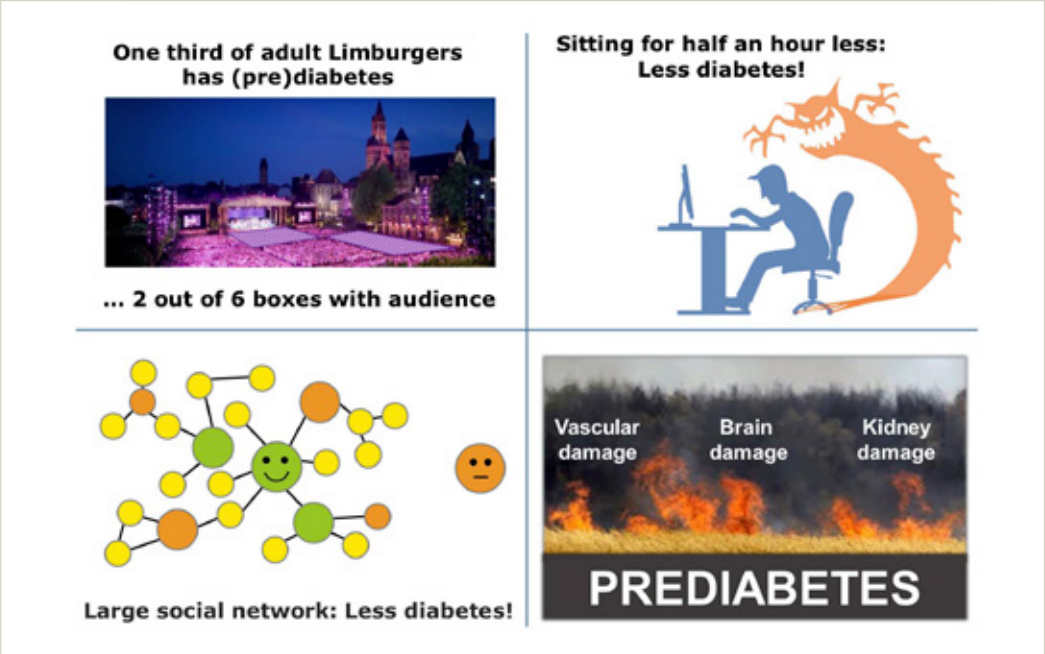


FIGURE 3 Societal impact of results of The Maastricht Study

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.

8 The Digital Twin

Uyen Chau Nguyen,[1,2] Dr. Matthijs Cluitmans,[1] Dr. Jordi Heijman[1] and Prof. Joost Lumens[3]
Departments of Cardiology,[1] Physiology[2] and Biomedical engineering[3]

