School for Cardiovascular Diseases

CARIM
School for
Cardiovascular Diseases

Self Evaluation 2013 - 2018 Societal Impact in Narratives

Maastricht UMC+

Maastricht University

Contents

Computational Cardiac Electro-Mechanics and Hemodynamics

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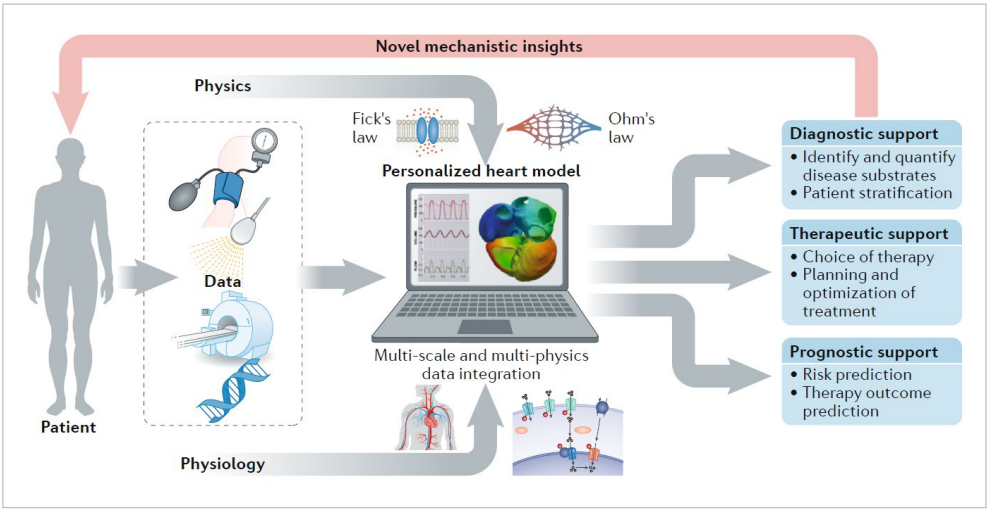
VES

Dr Joost Lumens, Department of Biomedical Engineering

The virtual patient: from simulation to care innovation

The treatment of individual patients in cardiology practice increasingly relies on advanced imaging, genetic screens, and devices. As the amount of imaging and other diagnostic data increases, paralleled by the greater capacity to personalised treatment, the difficulty of using the full array of measurements of a patient to determine an optimal treatment seems also to be paradoxically increasing. Computational models of the human heart and circulation are progressively addressing this issue, by providing a common framework for integrating multiple data sets from individual patients. These models, which are based on physiology and physics rather than on population statistics, enable computational simulations to reveal diagnostic information that would have remained concealed otherwise and to predict treatment outcomes for individual patients. A patient-specific simulation is obtained by adjusting a well-chosen set of relevant parameters in the computational model, so that model simulation and clinical measurements agree (Figure 1). The capacity of the model to replicate validation data sets provides confidence that the model can be used to make reliable predictions and simulate the most likely status of a patient given the available measurements. The resulting 'virtual patient' can be used for further improvement of diagnosis and for *in silico* optimisation and planning of a treatment.

Figure 1 How can computational models improve current cardiology care?



A computational model of the human heart and circulation enables synergistic integration of multiple diagnostic data, obtained with the use of different clinical modalities (such as echocardiography, MRI, electrocardiography, genetics and blood-pressure measurements) in one personalised heart simulation, based on widely accepted physical and physiological principles. The personalised integrative nature of such a virtual- patient simulation adds value to the existing clinical workflow by offering more quantitative and objective insight in the underlying disease substrates of a patient. In addition, the model provides a platform for virtual evaluation and optimisation of a therapy. Adapted from Niederer S, Lumens J, and Trayanova NA. Nat Rev Cardiol 2018 In Press.

My team's research is characterised by a multidisciplinary approach combining computer modelling/simulation with experimental and clinical data to gain mechanistic insight in heart failure and its treatments. Importantly, translation of novel mechanistic insights into diagnostic, therapeutic and educational improvement is always pursued. My group develops a unique virtual patient simulation technology that enables personalised simulation of an individual patient's cardiac function. Our research of the next five years will focus on determining the added diagnostic and therapeutic value of our virtual patient simulation approach. In a proof-of-concept study funded by the Dutch Heart Foundation, we aim to predict patient outcome after cardiac resynchronisation therapy (CRT), a special pacemaker therapy, before actual implantation of the pacemaker through patient-specific simulation of the patient's failing heart and of the intended treatment with CRT.

proof-of-concept study

Large trials have shown that 30 to 50% of the patients receiving CRT do not benefit from this invasive and expensive therapy. It is therefore in the interests of patients that CRT pacemakers are only implanted when there is a high chance of clinical response to the therapy. Reducing the number of unnecessary CRT device implantations will also have major benefits for healthcare providers, including hospitals, governmental departments, and insurance providers given the high costs associated with CRT, thereby ensuring that limited healthcare budgets are spent as efficiently as possible. Since our research is likely to reduce the burden of cardiovascular diseases for both the patient and the society, I was invited by the Dutch Heart Foundation to contribute to a promotional video of their Dr E. Dekker personal grant programme that was attached to a national press release, and to participate in a workshop on societal impact organised by the Rathenau Institute.

promotional video

Since twelve years, I work with the CircAdapt software for advanced cardiovascular simulation that has been entirely developed by a team of CARIM researchers (Figure 2). My PhD research (2006-2010) focussed on CircAdapt model development and its application to unravel the mechanisms of right heart failure in patients with pulmonary arterial hypertension. My research presentations at international conferences caught the attention of clinical experts in the field, which led to my co-authorship on a high-impact position paper as the youngest invited Task Force member of the 5th World Symposium on Pulmonary Hypertension.

CircAdapt
team of CARIM researchers

high-impact position paper

Figuur 2 CircAdapt research team members. From left to right: Dr Joost Lumens, Prof. Tammo Delhaas, Dr Koen Reesink, Dr Theo Arts and Dr Willem Dassen

International and Maastricht UMC+ collaborations

A crucial phase for my research line has been my postdoctoral fellowship in the Cardiac Rhythm Department of the Bordeaux University Hospital (CHU de Bordeaux), headed by Prof. Michel Haïssaguerre. By a unique integration of clinical, animal experimental and computational data, I shed new light on the working mechanism of CRT in patients with heart failure, published in a high-impact Cardiology journal. I initiated a strong collaboration between CARIM and the LIRYC Electrophysiology and Heart Modeling Institute in Bordeaux. Since 2015, I'm appointed as Visiting Professor at the LIRYC Institute. I have established a joint PhD agreement together with LIRYC researchers. Currently, a joint PhD candidate (Peter Huntjens, MSc) spends 50% of his time in Bordeaux and 50% in our group in Maastricht.

high-impact Cardiology journal
LIRYC Electrophysiology and Heart Modeling Institute

My group currently counts five PhD students, one postdoc and two Master students (November 2018). With their projects, they all bridge the different but complementing disciplines of biomedical engineering, physiology, and clinical cardiology. In a monthly joint lab meeting with the experimental research group of Prof. Frits Prinzen and the clinical research group of Dr Kevin Vernooy, we discuss our research, initiate Maastricht UMC+-based translational research collaborations and develop unique multidisciplinary communication skills. I truly enjoy the dissemination of my group's scientific output among colleagues in the field, medical doctors, and patients. The latter can be appreciated from the invitation to present my work for patient organisation meetings such as Lotgenotendag Stichting PHA and the RESCAR congress, and for the Maastricht UMC+ event '*Dag van de Wetenschap*' and PAS Festival.

Lotgenotendag Stichting PHA
'*Dag van de Wetenschap*'
PAS Festival

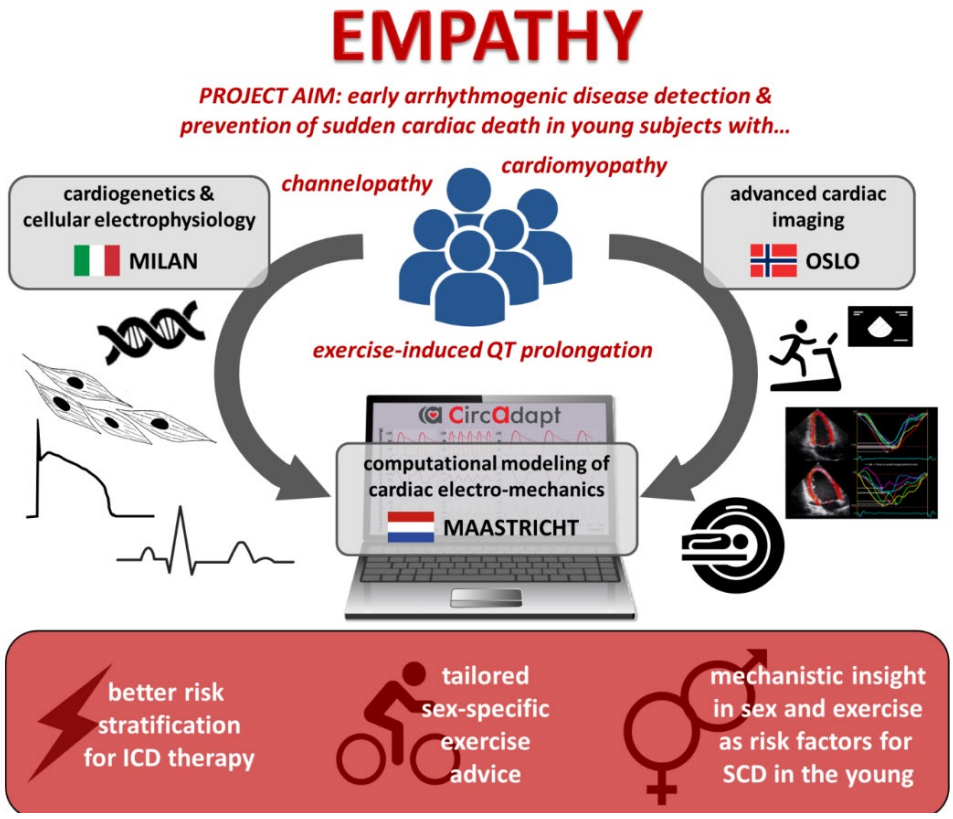
Research quality

In the last six years (2013-2018), my group published several papers in the Journal of the American College of Cardiology and was I awarded two personal grants by the Dutch Heart Foundation (2012 and 2015) and a Vidi grant by NOW ZonMw (2017) on personalised cardiovascular modelling. Furthermore, I am work package leader in a Horizon 2020 programme (EraCoSysMed), entitled 'Personalized MultiSystems simulations for Honing Cardiac Resynchronization Therapy (PUSHCART)'. I am also the coordinator of the recently awarded H2020 consortium grant in the ERA-CVD programme, entitled 'Electromechanical Presages of Sudden Cardiac Death in the Young: integrating imaging, modelling and genetics for patient stratification (EMPATHY)' (see Figure 3). Each year since 2014, I present my team's research findings on cardiac simulation as an invited faculty at large clinical conferences on cardiac imaging (ESC-EACVI EuroEcho-Imaging), cardiac rhythm (ESC-EHRA Europace) and general cardiology (ESC Scientific Sessions).

Journal of the American College of Cardiology

EraCoSysMed

Figure 3 EMPATHY project overview



Personalised medicine and an alternative to animal experiments

My group's virtual patient simulation technology will facilitate personalised medicine in the field of cardiac care and already provides new mechanistic insights in a large variety of cardiac diseases (CircAdapt publication overview). The fact that many other (inter)national research groups are using CircAdapt for their research, both in consultation with or independent from our group, proves that our software stimulates other scientists to use computer models of the human heart and circulation as a reliable and cheap alternative to animal experiments for the investigation of mechanisms and responses to novel therapies for cardiovascular diseases.

CircAdapt publication overview

Educational impact: the CircAdapt Simulator, a free educational tool

Large educational impact has been achieved through the development of the CircAdapt Simulator, a freely available interactive teaching tool for education of cardiovascular (patho) physiology to medical students, clinical trainees, and biomedical engineers. The software is structurally used for teaching medical students of Maastricht University (1st-, 2nd-, and 3rd-year GEN/ITM, 1st-year AKO), Radboud University Nijmegen and several international universities. I amm the webmaster of the CircAdapt Portal www.circadapt.org through which the CircAdapt Simulator freeware is disseminated. Since September 2013, the software has been downloaded more than 7,000 times by students, academic researchers, and medical teachers from >40 different countries spread over all continents. Currently, the CircAdapt educational software is also being implemented in the programme of the Papendal course on Cardiac Function and Adaptation of the Dutch Heart Foundation, annually attended by ~50 PhD canidate of cardiac research institutes of Dutch universities.

European Society of Cardiology (ESC): Working Group on e-Cardiology

The ESC Working Group on e-Cardiology provides the perfect infrastructure for scientists from various fields to interact on new topics and new applications of information technology and e-health in cardiology. My roles as Chair-Elect (2016-2018) and Chair (2018-2020) enable me to actively advocate the use of computer simulations for education, research and clinical decision taking in cardiology through organisation of sessions on this topic at international conferences (i.e., ESC Scientific Sessions, EuroEcho-Imaging, and EHRA-EuroPace). During my current mandate as Chair of this working group, I will propose a position paper on 'In Silico Clinical Trials and Simulation-Based Clinical Decision Support Tools' to be jointly endorsed by the WG on e-Cardiology and the ESC Council on Basic Cardiovascular Science.

Industry

From a commercial standpoint, medical imaging companies and biomedical device manufacturers all stand to gain from our virtual patient simulation technology. It will increase the diagnostic, therapeutic, and economic efficiency of existing imaging techniques and cardiac device therapies. Another commercially interesting aspect of our research is that the CircAdapt cardiovascular model can serve as a clinically validated platform for *in silico* clinical trials for developing and evaluating novel biomedical devices/products for cardiovascular care. Several health care industry partners have invited me to their headquarters to present my group's research, i.e. Medtronic (Minneapolis), Philips-TomTec (Munich), and Siemens (Erlangen). Medtronic contracted me (consultancy service agreement) for testing the functional consequences of a novel artificial valve implant in the CircAdapt model. The results will be used by Medtronic to decide on further investment in the biomedical device. This ongoing public-private collaboration is an example of a true *in silico* clinical trial.

