School for Cardiovascular Diseases

CARIM School for Cardiovascular Diseases

Self Evaluation 2013 - 2018

Maastricht UMC+

Maastricht University

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1 Objectives and research area

1.1 Vision, mission and objectives

CARIM

CARIM's mission is to study general and individual mechanisms of cardiovascular disease in a curiosity-driven way, to apply findings to early diagnosis, mechanistic classification and individual risk stratification of cardiovascular disease, and to develop novel therapeutic concepts. By combining broad coverage of all major cardiovascular pathologies in blood, vessels, and heart with tight connections between fundamental researchers and clinicians, CARIM is able to evaluate and apply new findings, products and techniques in practice, often in collaboration with private and industrial partners.

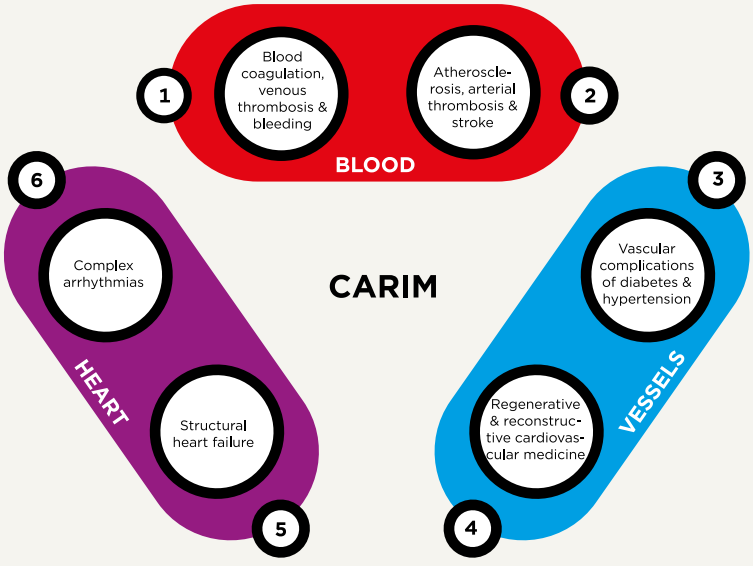
The vision of sustained interaction with the hospital, governing basic science driven by clinical needs and applying basic results and ideas to clinical practice, enables CARIM to act on the forefront of cardiovascular science. CARIM publishes in high-ranking international journals and disseminates research output to society as a whole. A major focus within CARIM is the identification and mentoring of young talent for which programmes are in place to teach and coach Masters students, PhD candidate and MD students to become independent researchers, and postdocs to become leading scientists in the field of cardiovascular disease.

CARIM's objective is to define and address key scientific questions through optimal application of CARIM programmes, involving Principal Investigators (PIs), researchers, and infrastructure in a team science setting combining track records, expertise, and innovative content and to disseminate results to scientific communities and society in general. With this, CARIM's rank among Europe's top cardiovascular institutes is secured[1].

1.2 Strategy and research area

Based on previous ERC recommendations, CARIM was restructured to stimulate better accessibility, connectivity and transparency in the international cardiovascular research community. CARIM is now built around three comprehensive research Divisions of 'Blood', 'Vessels' and 'Heart' comprising six programmes: 1. Blood coagulation, venous thrombosis & bleeding; 2. Atherosclerosis, arterial thrombosis & stroke; 3. Vascular complications of diabetes & hypertension; 4. Regenerative & reconstructive cardiovascular medicine; 5. Structural heart failure and 6. Complex arrhythmias (Figure 1). These six programmes together host 22 PI groups that represent specific research, infrastructural and financial units within CARIM.

Figure 1 CARIM Divisions and programmes after restructuring



1 Van Welie SD, Van Leeuwen TN, Bouma CJ, Klaassen ABM. The joint cardiovascular research profile of the university medical centres in the Netherlands. Neth Heart J 2016 May;24(5):308-16

Division Blood (Division leader: Prof. Hugo ten Cate) involves the programmes 'Blood coagulation, venous thrombosis and bleeding' and 'Atherosclerosis, arterial thrombosis and stroke' and is directed at deciphering impairments of proteins, platelets and the vessel wall with molecular and imaging approaches. The programmes include the development of novel (molecular) imaging techniques and translation of these techniques to clinical practice for tailored patient treatment. Due to a strong integration of the specialty atherosclerosis from former Theme III 'Vascular biology and medicine' with thrombosis from former Theme I 'Thrombosis and haemostasis', it was decided to transfer thrombo-inflammatory aspects of atherosclerosis and arterial thrombosis (*from-out-of-the-circulation*) to new Division Blood. Since 'stroke' comprises different neurovascular diseases, divided into large vessel disease and small vessel disease, it is represented in two divisions: Blood and Vessels.

Research in Division Vessels (Division leader: Prof. Coen Stehouwer) focusses on vascular complications of diabetes and hypertension and regenerative and reconstructive cardiovascular medicine. These programmes include research on specific cardiovascular diseases that pose major burdens to an ageing society, namely diabetes and metabolic syndrome, hypertension and chronic kidney disease, cognitive impairment and depression in relation to diabetes, hypertension and aortic aneurysm. There is extensive collaboration with Division Blood, notably with regard to atherosclerosis, arterial thrombosis and stroke.
Research in Division Heart (Division leader: Prof. Harry Crijns, former Theme II 'Complex Arrhythmias and Structural Heart Disease') focusses on complex cardiac arrhythmias and structural heart disease. The former includes atrial fibrillation, ventricular arrhythmias and sudden death, the latter relates to hypertrophic and dilated cardiomyopathies (thick heart failure and thin heart failure).

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

Heart+Vascular Center

Due to the increasingly complex and multidisciplinary cardiovascular research objectives, CARIM's new structure facilitates much needed interdivisional and translational research. Interdivisional collaborations have led to high impact publications (e.g. Division Blood and Heart: Spronk et al; paragraph 3.1.1) and for example several joint PhD projects are funded between the clinical Heart+Vascular Center (HVC) and Division Blood. See Part B for more detailed information on collaborations between the CARIM Divisions.

CARIM 2013-2018		
Theme I Thrombosis and Haemostasis		
1	Tilman Hackeng	Blood proteins & engineering
2	Chris Reutelingsperger	Vascular aspects thrombosis and haemostasis
3	Johan Heemskerk	Cellullar biochemistry of thrombosis and haemostasis
4	**Hugo ten Cate**[1]	Clinical thrombosis and haemostasis
5	Christian Weber	Structure-function analysis of the chemokine interactome
6	Monika Stoll	Complex cardiovascular genetics
Theme II Cardiac Function and Failure		
7	Hans Peter Brunner-La Rocca[2]	Clinical heart failure
8	**Harry Crijns**	Clinical atrial fibrillation
9	Matthijs Blankesteijn	ECM + Wnt signalling
10	Leon de Windt	Gene regulation
11	Tammo Delhaas	Cardiovascular system dynamics
12	Jan Glatz[2]	Intermediate cardiac metabolism
13	Stephane Heymans	Cardiomyopathy
14	Jos Maessen	Surgical intervention
15	Frits Prinzen	Electro mechanics
16	Uli Schotten	Experimental atrial fibrillation
17	Bert Smeets[2]	Mitochondrial disease
18	Paul Volders	Arrhythmogenesis and cardiogenetics
Theme III Vascular Biology		
19	Ilja Arts	Systems medicine of cardiometabolic disease
20	Erik Biessen	The vulnerable plaque: makers and markers
21	Leo Koole[2]	Cardiovascular biomaterials
22	Bram Kroon	Hypertension and target organ damage
23	Mark Post	Regenerative and reconstructive medicine for vascular disease
24	**Coen Stehouwer**	Vascular complications of diabetes and the metabolic syndrome
25	Harald Schmidt[2]	Network pharmacology and cardiovascular drug discovery
26	Harry Struijker-Boudier[3]	Vascular remodeling in cardiovascular disease
27	Robert van Oostenbrugge	Cerebral small vessel disease
28	Hans Vink[2]	Macrovascular dysfunction and glycocalyx
29	Joachim Wildberger	Imaging

CARIM 2019		
Division BLOOD		
1	Blood coagulation, venous thrombosis & bleeding	Tilman Hackeng Johan Heemskerk **Hugo ten Cate** Monika Stoll
2	Atherosclerosis, arterial thrombosis & stroke	Erik Biessen Chris Reutelingsperger Robert van Oostenbrugge Christian Weber Joachim Wildberger
Division VESSELS		
3	Vascular complications of diabetes & hypertension	Ilja Arts Bram Kroon **Coen Stehouwer**
4	Regenerative & reconstructive cardiovascular medicine	Jos Maessen Mark Post
Division HEART		
5	Structural heart failure	Matthijs Blankesteijn Stephane Heymans Leon de Windt
6	Complex arrhythmias	**Harry Crijns** Tammo Delhaas Frits Prinzen Uli Schotten Paul Volders

Old and new Principal Investigator structure (left) and programme structure (right) of CARIM
1: Prof. Hugo ten Cate took over Theme leadership from Prof. Tilman Hackeng on 1 April 2017.
2: Some PI ships were revoked as a result of ERC recommendations 2014 and CARIM restructuring.
3: Prof. Harry Struijker-Boudier retired in 2018.

1.3 Specific targets of the past six years

CARIM was evaluated by an External Review Committee (ERC) in 2014. The School received a very positive general assessment (reporting on the period 2007-2012). Overall, the School was evaluated as 'very good to excellent' (4-5). At the Division/ Theme level, the School received ratings from 'very good' to 'excellent' for all aspects: Quality, Productivity, Societal relevance and Vitality and feasibility within Themes I and III.

Table 1 Assessment of the period 2007-2012

Themes (currently Divisions)	Quality	Productivity	Societal relevance	Vitality and feasibility
Theme I (currently Division Blood)	5	4-5	5	4
Theme II (currently Division Heart)	3-5	3-5	3-5	2-5
Theme III (currently Division Vessels)	4-5	4-5	5	4
CARIM overall	4-5	4-5	5	4

The relatively low rating of the Vitality and feasibility of Theme II (between two and five) was mainly caused by a few less performing programmes, which since then have been discontinued. The official Report of the External Review Committee was written in 2015. Prof. Albert Scherpbier, Dean of the Faculty of Health, Medicine and Life Sciences (FHML), invited the Scientific Director of CARIM to follow up on the recommendations and write a plan of action, indicating how each of the recommendations would be addressed. The CARIM Scientific Director and board addressed the recommendations in the Midterm Review 2013-2015. In July 2016, the CARIM Midterm Review was officially approved.

Three main recommendations from the ERC in 2014 have been addressed and implemented since then:

- Implement FHML's policy of limiting the direct funding research labelling to max 0.5 fte (fulltime equivalent) per researcher;
- Discontinue underperforming research programmes from CARIM's research portfolio and relocate their PIs;
- Restructure CARIM to a more accessible and recognisable six-programme institute.

By setting a ceiling to the labelling of scientific staff paid for by direct funding to a maximum of 0.5 fte per person, a financial annual gain of about 600 K€ (reduction of 6.5 fte) was achieved. This financial annual gain was reserved to cover the expected loss of direct funding due to expected declines in PhD incentives. Therefore, additional measures had to be taken by the CARIM board to secure a strategic reserve to implement new initiatives. Therefore, the number of PI groups were reduced, and the corresponding PIs and their group members were placed outside CARIM, in consultation with – and supported by – the board of FHML, leading to an additional annual budget gain of 650 K€. The remaining PIs and their groups have since been re-allocated based preferentially on defined translational topics, which led to a stronger focus on six, rather than the former 22, programmes. This measure was in line with the recommendation of the ERC, to find a way to cut poorly performing programmes: six out of 29 PIs and their programmes were redrawn (including three that were mentioned in the ERC report), and one PI stopped due to retirement.

In contrast to expectations of declining external funding, CARIM researchers have been very successful in EU networking activities and in establishing international alliances. In total, CARIM is currently involved in nine Innovative Training Networks (ITNs) with a total number of 29 Early Stage Researchers allocated to CARIM. Two Horizon 2020 ITNs, INTRICARE (3.8 M€) and TRAIN-HEART (3.9 M€), are coordinated by CARIM. Furthermore, CARIM researchers have been successful in the acquisition of (national) personal and consortium grants from the Netherlands Organisation for Scientific research (NWO) and the Dutch Heart Foundation (Cardiovascular Research in the Netherlands: CVON).

Additional recommendations emerging from the ERC 2014 report were as follows:

- Strengthen translational axis CARIM-HVC;
- Connect to recently installed university professors from the Maastricht MultiModal Molecular Imaging Institute (M4I) and The Institute for Technology-Inspired Regenerative Medicine (MERLN);
- Connect to other FHML research Schools/institutes;
- Re-evaluate rigid PI structure;
- Improve transparency on processes of evaluation, decision making and tenure track procedures;
- Decrease duration PhD trajectories to four years;
- Strengthen research infrastructure (research platforms) including animal facilities;
- Invest in talent recognition and development.

M4I
MERLN

Strengthen translational axis CARIM-HVC

The earlier adopted strategy to merge CARIM and HVC was aborted and a new strategy of developing and stimulating fertile translational interactions was chosen. CARIM and HVC invested in two translational scientists as well as in joint PhD projects, in which translational activities were strengthened and PhD candidates were supervised by a joint CARIM-HVC promotion team. In addition, joint cardiac modelling and vascular network activities between researchers of CARIM and HVC were organised, and a monthly management team meeting of CARIM and HVC board was established. The bottom up strategy of identifying and stimulating joint activities has since then resulted in considerable advances in understanding vascular and aortic valve calcification and complex arrhythmia, and the development of a (pathological) stem cell research line within CARIM-HVC. Nevertheless, strengthening of interactions between CARIM and HVC is an opportunity that requires more investment and attention.

Connect to recently installed university professors from M4I and MERLN

CaReSyAn

Connections to university professors have been established through joint research projects and PhD candidates with M4I (Prof. Ron Heeren), and through joint activities with MERLN (Prof. Clemens Van Blitterswijk and Prof. Pamela Habibovic). In the Horizon 2020 ITN CaReSyAn, CARIM has a joint PhD project with M4I (PhD candidate Niko Rapp. CARIM and MERLN took the lead in initiating an international research programme on stem cell research (iPSCs; organoids) that is now being developed in close conjunction with the Stem Cell Research Center of the University of California at Irvine. In addition, CARIM and MERLN are both involved in the framework of the international REGMED XB programme on regenerative medicine.