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

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

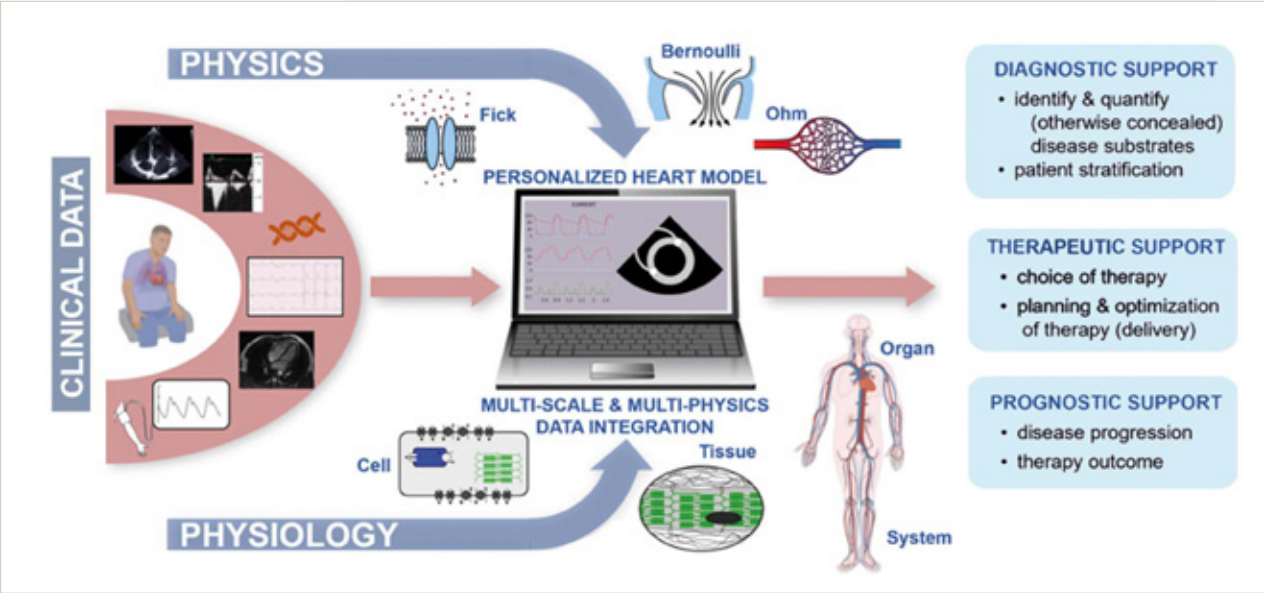


FIGURE 1 How can Digital Twin technology improve current cardiology care? A computational model of the human heart and circulation enables synergistic integration of an individual's diagnostic data obtained with the use of different clinical modalities in one personalized heart simulation. The Digital Twin of a patient's heart 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 (i.e., from ion channel function to system hemodynamics) obtained by adjusting a well-considered set of relevant parameters in the computer model to match the clinical phenotype of the individual patient as closely as possible (Figure 1). When biophysical processes are not (yet) fully understood, such mechanistic models can alternatively be augmented by artificial intelligence fueled with population-based data. Personalised primarily with non-invasive data from various clinical data sources, the Digital Twin provides highly relevant biophysical parameters and properties of the patient's heart and circulation (e.g. local electrical activity, hemodynamics and structural properties of the heart) that would remain concealed otherwise or would only be measurable in an invasive manner. These insights can be leveraged to improve patient stratification and guide disease management, especially in complex multifactorial diseases such as cardiac arrhythmias and heart failure.

Within CARIM, several teams have a long-standing interest in the development of Digital Twin approaches for personalized cardiovascular care. [1-3] Here, we present an example of a Digital Twin application developed by CARIM

researchers that demonstrates the potential academic, clinical and societal impact of these efforts.

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 electrocardiogram (ECG). Although the ECG is a very accessible technique, it 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 information obtained from cardiac magnetic resonance imaging (MRI) or computed tomography (CT) of the heart, one can tailor the treatment of arrhythmias and heart failure. CARIM researchers were the first to integrate electro-anatomic mapping from the coronary veins

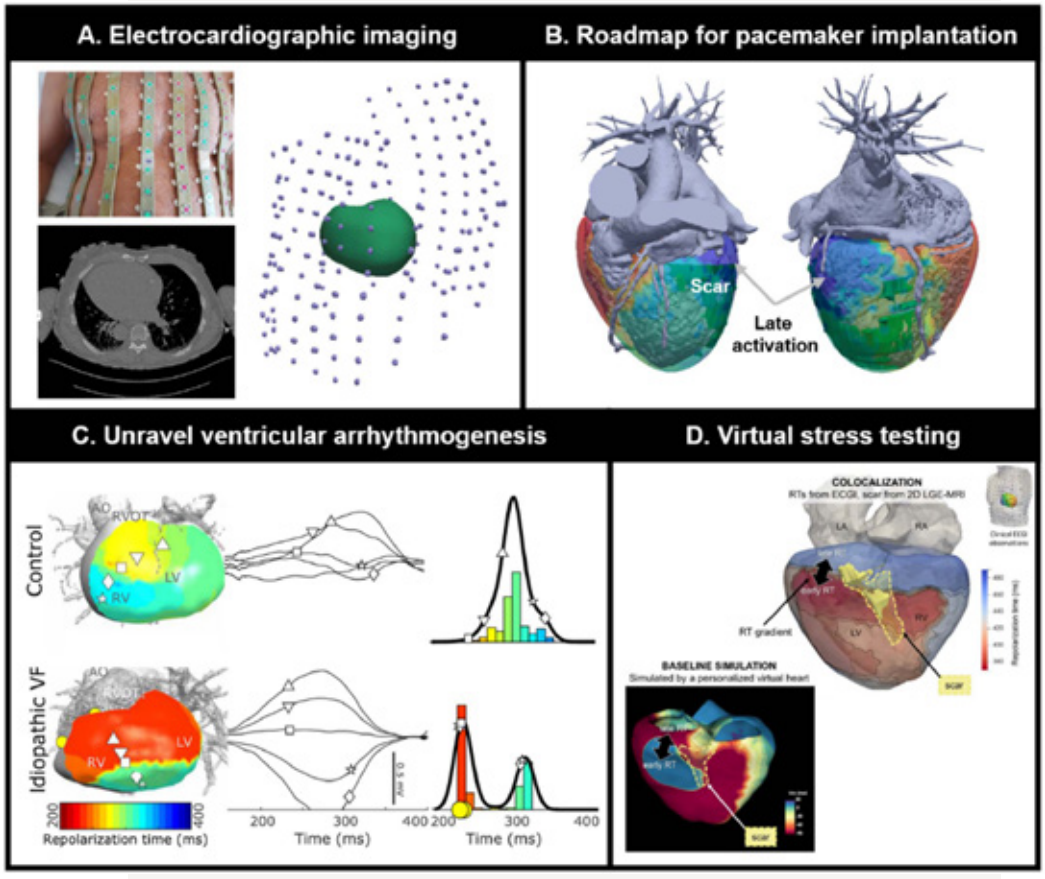


FIGURE 2: ECG-imaging workflow in Maastricht (A) with two representative clinical applications in the electrical treatment of heart failure (B) and assessment of idiopathic ventricular arrhythmias (iVF; C). The "electrical twin" based on individual ECG-imaging reconstructions can virtually test the inducibility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

with MRI for the electrical treatment of heart failure. [4] More specifically this was done to guide the implantation of a biventricular pacemaker to a region within the heart that requires the most electrical stimulation and is remote from scar. This 'road mapping approach' was further refined by replacing the invasive procedure with a more patient-friendly alternative approach, (ECG-imaging, Figure 2A-B). [5] ECG-imaging is a technique that non-invasively reconstructs the electrical activity of the heart using measurements from ~200 electrodes and a patient-specific geometry derived from CT or MRI, creating a virtual 'Electrical Twin' of the heart.