Unravelling mechanisms underlying ventricular tachyarrhythmias in the genetically-susceptible heart

Dr Rachel M.A. ter Bekke, Department of Cardiology

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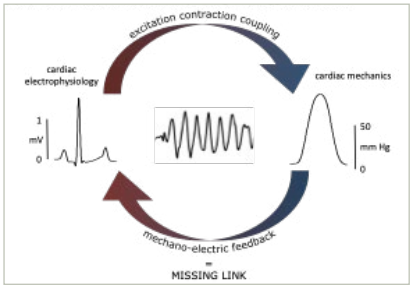
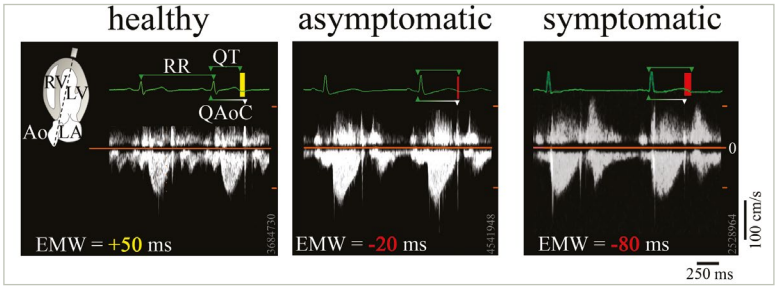
Ventricular arrhythmogenesis: an electromechanical interaction

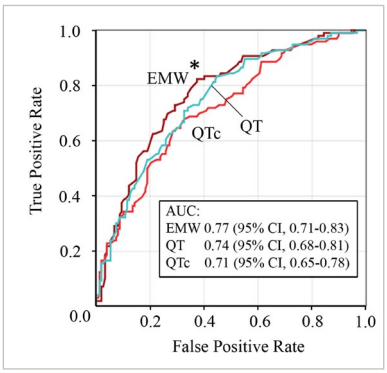
I defended my PhD thesis 'Ventricular arrhythmogenesis in the genetically-susceptible heart: time to change concepts of mechanisms and therapy' in June 2018. Prior to this, it was often overlooked that the heart is also a mechanosensory organ that can convert mechanical deformation into electrical signals. Through our research, it became clear that such mechanoelectrical feedback mechanisms can contribute to ventricular arrhythmogenesis at least in inherited channelopathies like the long-QT syndrome (LQTS). Altered electromechanical relations are appreciated under baseline conditions, but are more pronounced in the final moments before ventricular fibrillation (VF) or torsades-de-pointes ventricular tachyarrhythmias.



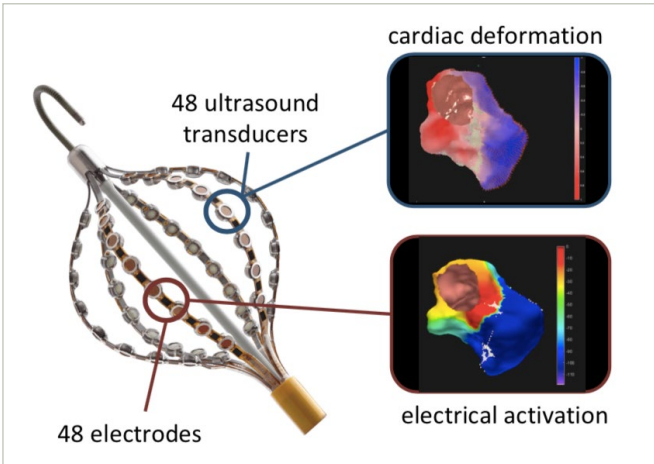
Major breakthroughs

A breakthrough in our research was the demonstration that increased arrhythmogenic mechano-electric heterogeneity predicted major arrhythmic events (including sudden cardiac death) better than traditional repolarisation markers in a large LQTS population [1, 2]. After initiating this research in patients in Maastricht, by combined electro- and echocardiography, two other academic centers (Mayo Clinic, Rochester, MN, USA, and University of Oslo, Norway) joined our project, which substantially increased the patient numbers. It became clear that symptomatic LQTS patients not only had a more prolonged electrical systole (QT interval on ECG), but also that the so-called 'electromechanical window' (mechanical minus electrical systole) became negative, mostly in symptomatic patients and those with Jervell and Lange Nielsen syndrome [2]. Our data indicated that the simultaneous assessment of electromechanical coupling has benefit for arrhythmia-risk analysis. The results of this research, together with other reports on aberrant cardiac mechanics in LQTS [3, 4, 5], led to a paradigm shift: the LQTS is no longer considered a 'purely electrical disease' but an electromechanical disease with mechano-electric consequences [6].





We further investigated the discordant mechano-electric coupling in an experimental animal model of drug-induced long-QT1 syndrome with superimposed unilateral sympathetic stimulation [7]. Two leading international cardiologists with specific expertise on neuroaxial modulation of the heart joined our experiments. Left-stellate ganglion stimulation provoked ventricular tachyarrhythmia and VF only when repolarisation was prolonged and the electromechanical window turned significantly negative. Our research hinted towards a proarrhythmic role for vagal-tone rebound under these conditions, consistent with the concept of 'autonomic conflict'.



This translational work opened new avenues for refined arrhythmia risk stratification, therapeutic drug and innovative device development. Future directions including high-density intracardiac and noninvasive electromechanical mapping are described in a recent Veni ZonMw/NWO grant application (2019). To this aim, I have established a collaboration with the Preclinical Development & Safety Laboratory of Dr David Gallacher at Janssen Research & Development in Beerse, Belgium and Acutus Medical, Inc. Carlsbad, US to embark on in vivo, high spatiotemporal resolution 3D intracardiac mapping in our experimental model and patients at risk of sudden cardiac death.

Furthermore, we set-up a collaboration with Prof. Katja Odening from the University of Freiburg (Germany) to advance noninvasive electromechanical mapping of LQTS patients by the concomitant use of ECG-imaging and mechanical profiling using cardiac ultrasound and MRI techniques.

Times of 'Ignorance Is Bliss' are over

A second pillar of our research, besides these mechanistic studies to unravel the electromechanical underpinnings of life-threatening ventricular arrhythmias, encompasses the disentangling of genotype-phenotype relations in inherited arrhythmia syndromes. The field of Cardiogenetics evolves at a rapid pace and becomes more complex every day. The easy times of high-effect size mutations with monogenic inheritance patterns and unidirectional functional impact are over and have made way for an ever-growing complex-genetic understanding. Many allelic variations are associated with mediocre or uncertain significance and pleomorphic biophysical profiles. As genetic determinants are increasingly incorporated in individual clinical-decision making and risk assessment, a vigilant attitude is warranted. I have captured such emerging complexities on an individual [8] and population level [9]. For the latter, I built on the availability of a large founder population segregating the SCN5A-p.(Phe1617del) mutation [9]. Patients with this mutation exhibited overlapping cardiac phenotypes including LQTS, cardiac conduction disease, Brugada syndrome, and isorhythmic atrioventricular dissociation. Meticulous phenotyping uncovered clinical manifestations atypical for sodium channelopathies: polymorphic ventricular tachyarrhythmias occurring mostly at daytime, proarrhythmic triggers including auditory stimuli, strong emotions, exercise, and postpartum periods. Besides, female sex was an independent risk factor for cardiac events (hazard ratio 5.1; 95% confidence interval 1.6–16.3). Such founder population constitutes an ideal source for the identification of 'modifier genes' that influence phenotypic expressivity, including sudden cardiac death [10]. In collaboration with Prof. Monika Stoll (CARIM) we have already found that single nucleotide polymorphisms on the non-carrying haplotype affect the trait's expression.

Scientific achievements

I successfully defended my PhD thesis entitled 'Ventricular arrhythmogenesis in the genetically-susceptible heart: time to change concepts of mechanisms and therapy' on 22 June 2018. I have published 14 articles, of which I was the first author in seven in highly-ranked journals. Renowned experts rewarded three publications (related to my PhD research) with an editorial. The mean impact factor of my research is 9.5 and the median impact factor 4.4. The median impact factor of the field Cardiac & Cardiovascular Systems is 2.264. My h-index increased substantially the last years to reach seven at this point in time. Furthermore, I have been the finalist of the Young Investigators Award competition at the 37th Annual Scientific Sessions of the Heart Rhythm Society, and have obtained several awards including the prestigious Seymour Furman Travel Scholarship of the 32nd Annual Scientific Sessions of the Heart Rhythm Society, the Travel Grant of ESC Working Group on Cardiac Cellular Electrophysiology, and the Young Talent Award of CVON-PREDICT consortium. I have been invited as a speaker at the European Society of Cardiology, the Dutch-German Joint Meeting of the Molecular Cardiology Working Groups, Diploma of Advanced Studies in Cardiac Arrhythmia Management, the German Gesellschaft für Kardiologie and the Norwegian Center for Heart Failure Research. Finally, I am involved in two CVON projects namely VIGILANCE (research leader: Prof. Paul Volders; co-investigators Prof. Arthur Wilde, Dr Rutger Hassink, Prof. Joachim Wildberger) and PREDICT (research leaders: Prof. Arthur Wilde and Prof. Marc Vos).

Research collaborators

Initially, our joint research projects involved the Dept. of Cardiology and the Dept. of Radiology and Nuclear Medicine of the Maastricht UMC+, but also other academic hospitals in the Netherlands including the University of Groningen, Amsterdam and Utrecht, and, internationally, University of Oslo (Prof. Thor Edvardsen, Dr Kristina Haugaa Herman), The Long QT Syndrome/Genetic Heart Rhythm Clinic and The Windland Smith Rice Sudden Death Genomics Laboratory (Prof. Michael Ackerman), the Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milano (Prof. Peter Schwartz), and the University of Pavia (Dr. Emilio Vanoli) and Washington University, St. Louis (Prof. Yoram Rudy). As a direct spin-off of my PhD work we have set-up collaboration with the Universities of Freiburg (Prof. Katja Odening) and Hasselt (Prof. Paul Dendaele) to join forces to improve high-resolution noninvasively electromechanical profiling of patients with a genetic susceptibility to VF and sudden cardiac death. A clinical trial is anticipated to start medio 2019. At the experimental side, I instigated collaboration with two commercial partners (Preclinical Development & Safety Laboratory of Dr David Gallacher at Janssen Research & Development in Beerse, Belgium and with Dr Derrick Chou at Acutus Medical, Inc. Carlsbad, US) to pioneer in high-density invasive electromechanical mapping using the noncontact AcQMap catheter in an animal model of drug-induced ventricular (pro)arrhythmia.

Societal impact

www.claudiavolders.nl

https://hartenvaatcentrum.mumc.nl/heart-project,

http://www.claudiavolders.nl/index.php/en/art-projects/zenderdna-2/heart-project

https://www.youtube.com/watch?v=SHxSIjXNNEw)

I have established a unique unconventional collaboration with a social process artist (Claudia Volders, www.claudiavolders.nl) to enhance my scientific outreach to patients, their family members, and policy makers. We created art inspired by the genotype-phenotype relations of the large SCN5A founder population described above. We printed scientific results and artistic interpretations at tablecloths and displayed these at outpatient clinics of Maastricht UMC+ and Zuyderland Medical Center in Heerlen. Patients were invited to write any thought or emotion on these artistic tablecloths. These unconventional means to improve the patient-doctor communication had a stimulating effect and was subsequently published. The so-called HeArt exposition travelled to the main building of Maastricht University (https://hartenvaatcentrum.mumc.nl/heart-project, http://www.claudiavolders.nl/index.php/en/art-projects/zenderdna-2/heart-project and https://www.youtube.com/watch?v=SHxSIjXNNEw).

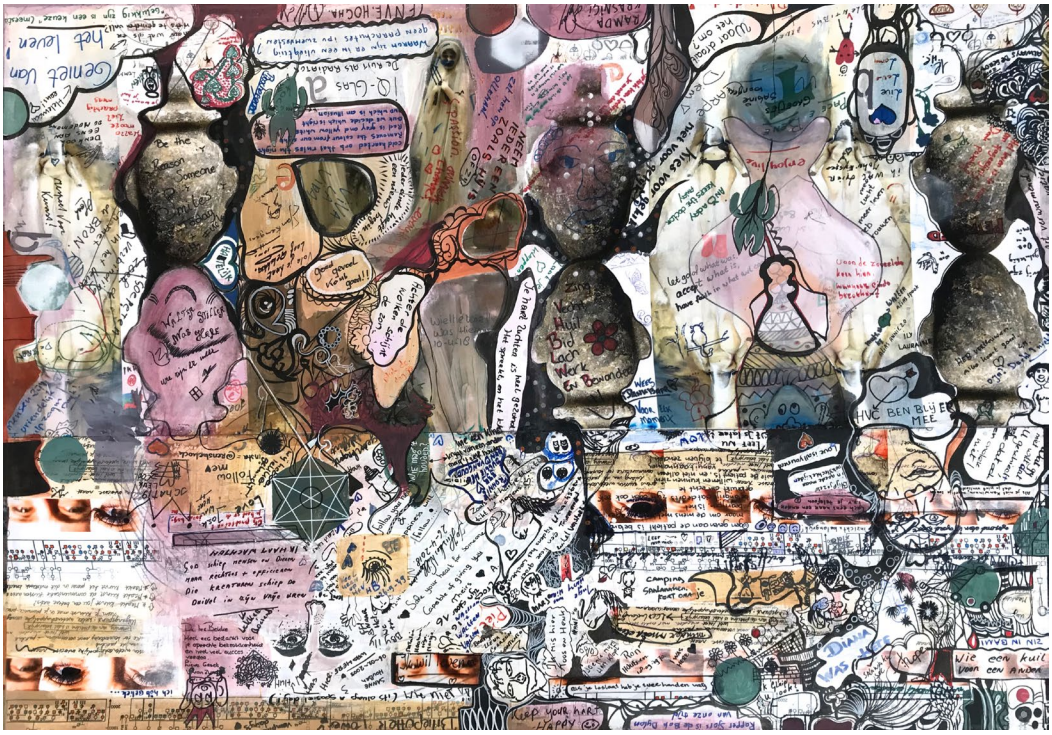
Our research has been widely covered in the media:

- *De Cardioloog: 'Kunst stelt het hart open'* (October 2018).
- Mergelland TV: Sudden cardiac death and the Worm study (October-November, 2018).
- YouTube: '*Opzienbarende ontdekking hartstilstand*' (October, 2018).
- Number 1: *Speurtocht naar oorzaken plotselinge hartstilstand* (June 2017).