Connect to other FHML research Schools/institutes

MHeNs
MaCSBio

Connections to other Schools and institutes have been intensified during recent years, as evidenced by interactions with institutes MERLN and M4I (vide supra), School for Mental Health and Neurosciences (MHeNs), and the appointment of staff from MHeNs and the Maastricht Centre for Systems Biology (MaCSBio) as PIs in CARIM. As a result, parts of MHeNs research lines that involved stroke (Prof. Robert van Oostenbrugge) and microcirculation (Dr Julie Staals) were transferred to CARIM's new Programme 2 (Atherosclerosis, arterial thrombosis and stroke), and linked to translational (neuro-)imaging (Prof. Walter Backes) and the new Programme 3 (Vascular complications of diabetes and hypertension). Currently, a joint PhD project is running between CARIM and MHeNS on the effects of smooth muscle cell extracellular vesicles on the blood brain barrier (Luise Klein). This crossover to MHeNs results in a strong opportunity for the involvement of CARIM within the Brain and Nerve Centre in which a multidisciplinary approach on Atrial Fibrillation (AF) and atherosclerosis with stroke, imaging, cognitive impairment and depression in relation to diabetes, and cognitive impairment as a result of microvascular stiffening will provide powerful opportunities. In appointing a new PI on microcirculation, pertinent attention to neurosciences and ageing will be required. In addition, MaCSBio research lines on cardiovascular systems biology were adopted by CARIM's new Programme 5 (Structural heart failure). Many of the CARIM initiatives that reached out to adjacent Schools, institutes, and faculty have now led to flourishing strongholds within MHeNs and MaCSBio, and within the Faculty of Science and Engineering (FSE) leading to more intense collaboration and exchange of ideas and staff. Department of Cardiology from CARIM Division Heart has appointed joint staff members (Prof. Leon de Windt and two staff members) with FSE (50/50).

Brain and Nerve Centre

FSE

Re-evaluate rigid PI structure
The rather inflexible PI structure and a certain lack of transparency in communication and processes of decision making (e.g. tenure track procedures) have been a subject of discussion in recent years. CARIM has re-evaluated the position and tasks of PIs in a memo 'on being a CARIM PI' and has come to the following conclusions: The main task of a PI is to facilitate research in the PI domain, and to coach young researchers in their choice of research areas and future career. In addition, a PI is responsible for the organisational and financial aspects of the PI's research group. Finally, the PIs facilitate research between CARIM programmes. All these tasks implicate that a PI should be a senior researcher.

Improve transparency on processes of evaluation, decision-making and tenure track procedures
In order to engage junior staff in CARIM research management and to create transparency in the development of CARIM procedures and policies, since 2014 all research staff and junior staff are invited to attend annual planning and control interviews with their CARIM PIs. In addition, they are invited to the quarterly CARIM School Council meetings to be kept updated on recent policy developments and new proposal by CARIM governance. During School Council meetings, invitees can participate in the discussion, but they are exempt from voting.

Decrease duration of PhD trajectories to maximum 4 years
CARIM delivers a high quality international PhD programme with an annual average of 40 PhD theses. The average duration of a PhD trajectory in CARIM (62 months in the period 2013-2018) is longer than the FHML target of 48 months. A reduction in the average duration of the PhD projects is discussed and monitored in the Planning & Control meetings with the PI groups. While the average duration has not declined over the past years, the number of PhD candidates that defend their thesis within four to five years has increased. FHML in turn stimulates the reduction in duration by disbursing an incentive of 5 K€ in case of official approval by the PhD assessment committee within 48 months. By giving more attention to planning and by closer monitoring of the PhD trajectories using the digital platform PHD TRACK, CARIM supports the FHML policy on reducing the average duration. However, in the end, the quality of PhD thesis prevails over the duration of the PhD trajectory.

PHD TRACK

Strengthen research infrastructure (research platforms) including animal facilities
CARIM has a broad spectrum of research infrastructure, from molecular design to clinical and population medicine (Annex 2). Investments have been made in the state of art facilities such as structural protein NMR (700 MHz), complex genetics, Imaging, the Maastricht Study, the CardioResearch-HVC unit, and a stem cell facility, and strategies are being prepared to create open access structures in which the sharing of these facilities between departments, Schools, and institutes can be improved. This also includes sharing infrastructures within the clinical setting to enable translational science. Plans are underway for the establishment of FHML research platforms, core facilities under 'fee for service', in which existing technologies will be centrally organised. CARIM researchers were strongly involved in the planning of a new animal facility building (Biomedical Centre: BMC). The final design has been approved and the construction will start in 2020.

Invest in talent recognition and development
CARIM has attained a unique position within Maastricht University by offering comprehensive talent development opportunities for its candidates at all academic levels from bachelor, master, pre-PhD, PhD, to postdoc in its 'Harry Struijker-Boudier award for talented academics' (HS-BAFTA) programme. CARIM believes that this programme will add to the personal, cultural, and professional development of young talent, and to a better preparation for a scientific career and grant acquisition. Laureates of these programmes are mentioned in the CARIM annual reports.

2 Description of the School's organisation, composition and financing

2.1 Organisation and embedding of the School

Maastricht University was founded in 1976 and is the youngest university of the Netherlands. Maastricht University is characterised by its multidisciplinary and thematic approach to research and learning. Maastricht University was the first Dutch university to make internationalisation a top priority. More than half of the students and 40% of the academic staff within Maastricht University come from abroad, making Maastricht University one of the most international universities in the Netherlands, reaching place eleven for internationalisation in the Times Higher Education World University Rankings 2018 (place 106 overall, place six in the Under 50 ranking of 2017). Maastricht University has extensive international partnership networks, and the university encourages international research collaborations. Students and researchers have many opportunities to study and work abroad, and graduates are eagerly sought in the international labour market and research community.

Maastricht UMC+

The Faculty of Health, Medicine and Life Sciences is Maastricht University's largest faculty, comprising 65% of the total staff and budget of Maastricht University. The FHML has officially existed since 1 January 2007, after a merger of the former faculties of Health Sciences and Medicine. Since 2008, the FHML cooperates with Maastricht's academic hospital under the name Maastricht University Medical Centre+ (Maastricht UMC+). This is a centre for integrated health care, research and education that covers the entire spectrum of the health sciences, medicine and molecular life sciences. The '+' added to the name is an expression of its focus on health instead of (only) on medicine, cure or care. The mission of Maastricht UMC+ is 'To provide the best possible care and improve health in the region through the integration of patient care, research and education' under the motto: Healthy Living. Within this mission, there is a strong focus on integrated care and prevention of disease.

Through a combination of biomedical, applied clinical, public health and primary care research concentrated in Graduate Schools and institutes, the FHML aims to strengthen the research and increase knowledge transfer by incorporation and implementation of the 'integrated care concept' within Maastricht UMC+. The cooperative alliance between FHML and Maastricht UMC+ is a breeding ground for innovation. It connects scientific research and education in the field of health, contributing to better care. In 2015, the Maastricht UMC+ created a new working method, called the 'Circle of Innovation©', which is a universal visualisation tool that reflects the circular process of knowledge, innovation and societal impact.

Figure 2 Maastricht UMC+ Circle of Innovation©

The 'Circle of Innovation©' shows how our researchers and specialists acquire new knowledge and put it into practice, create value and stimulate healthy living. 'Circles of Innovation©' are the foundation for health promotion in the broadest sense of the word. This method also stimulates collaboration between Schools and institutes, the hospital, different departments, regional health care and patient organisations and other knowledge institutes, governmental organisations and industry.

Within this framework, there is a strong focus on integrated care and prevention of disease within CARIM, in close collaboration with HVC. In general, several of the topics addressed within CARIM have clear parallels at HVC (e.g., venous and arterial thrombosis, complex arrhythmias and structural heart disease). Similarly, strong emphasis on microvascular research in the Departments of Internal Medicine and Neurology has created a need for microvascular expertise on the preclinical side as well. Here, CARIM already took action by deciding that additional expertise on microcirculation will be attracted. For other topics (e.g. diabetes) there are clinical correlates outside of HVC at other departments within Maastricht UMC+, and e.g. within NUTRIM. However, there are also various topics where CARIM and HVC are not aligned. For example, regenerative medicine does not yet have a HVC counterpart (which may be understandable given the technology-readiness of this topic), and minimally invasive surgery is not very visible within CARIM.

NUTRIM

To facilitate the CARIM-HVC axis, Maastricht UMC+ structurally supports translational research through funding of four research lines (@ 250 K€/annum). The first is biomedical engineering (Prof. Tammo Delhaas), the other three resulted from a joint CARIM and HVC request to the Maastricht UMC+ Board to promote translational cardiovascular research through the programme 'Broad Achievements (Pieken vanuit de breedte): Bringing Mechanisms into the Clinic'. As a result, three out of four research lines were supported: 1) Clinical Thrombosis, in the Thrombosis Expertise Centre (Prof. Hugo ten Cate); 2) Clinical Diabetes, in the Maastricht Study (Prof. Coen Stehouwer; and 3) Clinical Heart Failure (Prof. Hans-Peter Brunner la Rocca). The fourth, Radio-Biochemistry, was never activated and attempts of revival are underway by incorporating it in a newly designed translational initiative of radiobiochemical cardiovascular imaging (See Part B Blood). In parallel, negotiations are ongoing between CARIM Departments of Pharmacology and Toxicology, Internal Medicine, Cardiology, and Clinical Departments of Anaesthesiology and Pharmacy to establish a new Department of Clinical Pharmacology focussed on research, education, specialisation, and drug awareness.

CARIM is one of six Graduate Schools of the FHML, embedded within the Maastricht UMC+. The Scientific Director (Prof. Tilman Hackeng, as from 1 April 2017) has the final responsibility for the School, including the organisation and management of the research programme, the scientific output, the training of Master's students, PhD candidates and postdoctoral fellows, and the School's financial management and public relations.

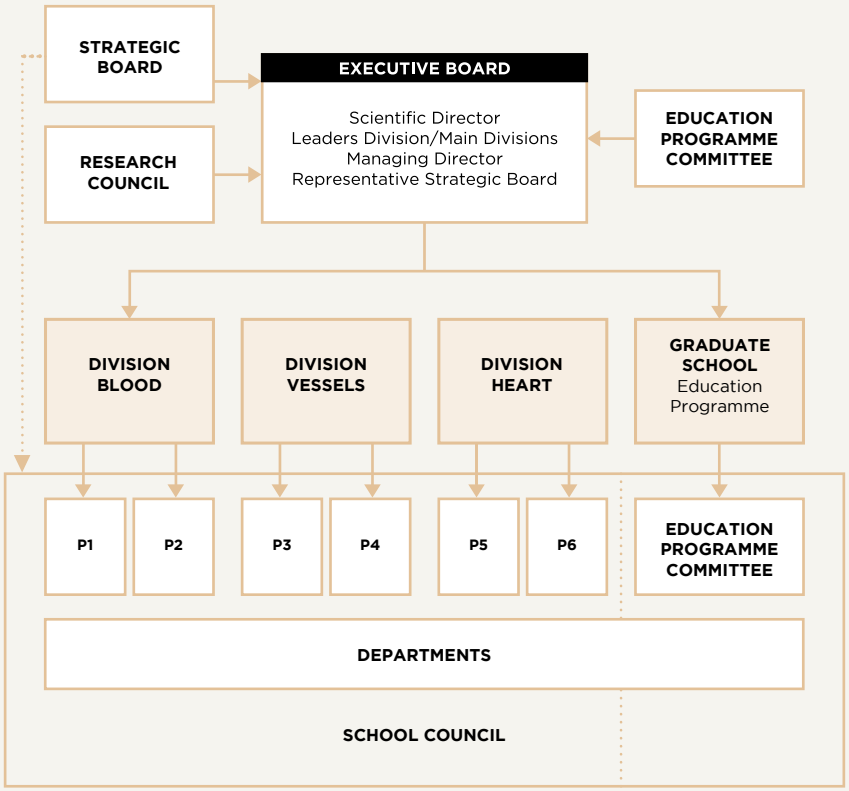
The Scientific Director is assisted by the Managing Director, who takes care of the financial and human resource management. Together with the three leaders of the Divisions and a representative from the Strategic Board, the Scientific and Managing directors constitute the Executive Board of the School. The Executive Board meets monthly to discuss and decide upon issues at a strategic and operational level. The Executive Board is advised by the Strategic Board, Education Programme Committee (EPC) and CARIM Research Council.

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

The EPC coordinates both the PhD and Masters training programmes. Furthermore, the Research Council advises the Executive Board and PIs on the quality of research proposals and meets regularly to discuss and guide grant applications.

The School Council consists of all PIs and Department Chairs and meets four times a year. The School Council is informed by the Executive Board on ongoing matters and advises the Scientific Director on research within the School and the related education programmes.

The research in CARIM's Divisions involved the research activities of employees working in 17 (seven basic and eleven clinical) departments of Maastricht UMC+. Basic departments: Biochemistry; Physiology; Biomedical Engineering; Epidemiology; Genetics & Cell Biology; Pharmacology/Toxicology; and Immunology. Clinical departments: Clinical Chemistry; Internal Medicine; Neurology; Pathology; Cardio-Thoracic Surgery; Radiology and Nuclear Medicine; Intensive Care; Anaesthesiology; Pharmacy; Cardiology; and Vascular Surgery.



CARIM's researchers are part of broad networks on the regional (Euregion), national (Center of Translational Molecular Medicine: CTMM; CVON) and international (Horizon 2020; Fondation LeDuc; ERA-CVD) level, and participate in internationally renowned research platforms such as the Maastricht Study (with support of Maastricht UMC+ and the Province of Limburg). In addition, strong and sustained alliances have been established with the Universities of Mainz (DE), Aachen (DE), Munich (DE), Münster (DE), Padova (IT), Stockholm (SE), Birmingham (UK), Bordeaux (F), and Irvine (USA), with which CARIM in general has a joint or double PhD degree programme in place. In addition, CARIM engages in broad and sustained public private partnerships with Medtronic; Bayer; Philips; Boehringer; NattoPharma; Roche and Siemens.