We have an in-house developed 'Maastricht' ECG-imaging system (Figure 2A) that was validated in a pre-clinical setting in anesthetized animal models. [6] This system has since then been employed to provide patient-specific electrical twins of >80 patients, e.g., providing clinically relevant information that could not be seen on the 12-lead surface ECG in patients with unexplained life-threatening ventricular fibrillation (Figure 2C), contributing to our understanding of arrhythmogenesis in these patients. [7] In the future, CARIM researchers aim to define the optimal treatment options for patients at risk of such life-threatening arrhythmias by evaluating the inducibility of these arrhythmias and treatment possibilities in the Electrical Twin based on ECG-imaging data (Figure 2D).

The 'Mechanical Twin'

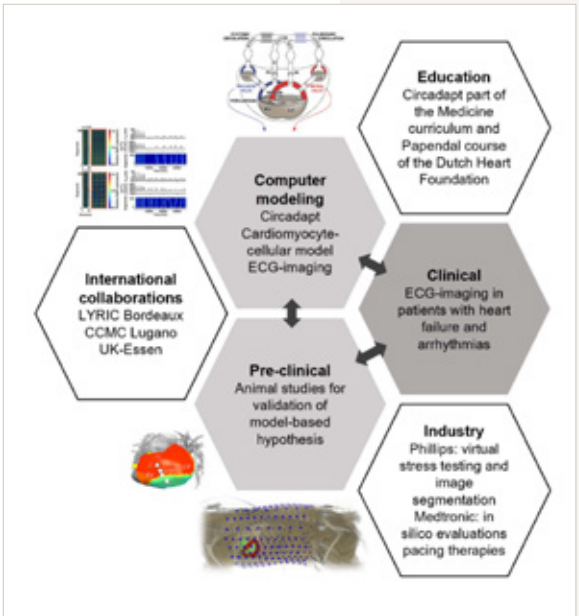
At CARIM similar Digital Twin approaches have been developed for the mechanical aspects of the heart ('Mechanical Twin') based on non-invasive strain imaging.- [8] Current efforts aim to link both electrical and mechanical components in a combined 'ElectroMechanical Twin', e.g., as part of the European Research Area Network on Cardiovascular Diseases (ERA-CVD) EMPATHY project.

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, Dr Jordi Heijman, Prof. Paul Volders). We have a diverse training background (engineering, applied mathematics, clinical technology, physiology, clinical cardiology) and share a common interest in computational cardiology. Importantly, the unique CARIM environment with clinical researchers welcoming and actively contributing to digital health solutions and technology-oriented researchers being well-educated in cardiovascular (patho)physiology makes Maastricht UMC+ the ideal breeding ground for Digital Twin innovations.

Users and collaborations

Institutional: There is a strong synergistic environment within CARIM (Figure 3). We organise monthly joint research meetings (e.g., on translational cardiac electromechanics between the basic science group of Prof. Frits Prinzen, clinical cardiology group of Prof. Kevin Vernooy, and computational cardiology group of Prof. Joost Lumens; on translational atrial fibrillation research between the groups of Prof. Uli Schotten, Prof. Kevin Vernooy, Dr Dominik Linz and Dr Jordi Heijman). Additionally, every three months we organize a cross-faculty computational cardiac electromechanics (CODE) research meeting with the research groups of Prof. Joost Lumens, Prof. Peter Peeters (Faculty of Science and Engineering), Dr Jordi Heijman, and Dr Matthijs Cluitmans.



International: Numerous important international collaborations exist, e.g., between Prof. Joost Lumens, Dr Matthijs Cluitmans, and Uyen Chau Nguyen and Prof. Dubois, Dr. Vigmond, Dr. Bear, and Dr. Potse from the Electrophysiology and Heart Modeling Institute (LIRYC) in Bordeaux, or between Prof. Frits Prinzen and Prof. Uli Schotten, and Prof. Auricchio, a scientific partner at the Center for Computational Medicine in Cardiology in Lugano. ***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

FIGURE 3 Integrative digital twin network within CARIM

and valve implant technologies in the CircAdapt cardiovascular model. [9] 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 personalSzed electrophysiology modeling. [10]

Education: An important and rapidly growing group of users of our modeling 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, >20,000 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 Maastricht University, the tool is implemented in several semesters of the medical curriculum. In addition, the tool is used for teaching during the national Papendal course organized by the Dutch Heart Foundation (DHF) and plays a major role in International Training Networks subsidizsed by the European Union (PIC (Personalized In-silico Cardiology); MARCIUS). Another tool developed by CARIM researchers that is used for teaching in the master Systems Biology at Maastricht University is Myokit. Myokit is a software tool for modeling of cardiac electrophysiology at the cellular level. [11]

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 270 papers within the digital twin/ computational cardiology topic. Additionally over 60 scientific papers involving the CircAdapt team and model have been published. [12]

Uyen Chau Nguyen was awarded the Dekker Clinical Scientist grant from the Dutch Heart Foundation (DHF, 2021). Dr Matthijs Cluitmans was awarded the Dekker Junior Postdoc grant from the Dutch Heart Foundation and the Veni grant from the Dutch Research council (NWO; both in 2018). Dr 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) and a Vidi from NWO (2017). All these prestigious individual grants were awarded to fund Digital Twin-based projects, showing that CARIM is the leading institute in this field at national level.