Opzienbarende ontdekking hartstilstan

Newspapers:

- 1Limburg press announcement "*Maastrichtse cardioloog wint 'zilver'*" (May 2016)
- *Belang van Limburg* (Belgium): *Worm studie* (June, 2013).
- Amigoe (Curaçao): '*Genfout bedreigt Zuid-Limburgse families*' (13 June, 2013).
- *Dagblad de Limburger*: 'Dodelijk genfoutje in Limburgse families' (February 2013).
- University of Maastricht's Gezond Idee: '*Plotselinge hartdood voorkomen' in rubriek Mijn Ontdekking* (June, 2013).



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[7] ter Bekke RMA, Moers AME, de Jong MMJ, Johnson DM, Schwartz PJ, Vanoli E, Volders PGA. Proarrhythmic proclivity of left-stellate ganglion stimulation in a canine model of drug-induced long-QT syndrome type 1. Int J Cardiol 2019:Epub ahead of print.

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[10] Brink PA, Schwartz PJ. Of founder populations, long QT syndrome, and destiny. Heart Rhythm 2009;6(11 Suppl):S25-S33.

Type 2 diabetes and brain disease within The Maastricht Study

NAR
RATI
VES

Dr Miranda T. Schram, Department of Internal Medicine

What is the impact of type 2 diabetes on the brain?

In 2007, I wrote the RIVM report 'Diabetes and depression a troublesome combination'. Depression appeared to be twice as prevalent in type 2 diabetes, and I published that diabetes and depression are accompanied by a considerable reduction in quality of life [1], and a 50% increased mortality risk [2]. However, the evidence on any pathophysiologic pathway that explained the co-occurrence of diabetes and depression was lacking. I hypothesised that early vascular disease, as abundantly present in type 2 diabetes, may be responsible for the overrepresentation of depression in diabetes. From 2008 onwards, I initiated the population-based Maastricht Study and successfully implemented a comprehensive battery of early markers of vascular dysfunction, including brain MRI, and state-of-the-art assessment of depression within this study [3], to overcome the paucity of data on this topic. This has led to important contributions in our understanding of the etiologic pathways that are be involved in the development of both depression and type 2 diabetes.

Who is involved?

The Maastricht Study is a population-based cohort study that currently includes over 8,000 participants living in Maastricht and surroundings that undergo three to four day parts of state-of-the-art measurements (advanced phenotyping). From 2008 until 2014, I was initiator and project leader of the Maastricht Study. My responsibilities included the scientific design of the study, establishing the content of the protocol in close collaboration to numerous scientists, and setup of the operational structure of the study. This resulted in the multidisciplinary research infrastructure that the Maastricht Study is today; the largest epidemiological study focusing on type 2 diabetes world-wide. In that period, I managed the multidisciplinary Maastricht Study team, which increased from three towards over 50 employees, at the novel research centre. I stepped down as project leader in 2014 to focus on my scientific work. At present, I am member of the Management Board of the Maastricht Study.

Diabetes and depression

Based on the unique data on early markers of vascular dysfunction, including brain MRI, and state-of-the-art assessment of depression in both individuals with and without type 2 diabetes, I confirmed that markers of endothelial dysfunction, arterial stiffness, low-grade inflammation and advanced glycation are indeed associated with depression [4, 5, 6]. In an extensive meta-analysis we were able to demonstrate that microvascular damage to the brain can predict depression over time [7], which suggests an etiologic link. In my future work, I will further investigate the role of early vascular dysfunction in the development of depression in type 2 diabetes in longitudinal data to further assess causality. Moreover, I will assess the impact of social relationships and diabetes distress on the development of depression in type 2 diabetes, in order to prevent the development of depression.

Users and collaborations

To perform this type of multidisciplinary research, I have initiated many collaborations with local (Maastricht UMC+), national and international partners. Important to note are the close collaborations with MHeNs scientists of the Dept. of Psychiatry and Neuropsychology (Prof. F Verhey, Prof. M. de Vugt, Dr S. Köhler, Dr M. van Boxtel) and the Dept. of Radiology (Prof. W. Backes, Dr J.J. Jansen) on depression, cognitive decline and MRI imaging of cerebral small vessel disease and connectivity. With CAPHRI, I work on the impact of social network characteristics on type 2 diabetes (Prof. P. Savelkoul Dept. of Medical Microbiology, and Prof. C. Hoebe, Dr N. Dukers Dept. of Infectious Disease/GGD Zuid-Limburg). To assess the societal and financial impact of type 2 diabetes I collaborate with Prof. S. Evers (Department of Health Services Research). In addition, Scannexus is an important contract partner for MRI assessments in the Maastricht Study (K. Feron, Prof. A. Scherpbier), and Datahub (P. Suppers) is a preferred partner for data storage. My (inter-)national collaborations include a collaboration with Drs E. Janssen, psychiatrist at Mondriaan, with Dr S.S. Soedamah-Muthu and Prof. J. Denollet at Tilburg

University on nutritional behaviour and personality traits in type 2 diabetes. Furthermore, I am member of several consortia including:

- The Memorabel Consortium of ZonMW with members from all large scale cohort studies on cognitive decline and dementia in the Netherlands (Prof. M. Ikram (Rotterdam Study), Dr PJ Visser (Alzheimer Center VUMC), Dr M. Geerlings (SMART study), Prof. P. de Deyn (Lifelines), Prof. P. Slagboom (LUMC), Dr M. Verschuren (Doetinchem cohort study), Prof. W. van der Flier (Alzheimer Center VUMC), Prof. M. Huisman (LASA Study).
- The Geohealth Cohort Consortium (GECCO, NWO middelgroot project by Dr J. Lakerveld, Prof. M. Huisman, Prof. B. Penninx, Dr E. Timmermans, Dr J. Beulens, Prof. J. Dekkers, Prof. I. Boomsma, Dr E. Generaal, Prof. K. Stronks, Dr K. van den Hurk, Dr W. Mulder, Dr F van Lenthe, Dr M. Verschuren, Prof. M. Ikram, Prof. V. Jaddoe, Dr C. Vaartjes, Prof. C. Stehouwer, Dr C. Schuengel, Dr M. Dijst, Dr A. Willemsen, Dr R. de Mutsert, Dr A. Dottinga, Dr A. Koster).
- Diabetes Pearl String Initiative (Diabetes experts from all eight UMC's in the Netherlands)
- The European Depression in Diabetes consortium (EDID)
- Initiator of Danish-Dutch Taskforce 'Diabetes and Depression, a burdensome combination that warrants further research'.

Scientific quality

The Maastricht Study laid the foundation for multiple PhD projects and internships. Currently, over 30 PhD projects are running, of which 19 have been successfully finished, as well as over 90 internships for Bachelor and Master students of Maastricht University. In the beginning of 2018, over 60 manuscripts have been published in peer-reviewed journals. The Maastricht Study has built a scientific reputation over the years, which resulted in at least ten so-called high impact papers (impact factor >10) on Maastricht Study data today.

Societal impact

I highly value the sharing of new insights with both the general and scientific public. Therefore, I initiated two annual symposia from 2012 onwards: The Scientific Meeting of The Maastricht Study, Maastricht, The Netherlands and the *Publiekssymposium* about The Maastricht Study, for participants of the Maastricht Study, Maastricht, the Netherlands. Results of the study are also highlighted on the Maastricht Study website in several media publications (please see: https://www.demaastrichtstudie.nl/actueel/nieuws). Specific scientific publications have been highlighted by press releases as well:

https://www.demaastrichtstudie.nl/actueel/nieuws

- December 2017: Brinkhues et al. Socially isolated individuals are more prone to have newly diagnosed and prevalent type 2 diabetes mellitus - the Maastricht study – BMC Public Health 2017. Metrics: 1085 media hits, 27 tweets, 74% members of the public, 19% health care practitioners, 7% scientists (https://biomedcentral.altmetric.com/details/30638368).

https://biomedcentral.altmetric.com/details/30638368

- December 2017: Persbericht MUMC+: Sociaal isolement gerelateerd aan diabetes type 2. *Onderzoeksresultaat Maastricht Studie van belang in het kader van preventie*
- Juni 2017: Persbericht MUMC+: Schade aan haarvaten kan tot depressie leiden. *Metingen aan de microcirculatie specialisme van De Maastricht Studie*
- 2016: Interview in CARIM annual report

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Vitamin K and vascular smooth muscle cell involvement in calcification of arteries and heart valves

Prof. Leon J. Schurgers, Department of Biochemistry

NAR
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What is vascular calcification?

I started my research on vitamin K and vitamin K-dependent proteins in relation to vascular calcification some 20 years ago. In these times, vascular calcification was regarded as an innocent bystander in cardiovascular disease. It was considered to be the passive chemical nucleation of calcium and phosphate ions on vascular smooth muscle cell debris and therefore the end-stage of CVD.

Our research in Maastricht significantly contributed to the understanding that vitamin K-dependent proteins are involved in vascular calcification which boosted our mechanistic understanding of this process and offers targets for diagnosis and intervention. This has now resulted in the Horizon2020 grant INTRICARE with CARIM as coordinator and beneficiary in Horizon2020 grants EVOluTION, CaReSyAn, and TICardio.

Major breakthroughs in our research

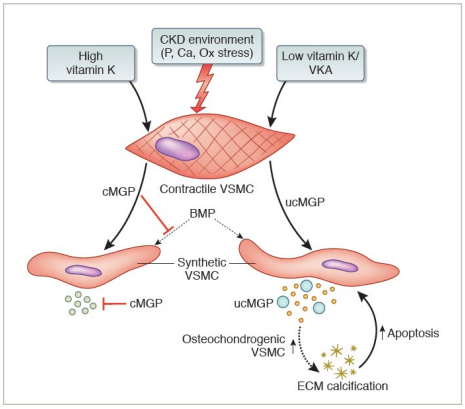
An important breakthrough in our research was the generation of conformation specific antibodies against the vitamin K-dependent matrix Gla-protein (MGP) [1]. During my postdoc, I designed and developed antibodies against active carboxylated and inactive uncarboxylated MGP. In the spin-off company VitaK BV we built our own MGP elisas as biomarker for vascular calcification and to detect vascular vitamin K deficiency. This has led to numerous publications with many renowned institutes [2, 3, 4, 5]. More recently, the antibodies and patents around MGP were sold to the British company IDS and within the Dept. of Biochemistry we are one of the few analysing centre for clinical samples.

In atherosclerotic disease research, calcification was only recently added to the growing list of biological events that play a role in driving vascular disease, and is commonly used as a measure of atherosclerotic burden and cardiovascular mortality [6]. What was not known at the time, is that under certain conditions, the current thrombosis treatment using vitamin-K antagonists (VKAs) could paradoxically lead to a high risk of calcification. VKAs are the most widely used anti-thrombotic drugs, with substantial efficacy in reducing the risk of arterial and venous thrombosis. Our research discovered that the inhibition was not restricted to coagulation factors, but also affected synthesis of functional extra-hepatic vitamin-K dependent proteins (VKDPs), thereby eliciting adverse side effects. It all started with a joint study by the universities of Maastricht and Tübingen – the university where Monckeberg (classical medial calcification; Monckebergsclerosis) was rector magnificus -, which showed that patients on VKA had significantly more vascular calcification than matched patients not on VKA[7]. This was an aspect of research that opened up an entirely new and unexpected field to the coagulation-based research performed at our Department of Biochemistry.

Who is involved?

Joint research projects involving the Biochemistry Department and the Departments of Internal Medicine [8] and Cardiology [9], and with other institutes such as Harvard [10]. This research line now flourished with collaborations in academia and industry (contracts with Bayer, Daichio Sankyo, Boehringer Ingelheim).

After we demonstrated that VKA treatment resulted in increased and accelerated vascular and valvular calcification, our research group got back in contact with the Norwegian stock-exchanged company NattoPharma ASA. With VitaK the research with NattoPharma resulted in a five-year research budget exceeding 3 M€. My research within CARIM led to a renewed collaboration with currently two PhD positions sponsored by NattoPharma. Furthermore, the academic collaboration with the Klinikum Aachen (Helmholz institute, cardiology and

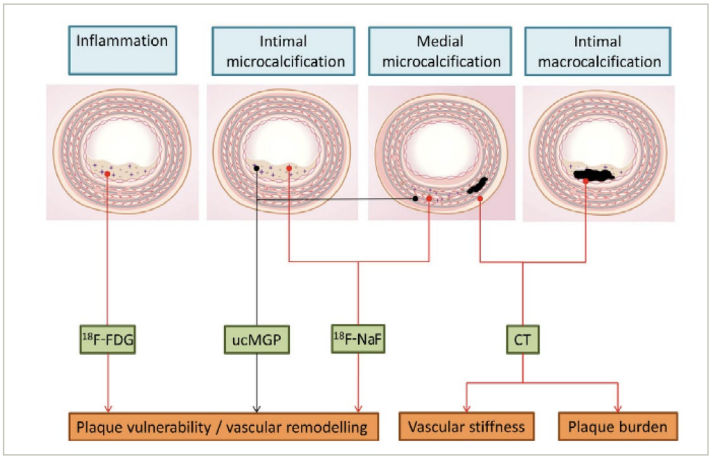


nephrology) and with our own Maastricht UMC (Vascular surgery/ HvC, Cardiology and Internal Medicine), is based on our initial work on differential roles of vitamin K1 and K2 – my former PhD work. The first clinical trial showing hold on progression of aortic valve calcification has now been accepted by Circulation (Brandenburg,...Schurgers/Koos) and three more clinical trials are currently being on going (VitaK-CAC NCT01002157, VitaVasK NCT01742273, BASIK2 NCT02917525).