2.2 Composition

The number of CARIM staff has decreased over the past six years. At the end of 2013, CARIM had 264 research staff members (177.0 fte), of which 34 staff members (5.9 fte) employed by Maastricht UMC+ with dedicated research time from the hospital. At the end of 2018, both the numbers of scientific staff as well as the support staff have decreased. The support staff was disproportionately affected as the decrease was governed by a first relative decrease of 0.89 fte to 0.70 fte technical support per fte scientific personnel, followed by an additional decrease in scientific fte as a result of an imposed scientific ceiling to a maximum of 0.5 fte per scientific personnel. As a result, the amount of support staff was almost halved. The decrease in research staff in 2015 and 2016 is caused by the reduction in research labelling to max 0.5 fte per researcher. The fte scientific staff employed by the academic hospital, however, has doubled from 5.9 in 2013 fte to 12.0 fte in 2018. The rise in the number of external PhD's reflects CARIM's investments in the international recruitment of PhD candidates from India, China, UK, Portugal and the Middle East, and the developing joint/double PhD programmes with the aforementioned established European partners.

Table 2 | Research staff at School level

	2013		2014		2015		2016		2017		2018	
School	#	fte	#	fte	#	fte	#	fte	#	fte	#	fte
Scientific staff FHML(1)	80	40.4	78	38.9	76	34.5	72	29.4	73	29.5	70	28.5
Scientific staff academic hospital	34	5.9	32	9.2	29	12.3	36	13.8	33	13.3	30	12.0
Post-docs (2)	59	46.7	43	35.2	38	30.3	46	35.2	38	29.7	37	28.0
Internal PhDs (3)	91	83.8	89	81.1	82	77.3	90	84.2	97	94.4	103	101.3
Total research staff	**264**	**177.0**	**242**	**164.4**	**225**	**154.4**	**244**	**162.6**	**241**	**166.9**	**240**	**169.7**
Support staff (research)(4)	104	71.3	83	57.5	75	51.7	61	48.9	51	42.4	54	42.4
Support staff (managerial)(5)	6	4.2	6	4.2	6	4.2	6	5.2	6	4.9	6	5.1
Total staff incl academic hospital	**374**	**252.3**	**331**	**226.1**	**306**	**210.4**	**311**	**216.6**	**298**	**214.2**	**300**	**217.2**
Total staff excl academic hospital	**339**	**246.4**	**299**	**216.9**	**277**	**198.1**	**275**	**202.8**	**265**	**200.9**	**270**	**205.2**
External PhDs (6)	**56**		**50**		**65**		**130**		**141**		**148**	
Visiting fellows/professors (7)	22		26		20		22		20		26	

#: Number of persons active on the School research activities on 31-dec of any year/average MJE (men year equivalents)
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the School research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML.
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the Scientific Director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Visiting fellows are researchers/professors who visit the School for a period of typically one week up to three months to work with School's staff members.

Finally, CARIM hosts at least 20 visiting international fellows and professors every year. CARIM has a renowned reputation in hosting Marie Curie Early Stage Researchers as well as Marie Curie Post-docs coming from various European countries. Co-financed by St. Annadal foundation (Wellens chair), the Van de Laar Fund and the Hemker fund, CARIM has been able to attract new expertise in a structural manner through the appointment of visiting professors who work in Maastricht for on average six months to one year. Not only the Maastricht cardiovascular research benefits from the expertise that comes available through visiting professorships, but the renowned candidates also give fresh impetus to CARIM's PhD programme and enhance personal experiences of PhD candidates (see chapter 5).

2.3 Financing

An overview of the total funding of research staff at the level of the School is provided in Table 3. The total research funding expressed in ftes has decreased from 171.8 fte to 158.4 fte, which is caused by a decrease in direct funding (34.1 fte in 2018 compared to 57.9 fte in 2013). The table shows a slight shift in the overall funding of the School towards more research grants and contract research (79% in 2018 compared to 66% in 2013) and less direct funding (22% in 2018 compared to 34% in 2013).

The total expenditures (including costs of technical and support staff) have decreased in the last six years, from € 24.492 in 2013 to € 18.721 in 2018, which is explained by a decrease of the number of staff members, both OBP and scientific staff, from 252.2 fte in 2013 to 208.0 fte in 2018 (see chapter 2.2).

Table 3 Funding at School level

School	2013		2014		2015		2016		2017		2018	
Funding	fte	%	fte	%	fte	%	fte	%	fte	%	fte	%
Direct funding (1)	57.9 (4)	34	52.9	34	42.0	29	36.6	24	33.6	22	34.1	22
Research grants (2)	19.3	11	21.7	14	24.9	17	19.5	13	22.4	15	18.8	12
Contract research (3)	94.7	55	82.9	52	77.3	54	93.6	63	98.3	64	105.5	67
Total funding	**171.8**	**100**	**157.4**	**100**	**144.1**	**100**	**149.7**	**100**	**154.3**	**100**	**158.4**	**100**
Expenditure	K€	%	K€	%	K€	%	K€	%	K€	%	K€	%
Personnel costs	16,456	67	15,341	71	13,865	71	13,241	69	13,572	68	13,078	70
Other costs	8,036	33	6,145	29	5,623	29	6,070	31	6,249	32	5,643	30
Total expenditure	**24,492**	**100**	**21,486**	**100**	**19,488**	**100**	**19,310**	**100**	**19,821**	**100**	**18,721**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering'/lump sum budget)
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charity organisations
Note 4: The funding in fte includes the total research staff but excludes the academic hospital staff

In addition to the numbers listed in Table 3, CARIM researchers accumulate external clinical trial funding. In our organisation, this part of the external contract funding is administrated by Maastricht UMC+ and/or the Clinical Trial Centre Maastricht (CTCM):

	2013	2014	2015	2016	2017	2018
Maastricht UMC+	316,588	1,661,441	2,269,550	6,999,720 *	2,082,620	1,795,409
CTCM	1,705,062	1,847,376	2,191,289	2,079,421	1,712,096	1,494,817
Total	**2,021,650**	**3,508,817**	**4,460,838**	**9,079,141**	**3,794,716**	**3,290,226**

* Increase in funding by incidental Maastricht Study support from Maastricht UMC+ (4.4 M€).

3 Research quality

3.1 Demonstrable research products for peers: a description of the research output

The results of CARIM's scientific output are presented in Table 4. The number of publications within CARIM has increased, while the number of scientific personnel declined. The number of refereed articles with an impact factor increased from 518 in 2013 to 581 in 2018. On average, CARIM has about 40 PhD graduations per year, with a peak in 2016 (55 theses). The average Impact Factor (IF) of CARIM's publications in scientific journals has increased from 4.86 to 5.57 between 2013 and 2018.

Table 4 Main categories of research output at School level (date: 7 June 2019)

School	2013	2014	2015	2016	2017	2018
Refereed articles with IF (SCI/SSCI) (1)	518	526	548	540	501	581
Other refereed articles (2)	117	87	120	107	123	115
Total refereed articles (3)	635	613	668	647	624	696
Books	1	1	16	2	1	n.a.
Book chapters	5	9	6	4	10	2
PhD theses	35	35	41	55	38	45
Total publications	**676**	**658**	**731**	**708**	**673**	**743**

Note 1: Refereed articles published in an international journal, which is mentioned in the (Social) Science Citation Index (SCI or SSCI) of Journal Citation Reports (JCR) ('wi-1')
Note 2: Refereed articles published in an international journal, not included in the SCI/SSCI ('wi-2'), editorial materials, letters to the editor and refereed articles in a national (Dutch) journal ('wn')
Note 3: The sum of the refereed articles (SCI/SSCI) and the other refereed articles

Please note that conference papers, abstracts, popular press articles, non-refereed articles, interviews and media appearances are not collected systematically. They will be, however, discussed during the annual Planning & Control meetings with the PI groups.

3.1.1 Most important scientific publications

The following publications have been selected because of their high impact and/or representation of the research foci within CARIM.

Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation

von Hundelshausen P, **Agten SM**, Eckardt V, Blanchet X, Schmitt MM, **Ippel H**, Neideck C, Bidzhekov K, Leberzammer J, **Wichapong K**, Faussner A, Drechsler M, Grommes J, **van Geffen JP**, Li H, Ortega-Gomez A, **Megens RT**, Naumann R, **Dijkgraaf I**, Nicolaes GA, Döring Y, Soehnlein O, Lutgens E, **Heemskerk JW**, **Koenen RR,** Mayo KH, **Hackeng TM**, **Weber C**. Chemokine interactome mapping enables tailored intervention in acute and chronic inflammation. Sci Transl Med. 2017 Apr 5;9(384). IF: 16.7
In a team science setting of chemical protein synthesis, structural NMR, biophysical analysis and in vivo atherosclerosis models, this paper describes a conceptual change on views on thromboinflammation in which fluid existence of chemokine heteromers govern pro- and anti-imflammatory processes during development of atherosclerosis. As proof of concept an oxime-linked obligate chemokine (RANTES-PF4) heterodimer has been designed and chemically synthesised of which pro-atherogenic activity could not be reversed by a previously designed RANTES-PF4 disruptive peptide MKEY.

Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation.

Spronk HM, De Jong AM, **Verheule S**, De Boer HC, Maass AH, **Lau DH**, Rienstra M, **van Hunnik A**, **Kuiper M, Lumeij S, Zeemering S**, Linz D, Kamphuisen PW, **Ten Cate H**, **Crijns HJ**, Van Gelder IC, van Zonneveld AJ, S**chotten U**. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. Eur Heart J. 2017 Jan 1;38(1):38-50. IF: 23.4
Atrial fibrillation is known to be associated with an increased risk for thromboembolic stroke; this study provided the first evidence for a reverse association, in which

hypercoagulability is a driver of atrial fibrillation, through thrombo-inflammatory effects in the heart. This publication laid the foundation for the CVON RACE-5 consortium.

A randomized trial of intra arterial treatment for acute ischemic stroke

Berkhemer OA, Fransen PS, **Beumer D**, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, **Staals J**, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, **van Zwam WH**, Roos YB, van der Lugt A, **van Oostenbrugge RJ***, Majoie CB, Dippel DW; MR CLEAN Investigators. A randomized trial of intra arterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11-20 IF 55.87
*Shared last author
This study was a game changer. For the first time, it was shown that immediate intra-arterial treatment for acute ischemic stroke is effective, also in terms of outcome. The results of this trial prompted to change the treatment guidelines for acute ischemic stroke worldwide. Received the biannual Science and Innovation Price of the Netherlands in 2017 (Federatie Medisch Specialisten).

Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: The Maastricht Study

Sörensen BM, **Houben AJ**, Berendschot TT, Schouten JS, **Kroon AA, Van der Kallen CJ, Henry RM**, Koster A, **Sep SJ, Dagnelie PC, Schaper NC, Schram MT, Stehouwer CD**. Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: The Maastricht Study. Circulation 2016;134(18):1339-1352 IF 17.20
This study showed the potential of the Maastricht Study to derive important insights from deep phenotyping. Prediabetes (a metabolic phenotype present in ~20% of individuals over 40 years of age in the general population) was shown to be accompanied by generalised microvascular dysfunction which was similar, although less severe, than that observed in type 2 diabetes. This study concluded that microvascular dysfunction is present before the diagnosis of type 2 diabetes and at lower levels of hyperglycaemia than previously thought.

Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy: Applying the MOGE(S) Classification

Hazebroek MR, Moors S, Dennert R, **van den Wijngaard A**, Krapels I, Hoos M, **Verdonschot J**, **Merken JJ, de Vries B**, Wolffs PF, **Crijns HJ, Brunner-La Rocca HP, Heymans S**. Prognostic Relevance of Gene-Environment Interactions in Patients With Dilated Cardiomyopathy: Applying the MOGE(S) Classification. J Am Coll Cardiol, 2015. 66(12): p. 1313-23 IF 16.83
This study showed that prognosis of DCM patients depends on gene-environment interactions according to the novel MOGE(S) classification. The presence of multiple attributes was a strong predictor of adverse outcome and the application of the MOGE(S) involving multiple possible aetiologies is clinically recommended.

Right ventricular deformation imaging and computer simulation for electromechanical substrate characterization in arrhythmogenic right ventricular cardiomyopathy (ARVC)

Mast TP, Teske AJ, **Walmsley J**, van der Heijden F, van Es R, **Prinzen FW, Delhaas T**, van Veen TA, Loh P, Doevendans PA, Cramer MJ, and **Lumens J**. Right ventricular deformation imaging and computer simulation for electromechanical substrate characterization in arrhythmogenic right ventricular cardiomyopathy (ARVC). J Am Coll Cardiol, 2016; 68(20): 2185-2197 IF 16.83
This study provided evidence for echocardiographic myocardial deformation imaging being a valuable tool for early disease identification in and diagnostic stratification of patients with arrhythmogenic cardiomyopathy and their genotype positive but asymptomatic family members. Additionally, this paper demonstrates the added mechanistic value of the CircAdapt model. Model simulations provided insight into the pathophysiological substrates underlying the abnormal right ventricular deformation patterns observed in the index patients and their seemingly healthy family members, and guided the design of the novel patient stratification scheme presented in this manuscript.

Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial

Nijssen EC, **Rennenberg RJ**, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, **Ommen VV, Wildberger JE**. Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial. Lancet. 2017; 389: 1312-1322 IF 47.83
The AMACING trial is the first (and only) study to show that guideline-recommended prophylactic hydration prior to intra-arterial and intravenous contrast administration is not (cost-) effective for the largest part of the eligible population. The results prompted an amendment to several guidelines (e.g. NL, EU, UK), and clinical practice has been demonstrably altered: complications such as symptomatic heart failure are avoided and bed occupancy has been much reduced, relieving patient and hospital burden. In the

Netherlands alone the reduction in health care costs is an estimated 50-100 million euro a year. The study has promoted a paradigm shift in the scientific discussion surrounding contrast-induced nephropathy and clinical practice guidelines, featuring in many editorials and blogs.

3.1.2 *Scientific events organised by CARIM*

CARIM organises a variety of scientific events during the year. In addition to the Annual CARIM Scientific Symposium, the weekly Cardiovascular Grand Rounds Maastricht (40 per year) and the Cardio Renal seminars (in collaboration with RWTH Aachen), lectures and mini symposia are organised by CARIM on a regular basis.

CARIM engages in organising recurrent international scientific congresses, such as the Maastricht Consensus Conference on Thrombosis (MCCT: founder and organiser: Prof. Hugo ten Cate), this year successfully organised for the third time, the European Congress on Thrombosis and Haemostasis (ECTH: founder and organiser: Prof. Tilman Hackeng), also successfully organised for the third time. In addition, renowned international courses are organised such as the European Vascular Course (EVC: founder and organiser: Prof. Michael Jacobs), this year successfully organised for the 24th time, and the two-year course Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM: founder and organiser: Prof. Harry Crijns), organised for the second time.