Societal impact

Patient involvement and their families are essential for clinical translation of our study findings and for generating patient-friendly study protocols. Prof. Joost Lumens and Uyen Chau Nguyen gave a presentation about CRT and advanced computational techniques to guide implantation at the annual patient congress from the RESCAR (Research Cardiology) foundation in Maastricht. Furthermore, the CARIM Digital Twin team was involved in a DCVA-initated (Dutch Cardiovascular Alliance) initiated inventory and policy document on animal-free innovations for cardiovascular research, commissioned by the National Committee for the Protection of Animals Used for Scientific Purposes (NCad, see link) and published in an expert consensus document entitled ‘Animal models and animal-free innovations for cardiovascular research: current status and routes to be explored. Consensus document of the ESC Working Group on Myocardial Function and the ESC Working Group on Cellular Biology of the Heart’. [13] Generic and personalised computational models of the heart and circulation have been extensively discussed and included as an animal-free alternative for cardiovascular research. A selection of CARIM’s Digital Twin team media exposure is additionally provided below:

Media exposure

- *'Bijna 1 miljoen euro voor onderzoek hartritmestoornis*' - RTV Maastricht 2016: link
- '*UT studente Uyen Chau Nguyen ontdekt een methode om goede plaats voor pacemaker te vinden en wordt beloond met de Prof. Dr. G.P. Vooijs award*' - University of Twente 2017: link
- '*Bijna 1 miljoen euro voor onderzoek hartritmestoornis*' - Maastricht University 2017: link
- '*De hybride onderzoeker*' - Maastricht University 2018: link
- '*Welke onderzoekers kregen in 2021 een Dekkerbeurs*?' - Dutch Heart Foundation 2021: link
- '*Beter voorspellen of pacemaker helpt bij hartfalen*' - interview with Joost Lumens. Publications ZonMw 2020: link
- 'Implementation of technological innovations' - Dutch Cardiovacular Alliance 2020: link
- "Digital heart" to help doctors make a diagnosis. Better care thanks to computer models and artificial intelligence' - Observant 2022: link
- '*Streefbeeld Cardiovasculair onderzoek is vergevorderd*'. *Nationaal comite advies dierproevenbeleid 2022*: link

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9 Determinants and cardiometabolic consequences of non-alcoholic fatty liver disease

Prof. Martijn Brouwers, Department of Internal Medicine

Non-alcoholic fatty liver disease: at the heart of cardiometabolic complications

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent disorder that is histologically characterised by simple steatosis, steatohepatitis and fibrosis in individuals who do not consume excessive alcohol. It has been estimated that 30% of the general population is affected by NAFLD, which is mainly explained by unhealthy lifestyle habits. NAFLD 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 NAFLD per se is causally involved in the pathogenesis of cardiovascular disease, or whether it is an innocent bystander. Furthermore, given the high prevalence of NAFLD 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 five years I have setup a translational research line to disentangle the specific role of fructose in the pathogenesis of NAFLD, and the role of NAFLD 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 and genetic epidemiology (i.e. Mendelian randomization).

Users and collaborations

Translational research is team work: it is naïve to assume that all these diverse scientific skills can be possessed by one individual. I have, therefore, carefully invested in local, national and international collaborations:

- Local: Maastricht UMC+/Maastricht University: Prof. Coen Stehouwer (classical epidemiology in The Maastricht Study), Prof. Casper Schalkwijk (animal studies), Prof. Patrick Schrauwen (metabolic imaging in in-depth phenotyping and intervention studies)
- National: Prof. Feskens (Wageningen University; sugar composition tables for intervention studies) and Dr Oosterveer (University of Groningen; animal studies)
- International: Dr Burgess (University of Cambridge, UK; Mendelian randomisation), Dr Tolan (University of Boston, USA; animal studies), Dr Cassiman (University of Leuven, Belgium; inborn errors of metabolism).

Scientific quality

We used different approaches, including traditional epidemiology, in-depth phenotyping of patients with an inborn error of fructose metabolism and a randomised controlled trial, to unequivocally show that fructose per se is involved in the pathogenesis of NAFLD. 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 NAFLD 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 (1-10).