Finally, our research investigates the role of vascular smooth muscle cells (VSMCs) in CVD. VSMCs in the tunica media regulate vessel tone and diameter in order to maintain haemodynamic balance. Phenotypic flexibility of VSMCs is necessary to cope with the varying conditions of vascular tissue [11]. However, phenotypic switching of VSMCs plays a key role in vascular disease and is a precondition for vascular calcification.

Vitamin K-dependent proteins such as the matrix Gla protein (MGP) produced by VSMCs are key factors in the inhibition of vascular calcification [12]. We have set-up collaboration with Cambridge University (group of Prof. Bennett) and are working with mice that harbour a unique VSMC receptor to induce apoptosis of VSMCs so that we are able to investigate the role of VSMCs in CVD. This has resulted in a collaboration between HvC (Prof. Jacobs) and CARIM (Schurgers) [13] to further establish – next to the clinical aneurysm research – a basic research line investigating VSMC involvement in aneurysm formation. Finally, we have created our own 'UMouse", in which we knocked-in a cherry (red signal) construct after the smoothelin promotor. Smoothelin is the strongest marker for VSMC contractility and thus 'health.

All the above-mentioned work and established collaborations have gained extensive media exposure, and the research on active microcalcification will put forward Maastricht as expert centre in fundamental and clinical research, as well as state of the art imaging-probe design and imaging.



Users and collaborations

Our research attracts young students from all over Europe to Maastricht. Our group is an expertise centre for deliver young researchers, that have received a comprehensive training in basic and translational vascular research with a particular focus on vascular calcification.

Societal impact

Our research has received extensive media exposure:
Dr. Mercola Interviews Dr. Schurgers on Vitamin K
Articles *Nu.nl*, *GezondheidPlus*, *RTV Maastricht*, *1 Limburg*, *Nationale Zorggids*, *Blik op Nieuws* on INTRICARE.

Dr. Mercola Interviews Dr. Schurgers on Vitamin K

Nu.nl, *GezondheidPlus*, *RTV Maastricht*, *1 Limburg*, *Nationale Zorggids*, *Blik op Nieuws*

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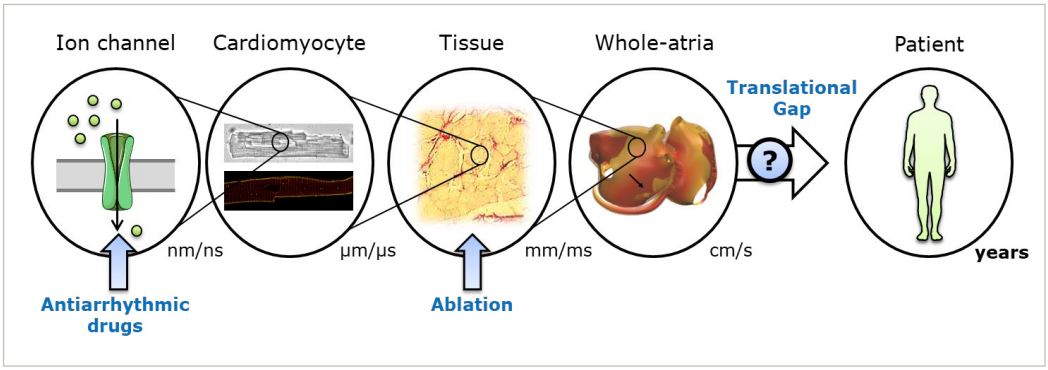
Computational modelling of cardiac arrhythmias

Dr Jordi Heijman, Department of Cardiology

Why do we need computational modelling of cardiac arrhythmias?

Cardiac arrhythmias have a major impact on the morbidity and mortality of millions of patients, a number that is expected to grow with the ageing of the population [1]. CARIM has a long-standing history and renowned expertise in clinical arrhythmology, exemplified by the previous (Prof. Hein Wellens) and current (Prof. Harry Crijns) chairman of the dept of cardiology, who are recognized experts in sudden cardiac death / electrocardiography and atrial fibrillation, respectively. In addition, several CARIM PIs have performed ground-breaking pre-clinical and translational research using large animal models to improve our understanding of atrial fibrillation (Prof. Ulrich Schotten), cardiac resynchronization therapy (Prof. Frits Prinzen) and ventricular arrhythmogenesis (Prof. Paul Volders). However, ethical and practical considerations have made the use of large animal models increasingly challenging. Although small animal models are commonly used to study cardiovascular diseases and have several advantages (notably the opportunity for genetic modification), their electrophysiological properties are significantly different from humans,[2] limiting their clinical relevance and making them less suitable for arrhythmia research. Regardless of species, experimental studies typically have limited options to modulate the system of interest (e.g., due to absence of selective pharmacological agents) and can only record a small number of parameters. In particular, it is not possible to reverse time and look at the exact same experiment from a new angle. Finally, it remains experimentally challenging to bridge the wide range of scales involved in cardiac arrhythmogenesis (Figure 1). Multi-scale computer models offer perfect control and perfect observability, making them highly suitable for testing causality and performing detailed analyses of arrhythmogenic mechanisms [3, 4]. Indeed, multi-scale computational models of cardiac electrophysiology have advanced significantly during the last 30 years, are now commonly used to study arrhythmia mechanisms and are starting to affect clinical cardiac arrhythmia management [5, 6].

Figure 1 Multi-scale complexity of cardiac electrophysiology and arrhythmogenesis.



Major breakthroughs in our research

I first came into contact with computational models of cardiac electrophysiology in 2006 during my Bachelor Thesis research, in which I could show that models available at that time did not show beat-to-beat variability of repolarisation duration, a parameter that had experimentally been suggested as an important risk marker for ventricular arrhythmias [7]. Since then, we have contributed significantly to the field of computational modelling of cardiac electrophysiology, in close collaboration with several people at CARIM (see section 'Who is involved', below).

We were among the first to integrate localised biochemical signalling pathways in cardiac electrophysiology models to simulate the effects of sympathetic stimulation [8]. Although such signalling pathways are essential for acute (seconds) and long-term (hours-days) regulation of cardiac electrophysiology and play a major role in multiple cardiovascular diseases, they have received relatively little attention in computational modelling efforts (with only 5% of PudMed publications on computational modelling of cardiac electrophysiology incorporating

signalling components[1]). Besides the β-adrenergic signalling pathway model, which has been used by several other groups, we have modelled the Ca^{2+}/calmodulin-dependent kinase-II (CaMKII) pathway [9] and have recently made the first steps in modelling transcription and translation of ion-channels to simulate long-term remodelling processes (MSc thesis of Lian Laudy; unpublished). We strongly believe that incorporation of these pathways will significantly advance the state of the art and create a unique opportunity to study the potential proarrhythmic effects of long-term cardiac remodelling during disease conditions, thereby creating an important connection between the programs on 'Complex Arrhythmias' and 'Structural Heart Disease' within CARIM.

A significant part of our work has focused on the role of abnormal Ca^{2+} handling in arrhythmogenesis, for example investigating its role in patients with paroxysmal atrial fibrillation together with Prof. Dobromir Dobrev (Essen, Germany) and Prof. Stanley Nattel (Montreal, Canada) [10]. As part of my NWO Veni project we also provided the first direct evidence that the subcellular distribution of Ca^{2+}-handling proteins, notably the cardiac ryanodine receptor (RyR2), has a major impact on Ca^{2+}-handling abnormalities [11]. This strongly suggests that simple Western blot experiments to assess total levels of RyR2 (or its phosphorylation) are not sufficient to evaluate the molecular basis of RyR2 dysfunction. Super-resolution microscopy experiments are needed to evaluate the RyR2 distribution. We are also working on alternative mechanisms through which Ca^{2+}-handling abnormalities can promote arrhythmogenesis, for instance through the regulation of other (non-Ca^{2+}) ion channels (PhD thesis of Henry Sutanto; unpublished). Finally, we are using computer models to study the mechanisms of ventricular arrhythmias in patients carrying the R14del founder mutation in phospholamban, an important regulator of cardiomyocyte Ca^{2+} handling, in collaboration with the large Dutch CVON-Predict consortium.

Besides providing important insight into arrhythmia mechanisms, computer models such as the ones developed at CARIM play an increasingly important role in risk prediction and treatment of arrhythmias. For example, the 'Comprehensive In vitro Proarrhythmia Assay' initiative, a collaboration between regulatory agencies (FDA), academia and pharmaceutical industry to improve the safety screening of new pharmacological compounds with respect to potential proarrhythmic side effects, includes an important role for computer models [12]. In addition, computer models may help to explain the complex effects of currently available antiarrhythmic drugs under diverse clinical conditions. For this purpose, we have recently developed a user-friendly framework encompassing a wide range of models and antiarrhythmic drugs, the 'Maastricht Antiarrhythmic Drug Evaluator' (MANTA; Figure 2) [13] Finally, computer models may help identify the antiarrhythmic potential of novel targets and/or (combinations of) drugs. For example, we have previously contributed to an investigation from Heidelberg University, Germany on the antiarrhythmic potential of two-pore-domain K^+ channels for the treatment of atrial fibrillation [14, 15]. These data have motivated further studies, including animal studies and a clinical study evaluating a compound affecting this channel that is currently ongoing in Heidelberg. Similarly, in collaboration with Prof. Ulrich Schotten, we employed computer models to study synergistic effects of drug combinations as part of the AfibTrainNet network (PhD thesis of Giulia Gatta; unpublished), enabling us to focus subsequent experimental animal studies towards the most promising combinations.

Taken together, computer models have provided import insight into cardiac arrhythmias with numerous translational applications both within CARIM and externally. Their use helps to refine (animal) experiments and in the near future may have important clinical applications, resulting in a large societal impact.

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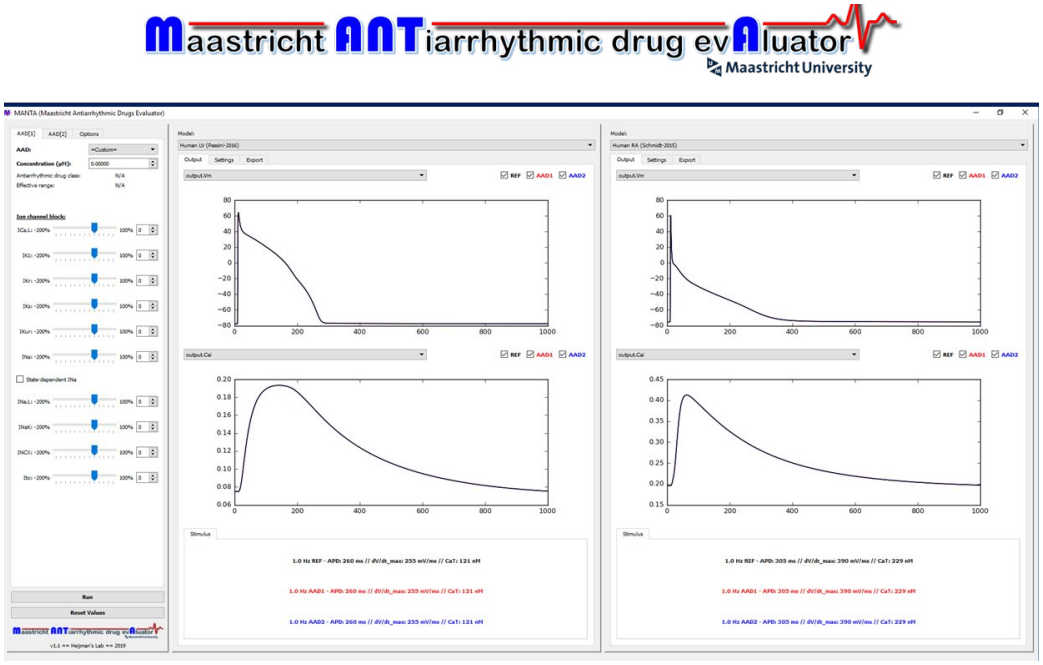
1 Defined as: "cardiac and (electrophysiology or "action potential" or "arrhythmia") and (simulation or "in silico" or "computer model" or "computational modeling")" with or without "("signaling" or "signalling")"

Figure 2 The Maastricht Antiarrhythmic Drug Evaluator. A freely available software tool to analyse the complex effects of antiarrhythmic drugs under different conditions.



Who is involved?

Computational modelling is inherently a collaborative effort, requiring a continuous ('ping-pong') interaction between experiments and modelling efforts. In addition, the clinical application of these models requires close collaboration with clinical partners. CARIM provides a unique environment in which all these stakeholders are integrated in the division 'Heart'.

For computational modelling of cardiac electrophysiology, there are active collaborations with the PI groups of Prof. Crijns, Prof. Volders and Prof. Schotten. Finally, although the fields of cardiac electrophysiology and mechanics have traditionally operated relatively independently, there is increasing awareness that there are important bidirectional interactions. Indeed, mechanical alterations can be important triggers for cardiac arrhythmias and abnormal excitation-contraction coupling affects mechanical function. Within CARIM, the Dept. of Biomedical Engineering (Dr Joost Lumens) has extensive experience with computer models of cardiac mechanics, both at the subcellular level (MechChem[16]) and at the organ/system level (CircAdapt[17]). We have recently started to combine the available electrophysiological and mechanical modelling expertise within CARIM in a fully coupled electromechanical model. This model will be used to investigate the proarrhythmic effects of exercise, which has important mechanical and electrical components, in the ERA-CVD project 'EMPATHY', a collaboration between CARIM (PI: Dr Joost Lumens, collaborator: Dr Jordi Heijman), Oslo University Hospital (PI: Prof. Kristina Haugaa) and IRCCS Istituto Auxologico Milan (PI: Dr Lia Crotti).

We organise regular Computational Cardiac Electromechanics (CODE) research meetings in which CARIM researchers from the Dept. of Cardiology, Dept. Physiology and Dept. of Biomedical Engineering, as well as collaborators from the Faculty of Science and Engineering, participate. These meetings provide a platform to exchange ideas, share expertise and identify new opportunities for joint projects. In addition, the topic of modelling cardiac electrophysiology is regularly part of the Maastricht Systems Biology Forum meetings, a quarterly event bringing together all researchers interested in Systems Biology within Maastricht University.