DAS-CAM

CARIM is also active in attracting major international congresses to a Maastricht edition, such as the 38th meeting of the EWGCCE (Meeting of the European working group for cellular cardiac electrophysiology of the ESC, organised by Prof. Paul Volders and Prof. Uli Schotten in 2014).

3.2 Demonstrable use of research products by peers

CARIM's publications (refereed with IF and other refereed) were cited 57,650 times in the period 2013-2018, as calculated by the University Library Maastricht. Table 5 provides an overview of CARIM's bibliometric statistics as calculated by the University Library Maastricht (based on refereed publications), including the number of articles (P); the average (mean) number of citations per paper (CI); the citation impact (citations per paper) normalised for subject, year and document type (CNCI); and the citation impact (citations per paper) normalised for journal, year and document type (JNCI).

These data show that CARIM's CNCI (the crown indicator) has remained fairly stable around 1.9 during the last 8 years. The CNCI indicates the impact of the research unit's publications compared to the world citation average (being between 0.8 and 1.2) in the subfields in which the research unit is active. That means that the publications of CARIM are cited approximately 1.9 times more frequently than the world average, reflecting a high research performance.

In addition, the JNCI is around 1.2, indicating that publications from CARIM are published in journals with a significantly above-average impact in the cardiovascular field.

Table 5 Bibliometric statistics CARIM 2013-2018 (refereed articles)

	P	CI	CNCI	JNCI
2013 - 2016	2,098	25.08	1.96	1.18
2014 - 2017	2,123	17.71	1.91	1.17
2015 - 2018	2,241	11.87	1.89	1.24

In the period between 2013 and 2018 approximately one-third of CARIM's publications ranked in the top journals (Table 6), i.e. those journals that have been ranked as the top 10% in various subject categories by the Journal Citation Reports of the the ISI[2] Web of Knowledge. An additional 30% to 40% of CARIM's papers are published in the top 10%-25% ranking journals. The average Impact Factor of CARIM publications has increased from 4.9 to 5.6.

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2 International Scientific Indexing

Table 6 Overview of the percentage of publications in the top 10% and top 10%-25% ranking scientific journals 2013-2018.

	2013	2014	2015	2016	2017	2018
Refereed articles with IF (SCI/SSCI)	518	526	564	543	502	581
Top 10%	32.4%	32.1%	35.6%	29.7%	28.3%	27.7%
Top 10-25%	33.5%	32.7%	30.0%	37.4%	36.1%	34.4%
Average IF	4.9	4.6	4.9	5.5	5.7	5.6

Finally, the Hirsch-index (Hirsch J., Proc Natl Acad Sci USA 2005;102: 16569) is a strong indicator of the academic reputation of individual scientists. Table 7 shows an overview of the Hirsch-index (H-index) for all CARIM PIs, including the Scientific Director.

Table 7 H-index and M-index of CARIM's PIs

Name	Department	H-index*	Year PhD mm/yyyy	Years after PhD	M-index**
Ilja Arts	Epidemiology	34	04/2001	17	2.0
Erik Biessen	Pathology	48	09/1989	28	1.7
Matthijs Blankesteijn	Pharmacology & Toxicology	28	09/1993	25	1.1
Harry Crijns	Cardiology	100	01/1993	25	4.0
Hugo ten Cate	Biochemistry	55	12/1987	31	1.8
Tammo Delhaas	Biomedical Engineering	36	12/1993	25	1.4
Tilman Hackeng	Biochemistry	44	12/1993	25	1.8
Johan Heemskerk	Biochemistry	55	06/1986	32	1.7
Stephane Heymans	Cardiology	53	05/2000	18	3.0
Bram Kroon	Internal Medicine	40	12/1996	22	1.8
Jos Maessen	Cardiothoracic Surgery	29	09/1988	30	1.0
Robert van Oostenbrugge	Neurology	35	06/1999	19	1.8
Mark Post	Physiology	54	11/1989	29	1.8
Frits Prinzen	Physiology	50	06/1982	37	1.6
Chris Reutelingsperger	Biochemistry	57	06/1987	32	1.8
Uli Schotten	Physiology	48	09/2003	15	3.2
Coen Stehouwer	Internal Medicine	110	10/1992	26	4.2
Monika Stoll	Biochemistry	44	06/1995	24	1.9
Paul Volders	Cardiology	39	07/1999	19	2.1
Christian Weber	Biochemistry	93	03/1994	25	3.4
Joachim Wildberger	Radiology	45	07/2002	17	2.6
Leon de Windt	Cardiology	47	12/1999	20	2.4

* H-indexes were provided by PI's and based on the Web of Knowledge using the time period 1988-2019. ** M-indexes were calculated in July 2019, using the date of the PhD defence instead of the date of first publication as the start of the publication record to prevent scientists from being disproportionally disadvantaged by their earlier publications (Pre-PhD).

3.3 Demonstrable marks of recognition from peers

The quality of the research output from CARIM scientists has been recognised by peers in many ways. An important mark of recognition is the number of prestigious personal grants a research institute has received. Table 8 shows the most prestigious grants received in the reporting period (2013-2018).

Table 8 Most prestigious personal grants received in reporting period (2013-2018)

Name	Department	Organisation*	Award	Year	Division
Eline Kooi	Radiology	NWO	Aspasia	2013	Blood (former Theme III)
Marjo Donners	Pathology	NHS	Dr E. Dekker Senior Scientist	2013	Blood (former Theme III)
Kristiaan Wouters	Internal Medicine	NHS	Dr E. Dekker Senior Scientist	2013	Vessels
Ingrid Dijkgraaf	Biochemistry	NWO	Vidi	2014	Blood
Blanche Schroen	Cardiology	NWO	Vidi	2014	Heart
Ellen Dirkx	Cardiology	NWO	Veni	2014	Heart
Blanche Schroen	Cardiology	NHS	Dr E. Dekker Senior Scientist	2014	Heart
Martijn Smulders	Cardiology	NHS	Dr E. Dekker Arts Junior Clinical Scientist	2014	Heart
Miranda Nabben	Genetics & Cell Biology	NWO	Veni	2015	Heart
Jordi Heijman	Cardiology	NWO	Veni	2015	Heart
Leon de Windt	Cardiology	NWO	Vici	2015	Heart
Marc Strik	Physiology	NHS	Dr E. Dekker Arts Junior Clinical Scientist	2015	Heart
Martijn Brouwers	Internal Medicine	NHS	Dr E. Dekker Senior Clinical Scientist	2015	Vessels
Joost Lumens	Biomedical Engineering	NHS	Dr E. Dekker Senior Scientist	2015	Heart
Judith Cosemans	Biochemistry	NHS	Dr E. Dekker Senior Scientist	2015	Blood
Anna Papageorgiou	Cardiology	NHS	Dr E. Dekker Senior Scientist	2015	Heart
Paula da Costa Martins	Cardiology	NHS	Dr E. Dekker Established Investigator	2015	Heart
Martina Calore	Cardiology	EC	Marie Curie Fellowship	2015	Heart
Blanche Schroen	Cardiology	NWO	Aspasia	2015	Heart
Ingrid Dijkgraaf	Biochemistry	NWO	Aspasia	2015	Blood
Judith Cosemans	Biochemistry	NWO	Aspasia	2016	Blood
Paola van der Meijden	Biochemistry	EHA-ISTH	EHA-ISTH Fellowship	2016	Blood
Judith Cosemans	Biochemistry	NWO	Vidi	2016	Blood
Judith Sluimer	Pathology	NHS	Dr E. Dekker Senior Scientist	2016	Blood (former Theme III)
Joost Lumens	Biomedical Engineering	NWO	Vidi	2017	Heart
Judith Sluimer	Pathology	NWO	Aspasia	2017	Blood (former Theme III)
Nordin Hanssen	Internal Medicine	NHS	Dr. E. Dekker Clinical Scientist	2017	Vessels
Christian Weber	Biochemistry	ERC	Advanced grant	2017	Blood
Eline Kooi	Radiology and Nuclear Medicine	NWO	Aspasia	2018	Blood (former Theme III)
Thomas van Sloten	Internal Medicine	NWO	Veni	2018	Vessels
Emiel van der Vorst	Pathology	NWO	Veni	2018	Blood (former Theme III)
Matthijs Cluitmans	Cardiology	NWO	Veni	2018	Heart
Thomas van Sloten	Internal Medicine	NHS	Dr. E. Dekker Clinical Scientist	2018	Vessels
Emiel van der Vorst	Pathology	NHS	Dr. E. Dekker Postdoc	2018	Blood (former Theme III)
Matthijs Cluitmans	Cardiology	NHS	Dr. E. Dekker Postdoc	2018	Heart
Judith Sluimer	Pathology	NWO	Vidi	2018	Blood (former Theme III)

* NWO: the Netherlands Organisation for Scientific Research; NHF: The Dutch Heart Foundation; EC: European Commission; EHA-ISTH: European Haematology Association-International Society on Thrombosis and Haemostasis; ERC: European Research Council.

Besides obtaining national personal grants from NWO and NHS and donations from large local private foundations (*Van de Laar; de Weijerhorst*), CARIM researchers have been very active in participating in national and EU networks and establishing (inter)national alliances. CARIM is involved in multiple NHF

Cardiovascular Research Networks (*Cardiovasculair Onderzoek Nederland*; CVON) as members in RACE, SHE-PREDICTS-HF, PREDICT 2, VIGILANCE, ARENA PRIME, EARLY-HFPEF, CONTRAST, RECONNECT YTP, and in multiple NHF young talent programmes. In total, CARIM is currently involved in almost 50 European projects, of which nine Horizon 2020 ITN programmes with a total number of 29 Early Stage Researchers allocated to the School. CARIM is coordinator of two of these ITNs; INTRICARE (3.8 M€) and TRAIN-HEART (3.9 M€). See Annex 3 for an overview of all European projects that started in the period 2013-2018.

Furthermore, CARIM scientists have received prestigious scientific awards and prizes (Annex 4) and have been invited for numerous plenary presentations at international conferences (Annex 5). In addition, CARIM scientists are members of (inter)national scientific research grants reviewing boards (Annex 6) and editorial boards (Annex 7).

3.4 In conclusion: quality

Researchers in CARIM produce a large number of frequently cited publications in high impact scientific international journals. The number of PhD candidates is increasing. CARIM researchers have a high international academic reputation, which is demonstrated by the invited lectures, the participation in large-scale European projects, the number of prestigious personal grants, awards and prizes, the memberships of scientific committees and editorial boards, and the editorships, which can all be found in Part B of this report.

4 Relevance to society

Part of CARIM's mission is to disseminate results, not only to scientific communities, but also to professional communities and to society as a whole. CARIM does this by contributing to expert and consensus committees, and guideline task forces, by creating awareness of the importance of research on cardiovascular disease, and by informing and warning members of our society about early warning signs of cardiovascular disease. To achieve this goal CARIM organises annual public events such as 'World Thrombosis day', every year on 13 October, to inform citizens of southern Limburg about the signs and risks of cardiovascular disease. In addition, CARIM-HVC organises a number of annual events, such as 'Walk (and cycle) with your Doctor' in which patients and relatives can engage in hiking and cycling trails accompanied by doctors aiming at healthy living and discussing early diagnosis, prevention, and healing of cardiovascular disease, the 'Awareness days' ('*Doe- en beleefdagen*'), in which the general public is informed of translational science and medicine and the yearly 'RESCAR/HFL' patient congress during which patients and relatives are interactively informed on PhD work they financially supported. Basic and clinical researchers of CARIM give lectures for patient associations and at elementary and high schools (Kidz college). Based on publications and expertise, CARIM's researchers are invited for interviews in local and national newspapers and perform on regional and national TV channels. CARIM clinicians are involved in major guideline and position papers, both as authors as well as reviewers, with the aim to improve general health care and treatment of cardiovascular disease.

Division-specific information on societal impact is described in Part B of this document. In this chapter, results are summarised.

4.1 Demonstrable research products for societal target groups

MyAF
AF manager

Uli Schotten and Harry Crijns: CATCH ME applications MyAF and AF manager, providing guidance for patients with AF and a platform for interaction with their care providers; in addition, the platform provides a repository for big data analyses. These apps are the official European Society of Cardiology (ESC) apps for health care professionals and AF patients. They have been designed as part of the CATCH ME projects and the ESC decided to further maintain and develop these apps in the context of future projects

Het vitamine K kookboek; gezond en lekker koken voor trombosedienstpatiënten

Leon Schurgers and Hugo ten Cate: Cookbook on vitamin K for patients of the oral anticoagulation clinic (*Het vitamine K kookboek; gezond en lekker koken voor trombosedienstpatiënten*. Trichis Publishing B.V. ISBN 9789490608460). This collaboration between the Dutch Thrombosis Foundation and scientists in the field of Biochemistry and Clinical Thrombosis and Haemostasis has yielded tried and tested recipes with known concentrations of vitamin K to create awareness amongst patients on oral anticoagulation with vitamin K antagonists.

www.circadapt.org

Joost Lumens and Tammo Delhaas: The educational version of the CircAdapt model of the human heart and circulation (freely downloadable from www.circadapt.org) is an example of educational valorisation, as it is used for teaching cardiovascular physiology and pathophysiology not only to medical students in Maastricht (>1000 per year), but also to medical students in other universities in the Netherlands and Abroad. The CircAdapt model is used in medical school curricula of the Dutch universities of Nijmegen and Utrecht, and on an international level it is introduced at the University of Utah and Duke University (USA), Stellenbosch University (SA), University of Cali (CO), University of Copenhagen (DK), and more (> 6000 external downloads between 2013-2018). In addition, the open-source research version of the CircAdapt model is used for basic cardiovascular science projects at several renowned international universities, such as Bordeaux University, University of Graz, King's College, University of Utah, Washington University in St Louis, and more.

https://www.sciencedirect.com/science/article/pii/B9780123983589000781?via%3Dihub

Mark Post: Prof. Mark Post's efforts with regard to tissue engineering for food constitute an important effort to enhance sustainability of meat consumption. It will be extremely challenging to make these products a reality for the consumer, but the reward and return in terms of value for our society will be tremendous. (https://www.sciencedirect.com/science/article/pii/B9780123983589000781?via%3Dihub)

Michael Jacobs: Prof. Michael Jacobs's European Vascular Course is held yearly and attracts vascular surgeons from the entire world, The course has increased standards and innovation in vascular surgery, thus affecting the lives of countless patients suffering from vascular insufficiency or degeneration. (http://www.vascular-course.com/root)

http://www.vascular-course.com/root

Casper Schalkwijk: Prof. Casper Schalkwijk recently published the first database of Advanced Glycation End products (AGEs) in 240 food items, as measured with state-of-the art UPLC-MSMS. He found that dietary AGEs are associated with AGEs in the body. (https://www.sciencedirect.com/science/article/pii/S0308814615009413?via%3Dihub)

https://www.sciencedirect.com/science/article/pii/S0308814615009413?via%3Dihub)

4.2 Demonstrable use of products by societal groups

During the period 2013-2018, CARIM staff members have been participating in several large public-private partnerships, such as CTMM and the Top Institute Biomedical Materials (BMM). It has been the explicit intention that expertise emerging from studies within these consortia should lead to patents and spin-off companies.