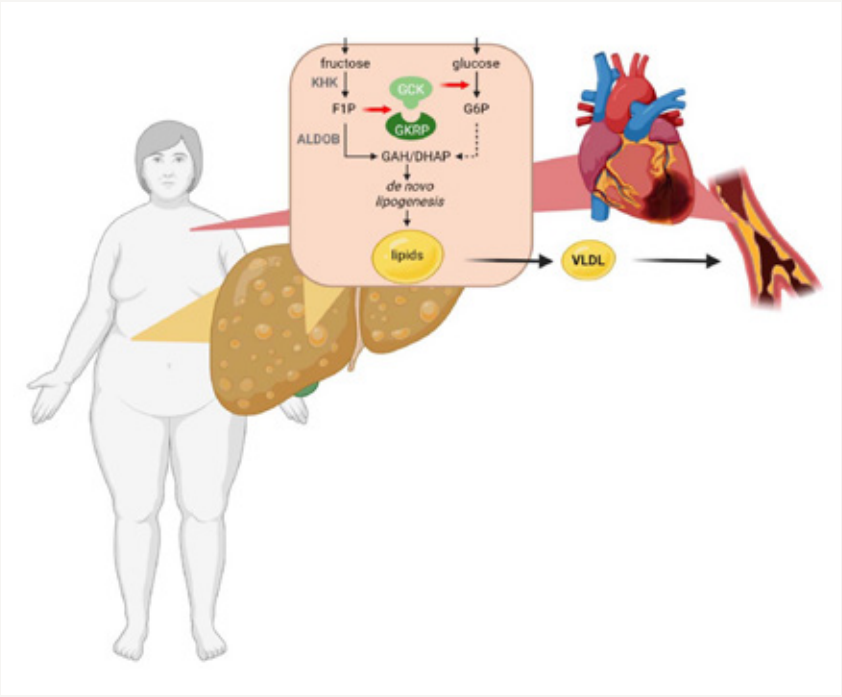

FIGURE 1 Based on my data I postulate that fructose contributes to NAFLD via direct pathways (by serving as a substrate for de novo lipogenesis) and indirect pathways (by stimulating hepatic glucose disposal and subsequent conversion into fat). NAFLD drives the overproduction of VLDL particles, which 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, online news sites and webinars and podcasts.
We are happy that our national government recently decided to implement such a sugar tax.

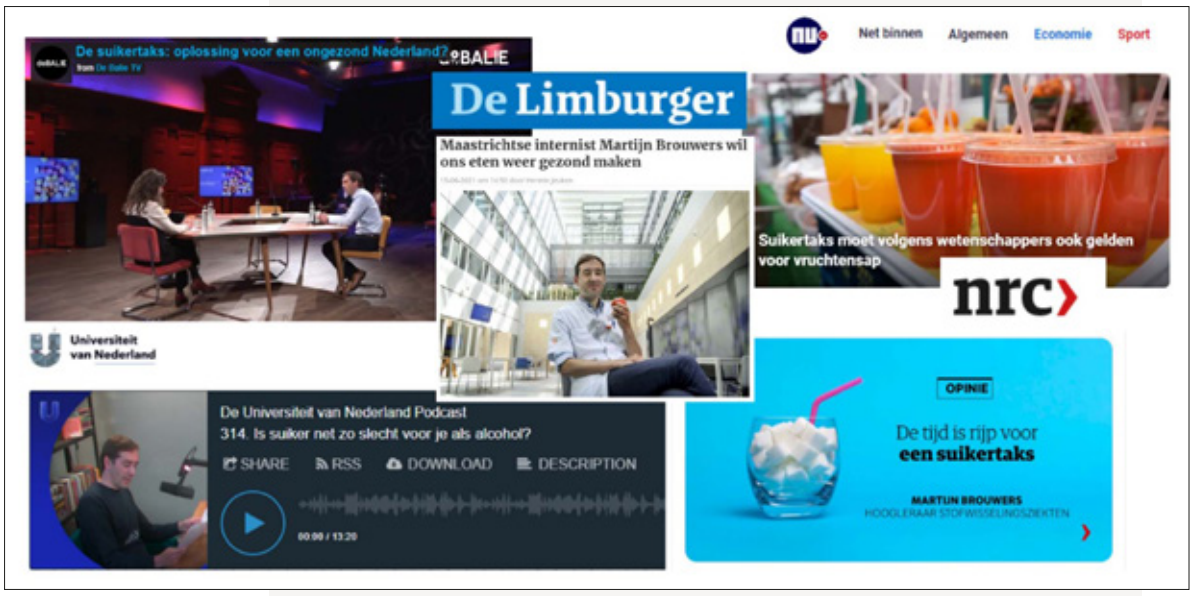

FIGURE 2 Selection of media attention, based on our research

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10 Cardiac Magnetic Resonance-Guided Electrophysiological Intervention (iCMR)

Dr Rob Holtackers, Department of Radiology & Nuclear Medicine
Drs 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 [1]. 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. The developed software and system in Maastricht are therefore unique in the Netherlands and leading in the world. 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. 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 visualization 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 visualization of the location and orientation of the catheters in the heart itself. Therefore, iCMR not only allows for real-time ablation through detailed visualization of the catheter and the anatomy of the heart but can also map tissue changes during and directly after ablation. Thanks to this detailed pre-, peri-, and post-procedural visualisation, treatments can therefore 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. In the MUMC+, however, we can temporarily transform one of our pre-existing MRI environments into an interventional cardiac MRI suite [2], 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 students, junior researchers/clinicians/technicians, senior staff members), affiliations (5 departments/ centres), and a large variety of complementary technical and clinical skills and expertise (mix of clinicians, engineers, technicians, visionaries, and finance).