Users and collaborations

Besides the interest in computational modelling from several PI groups within CARIM, the value of computational modelling has been shown in numerous international collaborations, leading to several high-profile publications (see below). Important active collaborations exist with respect to simulating the mechanisms of atrial fibrillation with Prof. Dobromir Dobrev (Essen, Germany) and Prof. Stanley Nattel (Montreal, Canada), elucidating the mechanisms of channelopathies (Prof. Katja Odening, Freiburg, Germany) and simulating the electrophysiological effects of alcohol (Dr Markéta Bébarova, Brno, Czech Republic), among others.

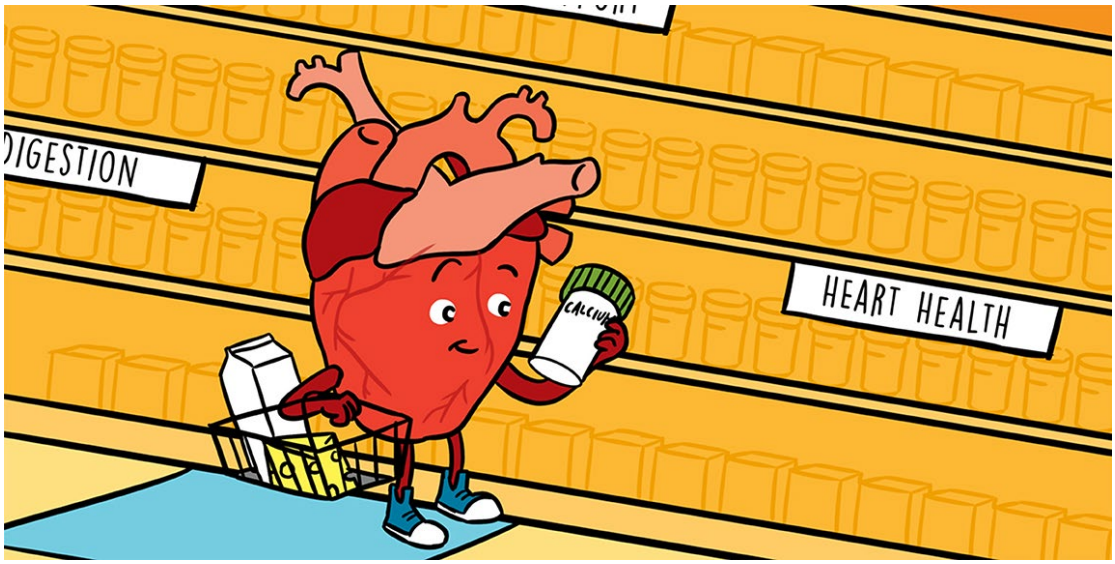
Of note, the models that we develop are made freely available to everyone who is interested. This has led to numerous downloads and studies employing our models for further research,

both within academia and from the pharmaceutical industry. We are regularly approached by other scientists (users of our models) with specific questions. Finally, MANTA is designed to be used by cardiologists and students who want to better understand the complex effects of antiarrhythmic drugs (rather than experts in computational modelling), creating a different group of users that may benefit from our models.

Societal impact

Both the relevance of computer modelling to study cardiac arrhythmias, as well as the expertise of CARIM in this area is increasingly recognised. In addition to the societal impact regarding animal experiments and patient care described earlier, this has resulted in a number of lectures for general audiences, as well as publications in the general press (summarized below). In addition, we have recently published a manuscript in *Frontiers for Young Minds*, an international journal aimed at young aspiring scientists, about the role of calcium in heart rhythm disorders (https://kids.frontiersin.org/article/10.3389/frym.2019.00065). These initiatives help to inform and educate the general public about the impact of our work.

Cover image from our paper in Frontiers for Young Minds



Lectures for lay audiences:

- "Ons hart: hoe werkt het en waarom werkt het soms niet goed?" (in Dutch), KidzCollege Maastricht (https://www.maastrichtuniversity.nl/nl/nieuws-agenda/voorlichtingsactiviteiten/kidzcollege), June 19, 2019, Maastricht, The Netherlands.
- "De mechanismen van hartritmestoornissen: van (virtuele) hartspiercel tot gepersonaliseerde therapie" (in Dutch), Seniorenuniversiteit UHasselt (https://www.uhasselt.be/seniorenuniversiteit), November 13, 2017, Diepenbeek, Belgium (>450 attendees, presentation evaluated by attendees with 9 out of 10).
- "Hartritmestoornissen: het hart op hol" (in Dutch and English), Parcours of Arts and Sciences Maastricht 2017 (http://www.pasmaastricht.nl/), September 8-9, 2017, Maastricht, The Netherlands.
- "Pharmakologische Therapie bei Vorhofflimmern" (in German), 50th anniversary of the faculty of medicine, University Duisburg-Essen, October 4, 2013, Essen, Germany.
- "De virtuele hartcel onder stress" (in Dutch), 10th anniversary of the Hein J.J. Wellens Foundation, March 23, 2011, Maastricht, The Netherlands.

Publications in the general press:

- Radio interview on "Hartritmestoornissen en DAS-CAM" (in Dutch) on the RTV Maastricht show "Het beleg" (http://www.rtvmaastricht.nl/radio/het-beleg/46419959), March 2, 2017.
- Television interview on the evening talk show "L1 Avondgasten" (http://www.l1.nl/ video/hartkloppingen-wiskunde-29-nov-2016), November 29, 2016 (in Dutch).
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MR CLEAN: The endovascular treatment of acute ischemic stroke

Prof. Robert van Oostenbrugge and Prof. Wim van Zwam, Department of Neurology

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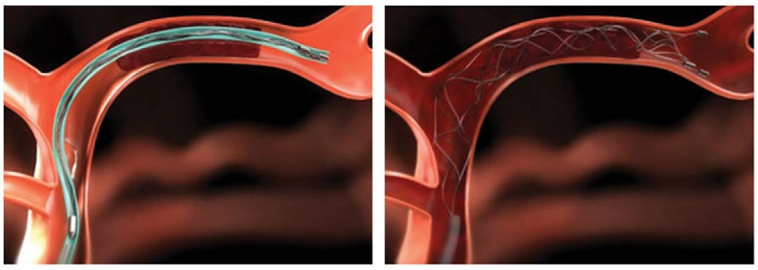
What is acute ischemic stroke?

Vascular neurology has a long-standing research tradition in cerebral small vessel disease, which is an umbrella term covering all pathological processes related to the small vessels of the brain. In the last few years, a novel area of research has opened up: the treatment of acute stroke. Now is a good moment to look back and see how this new line of research has developed, and to look at its future prospects. Stroke is one of the major causes of death, and the main cause of dependency in the western world. Intravenous thrombolysis to achieve early recanalisation has proved effective for acute ischemic stroke patients treated within 4.5 hours after stroke onset. However, despite the overall beneficial effect of this treatment, its effect in acute ischemic stroke patients with intracranial large-vessel occlusion is limited, leading to recanalisation in only 10% of treated patients. Furthermore, the linited time window of intravenous thrombolysis is a major drawback, as many patients arrive at the emergency department outside this time window.



MR CLEAN

MR CLEAN

For more than 20 years, studies (non-randomised as well as randomised) have suggested a benefit of endovascular treatment of acute ischemic stroke due to intracranial large-vessel occlusion. However, although likely, it remained unproven whether this treatment in an unselected sample of patients is indeed beneficial. This was the reason to set up MR CLEAN, a multicentre randomised clinical trial of endovascular treatment of acute ischemic stroke in the Netherlands, in collaboration with Erasmus Medical Center (Rotterdam) and the Academic Medical Center (Amsterdam). MR CLEAN has received funding from the Dutch Heart Foundation. The primary objective of MR CLEAN, was to estimate the effect of endovascular treatment on overall functional outcome after acute ischemic stroke, due to proven intracranial large-vessel occlusion of less than six hours duration. The treatment contrast was endovascular treatment versus no endovascular treatment, and the primary outcome was functionality at three months, estimated by the modified Rankin scale, a seven-point scale ranging from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence.

In December 2010, the first patient was included in MR CLEAN, which ran at 16 sites in the Netherlands. Patient accrual was faster than expected, partly because of the decision of the Dutch government to make reimbursement of the treatment costs conditional on participation in the trial. The last patient was included in the trial in March 2014.

First results

New England Journal of Medicine

Results were first presented at the World Stroke Congress in Istanbul in October 2014, and were published in the New England Journal of Medicine on 1 January 2015 (New Engl J Med 2015;372:11-20). The main finding was a shift in the distribution of the primary-outcome score in favour of the intervention with an adjusted common odds ratio of 1.67 (95% confidence interval [CI], 1.21 to 2.30). The shift toward better outcomes in favour of the intervention was consistent for all categories of the modified Rankin scale, except for death. The absolute between-group difference in the proportion of patients who were functionally independent (modified Rankin score, 0 to 2) was 13.5 percentage points (95% CI, 5.9 to 21.2) in favour of the intervention (32.6% vs. 19.1%). Importantly, there were no safety concerns as there was no significant between-group difference in the occurrence of serious adverse events during the 90-day follow-up period. Symptomatic intracranial haemorrhage, the most severe complication,

was equal in both arms. Shortly after publication of the results, the New York Times stated that the study was 'a game changer' in the treatment of acute ischemic stroke.

The favourable results of MR CLEAN also had a major impact on four other on-going randomised studies on the efficacy of endovascular treatment of acute ischemic stroke due to intracranial large-vessel occlusion, as all four were halted by the respective Data Safety Monitoring Boards. Interim analyses of these four halted randomized studies showed positive results supporting the results of MR CLEAN.

Scientific and societal impact of MR CLEAN

As the MR CLEAN trial included an unselected population, we had the opportunity to study pre-specified predictors of efficacy. This resulted in major new insights into patient selection for this treatment and provided directions for future studies. The most important findings were related to age and pre-treatment selection by imaging characteristics.

First, MR CLEAN showed that age did not modify treatment effect. Hence, it is currently accepted not to withhold endovascular treatment from acute ischemic stroke patients even at very high age.Second, although pre-selection on imaging characteristics led to an overall higher effect of endovascular treatment in the other randomized clinical studies, none of the characteristics, except degree of collateral flow, significantly modified the treatment effect in the unselected population included in MR CLEAN. Based on the findings of MR CLEAN it is now generally accepted that pre-selection of eligible patients is not warranted within the six-hour time window, and that collateral flow might be an important imaging characteristic to use in future trials aiming to determine the efficacy of endovascular treatment in patients who arrive at the hospital more than six hours after stroke onset. Third, it was shown that, like with intravenous thrombolysis, effect of endovascular treatment was strongly time dependent.

Besides its scientific relevance, MR CLEAN also has a huge societal impact. It has set a new stage for the treatment of acute ischemic stroke. To implement this new treatment in practice, stroke care in the Netherlands and in the rest of the world needs to be reorganised as the current system has to evolve into an effectively organised system of care that can provide endovascular treatment to eligible stroke patients as quickly as possible. More importantly, MR CLEAN established a novel effective treatment for major stroke that gives patients the hope of regaining independency.

Prof. Robert van Oostenbrugge and Prof. Wim van Zwam have received several prices related to MR CLEAN such as the Science and Innovation award of the Federation of Medical Specialists and the Award of Excellence and Innovation in Intervention Radiology from the Cardiovascular and Interventional Radiological Society of Europe (CIRSE).

Future perspectives

The near future of research in endovascular treatment in acute ischemic stroke looks bright. Two major prospects lie ahead of us. First, publication of the results of the five endovascular treatment studies led to the establishment of the HERMES collaboration. The main aim of this collaboration, in which MR CLEAN is the major contributor, is to analyse pooled individual patient data. The main paper of this study has been published and showed the effectivity of endovascular treatment in general and over a broad range of sub groups. The HERMES collaboration is still vivid and will continue to publish high impact pooled analyses on different subjects within the field of endovascular treatment of acute ischemic stroke.

Second, based on the success of MR CLEAN, a top-down programme of the Dutch Heart Foundation/CardioVascular Research Netherlands (CVON) was established to further improve the treatment of acute ischemic stroke in the Netherlands. The Vascular Neurology and Interventional Neuroradiology departments of CARIM were heavily involved in the preparation of the overall programme and are principal investigators of the successor to MR CLEAN, i.e. MR CLEAN LATE. This randomised clinical study investigates the efficacy of endovascular treatment in patients with acute ischemic stroke due to intracranial large-vessel occlusion who arrive at the hospital between 6 and 24 hours after stroke. Eligible patients are selected on the presence of collateral flow, the only imaging characteristic that modified treatment effect in MR CLEAN. In the end, what started a couple of years ago as a novel research topic in vascular neurology has now become a major research line and flagship programme for the years to come.

Arterial Thrombosis - More than Fibrin Formation

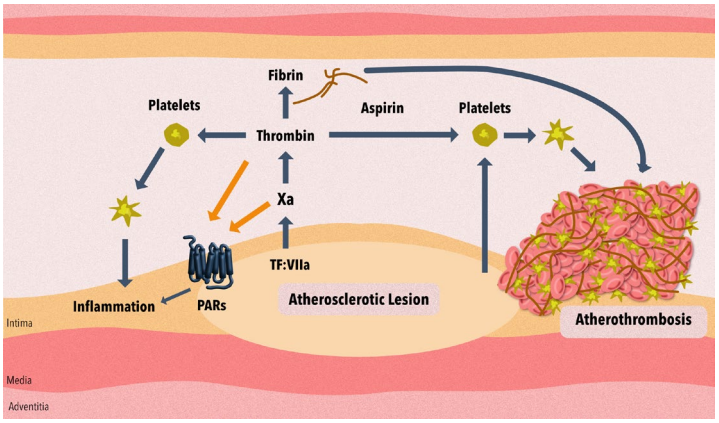
Dr Henri M. H. Spronk, Departments of Biochemistry and Internal Medicine

What is the role of coagulation beyond fibrin formation?