Several groups within CARIM have been successful in filing patents on results emerging from their studies, e.g. biomarkers for prevention and treatment (Prof. Hans-Peter Brunner-La Rocca, Prof. Blanche Schroen, Prof. Uli Schotten, Prof. Leon De Windt, Prof. Frits Prinzen), inhibitors or markers for treatment (Dr Gerry Nicolaes, Prof. Christian Weber, Prof. Hans-Peter Brunner-La Rocca), devices (Prof. Cees Wittens, Prof. Frits Prinzen, Dr Peyman Sardari Nia, Prof. Uli Schotten) and products (Dr Cees Vermeer, Prof. Tilman Hackeng).

Part of these patents were granted and have been licensed by existing SMEs, others have resulted in spin-off companies emerging from CARIM itself in the recent years. See Annex 8 for an overview and description of the CARIM spin-off companies.

Spin-off	Subject	Scientist(s)	Year	Division
Biotech Mirabilis Therapeutics BV	MicroRNA therapeutics	L. de Windt; P. da Costa Martins	2015	Heart
Qorium BV	Cultured leather	M. Post	2015	Vessels
C2T	Cell culture technology	M. Post	2016	Vessels
MosaMeat	Cultured meat	M. Post	2016	Vessels
YourRythmics	AF decision tool	U. Schotten	2016	Heart
FlowChamber	Blood platelet function and coagulation	J. Heemskerk	2017	Blood
Coagulation Profile	Coagulation phenotyping	H. Spronk; H. ten Cate; L. Schurgers; T. Hackeng	2018	Blood
Cartesio Therapeutics Inc.	Vascular inflammation	C. Weber; G. Nicolaes	2018	Blood

4.3 Demonstrable marks of recognition by societal groups

CARIM researchers contribute extensively to (inter)national clinical guidelines and serve on committees responsible for (inter)national (health) policy reports (see Annex 10 and 11). The most important contributions are described below:

Robert van Oostenbrugge: Member advisory group Ministry of Health regarding the implementation and concentration of Intra-arterial treatment in the Netherlands.

Hugo ten Cate: Chairman of Board Dutch Federation of Anticoagulation clinics. Chair national steering committee on anticoagulation management ('*Stuurgroep*' currently transformed into '*Kenniscentrum Antistolling*'; of which Prof. Hugo ten Cate is vice-chair).

Arina ten Cate-Hoek: Member of the working group European Society for Vascular Surgery (ESVS) 2020. Clinical Practice Guidelines for the Management of Venous Thrombosis; working group International Society on Thrombosis and Haemostasis (ISTH) committee on common data elements in reporting on venous thromboembolism (VTE) related outcomes.

Bram Kroon: European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the Management of Arterial Hypertension (2018) & ESH Position paper on Renal Denervation (2018). Hypertension is the single most important risk factor in terms of loss of DALYs. Prof. Bram Kroon's membership of guideline committees on the management of hypertension has resulted in caregiver and patient advice that will positively affect the lives of millions of individuals.

Nicolaas Schaper: Co-chair International Consensus on Peripheral Artery Disease in Diabetes (2015). Prof. Nicolaas Schaper is a world-renowned expert on the diabetic foot. His efforts over the years have resulted in clear multidisciplinary guidelines for this devastating and complex problem; these guidelines have been translated into 27 languages, clearly demonstrating their importance.

Uli Schotten: Guidelines for the management of Atrial Fibrillation 2016. These guidelines improve the clinical antithrombotic and heart failure treatment in patients with atrial fibrillation on a daily basis.

Stephane Heymans: Leading role in different ESC position papers/scientific statements in heart failure, including fibrosis and heart failure (EJHF, 2018), diabetes and heart failure (Eur. Heart J., 2018), metabolism in HCM (CVR, 2018), geno-phenotype in DCM (CVR, 2018), innate immunity in heart failure (EJHF, 2018), translational research in HFPEF (EJHF, 2018). Furthermore, Prof. Stephane Heymans was involved in other guidelines as well, including ESC guidelines on definition of dilated cardiomyopathy (EHJ, 2016), right heart failure (EHJ, 2017), management of HCM (EHJ, 2014), myocarditis (EHJ, 2013), and non-coding RNAs in vascular disease (CVR, 2018). Chair of Basic Science section within the Executive Committee of the ESC Heart Failure Association, Chair of the Committee on Translational Research, and Chair of the Working Group of Myocardial Function.

Leon de Windt: An ESC scientific statement from the Working Group on Myocardial Function on the innate immune system in chronic cardiomyopathy (2018). Activation of the immune system in heart failure (HF) has been recognised for over years. Prof. Leon de Windt's membership of this guideline committee on therapeutic opportunities to alter the immune system in the management of heart failure has resulted in caregiver and patient advice that will impact patients with chronic heart failure. A position paper from the ESC Working Group on Myocardial Function: an integrative translational approach to study heart failure with preserved ejection fraction (2018). ESC Working Group on Myocardial Function Position Paper: how to study the right ventricle in experimental models (2014).

Joost Lumens: Various leadership roles in the ESC, e.g. Chair-Elect (2016-2018) and Chair (2018-2020) of the ESC Working Group on e-Cardiology, ESC Working Group Liaison Officer in the ESC Digital Health Committee, Member of the ESC Conference Programme Committee, Ex-Officio Board member of the European Heart Rhythm Association (EHRA). Dr Joost Lumens also served as an invited Taskforce Member of the 5th and the 6th World Symposia on Pulmonary Hypertension (2013 and 2018) and co-authored the relating Consensus Papers on 'Right heart adaptation and pathophysiology in pulmonary hypertension' (JACC 2013 and Eur Respir J 2019).

Eline Kooi: Prof. Eline Kooi is a member of a study group from the American Society of Neuroradiology. This study group has provided perspectives and guidelines on vessel wall imaging in patients with carotid artery disease. These expert recommendations were recently published in a white paper (Saba et al, AJNR, 2018).

4.4 Narrative and anecdotal information

For the narratives and anecdotal information, we refer to an overview of narratives collected from researchers from all CARIM programmes, which can be found on our website.

5 PhD programme and overall talent policy

5.1 PhD programme

PhD programme
Part of CARIM's mission is to train Masters-, PhD- and MD students to become independent researchers and post-doctoral fellows to become leading scientists, capable of functioning in multidisciplinary research programmes at universities or other academic and non-academic institutions. In most cases, PhD candidatess are appointed for four years. However, in case of European grants, contracts can be three years. As of 2017, CARIM provides financial support to cover part of the salary costs for the fourth year appointment. At the same time, it is recognised that for the nearby future CARIM should aim for a reduction of the duration of the average trajectory to comply with international developments and to guarantee exchangeability in joint interuniversity PhD programmes.

In the previous external evaluation, the PhD programme was evaluated as flexible, clearly structured and as meeting the criteria of a high quality PhD training programme. The quality and timeliness of the PhD programme is subject to continuous evaluation by the Education Programme Committee (EPC) composed of PhD representatives and CARIM staff. The EPC meets on a monthly basis and reports to the CARIM board. The PhD coordinator, Dr Marc van Bilsen serves as a mentor for all CARIM PhD candidates and as a point of contact for their supervisors. The PhD coordinator acts as Chairman of the EPC and works closely with the CARIM management office, policy advisor and Scientific Director. He also is a member of the FHML- and Maastricht University PhD committees.

The cardiovascular training programme aims to introduce the PhD candidates into aspects of basic and applied science. This aim is reflected in the School's programme of five one-week courses, and the involvement of CARIM staff in the organisation and execution of the three PhD courses organised under the auspices of the Netherlands Heart Foundation. The CARIM courses include courses on new developments in molecular biology and sophisticated physical measuring methods, as well as courses focussing on clinical problems. The courses are based on the principles of active participation and problem solving. Seminars and Master classes organised by CARIM, as well as one-day scientific meetings organised by the various research groups or departments within the School, also address basic and applied aspects of research.

The ERC advice to put more effort into monitoring the quality of supervision of PhD candidates was acted upon with the implementation of the CARIM Research, Education and Supervision (CARES) plan, which was integrated in the faculty-wide web-based PhD monitoring platform 'TRACK.2' in April 2015. This platform allows PhD candidates to upload information relevant to their PhD programme and allows CARIM to monitor PhD progress in an easy and structured way. In accordance with the CARES plan, it includes the composition of an individual Training and Supervision Plan (TSP) and Personal Research Plan (PRP) to be written in the first three months of the PhD trajectory. Once completed the TSP is signed by the PhD candidate, supervisors and PhD coordinator (after formal approval). The TSP is integrated into the PhD candidate's TRACK portfolio and kept up to date with respect to ECTS credits earned with educational activities. The PRP is updated on a yearly basis and serves as a progress report. TRACK.2 also demands a twice-yearly assessment of the progress by supervisors.

Importantly, in an annual survey, PhD candidates assess their own progress, education, career development and quality of supervision (the latter being part of a confidential section of the survey only visible to the PhD coordinator). Insufficient scores (6 or lower) for progress or supervision are automatically relayed to the PhD coordinator enabling him to take action. Elements of the annual survey can be used as starting point for the annual assessment interview with the supervisors. From the time TRACK.2 was implemented until 2018, the PhD candidates rated the progress of their PhD project with an average score of seven (on a 10-point scale) in the annual survey. 18% of the PhD candidates indicated that they expected a delay of more than three months.

academictransfer.com

To reduce the time to obtain a PhD, recently FHML decided to provide an incentive to supervisory teams in case a PhD candidate would finish within four years and otherwise to enforce to pay for the extra salary in case a PhD candidate would need more than four years to finish the thesis. It is anticipated that this measure will help to reduce the average duration of the PhD trajectory.

Selection and admission

Most CARIM PhD positions are filled via vacancies posted on academictransfer.com, or by students from one of the FHML Masters programmes who demonstrated to be potentially talented researchers during their Senior Internship in one of CARIM's PI groups. In the latter case, the time and research efforts invested in their Senior Internship regularly serve as a starting point for their PhD-trajectory. As shown in Table 9, the average dropout rate is still relatively high (15% in the period from 2008-2014) and has only dropped marginally compared to the previous Self Evaluation (17%). In most cases, this concerns drop out of PhD candidates in their first year. The first year assessment is the moment (go/no-go decision for internal PhDs) at which the PhD candidate and supervisors decide if continuation of the PhD trajectory is likely to be successful or not. In order to reduce dropout rates, the FHML started a pilot in one of the other FHML Graduate Schools (CAPHRI) in 2017. The aim of this selection tool is to make the candidate more aware of personal rights and obligations during the PhD trajectory and to achieve better matching between PhD candidate and supervisors.

Supervision

PhD candidates are supervised by two to three researchers, one who is the principal supervisor ('promotor') and the other the daily supervisor ('co-promotor'). The supervisors meet on a regular basis, thereby assuring proper guidance during the entire PhD trajectory. The Training and Supervision Plan (TSP) includes agreements about the supervisory team (roles and responsibilities of each member). As indicated earlier, PhD candidates are asked to (confidentially) rate the performance of their supervisors. In the annual survey PhD candidates rated the performance of their supervisory teams with an eight on average (on a 10-point scale), with 89% of them rating the performance of their supervisors with a score of seven or higher. The majority of CARIM's research staff has extensive experience with the supervision of PhD candidates. New supervisors are urged to participate in the newly developed UM training 'Supervision of PhD students'. More recently, the Faculty PhD committee was involved in setting up a new, more extensive, five-day FHML training course 'Competence development for PhD supervisors'. A pilot of this course ran in 2018 and was well received by the participants. For younger staff it will become mandatory to follow this course before being allowed to supervise PhD candidates.

Guidance of PhDs to labour market

The CARIM education plan is not only designed to develop research skills, but also allows PhD candidates to develop various competencies and transferrable skills needed outside academia. Thereto, ECTS credits can be earned in different domains such as cardiovascular and general courses, participation in international conferences, co-supervising Master students and teaching Bachelor students. The PhD candidate is largely free to choose in which domains to invest and which courses to follow (in consultation with the supervisor). This will to a large extent depend on whether the candidate wishes to pursue a career in healthcare, academia, industry, or other. In addition, there are multiple opportunities to attend national or local PhD workshops on career management, valorisation, etc. This year the CARIM PhD representatives of I'M CARIM, organised a career workshop themselves. Career wishes and opportunities are discussed as part of the annual assessment with their supervisors.

Master programmes

CARIM is involved in several FHML clinical and preclinical Master programmes, including the Master in Medicine, the Physician-Clinical Master and the Master Biomedical Sciences (BMS). In each of these Master programmes, CARIM staff acts as coordinator of different modules and fulfils other important teaching roles. Importantly, part of the training of Master students in each of these programmes involves one or two internships (ranging from three to eight months) allowing many students to become acquainted with and to participate in clinical and preclinical cardiovascular research under the guidance of CARIM staff.

5.2 PhD duration and success rate

In 2018, the total number of PhD candidates (both internal and external) at CARIM amounted to 246 people of whom 98 PhD candidates were employed by the University (see chapter 2.2). Table 9 shows an overview of the number of regular (internal) PhD candidates who started between 2008 and 2014. The primary aim of those PhD candidates with an employee status at CARIM is to conduct research with the obligation to graduate. The enrolment of new PhD candidates in 2009, 2010 and 2011 was significantly higher than in other years. The most important reason for this increase was the Maastricht Study, which started in 2009. The ratio male/female PhD candidates is slightly shifting towards more female than male PhD candidates. In total, 71% of the PhD candidates who enrolled in 2008-2014 have finished their PhD trajectory. While the number of PhD candidates that finishes their theses within four or five years increases, the average duration of the PhD trajectory is still substantially longer than the originally intended four years: 62 months until the date of PhD defence in 2017. The date of approval of thesis manuscript is usually four months before. It should be noted however that much of the average delay in PhD duration is caused by a few PhD trajectories with a very long duration. To prevent this from happening, more intense personal monitoring and coaching is needed.