Within our iCMR team, we 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 the MUMC+ 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 several 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: drs. Miranda Bijvoet (imaging cardiologist), Dr Marisevi Chaldoupi (electrophysiologist), Dr 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 initiated 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.

Although the extensive project efforts only became visible recently and clinical procedures have just been performed since 2021, the efficient and close collaboration within the iCMR team already led to two publications in peer-review scientific journals [2,3] and various presentations at international conferences. Two additional research manuscripts from both an imaging and an electrophysiology perspective are in their final stages. Furthermore, the iCMR project was nominated for the very first 'Marja van Dieijen Award' in 2021 and became runner-up. A recent application for the NWO team research grant reflects our persisting scientific ambition and will form the basis for additional grant proposals in the future.

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 standardize 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 in one of our latest publications [2] 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' (in Dutch), article in magazine "Hartpatiënten Nederland" (https://www.hartpatienten.nl/nieuws/unieke-techniek-behandeling-hartritmestoornissen-in-mri/)
- 'Dit is wat mijn vak zo mooi maakt' (in Dutch), article in magazine 'Hartpatiënten Nederland' (https://www.hartpatienten.nl/nieuws/dit-is-wat-mijn-vak-zo-mooi-maakt/)

Scientific publications

- **Bijvoet GP, Holtackers RJ,** M J M Nies H, 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. doi: 10.1016/ j.ijcha.2022.101078.
- Nies HMJM, Gommers S, **Bijvoet GP,** Heckman LIB, Prinzen FW, Vogel G, van de Heyning C, Wildberger JE, Mihl C, **Holtackers RJ.** Histopathological validation of semi-automated myocardial scar quantification techniques for dark-blood LGE MRI. Eur Heart J Cardiovasc Imaging. 2022;jeac107. doi: 10.1093/ehjci/jeac107 (online ahead of print)
- **Bijvoet GP[†], Holtackers RJ[†],** Smink J, Lloyd T, van den Hombergh CLM, Debie LJBM, Wildberger JE, Vernooy K, Mihl C[‡], Chaldoupi SM[‡]. 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.

International congress contributions

- ***Bijvoet GP,*** Hermans BJM, **Holtackers RJ,** Luermans JGLM, Linz D, Maesen B, Mihl C, Nijveldt R, Vernooy K, Wildberger JE, Schotten U, Chaldoupi SM. Novel 3D dark-blood late gadolinium enhancement MRI to determine atrial ablation scar after pulmonary vein isolation. ESC congress 2022 (moderated poster presentation)
- ***Bijvoet GP,*** Hermans BJM, Linz D, Vernooy K, Wildberger JE, Mihl C, Chaldoupi SM, **Holtackers RJ.** Novel 3D dark-blood late gadolinium enhancement MRI for visualisation of atrial scar to guide atrial fibrillation ablation. ECR congress 2022 (oral presentation)
- Nies HMJM, Gommers S, Heckman LIB, Prinzen FW, Van De Heyning CM, Chiribiri A, Wildberger JE, Mihl C, **Holtackers RJ.** Histopathological validation of semi-automated myocardial scar quantification techniques for dark-blood LGE MRI.
  ECR congress 2022 (oral presentation)
- ***Bijvoet GP,*** Nies HMJM, **Holtackers RJ,** Vernooy K, Wildberger JE, Linz D, Mihl C, Chaldoupi SM. First clinical experience with cardiac magnetic resonance guided typical atrial flutter ablation with the integration of active catheter tracking and electro-anatomical mapping. EHRA congress 2022 (poster presentation)

- *Hermans BJM*, **Bijvoet GP, Holtackers RJ,** Mihl C, Luermans JGLM, Vernooy K, Linz D, Chaldoupi SM, Schotten U. Development and validation of a fully automatic algorithm to align 3D LGE MRI and electro-anatomical mapping anatomies of the left atrium.
  EHRA congress 2022 (poster presentation)
- Nies HMJM, **Bijvoet GP,** Chaldoupi SM, Vernooy K, Linz D, Wildberger JE, **Holtackers RJ,** Mihl C. Direct pre- and post-ablation cardiac magnetic resonance imaging of tissue characteristics in patients with typical atrial flutter.
  EHRA congress 2022 (poster presentation)
- ***Bijvoet GP*, Holtackers RJ,** Smink J, Lloyd T, van den Hombergh CLM, Debie LJBM, Wildberger JE, Vernooy K, Mihl C, Chaldoupi SM. Transforming a pre-existing MRI environment into an interventional cardiac MRI suite. ESCR 2021 (poster presentation)
- ***Bijvoet GP,* Holtackers RJ,** Mihl C, Chaldoupi SM. CMR-guided typical atrial flutter ablation in the Maastricht University Medical Centre (NL) - Choose your optimal path through the isthmus towards the inferior caval vein.
  ESC congress 2021 (oral presentation) – best clinical cases o f the young.
- Invited lecture on our experience regarding CMR guided atrial flutter ablations at the Heart Rhythm Society (HRS) congress 2021. Presenter: Dr. S.M. Chaldoupi
- Invited lecture on our experience regarding CMR guided atrial flutter ablations at the Imricor Realtime iCMR Ablations Summit 2022. Presenter: Dr. S.M. Chaldoupi

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11 Ticknology: bio-inspired diagnostics and therapeutics

Dr Ingrid Dijkgraaf, Dept. of Biochemistry

What is the benefit of tick proteins for our health?