Upon completion of the PhD thesis 'Effects of impaired vitamin K-dependent protein carboxylation', I started as a post-doc in the new laboratory for Clinical Thrombosis and Haemostasis under the supervision of Prof. Hugo ten Cate. At that time, 2002, the research was focussed on biomarkers and prediction of both arterial and venous thrombosis. However, the broad approach and enthusiasm of Prof. Hugo ten Cate for anything related to coagulation and thrombosis, encouraged me to develop my own research line with the focus on activity of coagulation enzymes beyond the generation of a fibrin clot. Following our observation that almost all coagulation factors are present or expressed within the arterial vessel wall, and more precisely, within atherosclerotic lesions [1], the research elaborated on the role of hypercoagulability and cardiovascular disease [2]. Using experimental models, we demonstrated that active coagulation enzymes, mainly thrombin and factor Xa, contribute to the development and progression of atherosclerosis [3, 4]. Inhibition of the coagulation enzymes causes diminished plaque formation and recent data suggest that regression of atherosclerosis is possible through inhibition of factor Xa [4], thereby providing a vascular protective role for antithrombotic medication. Using a sophisticated animal model for myocardial ischemia/reperfusion injury, we were able to demonstrate that inhibition of coagulation reduced the area of infarction in a fibrin independent manner, suggesting a role for coagulation enzymes in inflammation and fibrosis [5, 6]. Besides atherosclerosis and myocardial infarction, the impact of hypercoagulability on the development and progression of atrial fibrillation was demonstrated [7], thereby providing additional evidence that coagulation is a key player in development of cardiovascular disease. This novel concept reversed the commonly accepted fact that atrial fibrillation causes thrombosis into a novel mechanism in which activation of coagulation is a substrate for the development and progression of cardiovascular disease.

Atherothrombosis involves atherosclerotic plaque rupture or erosion and the formation of an intravascular thrombus. The atherosclerotic plaque contains agents, such as collagen, that activate platelets, and tissue factor (TF) which activates the coagulation cascade. Aspirin reduces the thrombus by inhibiting platelet activation. Anticoagulants reduce the thrombus by inhibiting fibrin generation, and also by reducing thrombin activation of platelets. Activated platelets and activation of protease-activated receptors (PARs) by coagulation proteases enhances inflammation in the vessel wall. Aspirin and anticoagulants may also reduce vascular inflammation and limit the progression of atherosclerosis (see Figure 1).

Figure 1 Role of platelets and the coagulation cascade in atherothrombosis and vascular inflammation.

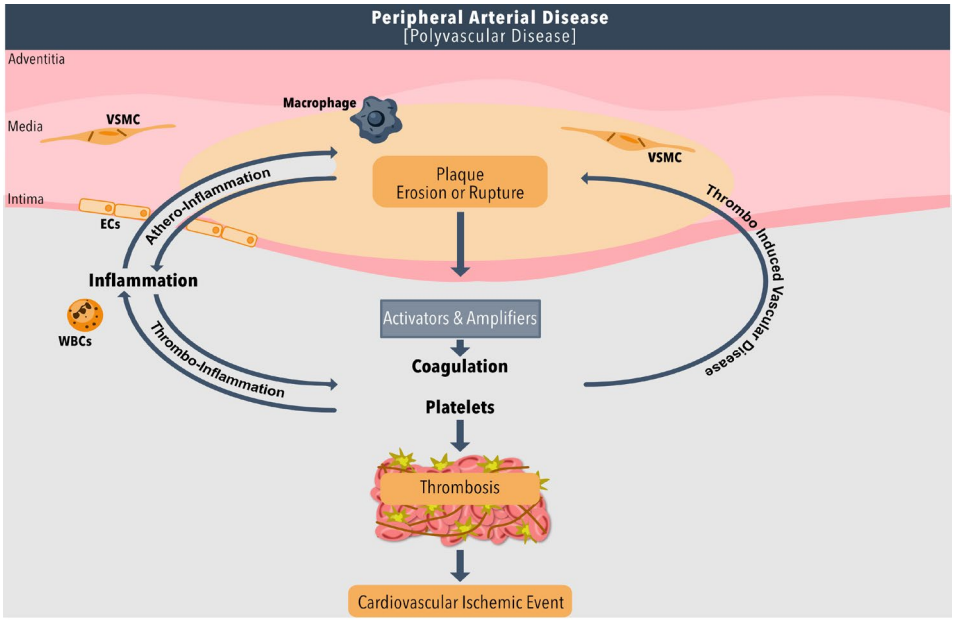


Who is involved?

Our work is recognised by a long history of joined efforts in research on activators of coagulation [8], biomarkers of hypercoagulability, and animal models for arterial and venous thrombosis. Currently, the research line has yielded several flourishing collaborations with academia and industry. Upon demonstration of the concept that active coagulation enzymes are a substrate for atrial fibrillation [7], the Dutch Heart Foundation granted the 5M€ CVON 'Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodelling, and Vascular Destabilisation in the Progression of AF (RACE V)' consortium, led by Prof. Isabelle van Gelder (Groningen) and Prof. Uli Schotten. In this national network, the team of clinicians, epidemiologists and basic scientists investigates the complex interactions between coagulation in atrial fibrillation. To further explore the vascular protective effects of antithrombotic medication, we have set-up a collaboration with the University of North Carolina (Chapel Hill, NC: group of Dr Nigel Mackman) and the University of Cincinnati (group of Dr Phil Owens) [9, 10]. Activators or enhancers of atherothrombosis are studied in a three-year project funded by Bayer AG (Germany, 1.5 M€), including collaborations with Prof. Esther Lutgens (Amsterdam) and Prof. Gerard Pasterkamp (Utrecht), resulting in one D1 target approval, several articles in progress and appointment of two PhD candidates.

Atherosclerosis in PAD leads to the athero-inflammation and finally into thrombo-inflammation. Coagulation proteases induce inflammation in return, thereby indirectly contributing to progression of atherosclerosis or directly to thrombo induced vascular disease. Spronk 2019, unpublished (see Figure 2)

Figure 2 Concept of bidirectional pathways induced by atherothrombosis in Peripheral Arterial Disease (PAD).



In line with the role of coagulation in cardiovascular disease, we study the applicability of assays for plasma thrombin generation and active coagulation enzymes as predictors for thrombotic cardiovascular events, both in animal models and patient cohorts. In a collaboration with the University of Aachen (group Dr Oliver Grottke), and funded by Boehringer Ingelheim, we demonstrated the applicability of a pig standardised blunt liver trauma coagulopathy model for the pre-clinical approval of an antidote for the direct thrombin inhibitor dabigatran [11, 12].

Finally, we established a long-lasting collaboration with the Center for Thrombosis and Haemostasis, Gutenberg University, Mainz. Together with the team led by Prof. Philipp Wild, we explore the applicability of thrombin generation and coagulation biomarkers for the prediction of arterial and venous thrombosis [13], extending into a new GWAS study including 20,000 subjects with thrombin generation measured. A next large study to address thrombin generation, in conjunction with a series of enzyme-inhibitor coagulation biomarkers, is the heart failure study MyoVasc, led by Wild and Dr Jurgen Prochaska, CTH, Mainz. We anticipate additional pre-clinical studies with the team led by Prof. Wolfram Ruf, on the specific contribution of macrophage PAR-2 (mutants), in models of CVD, including our myocardial

TICARDIO infarction and atherosclerosis models in mice. The Mainz collaboration paved the way for a more extensive collaboration, formalised in the recently acquired Horizon 2020, **T**hrombo-Inflammation in **CARDIO**vascular disease 'TICARDIO' grant between the University of Mainz, the University of Marseille and Maastricht University.

The experience and knowledge from the biomarker focussed research, has been utilised for the development of a new diagnostic device for routine measurement of thrombin generation in the clinical chemistry laboratory (Genesia, Stago) and in three subsequent Stimulus *OpZuid* grants for the development of a novel point of care platelet biomarker device in collaboration with 2M Engineering, Valkenswaard. Finally, we started our own Maastricht University spin-off company Coagulation Profile BV, offering a wide variety of assays to assess the 'Coagulation Profile' of a person.

Users and collaborations

Our research group provides an expertise center for translational thrombosis and haemostasis research with a strong basic science background, attracting young enthusiastic students and collaborators from all over the world.

Societal impact

1. Organiser and host of the bi-annual Maastricht Consensus Conference on Thrombosis (2015, 2017, 2019).
2. Workshop on the importance of biochemical research for 8-years old students (group 4, basic school).
3. Various publications in national newspapers and magazines.

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Electro-Mechanics of the Heart

Prof. Frits Prinzen, Department of Physiology

What is Electro-Mechanics of the Heart

We study the relation between the sequence and synchronicity of electrical activation of the ventricles and the resultant pump function of the heart. This line of research started about 25 years ago, when we discovered that electrical stimulation (pacing) of the ventricles results in abnormal electrical activation and an even more abnormal contraction pattern. An important step was my sabbatical leave at the Johns Hopkins University, 1995-1996, where for the first time MRI studies were performed in the paced (animal) heart. We were able to determine the enormous regional differences in stretch and shortening within a paced heart (Figure 1). This resulted in a still frequently cited article in JACC [1]. Currently, the focus is on finding better pacing sites, better selection of patients who may benefit from pacemaker therapies and algorithms that provide the best modes of pacing. Beside improving conventional pacemaker therapy (for maintaining a normal rhythm), pacing at the right (RV) and left ventricle (LV) is used to synchronise the heart, especially of patients with heart failure (cardiac resynchronisation therapy, CRT).

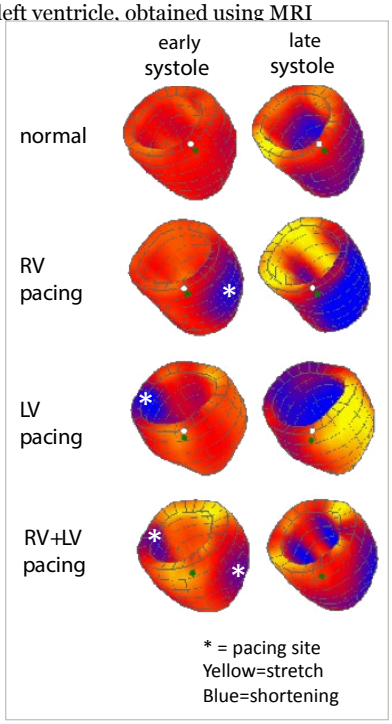


Figure 1 Color-rendered myocardial strain (fiber length changes) in the left ventricle, obtained using MRI tagging in a canine heart [1]. During normal (synchronous) conduction contraction is uniform, as shown by the almost uniform blue color (shortening) at late systole. During RV and LV pacing, regions remote from the pacing site (*) are stretched (yellow color), and abnormality that becomes less when pacing LV and RV together.

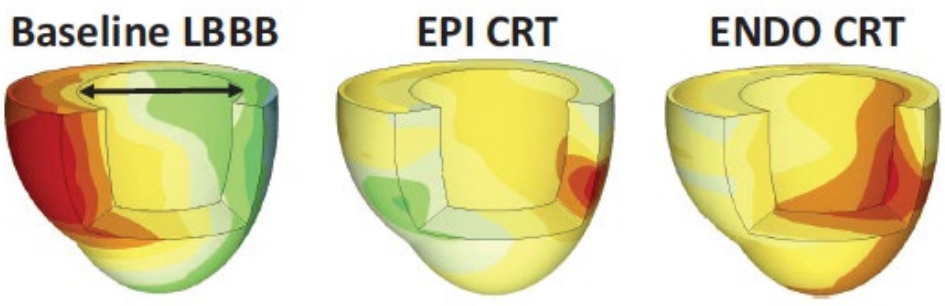
Major breakthroughs

In 2003, we reported the first evidence from animal experiments that pacing at the apex (=tip) of the LV or at the left side of the interventricular septum (LV septum) provides the best pump function [2]. This was subsequently supported by proof in patients. A case report in *the New England Journal of Medicine* showed how LV apex pacing cured one child [3]. A few years later a large clinical trial, published in *Circulation* [4] showed the superiority of LV apex as pacing site in children. LV septum pacing was proven feasible in patients [5] and its benefits are currently tested in patients with heart failure who are candidate for CRT.

In animal experiments we also discovered that positioning the LV electrode at the inside (endocardium) of the LV wall provides better electrical resynchronization (Figure 3) and pump function than conventional epicardial placement [6, 7]. Other groups are following this up in clinical studies, some of which with promising results.

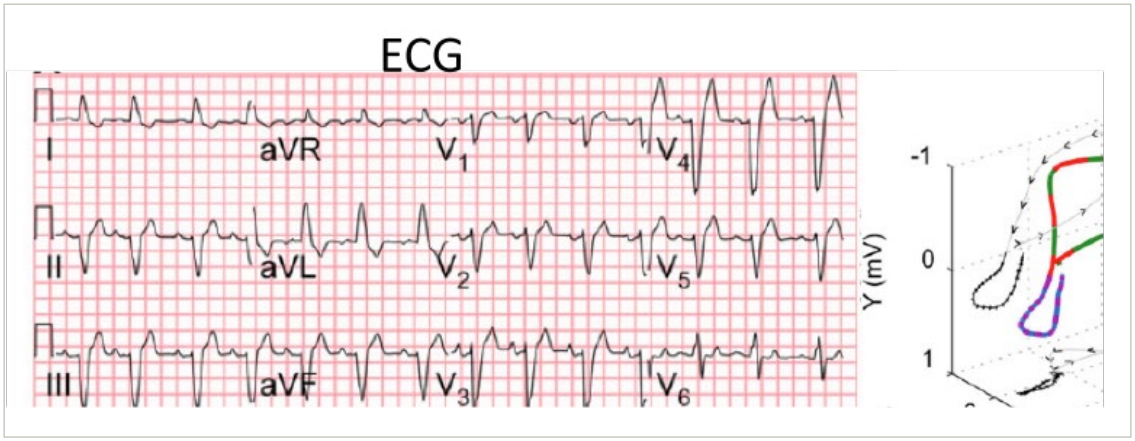
Figure 2 3D-activation patterns during left bundle branch block and during conventional epicardial and novel endocardial CRT. Red and green indicate early and late activation, respectively. The disappearance of the green color during endocardial CRT indicates better resynchronisation. (Strik et al, 2012)

Regarding the selection of patients for CRT, we discovered in a series of animal and patient



studies that the use of vectorcardiography (VCG) can improve identification of patients who benefit from CRT. Most recently, in a large registry of 1500 patients the VCG-derived area under the QRS complex, (QRSarea, Figure 3) proved to select patients better than the ECG characteristics recommended by the current clinical guidelines [8]. Therefore, we are currently analysing data from a large randomised clinical trial in order to collect the ultimate prove that QRSarea should be added to the guidelines for CRT.