Table 9 Standard PhD candidates (1)

Enrolment				Success rates						
Starting year	Enrolment (male / female)		Total	Graduated in year 4 or earlier	Graduated in year 5	Graduated in year 6	Graduated in year 7 or later	Total graduated	Not yet finished	Discon-tinued
	M	F								
2008	10	9	19	0/0%	5/26%	6/31%	3/16%	14/74%	0/0%	5/26%
2009	21	17	38	2/5%	9/24%	10/26%	8/21%	29/76%	2/5%	7/18%
2010	13	20	33	1/3%	13/39%	8/24%	5/15%	27/82%	0/0%	6/18%
2011	18	15	33	1/3%	15/45%	8/24%	4/12%	28/85%	5/15%	0/0%
2012	9	12	21	3/14%	7/33%	3/14%	n.a.	13/62%	3/14%	5/24%
2013	7	15	22	4/18%	8/36%	4/18 %	n.a.	16/73%	3/14%	3/14%
2014	12	15	27	2/7%	8/30%	n.a.	n.a.	10/37%	14/52%	3/11%
Total	**90**	**103**	**193**	**13/7%**	**65/34%**	-	-	**137/71%**	**27/14%**	**29/15%**

Note 1: Standard PhD candidate with employee status and conducting research with primary aim/obligation to graduate; ('AiO', 'promovendus')

As shown in Table 10, CARIM graduates are successful in obtaining jobs in various categories of employment. Of note, most of the CARIM graduates with the Dutch nationality have an MD and end up in the healthcare sector (55%), whereas the far majority of graduates from abroad continue their career in academia as researcher (61%). The high number of PhD graduates that continue their career as medical specialists in training also requires flexibility in the education programme as the career path for these PhDs is rather well defined from the start and their PhD often involves practical clinical work as well.

Table 10 Career after obtaining PhD degree (sum 2013-2018)

Field	Netherlands	Abroad	Total
Health Care	98	11	109
Industry	16	4	20
University General	2	1	3
University Research	46	33	79
Other	16	4	20
Unknown	-	-	18
Total	**178**	**54**	**247**

5.3 The School's talent policy

Early recognition of talent is one of the key strategies of CARIM to coach and prepare gifted young academics for their future academic career. CARIM stimulates and supports talented students and staff by offering grants for research programmes at each step of their career, be it at Bachelor, Master, postgraduate, PhD or postdoc level. UM students who pursue a career in cardiovascular sciences and who are identified by their supervisor as promising researchers can enroll in CARIM's Talent programme established in honour of one of the previous directors: the HS-BAFTA programme. Within the annual HS-BAFTA programme the possibility exists to perform a fully paid one year research rotation within CARIM for bachelor students (once per year); Master Students (once per year); a six month pre-PhD-candidate preparation period (once per year), a 3-6 month PhD candidate visit to an internationally renowned research lab (four per year), and a one year postdoctoral fellowship at an internationally renowned research lab (once per year).

In order to keep internal talent at CARIM or attract external talent, CARIM has introduced the Tenure Track Programme in 2008. Following a five-year programme, young researchers are given the opportunity to obtain a permanent employment contract if they meet the criteria laid down in CARIM's Tenure Track procedure, based on excellence, independence, flexibility, diversity, personal development and recognition. Tenure track candidates are annually evaluated by their personal evaluation committee involving supervisors, department chairs, CARIM board members and junior staff members. The following researchers have successfully completed their tenure tracks: Prof. Blanche Schroen (Heart), Dr Judith Cosemans (Blood), Dr Marjo Donners (Blood, former Theme III), Dr Judith Sluimer (Blood, former Theme III), Dr Paula da Costa Martins (Heart), Prof. Leon Schurgers (Blood), Dr Jan Bucerius (Blood, former Theme III), Dr Dietbert Neumann (former Theme III), Dr Rory Koenen (Blood), Dr Kristiaan Wouters (Vessels).

CARIM focusses on acquisition of prestigious personal grants, both at the junior (Veni grants) and the senior level (Vidi, Vici, ERC). CARIM has installed the Research Council, an instrument that guides researchers through their grant applications, from pitch presentation to reviewing the proposal, to practicing the interview. All CARIM employees that have received an important personal research grant are mandatory members of the research council, creating a large group where the CARIM Research Council board can select from depending on specialty. In addition, the FHML Research Office supports the School in creating a stimulating and supporting environment and operates a transparent and effective policy to help researchers in the entire process of acquiring grants and establishing international networks. The Research Office collects and shares data and information, provides analyses and syntheses, and safeguards focus and quality. The Research Office is a point of contact when it comes to procedures and protocols.

Finally, CARIM is part of the Faculty's central policy in identifying young talent at the faculty level by enabling the postdoctoral Kootstra Talent Fellowship, and by actively nominating researchers for their Toptalent Programme. At the highest level, Maastricht UMC+/FHML offers this toptalent programme to potential professors to offer them a track towards Chair with a specialised remit (*profileringsleerstoel*) with the prospect of moving on to a full professorship with a personal chair or a full professorship with a key domain chair after assessment of their performance and professional growth potential. This track includes course work on personal development and leadership skills. In the past three rounds, ten CARIM researchers have been selected for the programme, of which three have been appointed to professor: Dr Judith Cosemans, Dr Rory Koenen, Prof. Eline Kooi, Dr Bas de Laat, Prof. Blanche Schroen, Dr Paula da Costa Martins, Prof. Leon Schurgers, Dr Joost Lumens, Dr Judith Sluimer and Dr Julie Staals.

6 Research integrity and research data management

Maastricht UMC+ Research Code

Every new researcher (including PhD candidates) who receives his/her contract from the human resources department of the Maastricht UMC+/FHML is informed about the existence of the Maastricht UMC+ Research Code. The Maastricht UMC+ Research Code provides those involved in research with a clear description of the rules for ethical and socially responsible conduct in scientific research.

VSNU; Association of Universities in the Netherlands

All scientists and PhD candidates are obliged to follow the national guidelines for research integrity (VSNU; Association of Universities in the Netherlands). All staff members involved in academic research and teaching at CARIM share the responsibility for maintaining academic integrity at the university level, the Executive Board has appointed a Counsellor for scientific integrity and a Committee for Scientific Integrity, which advises the Executive Board on complaints filed regarding scientific integrity.

dilemma games on scientific integrity

In 2018, Maastricht University has setup a Research Ethics and Integrity platform to increase awareness on research integrity among students and staff by further stimulating discussion on relevant topics in a constructive and positive manner. Dr Marc van Bilsen, the PhD coordinator of CARIM, is a member of the FHML faculty platform Scientific Integrity, which was installed in 2018. This platform is developing an online course on scientific integrity, which will be obligatory for all scientific staff, including PhD candidates (in their first/second year). Moreover, the platform has ordered several dilemma games on scientific integrity (developed by Erasmus University Rotterdam), which are now being used by small groups of PhD candidates or researchers within the Schools, including CARIM.

One important aspect in this respect is the protection of storage and proper handling of research data. CARIM considers it very important to manage data with care and integrity, and to ensure the reuse and verification of research data following principles of FAIR (Findable, Accessible, Interoperable, and Reusable) and Open Science. Accurate management of research data is essential in terms of accountability and scientific integrity, but also in terms of better retrieval, sharing, and storage of research data. The Maastricht Study is a forerunner with respect to the above principles. Maastricht UMC+/FHML adheres to the principles as defined in the Maastricht University Research Data Management Code of Conduct. This code contains guidelines for the management of research data to safeguard the accessibility of research data and protect it against theft, misuse, damage and loss. Additional guidelines apply for research with human material. For these guidelines Maastricht UMC+/FHML has developed a Quality System Research (QSR). The Datahub unit offers support and facilities for Research Data Management.

7 Diversity

CARIM aims at creating diversity and equality within its community. By securing diversity and inclusivity, CARIM pursues to reflect the composition of our modern society, with a creative mix of age, race, colour, sex, culture, and character. The many European consortia in which CARIM participates also promote diversity and mobility, and CARIM's PhD candidates come from 31 countries, 51% is female and 20% non-Caucasian. Also in recruitment and tenure track policies, CARIM aims at inclusivity, and although during the previous ERC Review in 2014, PIs and staff members were predominantly male and Dutch, currently this situation is changing. Today, from the 55 professors in CARIM 15% is female, and 29% is non-Dutch, and from the junior scientific staff members and tenure trackers, 42% is female and 26% is non-Dutch (OBP: 62% female). As diversity includes many more aspects than race and gender, CARIM also supports diversity in character among their researchers. Different characters pose different views on scientific challenges, which will lead to essential scientific discussions on research objectives. In 2018, CARIM successfully applied for the pilot programme Refugees for Science from NWO and appointed a Syrian refugee.

8 Trends, SWOT and strategic plans

8.1 Trends

Translational research: Today more emphasis on translational research is requested by the general public, patient associations and society as a whole, and CARIM aims at closing translational gaps between experimental research and clinical investigations into the application of scientific results in broad-scale clinical practise. CARIM has developed several strategies to achieve this goal. Close contact and interaction between clinicians and basic researchers is stimulated by joint PhD projects and by facilitating meetings and lecture series between clinical and basic researchers. Traditional curiosity-driven research and identifying clinically relevant findings for translational application heavily relies on bringing people together who do not interact on a regular basis. To enable this, CARIM invests in translational programmes and research lines, for example at the HVC, which has led to recent spectacular results in the area of pathological stem cell generation, differentiation and repair. A national initiative called the 'science agenda' (*wetenschapsagenda*) further stimulates these translational efforts by allocating part of governmental funding power to research responding to societal needs concerning personalised, regenerative, and early detection of cardiovascular disease. CARIM researchers very actively participate in current calls of the national science agenda. Translational research plays a fundamental role in the main strategy of the Dutch Heart Foundation (NHF), which is important to CARIM as the NHF is one of the main funding organisations for contract research. The Dutch Heart Foundation plays a very central role in the recently established joined initiative Dutch CardioVascular Alliance (DCVA), which will shape the Dutch subsidy landscape on cardiovascular research in the coming years. Many CARIM researchers actively participate in this process either as coordinators or work package leaders of large national networks financed by the NHF (CVON networks) or as chair (Prof. Harry Crijns) or members of the advisory boards of the NHF.

DCVA

Personalised medicine, precision medicine and data science - Integrative diagnostics: Cardiovascular science is witnessing a shift from research on the main general pathophysiological mechanisms of cardiovascular disease towards the heterogeneity of individual mechanisms and the relative contribution of them in individual patients. Identification of disease mechanisms that are operative in individual patients offers opportunity for personalised medicine, increased cost-effectiveness of existing therapeutic interventions, more safety and efficacy of treatment. As such, studies can only be performed in large and well-characterised cohorts with rich datasets, and a shift from wet-lab experiments to data analysis, bioinformatics, and computational techniques is foreseeable. Critical expertise to implement such research approaches are non-invasive diagnostics, large-scale signal analysis, computer modelling (mechanistic and prediction models), access to biomarker development pipelines, hardware and bioinformatics for omics technologies, and novel research to integrate information from different research modalities. To homogenise and enhance this development, Prof. Hugo Aerts from Boston has been recently appointed Professor in Artificial Intelligence within Imaging. In the context of integrated diagnostics for optimised therapy, further cross-division and faculty connections are pursued.

Big data: Big data technologies offer an opportunity to expand the usage of individual data for better understanding of health and disease even more. Large efforts and investments have been undertaken to establish and secure large data infrastructure and Biobanks. A pioneer on big data analysis has been recruited from the Stanford Center for Biomedical Informatics Research to Maastricht University (Prof. Michel Dumontier) who will aid us in the future in combining large databases (e.g. Maastricht Study to central (national) bureau of statistics and geographic information (GECCO Consortium)). Big data analyses can result in better and more effective prevention of depression and anxiety and other age-related diseases such as diabetes, cancer and cardiovascular disease.

Regenerative medicine: By using new insights into new applications, regenerative medicine offers an outlook on the treatment of untreatable disease and the ageing population, improved quality of life and reduced medical costs. However, so far, regenerative medicine has not yet proved itself in the clinic beyond rare diseases or conditions of limited public health importance. With recent scientific discoveries opening up new approaches to regenerative medicine, the challenge is to use these to extend the regenerative approach

to major diseases and conditions. CARIM applies (murine) in vivo cardiac regeneration with miRNA and antagomir therapy in the challenged heart, and applies stem cell differentiation and CRISPR-Cas9 editing to repairing and culturing patient-own tissue.

Open access & data management: Currently national and international discussions are ongoing on revenue models of main scientific publishers. The European Research Council promotes and actually requires open access publishing, which affects the choice of journals for publishing scientific output. The NWO is now considering banning journals that do not comply with open access publishing guidelines for the dissemination of research results from NWO funded projects and programmes. CARIM strongly supports open access and advises the UM library on this issue who take part in national and governmental discussions.

Reduce grant acquisition pressure: To reduce grant acquisition pressure and to better prepare CARIM researchers for a well-funded scientific career, CARIM has installed a Research Council that individually maps funding strategies for CARIM's researchers for better career planning. The CARIM Research Council guides and coaches researchers who work on grant applications, for example by interview training, to stimulate the acquisition of research grants and contract research.

Next generation RNA sequencing: Infrastructure and personnel for bioinformatics analysis is crucial. CARIM observes a progressive shift in routine diagnostics to Next Generation Sequencing (NGS) for routine diagnosis, and more particularly in personalised medicine practice, from a growing number of molecular tests to NGS. NGS can provide insights into a person's genetic susceptibility to disease, diagnostic information, and predictive indications about treatment outcome. It also allows to embrace simultaneously different molecular pathways of disease evolution and to identify actionable mutations in a patient for medical decision and further research. In addition, it requires less sample material than multiple tests and therefore reduces risk and inconvenience for patients. However, the introduction of NGS in clinical practice is hampered by its cost, the availability of proper NGS tests, and diagnostic errors resulting from insufficient quality assurance, technological bias and complex interpretation of data.