My research on tick proteins started approximately 10 years ago when I just worked at Maastricht University for a few months. At the time, in Department of Biochemistry, we were looking for proteins and peptides that could serve to distinguish the unstable from the stable plaque by molecular imaging techniques. It appeared that tick saliva contains a family of proteins that specifically bind to chemokine proteins [1, 2], the driving forces behind the formation of atherosclerotic plaques and thus an indicator for the inflammatory process and plaque stability. These chemokine-binding proteins, so-called evasins, were subsequently produced via chemical protein synthesis techniques and recombinant expression methods. Since then, research on tick proteins has expanded further. We mainly focus on structure-activity relationships of tick proteins, whereby tick proteins can be used to unravel molecular pathways of hemostasis and other (patho)physiological processes as well. In addition, we aim to develop these proteins into diagnostic (molecular imaging) and therapeutic agents. Finally, tick proteins are used for the design of 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.

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, [3]).

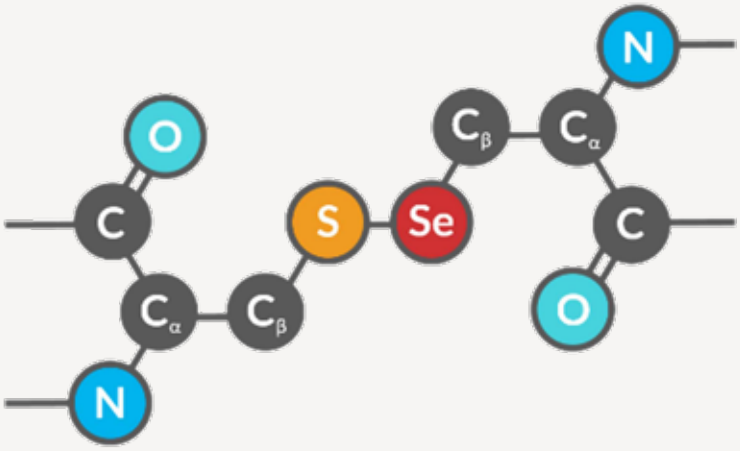

FIGURE 1 Schematic representation of the mixed Cys-Sec bond indicating Cα/Cβ carbons

Subsequently, we could solve the 3D structure of evasin-3 and identify how it binds to chemokines CXCL1- and -8 by NMR [4, 5]. In a fellow-up project, we showed that fluorescently labeled evasin-3 is able to visualize inflamed endothelium, a hallmark of progressive atherosclerosis (Figure 2, [5]).