Figure 3 Determination of QRSarea: from PDF files of the normal 12-lead ECG the digital signals are extracted and a 3D-vectorcardiogram (VCG) is constructed, from which the area of the QRS complex (red-green line in right panel) is determined. This approach is currently so popular, that our center is the corelab for the ECG in four clinical trials.



The close collaboration with the Department of Biomedical Engineering resulted in the use and rapid further development of *the CircAdapt computer programme* for CRT research, solving questions like how to optimise CRT and development of a new echocardiographic parameter for better selection of candidates for CRT (collaboration with Prof. Tammo Delhaas and Dr Joost Lumens). Several publications [9, 10, 11] describe studies that are close to clinical trials and approach the goals described in the Avicenna document on 'how computer simulations will transform the biomedical industry'. Altogether, the unique combination of animal experiments, computer simulations and patient studies enables to move the field forward in both mechanistic understanding and clinical application.

Who is involved?

Within CARIM, the researchers are in the Dept. of Physiology, Dept. of Biomedical Engineering, Dept. of Cardiology and and Dept. of Cardiac Surgery. Strong national collaboration exists with cardiologists from UMCU, UMCG and AUMC. Internationally, close collaboration exists with the Cardiocentro Ticino and the Center for Computational Medicine in Cardiology within the University of Lugano (Prof. Auricchio and Prof. Krause); the LIRYC institute at the University of Bordeaux (Dr Bordachar, Dr Vigmond); Washington University (St. Louis; Dr Gorcsan), Rovigo (Dr Zanon); Prague (Prof. Janousek); Brno (Dr Jurak, Dr Plesinger) Kings College London (Prof. Rinaldi; Dr Niederer) and the University Hospital Oslo (Prof. Smiseth; Dr Remme).

Users and collaborators

The translational nature of our research attracts students with medical background as well as biomedical engineers, medical technician and biomedical scientists. Many of these students continue in the field by specialisation in disciplines like cardiology or cardiac surgery. There is a regular exchange of investigators between our group and the abovementioned institutes, frequently resulting in internships or secondments at each other's labs as well as visiting professorships.

Scientific quality

The scientific quality of the research is apparent from the publications in major and high impact journals, including review articles [12,13], as well as research grants obtained (NHS junior and senior fellowships, junior staff member; ZonMW clinical fellow, Vidi; EracoSysmed, Horizon 2020 grants: AXONE, CARDIS and Marie Curie ITN grant 'PIC'; and the COHFAR project within CTMM)

Societal impact

An important societal impact concerns the application of the findings of our studies to patients. Partly, this is possible also through collaboration with companies, especially vendors of pacemakers. They were, and are, involved in several of the abovementioned research grants (public-private partnerships), while these companies have also supported us in investigator-initiated studies. With all the experience in the field of CRT, Prof. Frits Prinzen participated in the committee writing the 2012 Expert Consensus Statement for CRT, of EHRA/HRS, the European and American organisations for cardiac arrhythmia. This statement supports the guidelines for professionals in the field:

Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, DeLurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld JA, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace 14:1236-1286, 2012.

Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, Delurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld J, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm. 2012 Sep;9(9):1524-76.

Between 2014 and 2017 Prof. Frits Prinzen was the chairman of the EHRA Innovation Committee and he is currently a member of the EHRA scientific initiatives committee. One of the spin-offs of this activity is a strategic document on innovation in the area of cardiac electrophysiology [14].

Dr Joost Lumens is chairman of the working group on eCardiology of the ESC. In this working group, all novel digital technologies, for therapies and training in cardiology, are discussed and stimulated, ranging from information provided by smart phones to computer models.

Due to our experience in VCG, we are currently the core-lab ECG and VCG for three clinical trials. We also achieved a valorisation grant from the Center for Translational Molecular Medicine for further development of concepts derived from our understanding of the VCG.

Prof. Frits Prinzen and other members of his group (Dr Kevin Vernooy; Dr Joost Lumens) contribute significantly to the training of residents in cardiology, cardiologists as well as pacemaker technician. As an example, together with Prof. Angelo Auricchio, Prof. Frits Prinzen developed and presented the module 'Cardiac Pacing, Defibrillation and Electrical Management of Heart Failure' of the post-doctoral 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM), organised by the European Heart Rhythm Association (EHRA) and Maastricht University. The 30 participants of this DAS-CAM course are selected future leaders in electrocardiology within Europe.

Another expression of the international status of the research line and its societal impact is the first international congress on Electrical Management of Heart Failure, held in Maastricht October 2018, organised by Dr Kevin Vernooy and Prof. Frits Prinzen.

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Advanced Glycation Endproducts and vascular diseases

Prof. Casper G. Schalkwijk, Department of Internal Medicine

NAR
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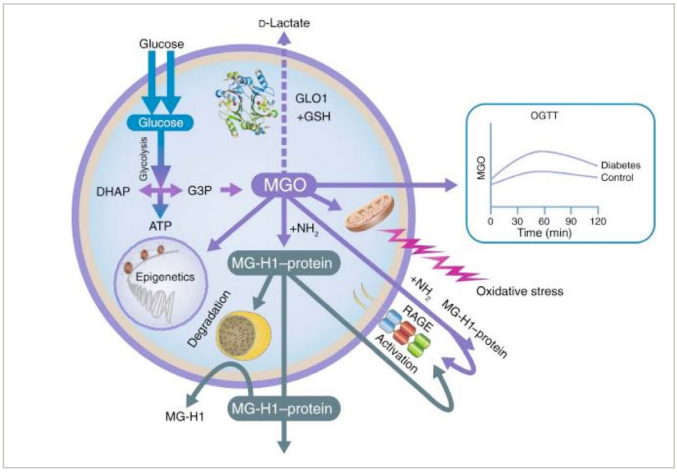
VES

How it all started

My work on advanced glycation endproducts (AGEs) started at TNO-PG in Leiden 25 years ago. At that time, Prof. Victor van Hinsbergh, Prof. Coen Stehouwer and I decided to start studying the role of AGEs in the development of vascular complications in diabetes. It initially looked like low-hanging fruit, but it was definitely not. It turned out that it is an unruly but exciting subject; up until today.

Traditionally, the formation of advanced glycation endproducts (AGEs) is viewed as a post-translational modification of proteins by reduced sugars, that accumulate slowly on extracellular and long-lived proteins throughout life. Formation of AGEs can be regarded as a naturally occurring process, resulting from normal metabolism, but increased under hyperglycaemic conditions, as well as under conditions of increased oxidative stress. Several mechanisms have been proposed, by which AGEs contribute to the development of pathological conditions, including aberrant cross-linking of extracellular matrix proteins leading to arterial stiffness. This knowledge is mainly due to excellent experimental work by Prof. Harry Struijker-Boudier and other CARIM researchers in the late 1990s. In the same time, I moved from TNO-PG to VUMC in Amsterdam to continue my work on glycation, and to start a laboratory of vascular biology and biomarker measurements. Because of the focus of my work on AGEs and vascular function, I accepted an invitation to continue my work at CARIM, one of the roots of AGE research. I moved from Amsterdam to Maastricht in 2005. I had also the opportunity to continue my fruitful collaboration with Prof. Coen Stehouwer. For our AGE research, we developed analytical techniques to measure AGEs and quantified several AGEs in large cohorts. We continued collaborations with many prominent groups in the field of diabetes research, and reported about the association of AGEs with vascular complications in type 1 diabetes (in the EURODIAB study; in collaboration with Prof. Nishi Chaturvedi from Imperial College London and in the LEACE study; in collaboration with Prof. Peter Rossing from Steno Diabetes Centre Copenhagen) and in type 2 diabetes (in CODAM and Hoorn study and in the EPIC-NL study in collaboration with Prof. Yvonne van der Schouw, UMC Utrecht). By providing data from multidisciplinary and translational research including data from large cohort studies, basic science and animal models, our research group has contributed significantly to the knowledge we have nowadays about the impact of the formation of AGEs for vascular diseases.



The game changer in our research; methylglyoxal

It was long believed that AGEs accumulate only on long-lived extracellular proteins. In recent years, however, the importance of very fast AGE formation has become increasingly clear, with the highly reactive methylglyoxal as a key compound involved in the very fast generation of glycation adducts on cellular and short-lived extracellular proteins, lipids and DNA [1, 2]. In fact, methylglyoxal mainly generated as a by-product of glycolysis, is believed to be the most potent glycation agent (Figure). In the last five years, our research on AGEs focusses on methylglyoxal. Dr Jean Scheijen developed state-of-the art UPLC/MSMS detection techniques to quantify methylglyoxal. We have very recently found that diabetes is associated with a sharp increase in methylglyoxal stress after a meal in which blood sugars peaks, demonstrating the very fast formation of methylglyoxal [3, 4]. We were among the first to show, in several experimental studies, that there is a significant role of methylglyoxal in the development of microvascular complications in diabetes [5], but also in age-related diseases such as atherosclerosis and myocardial infarction. In collaboration with Prof. Jeroen Pasterkamp of UMC Utrecht, we showed for the first time, that methylglyoxal is associated with rupture-prone plaques [6]. To counteract the deleterious effects of methylglyoxal, organisms have an enzymatic glyoxalase defence system. Intra-plaque comparison of plaques, as stored

in the CARIM biobank, revealed that the expression of glyoxalase 1 was decreased in ruptured compared with stable plaque segments, which may explain increased levels of methylglyoxal. In agreement, we showed in cohorts from the Steno Diabetes Center and the SMART study from UMC Utrecht, that plasma methylglyoxal is associated with incident CVD [7, 8] . We conclude that methylglyoxal may act as mediators of the progression of stable to rupture-prone plaques, opening a window towards novel treatments and biomarkers in cardiovascular diseases.

Thus, reducing methylglyoxal accumulation is potentially of medical importance. Therefore, we have started, in collaboration with Prof. Toshio Miyata from the Tohoku University in Japan, to study the effect of pyridoxamine, a vitamin B6 analogue with methylglyoxal-quenching capacity, on vascular function. We found that in high-fat diet induced obesity in mice, a delayed intervention with pyridoxamine is associated with improvement of inflammation and vascular function, but also several aspects of obesity including insulin resistance. This very original and relevant study has drawn attention of many and has been published in the leading journal Diabetes [9] and in *'de Limburger'*. These results have led to our first ongoing clinical trial with pyridoxamine in individuals with overweight and with micro- and macrovascular function and insulin sensitivity as primary outcome measures (NCT02954588). Real translational research; from cells to the patient.

A team effort

It is obvious from our findings that methylglyoxal has deleterious effects on the vascular system. This has been studied in an epidemiological setting with experimental *ex-vivo* -, animal - and more clinical work. Our research takes full advantage of several excellent patient and population cohorts, including the Maastricht Study, and is based on a strong and synergistic collaboration between frontrunners with outstanding track records in the field of glycation research, vascular research, intervention studies and (nutritional) epidemiology. The creation of such a collaborative platform resulted in unexplored collaborative efforts to study the relationship between methylglyoxal and biological consequences thereof for vascular function. My lab is one of the most renowned labs in this field. Because of our expertise and leadership in the field, there are many excellent national and international collaborations. We hosted many PhD students and post-docs from all over the world to work on AGEs and methylglyoxal. The work in my lab has been supported by several grants, including the Diabetes Fonds Nederland CTMM, TIFN, BMM and is now granted by NWO, ZON-MW, EFSD, Dutch Heart Foundation and NVWA. I am regularly contacted by various groups and journalists who disseminate our research results, unsolicited, illustrating the interest in this topic of the general community.

the Maastricht Study

The future

Methylglyoxal and the glyoxalase system will be an ongoing focus of our research on biomarkers, pathophysiological pathways and prevention of vascular complications in people with and without diabetes. In addition to endogenously formed methylglyoxal and AGEs, modern diets and drinks contain high levels of methylglyoxal and AGEs and it has now become apparent that dietary levels of methylglyoxal and AGEs represent a significant source of circulating and tissue methylglyoxal and AGEs, manifesting similar pathogenic properties to their endogenous counterparts. In collaboration with food scientists, we will elucidate the contribution of (dietary) methylglyoxal and AGEs in the onset of chronic inflammatory diseases, diabetes and vascular diseases. To do so, we just started the deAGE-ing trial.

I am looking forward to continuing this work on this most exciting project.

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Optimising care for the patient with venous thrombosis

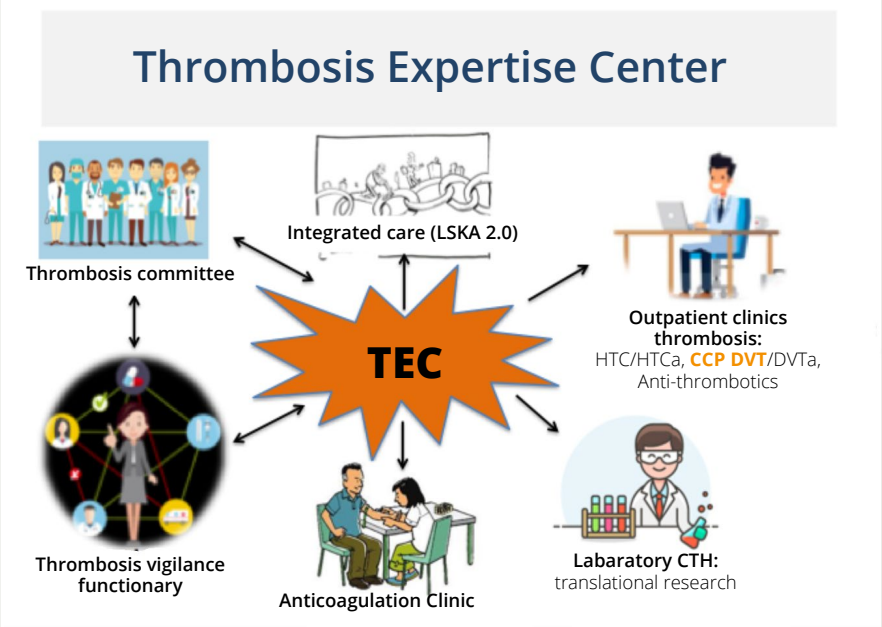
Dr Arina J ten Cate-Hoek, Department of Internal Medicine

What is venous thrombosis?