8.2 The SWOT analysis

STRENGTHS

- The entire cardiovascular spectrum - blood, vessels and heart – is completely covered by CARIM, which is unique for a cardiovascular institute;
- An integrative and interdisciplinary scientific research approach;
- Close collaboration with the clinical departments results in high quality translational research;
- Strong publication record with a high percentage of papers in top 10% (high impact) journals. This results in citation scores that are substantially above world average;
- Strong national and European cardiovascular profile;
- A high quality PhD training programme that offers PhD candidates a skilled and experienced supervisory team, thereby providing a stimulating and critical environment to further develop one's research skills;
- CARIM has strong scientific and social partnerships with other institutes on a national and international level;
- Strong track record in acquiring prestigious national and European grants, such as NWO, CVON and H2020;
- Increasing valorisation of CARIM-generated knowledge, in terms of patents and spin-offs;
- Long-lasting relationship with private partners: pharmaceutical, devices;
- Excellent research infrastructure within CARIM and FHML such as the Imaging facilities, the Maastricht Study, Biobank, Muroidean Facility, Computational biology (See Annex 2);
- CARIM stimulates and supports talented candidates and staff by offering grants for research programmes at each step of their career, be it at Bachelors, Masters, postgraduate, PhD or postdoc level: the HS-BAFTA talent programme;
- Dedicated Research Council for coaching personal grant applications.

WEAKNESSES

- Data management is inefficient in that the possibilities for the coupling of research data with clinical data are still limited. Efforts have been made to establish one data platform within the academic hospital ('Vendor Neutral Archive') with a dedicated team for support;

- While CARIM researchers have been successful in obtaining national personal grants (NWO talent scheme; Dr E Dekker programme), success in obtaining personal European Grants (ERC) has been limited;
- Under-representation at the most relevant committees of national and international funding agencies;
- Insufficient animal facility;
- Lack of optimal integration of the academic hospital and FHML at the administrative and cultural level, which challenges optimal interaction between basic and clinical departments;
- Absence of state of the art Immunology and Pharmacology (including ageing);
- Largely compliant with diversity policies, but insufficient gender diversity esp. level of professors;
- Average duration of PhD trajectory is too long (>48 months), due to a small number of exceedances.

OPPORTUNITIES
- The new programme structure with a focus on 'team science' stimulates interaction between scientists within CARIM amongst the programmes as well as between basic scientists and clinicians;
- Further integration of CARIM and the HVC in order to facilitate collaborations in a more optimal way. Currently, a major strategy change of Maastricht UMC+ is to couple research and care, and this will pose a major challenge and task for the clinical staff and CARIM PIs to further add to this integration
- Participation in a School-overarching Centre for Integrative Neuroscience;
- The presence of large cohorts and biobanks within CARIM offers possibilities for studies into personalised treatment of cardiovascular disease;
- Establishment of sustainable international collaborations with selected universities;
- Boost of molecular sciences by the establishment of the Faculty of Science and Engineering;
- A new BioMedical Centre containing a top-notch animal facility;
- Revival of early '*Pieken vanuit de Breedte*' integrated in Radiobiochemical vascular imaging;
- Development of a translational Department of Clinical Pharmacology.

THREATS
- Budgetary restrictions because of single output criterion for 25% of Faculty funding (number of PhDs only);
- Decreased research time (a.o. because of maximising the labelling of scientific staff paid for by direct funding to 0.5 fte per person and increased educational tasks;
- Deceased continuity of research infrastructure support due to decrease in technical staff (OBP) as a result of downlabelling of scientific personnel;
- Cardiovascular research does not have a prime position on national and international research agendas;
- Lack of funding programmes for senior research staff;
- Parallel to translational research, focus on basic (curiosity-driven) science should not be neglected;
- Costs (time and resources) of European Privacy Regulations;
- Increase in pressure on (human) resources on the clinical side.

8.3 Strategic plans

Stimulate acquisition of research grants and contract research: As currently the allocation of internal FHML funding to the Schools ('direct funding') depends for 25% on the number of delivered PhDs, one of the challenges and aims of CARIM is to increase the number of PhD's by acquiring more national and international project and programme grants. To this end, the CARIM will undertake regulation of these processes by the following actions: CARIM Research Council will continue to guide and coach research applications and applicants and recently has installed local office hours for FHML grant office representatives. In addition, the following plans will be implemented:
- Personal grant submission timeline planning for scientific personnel;
- Establishment of a CARIM Grants & Incentives Team.

CARIM-HVC: Implementing basic research findings in the clinic and performing fundamental research according to clinical need will strengthen the axis between the HVC and CARIM. Currently, PhD projects are funded on translational topics such as vascular calcification and thrombosis diagnostics, and a stem cell lab was founded as a result of successful generation of pathological iPSCs from HVC

patients. Using FHML research platforms (vide infra) CRISPR-Cas9 technology will be applied to repair pathological stem cells as potential therapy of the future. In addition, in patients with acute atrial fibrillation, novel monitoring schemes will allow diagnosing these patients, such as acute coronary syndrome patients, thereby improving their outlook. Installing the infrastructure for early diagnosis of vascular disease in these acute arrhythmias is one of the prime targets of CARIM and the HVC. Further to the above, after an advice of the Strategic Board, CARIM decided to install a HVC/CARIM Scientific Initiative Committee with the mission to define large collaborative translational projects, to identify funding opportunities, and to facilitate the application and implementation process.

Research platforms: Together with FHML, CARIM will engage in the design and development of technology platforms, making available open access technologies for FHML Schools and institutes. FHML research platforms offer opportunities for high quality technological analysis and diagnostics. CARIM contribution to the FHML research platforms will be in the area of: structural NMR; chemical protein synthesis; FACS; iPSC lab; immunohistochemistry, CRISPR-Cas9 lab; Biologics and PET/MRI/SPECT/Echo/CT Imaging. The FHML technology platforms will remain assigned to their home departments but will be (partly) centrally organised.

Data sciences: CARIM will stimulate the acquisition of large data sets and bio-banks in relevant and well-characterised patient cohorts. The School wants to involve both clinical and basic researchers in the planning, design, execution, and dissemination of larger clinical studies or registries.

Focus on research of multimorbid- and chronic disease among the ageing population: As the population is ageing because of better understanding and treatment of (cardiovascular) disease, we are entering an era of more chronic and multimorbid pathologies in which complex interactions of failing organs require interdisciplinary and translational approaches to study and prevent disease. To this end, emphasis will be put on successful cohort initiatives such as the Maastricht Study and investments will be made in studying the failing microcirculation as a cause of impairing physical condition and cognition.

Data management: All projects must adhere to legal and ethical standards regarding the participation of human subjects in the research and regarding data collection and management processes (see above). Our Institutional Review Board (Ethical Committee) consists of academic specialists, legal specialists, and as experts in medical ethics. The impact of big data analysis on peoples' privacy is ever expanding and CARIM realises that these aspects should be covered in a realistic and person-friendly manner. This holds even more in case data is collected on a continuous basis (e.g. the heart's rhythm using implanted monitors). All data shall be handled according to strict standards (FAIR and Fact criteria). After all, all personal data is owned by the persons themselves and only if they give permission, anonymised data can be made available for research. Annotation, synchronisation and maintenance are key.

9 Viability

Globally 17.9 million people die each year from cardiovascular disease (CVDs), which is an estimated 31% of all deaths worldwide. In Europe alone, each year 3.9 million deaths (45%) are caused by CVD. CVD is the main cause of death in men in all but 12 countries of Europe and is the main cause of death in women in all but two countries. Identifying those at highest risk of CVDs and ensuring they receive appropriate treatment can prevent premature deaths. Understanding the underlying mechanisms and developing new therapies in this area will be important for the decades to come. This is a motivation for CARIM to find solutions to problems and collaborate with stakeholders to ensure sufficient societal impact.

CARIM embeds high quality research and highly motivated researchers, as well as a large cohort of PhD candidates, both with fundamental scientific and/or clinical backgrounds. CARIM has a strong track record and growing earning power. CARIM flourishes in strongly embedded, long lasting (inter)national collaborations, resulting in many European networks and consortium grants. CARIM activities will engage in translational research, of gender and age related aspects of cardiovascular disease and effects thereof on multimorbidity settings and cognition of the ageing population. Above all, CARIM will apply early comprehensive diagnosis and targeted prevention, using longitudinal diagnostic techniques in early stage cardiovascular disease as well as cutting-edge interventions including gene regulation approaches. CARIM will continue to publish research results in high impact journals and apply economic and societal knowledge utilisation as a main responsibility.

In parallel to focussing on personalised approaches in disease prevention and treatment, CARIM will also start coaching its young talent in a more personalised way by tailored grant application timelines, and probing of the utility of diverse research specialisations for engagement in public awareness development. A special CARIM Grants & Incentives team has been established enabling close mentoring of CARIM's young talent on these aspects.

CARIM continues to have excellent research facilities and both continuity and potential growth is sufficiently secured: State-of-the-art infrastructure and other resources (Annex 2) will be expanded with iPSC and CRISPR/Cas9 technology (already implemented), Phage display antibody libraries, and participation in multiple FHML research platforms on organoids, bio mass-imaging, fluorescence imaging, electron microscopic imaging, nuclear imaging, and novel translational organisation of nuclear molecular imaging.

Due to budget cuts and restructuring beyond necessary financial compensation CARIM has reached ample financial reserves to invest in novel research groups (microcirculation), direct funding PhD candidates, revival of CARIM's tenure track system that was on hold since 2016, and investments in technological innovations such as a laboratory for iSPC and CRISPR/Cas9.

With the existing state-of-the-art infrastructure at CARIM and FHML as well as planned investments into our infrastructure and young, high potential researchers, CARIM will maintain its status as leading institution in cardiovascular research in the Netherlands and beyond. Its interdisciplinary approach to solving scientific and medical problems from basic research to clinical translation is right on target and fits many funding schemes in the European Union and the Netherlands, and will therefore enable CARIM to continue its success in the acquisition not only of third party funding, but also in attracting and securing bright scientists and medical doctors. As can be seen from the SWOT analysis, CARIM needs to improve on the number of female professors and PIs. First steps have been taken by appointing and coaching ambitious, female Associate Professors who are on track to become renowned scientists in the field, and will function as role models for the next generation of female researchers.

In terms of HR, it is worth mentioning that before 2021 six scientific staff members and two technical staff members will be eligible for retirement, and an additional eight scientific staff members will retire before 2026. Among these staff members are seven PIs (one-third of current PI group), who will leave before the end of 2024. This offers plenty opportunity for future tenure of our young talent that has currently been scouted, also with current policies of diversity and inclusivity in mind. With this, ongoing investments in novel technology governed by researchers on soft money can be firmly established in CARIM's future research and infrastructure portfolio. As a result, careful selection and seeding of talent and research initiatives combined with sufficient financial support allows a positive as well as cautious optimistic view on our future.

School for Cardiovascular Diseases

CARIM
School for
Cardiovascular Diseases

Self Evaluation 2013 - 2018 Part B

Maastricht UMC+

Maastricht University

1 Division Blood

1.1 Objectives and research area

1.1.1 Vision, mission and objectives

Up until 2018, research within the Theme 'Thrombosis and Haemostasis' was directed towards deciphering impairments of proteins, platelets, and the vessel wall in relation to the development of venous and arterial thrombosis. This Theme I, led by Prof. Tilman Hackeng, was divided into four programmes, including:

1. Blood proteins and engineering (Prof. Tilman Hackeng)
2. Vascular aspects thrombosis and haemostasis (Prof. Chris Reutelingsperger)
3. Cell biochemistry of thrombosis and haemostasis (Prof. Johan Heemskerk)
4. Clinical thrombosis and haemostasis (Prof. Hugo ten Cate)

Later, Theme I was extended to include the programmes of two newly appointed Principal Investigators with part time affiliations: Prof. Christian Weber and Prof. Monika Stoll:

5. Structure-function analysis of the chemokine interactome (Prof. Christian Weber)
6. Complex cardiovascular genetics (Prof. Monika Stoll)

In 2018, these six programmes were realigned in a new division structure, combining themes and topics in a more dynamic and integrated manner. Thus, the former Theme I 'Thrombosis and Haemostasis' continued as the new Division Blood, comprising two main comprehensive programmes:
Blood coagulation, venous thrombosis and bleeding;
Atherosclerosis, atherothrombosis and stroke.

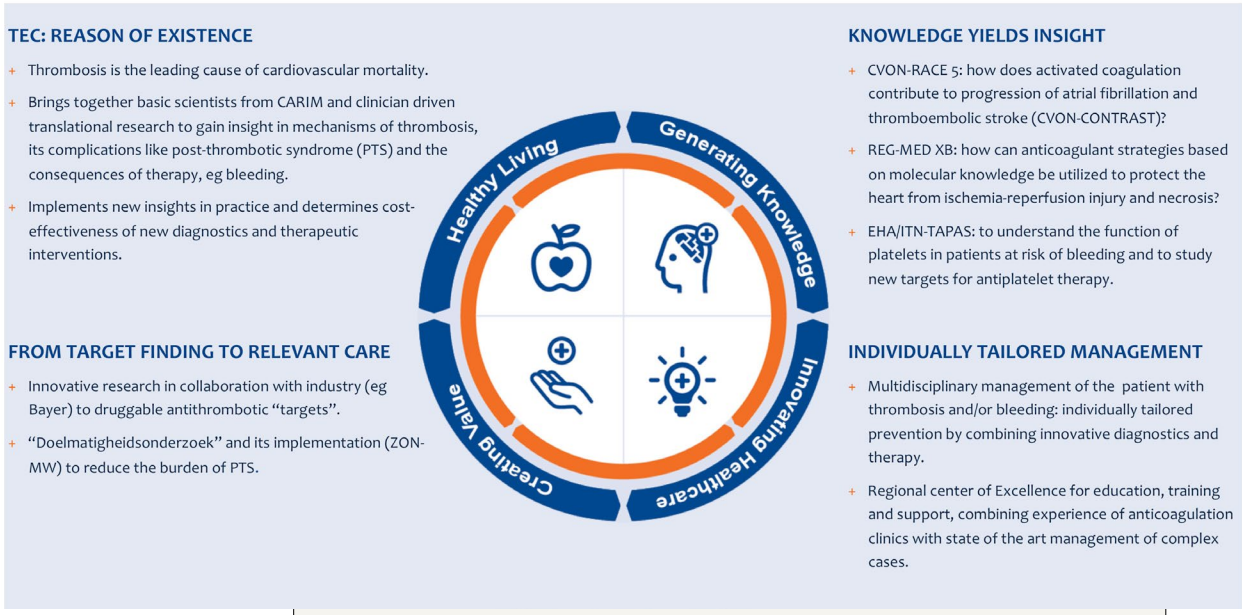
In Division Blood, the number of PIs has currently been extended to include include Prof. Erik Biessen, Prof. Robert van Oostenbrugge and Prof. Joachim Wildberger in Programme 2, as schematically indicated in the figure below.