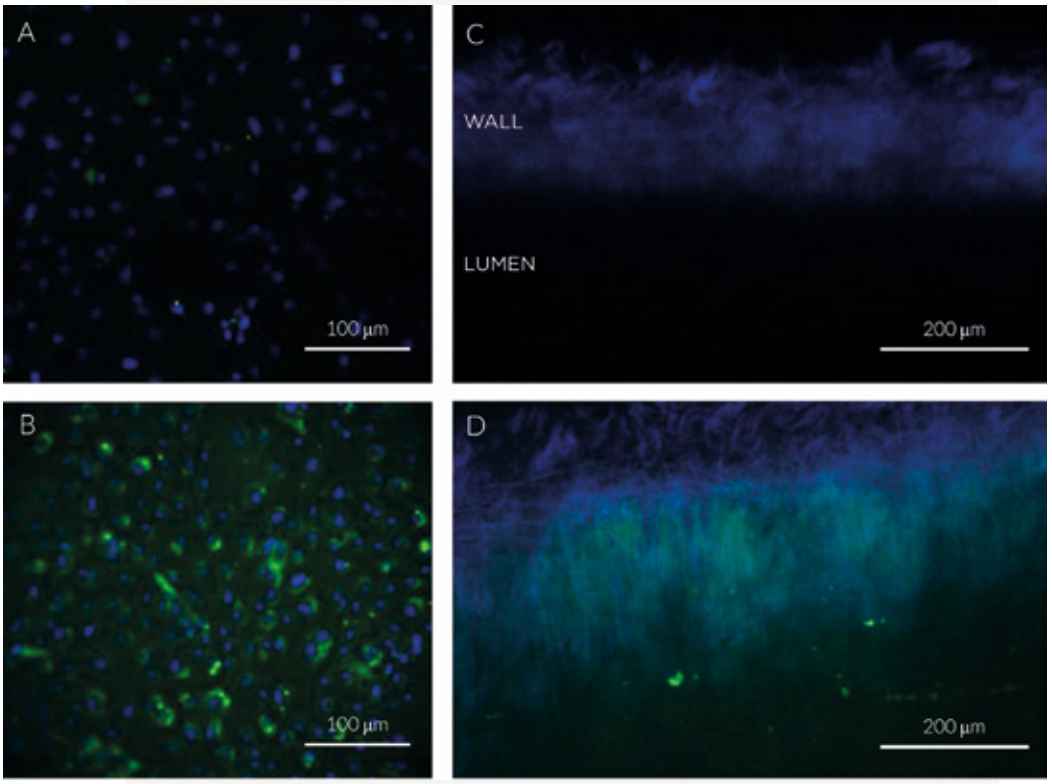

FIGURE 2 Fluorescently labeled Evasin-3 visualizes CXCL1 in stress-activated HMVECs and LPA-activated murine carotid arteries. HMVECs cultured under static conditions (A) and subjected to 2.0 Pa (20 dyne/cm2) shear stress for 72 h (B) (green = N56K Evasin-3 OG488, blue = Hoechst). Two-Photon Laser Scanning Microscopy of mounted murine carotid arteries without (C) and with LPA treatment for 10 min (D) (green N56K Evasin-3 OG488, blue autofluorescence collagen).

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 [6]. 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 3A-B).

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 [7].

Users and collaborators

Over the years, I have initiated many collaborations with local (Maastricht UMC+), national and international partners to perform our multidisciplinary research. In the field of chemokines, my team collaborates with Dr Rory Koenen, Prof. Oliver Soehlein (University of Münster, Germany), Prof. Philipp von Hundelshausen and Prof. Christian Weber (Ludwig-Maximilian University Munich, Germany). Structure elucidation is done with the support of Dr Hans Ippel (Biochemistry), Dr Bert Janssen (Utrecht University) and Prof. Kevin Mayo (University of Minnesota, USA). To design and develop chemokine-binding proteins, we collaborate with Dr Peter Timmerman and Dr Michael Goldflamm (Pepscan Therapeutics), Prof. Shoumo Bhattacharya (Oxford University, UK) and

Prof. Akane Kawamura (Newcastle University, UK). For nuclear and fluorescent imaging, we cooperate with Prof. Felix Mottaghy (Maastricht UMC+) and Dr Remco Megens (Maastricht UMC+). In the field of haemostasis, we collaborate with Dr Elisabetta Castoldi.

For the design, synthesis and evaluation of synthetic vaccines to prevent tick-borne diseases, several collaborations have been started in recent years. In the field of Lyme disease prophylaxis: Prof. Joppe Hovius (Amsterdam UMC), Prof. Tina Vermonden (Utrecht University), Dr Daniëlle van Manen (Janssen Vaccines & Prevention B.V.). To prevent other tick-borne diseases: Dr Hein Sprong (RIVM), Prof. Michalis Kotsyfakis (University of South Bohemia, Czech Republic), Prof. Anabella Gaspar (University of Pretoria, South Africa), Dr Ben Mans (University of South Africa, South Africa) Dr Esther Kanduma (University of Nairobi, Kenya) and Dr Siddharth Deshpande (Wageningen University).

Scientific quality

The fascination for and work on tick-derived proteins laid the foundation for two completed PhD projects (Stepan Denisov, 2019 and Danique van den Kerkhof, 2021) and various BSc (14), MSc (4) and technician (8) internships. Lately, two joint PhD projects with Leuven and Hasselt University were granted and will start last quarter of 2022 and first half of 2023, respectively. The two completed PhD projects have led to nine publications in renowned journals, such as Bioconjugate Chemistry, Journal of Biological Chemistry and Chemical Communications, thus far. Furthermore, a CARIM Kootstra Fellowship (2019) and NWO Rubicon (2021) grant were award to Stepan Denisov. To investigate tick salivary protein BSAP1, I received in 2018 an NWO ECHO grant. Lately, a visiting postdoc (Amine Jmel) in our group received an EMBO grant to extend his studies at Maastricht University.

Societal impact

To inform and inspire society about the relevance of our research, I voluntary give lectures and provide information about scientific research and my university studies to secondary school students in the Netherlands since 2012. After receiving an Outreach Lecturing Fund Travel Award in 2014 (US Department of State), I visited Mississippi Valley State University (USA), a historically black university. Here, I gave lectures about my research, participated in daily activities, and had lively conversations with students, broadening my horizons. In 2019, a KNCV eye opener movie was made in which I explain briefly for what our tick protein research serves.

Furthermore, our research into tick proteins was nominated for the Klokhuis Science Prize. In 2020, our research on the application of tick proteins as diagnostic in cardiovascular disease was highlighted in C&EN News March and C2W. This study was presented in the popular scientific journal Research Features in 2021. Later that year, I was interviewed by *BNR Nieuwsradio (Wetenschap Vandaag)* about my research. A short article based on this interview appeared in *Financieel Dagblad* a few weeks later.
Since 2020, I have been a board member of the Chemistry and Society Group (KNCV), which aims to inform society about the relevance of chemistry in daily life and to discuss challenges in which chemistry plays a role.

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