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are disorders that are usually categorised as the entity 'venous thromboembolism' (VTE), referring to the similarity in risk factors, aetiology and management. However, PE and DVT are diverse entities and there is marked heterogeneity among patients suffering from DVT. International guidelines tend to become simpler in addressing management, essentially recommending standard policies in those with provoked DVT (three months of anticoagulants) versus prolonged anticoagulation in patients with DVT of undetermined origin. This tendency, however, does not recognise the diversity in patient presentations. To recognise patient heterogeneity, to better understand the individual aetiology of DVT, and to better individually manage the patient with DVT, a Clinical Care Pathway for such patients at the Heart+Vascular Center of Maastricht UMC+ started in 2004. At present, this care pathway has been embedded in the Thrombosis Expertise Center.

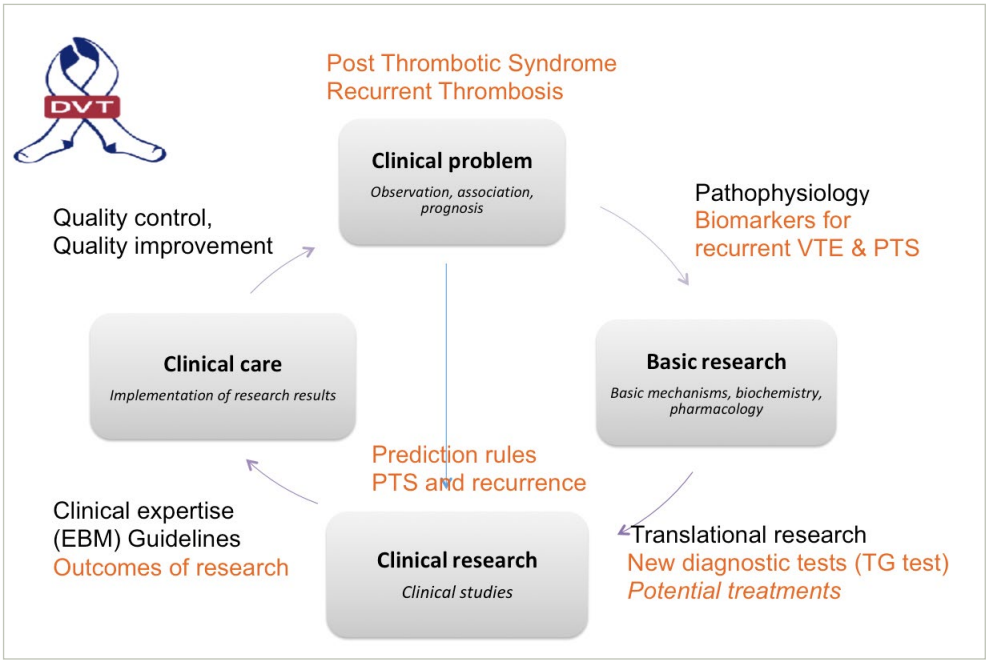
Thrombosis Expertise Center

Figure 1 The Thrombosis Expertise Centre at the Heart+Vascular Center of the Maastricht UMC+



The aim of this DVT care pathway is to provide optimal individual management of each patient with DVT, as well as to study mechanisms of recurrent DVT and to improve the prevention of post-thrombotic syndrome (PTS). Thus, patient management and clinical research go hand in hand, aiming to include each patient in an ongoing clinical study. Obviously, care and research need to be clearly defined and separated (also financially) to avoid 'contamination' of care.

Figure 2 The Clinical Care Pathway for DVT at the Heart+Vascular Center of the Maastricht UMC+



Risk factors for recurrent VTE

While many so-called 'thrombophilia risk factors' for thrombosis have been discovered over the past decades, including factor V Leiden, none of these sufficiently explain the risk of recurrent thrombosis. To address this predictive uncertainty, we instituted the prospective 'Endogenous thrombin potential' (ETP) study, referring to the potential importance of thrombin generation measurement for the identification of patients at risk for recurrent thrombosis and bleeding after initial anticoagulant treatment. Currently, over 450 consecutive patients with DVT are enrolled in this study. This year, we aim to finalise not only thrombin generation assays on plasma samples, but we will also perform an extensive intrinsic coagulation cascade analysis using Elisa's for activated clotting factors together with Prof. Hugo ten Cate and Dr Henri Spronk.

In addition, we are planning the analysis of proteins that could indicate differences in risk of recurrence, by using an omics strategy (O-link platform) together with our collaborators from the Center for Thrombosis and Haemostasis of the Johannes Gutenberg University in Mainz. We have previously published our quality findings on the management of patient in our CCP for DVT, showing that the recurrence rates were low (2.9 per 100 patient years), using a management strategy including residual vein occlusion as predictor of recurrence. Based on data from the CCP on DVT, a prediction score for recurrent VTE using fVIII measured during anticoagulant treatment instead of d-dimer measured after cessation of anticoagulant treatment for the prediction of recurrence, is constructed. This continue-8 score is developed together with Dr Sander van Kuijk (KEMTA) and Dr Michael Nagler (Bern, Switzerland). The clinical applicability of this prediction score is anticipated to be greater than current risk scores because fVIII levels may be measured during anticoagulant therapy resulting in a safer strategy.

Prevention of PTS

PTS occurs in almost half of all patients after a DVT, and comprises signs and symptoms reflecting chronic venous vascular damage. There is no gold standard diagnostic tool for PTS, but it can be diagnosed using a clinical consensus score as developed by Villalta. PTS can cause debilitating symptoms that markedly impair the quality of life; hence, measures to timely diagnose and to optimise the prevention are needed.

There has been considerable controversy regarding the use of compression therapy for the prevention of PTS after diagnosis of DVT. However, we recently showed that the use of immediate and adequate compression therapy in the acute phase reduces the occurrence of residual vein occlusion (RVO) and PTS. Furthermore, in our recent multicentre IDEAL DVT study (12 Dutch centres and two Italian centres) we clearly show that compression therapy could be individually tailored based on signs and symptoms of PTS using a clinical score. Based on the Villalta score it is possible to inform the decision on the need for extended duration of compression treatment after six months. This compression approach is highly cost-effective as over 55% of patients could stop compression therapy after six months of treatment. For VGZ, one of the largest insurance companies, this was reason to ask me to become their ambassador for PTS prevention in the Netherlands. Also, ZonMw asked us to initiate a Dutch

implementation initiative (*Verspreidings- en Implementatie impuls (VIMP)*) to firmly embed compression therapy on individual basis in daily practice.

Currently, PTS cannot be predicted at an early point in time in the individual patient and measures for prevention need to be applied in all. Ideally, the risk of PTS should be estimated upon presentation with DVT and for this purpose we developed a PTS prediction score that was externally validated in an Italian cohort (n=1100) in collaboration with Prof. Paolo Prandoni (Padua, Italy).

Figure 3 Investigators of the IDEAL DVT network

From left to right: Prof. K Meijer, UMCG (Groningen), Prof. S. Middeldorp, AMC (Amsterdam), Dr M. ten Wolde, Flevoziekenhuis (Almere), Dr S van Wissen, OLVG (Amsterdam), Dr E Klappe, Radboud ZH (Nijmegen), Dr G. Mostard, Zuyderland ZH (Heerlen/Sittard), Dr M vd Poel, (Roermond), Dr S vd Heiligenberg, WFG (Hoorn), Dr L. Tick, MMC (Eindhoven), Dr E. Serné, VUMC (Amsterdam), Prof. P. Prandoni (Padua), Prof. S. Villalta (Treviso), Dr A. Bouman (PhD), Dr E. Amin (PhD), Dr H.M. Otten, Slotervaart ZH (Amsterdam)

We are also studying the pathophysiology of PTS to further the process for optimisation of PTS prevention. PTS has many features of 'thrombo-inflammation' but also endogenous fibrinolysis plays a role in the process of venous vascular remodelling that follows the event of DVT. We studied the association of biomarkers with thrombo-inflammation and PTS and are currently, in collaboration with Prof. Monika Stoll, Dr Aaron Isaacs and Dr Elisabetta Castoldi, investigating gene expression profiles in patients with PTS. An important further objective is to use this knowledge on mechanisms and to be able to apply pharmacological preventive therapies. This may include novel targets, but also include currently available drugs with different indication profiles such as hydroxyethylrutoside (Venoruton) now used in patients with chronic venous insufficiency for the reduction of edema and inflammation, but also other drugs such as sulodexide or statins are mentioned as possible targets. We intend to study the mode of action of agents with potential 'anti-thrombo-inflammatory' activity. In part, the new class of anticoagulants (DOACs) may offer some benefit, potentially by increasing endogenous clot lysis as compared to vitamin K antagonists, but the evidence is weak and requires further study.

Invasive measures to prevent PTS

The team of Prof. Cees Wittens (Department of Vascular Surgery), in collaboration with TEC and the team of Prof. Michiel de Haan (Dept. of Radiology and Nuclear Medicine), offer a number of interesting and innovative approaches to tackle the PTS problem from an invasive perspective as well. In the Dutch CAVA study, we addressed the potential of catheter directed thrombolysis (CDT) in patients with clinical high risk of PTS, i.e. iliofemoral DVT. In this study, patients were randomised to conventional anticoagulant and compression management, or to CDT on top of conventional management for the initial treatment of DVT. This study has been completed and the data are under submission. Whether CDT will improve PTS outcomes remains to be seen. For patients with chronic PTS, the efficacy of intravenous stenting is unclear and studies to establish whether stenting of existing proximal venous obstruction could alleviate PTS complaints. These approaches raise many new questions regarding patient selection, optimal antithrombotic management etcetera.

International collaborations

The above studies thrive because of national and international collaborations. The IDEAL DVT study and the Dutch CAVA study are strong examples of national, multicentre studies that are founded on existing networks. Internationally, the collaboration with Prof. Paolo Prandoni was important to tackle PTS from a non-invasive approach. Prof. Robert Ariëns from Leeds, UK helped with our studies on fibrinolysis and he will be involved in subsequent studies. With Prof. Tom Wakefield and Prof. Peter Henke, vascular surgery from Michigan, USA we have reviewed the literature on the pathophysiology of PTS. With CTH Mainz Prof. Philipp Wild and Prof. Monika Stoll we intend to deepen knowledge on the underlying molecular mechanisms in order to improve diagnostic and management protocols. With CTH Mainz we extend this knowledge towards venous insufficiency, of which a recent collaborative study showed that it relates to mortality (under submission), a very important new observation. In 2019, the TICARDIO International Training Network (ITN) will start combining forces from Maastricht (CARIM), Mainz (CTH) and Marseille to tackle many aspects of 'thrombo-inflammation', including mechanisms in venous thrombosis. This will further strengthen existing collaborations and stimulate innovation.

Research quality

Over the past decade, our joint efforts have resulted in strong and internationally recognised lines of research. This is evident from our recent publications including *Lancet Haematology* and *Blood*, but also by a series of invited lectures including a state of the art lecture at the Berlin ISTH congress in 2017 and an interview for ISTH-TV. Last year, eight international invited lectures were given on PTS and it is evident that this established our work in the international community. Furthermore, our publications have led to invitations to take part in international guideline committees such as those of the European College of Phlebology (ECoP) and the European Society of Vascular Surgery (ESVS). During this period, I have been a co-promotor to seven PhD students (four on PTS, one on epidemiology, two on patient safety and anticoagulation) who have successfully defended their theses. Another three students will finish their thesis in the next two to three years.

interview for ISTH-TV

Societal impact

Our research, especially the moest recent randomised clinical trial, the IDEAL DVT study, already had great societal impact. When we published the results of the IDEAL DVT trial, this was accompanied by extensive covering in the media; *Dagblad de Limburger*, *Algemeen Dagblad*, and other papers as well as BNR radio, L1, and a one-hour live interview with a New York based medical radio station (doctor radio Sirius 110)). Our project was also chosen by in the external evaluation of research funded by *ZonMw Doelmatigheid* over the period 2006-2017 as one of ten successful projects out of 440 projects that were funded, to be presented in their magazine. These ten stories were chosen because they clearly show how the individual patient benefits of successful research.

ZonMw Doelmatigheid

We have shown that compression after DVT does matter and especially compression in the acute phase after DVT should be initiated in all patients, irrespective of complaints in order to improve thrombus resolution. The use of multi-layer bandaging is similar in efficacy as compression hosiery, comes at four-time greater costs and is associated with reduced scores on health related quality of life measures. For the long-term compression therapy for the prevention of PTS we showed that base on a clinical evaluation in over 55% of patients compression can be stopped early without impact on the incidence of PTS. Based on a formal cost-effectiveness analysis we calculated that this results in a 40 M€ reduction of costs each year in the Netherlands. We have already adapted our strategy for initial compression treatment in our hospital. In addition at least one guideline (ESVS guideline on venous thrombosis) is going to recommend initial compression and individual tailored compression in the subacute phase for the prevention of PTS.

Collaboration with the industry

The most important financial support for the IDEAL DVT study was derived from a grant from ZonMw. The IDEAL study was additionally supported by a grant from Medi a Dutchcompany that makes elastic compression stockings. For the more basic and translational research on PTS, industrial partners are involved. The initial studies on thrombin generation were part of the INCOAG consortium, a Dutch Heart Foundation supported university-industry network. Future work on biomarkers will be embedded in part in the TICARDIO consortium, involving CTH Mainz, CARIM and Marseille as well as industrial partners like Bayer and Boehringer that have strong interest in thrombo-inflammation. It also includes the Dutch SME 2M that brings in novel diagnostic tools to study platelet activation, also in the context of venous thrombosis. The CAVA study was partly financed by ZonMw but most importantly relies on collaborations with companies that make stents, catheters and other tools needed for further optimization of venous interventions. For the latter, Prof. Cees Wittens has played the most important role for the acquisition of financial support.