CARIM 2013-2018		CARIM 2019	
Theme I Thrombosis and Haemostasis		**Division BLOOD**	
1 Tilman Hackeng	Blood proteins & engineering	**1** Blood coagulation, venous thrombosis & bleeding	Tilman Hackeng Johan Heemskerk **Hugo ten Cate** Monika Stoll
2 Chris Reutelingsperger	Vascular aspects thrombosis and haemostasis	**2** Atherosclerosis, arterial thrombosis & stroke	Erik Biessen[1] Chris Reutelingsperger Robert van Oostenbrugge[1] Christian Weber Joachim Wildberger[1]
3 Johan Heemskerk	Cellular biochemistry of thrombosis and haemostasis		
4 **Hugo ten Cate**	Clinical thrombosis and haemostasis		
5 Christian Weber	Structure-function analysis of the chemokine interactome		
6 Monika Stoll	Complex cardiovascular genetics		

Old and new programme and Principal Investigator structure of Division Blood (formerly Theme I).
1: Prof. Erik Biessen, Prof. Wildberger and Prof. Oostenbrugge came from former Theme III 'Vascular Biology and Medicine'.

Our research follows the 'Circle of Innovation©' (See Part A, page 11) in which basic research at CARIM, including new technology, boosts translational research within the Clinical Heart+Vascular Center (HVC), thereby supporting high-level academic health care. Below, the Circle of Innovation for the Thrombosis Expertise Center is presented as a relevant example for Division Blood:

Figure 1 | Circle of Innovation 'Thrombosis Expertise Center'



1.1.2 Strategy and research area

Division Blood contains two major programmes involving nine PIs. A brief perspective on CARIM's PIs and their expertise is provided in Annex 9.

Programme 1 Blood coagulation, venous thrombosis and bleeding (PIs: Prof. Hugo ten Cate, Prof. Tilman Hackeng, Prof. Johan Heemskerk, Prof. Monika Stoll)

The programma 'Blood coagulation, venous thrombosis and bleeding' comprises the expertise of four PIs and encompasses research in the field of venous thrombosis, spanning the spectrum from molecular design and synthesis to therapy and epidemiology. Special attention is given to the analysis of impairments of blood proteins in relation to thrombosis, bleeding and vascular calcification, and due to the very broad representation of disciplines in Division Blood (from chemical to clinical), implementation of curiosity-based findings in the clinic is stimulated and obvious. It is becoming more and more clear that blood coagulation enzymes are not only involved in thrombosis and late stage thrombus generation as a result of instable atherosclerosis, but stand at the cradle of development and progression of atherosclerosis and complex arrhythmias. Understanding pro- and anticoagulant regulatory pathways has now become essential to the whole field of cardiovascular disease, and goes beyond just understanding thrombosis alone.. Therefore, pertinent cross interactions of this programme with all other CARIM programmes exist, especially with 'Atherosclerosis, arterial thrombosis and stroke', 'Regenerative and reconstructive cardiovascular medicine' and 'Complex Arrhythmias'.

Basic mechanisms of anticoagulant proteins
The group of Dr Rory Koenen, Dr Ingrid Dijkgraaf, Dr Elisabetta Castoldi, Dr Gerry Nicolaes and Prof. Tilman Hackeng applies a multidisciplinary approach to unravel functional properties of proteins involved in the regulation of thrombin formation and cardiovascular disease. Functional impairments of coagulation proteins can lead to the development of venous and arterial thrombosis, and a fundamental understanding of inter-protein and protein-vessel wall interactions is a prerequisite for understanding how anticoagulant proteins work in preventing thrombosis. A broad technology platform is applied to this programme, from automated thrombin generation, molecular dynamics simulation, *in silico* drug design, to total chemical synthesis of proteins, NMR protein structural analysis, molecular genetics, exosome research, and the development of clinical assays. Seminal advancements in the field have been made in deciphering contributions

of tissue factor pathway inhibitor (TFPI) and factor V short on regulation anticoagulant pathways and recurrence of venous thrombosis (full length TFPI correlates with recurrent VTE; MEGA study). Design of small molecules, peptides, and proteins for diagnosis or therapy is strongly supported by Programme 1's drug design unit focussing on integration of computational methods (structural bioinformatics, molecular dynamics simulation and *in silico* drug design), biophysical methods (SPR, ITC and DSC), recombinant protein expression and more classical biochemical techniques to study and modulate protein-ligand interactions. This allows the discovery and optimisation of biologically active small molecules, peptides and biologicals that serve as research tools, and as novel therapeutics or diagnostics. Essential contributions to understanding and treating thrombosis and haemostasis (protein C pathway), atherosclerosis (TRAF-family), immunothrombosis, inflammation and sepsis (extracellular histones and non-anticoagulant heparins) have been made.

Platelets in thrombo-inflammation and bleeding

The group of Dr Paola van der Meijden, Dr Rory Koenen, Dr Judith Cosemans, and Prof. Johan Heemskerk studies the complex way by which platelets are activated and regulate haemostasis. A combination of complex platelet phenotyping under flow and genomics has revealed subject-dependent (personalised) determinants that explain variance in human platelet activation properties. In collaboration with several other universities, it has been shown that, in combination with microspotting, whole-blood microfluidics can provide valuable high-throughput information on multiple platelet functions in thrombus formation at the same time. Based on the assessment of the inter- and intra-subject variability in parameters of microspot-based thrombus formation, relevant platelet factors contributing to this variation have been unravelled. Subsequent analysis of blood samples from patients with Glanzmann's thrombasthenia or storage pool disease revealed unique thrombus signatures of aggregation-dependent parameters that were subject-dependent. Blood proteins have intricate relations and interactions with blood platelets, not only coupling primary and secondary haemostasis, but also governing thrombo-inflammatory processes. It is therefore important to study effects of platelets and platelet-derived extracellular vesicles, also beyond haemostasis and thrombosis, as platelets can act as immune cells and their extracellular vesicles might serve as their extended arm by influencing the phenotype and responses of cells, distal to platelet activation. In a recent study, platelet extracellular vesicles were shown to induce a pro-inflammatory phenotype in smooth muscle cells.

Genetics of Thrombosis

Dr Elisabetta Castoldi and Prof. Tilman Hackeng study processes of genetic alteration of coagulation factor function. Using molecular genetics techniques (gDNA and mRNA analysis, antisense-based splicing modulation) and specific functional assays (thrombin generation in plasma, kinetic assays in model systems), molecular bases of (inherited) coagulation defects are unravelled that predispose to venous thrombosis or bleeding. In addition, antisense therapies with morpholinos are designed to correct protein impairment due to splicing variations. In recent years, Dr Aaron Isaacs and Prof. Monika Stoll have been successful in disentangling the genetic basis of paediatric stroke, venous thromboembolism and heparin-induced thrombocytopenia through GWAS and NGS applications. Following the initial publication of three genes belonging to the ADAMTS gene family as susceptibility genes for paediatric stroke, it was subsequently shown that these genes also play a role in cerebral aneurysms. In addition, it was discovered that rare genetic variants residing within the ADAMTS13 gene contribute to paediatric stroke through a direct effect on circulating ADAMTS13 levels. A recent GWAS study in children affected by venous thrombosis implicated three additional susceptibility genes for this complex disease: SMAP1, RIMS1 and B3GAT2, pointing towards a chronically activated coagulation system in these patients. A current GWA study on DVT in young adults for the first time, implicated ADAMTS13 in the pathogenesis of DVT, suggesting an impact of ADAMTS13 on thrombotic diseases in general. These studies clearly implicate the ADAMTS superfamily of proteases in the pathogenesis of (athero) thrombotic diseases and point towards an interaction between a chronically activated coagulation system and features of vascular fragility as underlying molecular mechanism.

Translational Cardiovascular Chemistry

Dr Ingrid Dijkgraaf, Dr Stijn Agten, Dr Hans Ippel, Dr Kanin Wichapong and Prof. Tilman Hackeng apply design and total chemical protein synthesis to understand, image, and treat cardiovascular disease. In addition, exogenous (tick) proteins are studied as a source for understanding human molecular mechanisms as

well as to discover leads for low immunogenicity imaging and therapy purposes. The anticoagulant and anti-inflammatory properties of tick proteins by which they evade the human immune response, makes them ideal candidates to study human coagulation and inflammatory pathways. By applying total chemical synthesis of proteins and NMR structural analysis, tick proteins are synthesised and analysed as candidates for *in vivo* multimodal imaging using PET, SPECT, MRI, and as candidates for therapy and synthetic vaccines.

Clinical Thrombosis Research

Many research activities of this programme reach into the clinic, whereas some are fully performed in the clinic. An example of the latter, related to venous thrombosis and post-thrombotic syndrome (PTS), is displayed as a narrative available at the CARIM website. Apart from clinical activities, strong interactions with Programme 2 are formed on research of coagulation enzymes on atherothrombosis by the research group of Dr Paola van der Meijden, Dr Henri Spronk, and Prof. Hugo ten Cate. Over the past six years, this research was extensively broadened and extended to atherothrombosis with a focus on thrombo-inflammation. Evidence of this is in the participation as work package leaders in the Dutch Heart Foundation CVON consortia RACE V and CONTRAST, involving the role and clinical significance of thrombo-inflammatory mechanisms in atrial fibrillation (AF) and ischemic stroke, respectively. The concept of thrombo-inflammation will be further explored in relation to venous and arterial thrombotic diseases in the Horizon 2020 ITN TICARDIO, that has been granted to three centres, including Mainz (coordinator), Marseille and CARIM, in particular the Department of Biochemistry. Our participation in these large teams of distinguished (inter)national scientists is based on our previous pioneering research on atherothrombosis, in a broad and translational team, spanning research from bench (biochemistry) to the clinic. The conceptual change that procoagulant activity is a cause of cardiovascular disease (atherosclerosis; arrhythmia) rather than a consequence has occurred particularly as a result of activities of this programme. Involvement in other consortia (ITN TAPAS, InScite and REGMED XB) give further credit to the programme's strong position in the field of thrombo-inflammation.

CARIM website

Programme 2 Atherosclerosis, arterial thrombosis and stroke

The programme 'Atherosclerorsis, arterial thrombosis and stroke' comprises the expertise of five PI groups and encompasses research in the field of atherosclerosis, arterial thrombosis and stroke, especially on events that trigger vascular remodelling from out of circulation and the effects thereof. Understanding vascular pathologies at the molecular level is of key importance to prevent or treat cardiovascular disease.

Thrombo-inflammation and atherosclerosis

The focus of the research group of Dr Dietbert Neumann, Dr Marjo Donners, Dr Judith Sluimer and Prof. Erik Biessen has gradually shifted from the role of dendritic cell subsets on cardiovascular inflammation, to the related myeloid subset, the macrophage. the group showed amongst others that disruption of macrophage's machinery for mesenchymal migration reduced plaque burden but paradoxically also destabilised the plaque due to sub endothelial accumulation of macrophages, eroding the protective cap. Major contributions have been made to the understanding of plaque destabilisation as a result of plaque hypoxia in atherogenesis, and it was recently demonstrated that these findings could be readily applied to human plaque imaging. In parallel, an intriguing link between oxygen sensors and cholesterol homeostasis was established and consequently published in The European Heart Journal, demonstrating the ability of the group to develop new concepts and lead breakthrough science. Using *in vivo* conditional knockout mice models, divergent macrophage and endothelial cell specific effects of ADAM10 in atherosclerosis were observed, suggesting a protective role of endothelial ADAM10 in maintaining endothelial homeostasis. The underlying mechanisms are currently investigated, but may well include LOX-1 cleavage, as we recently established, that after initial cleavage by ADAM10, LOX-1 is released by the intramembrane protease SPPL2, and that a deficiency of the latter emulated the phenotype seen with endothelial ADAM10 deficiency, and significantly enhanced atherosclerosis. Dr Hans Ippel, Dr Kanin Wichapong, Dr Remco Megens, Prof. Tilman Hackeng, Dr Philipp von Hundelshausen and Prof. Christian Weber have uncovered new dimensions to explain the plasticity and fine-tuning of chemokine activities in the context of athero-inflammation that has been introduced by the paradigm that chemokines engage in heterodimer formation. The systematic interactome mapping and structural analysis of

hetero-dimeric chemokine interactions, e.g. of CCL5 with CXCL4 or CCL17, which differentially modulate their function by synergistic or inhibitory effects, led to the design of cyclic or bundled peptides, which disrupt or mimic heterodimers to limit atherosclerosis. Protection can also be conferred by apoptotic micro particles, which deliver microRNA-126-3p to induce autocrine CXCL12 expression in endothelial cells and angiogenic cell influx by unleashing CXCR4 activity. This epitomises essential regulatory functions of non-coding microRNAs in atherogenesis. The long standing collaboration between *in silico* drug design, NMR, and translational cardiovascular chemistry from CARIM's Division Blood (Dr Gerry Nicolaes, Dr Hans Ippel, Dr Rory Koenen, Dr Ingrid Dijkgraaf, Prof. Tilman Hackeng) with *in vivo* thrombo-inflammation of The Ludwig Maximillans University In Munich (Dr Philipp Hundelshausen, Dr Remco Megens, Prof. Christian Weber), in combination with NMR expertise from the Unversity of Minnesota (Visiting Prof. Kevin Mayo), has reached the stage where it seems appropriate to submit an ERC Synergy grant which is currently being prepared.

Vitamin K-dependent proteins and vascular calcification

Prof. Leon Schurgers, Dr Pieter van Paassen and Prof. Chris Reutelingsperger work on vascular aspects of cardiovascular disease. Vascular smooth muscle cell (VSMC) phenotypic switching is an important contributor to vascular disease, and understanding underlying molecular mechanisms driving this switch is key for novel diagnosis and treatment. Prof. Leon Schurgers studies major conceptual changes of VSMC on how vascular calcification (VC) is initiated and contributing to cardiovascular disease (INTRICARE Horizon 2020 is based on this research line). In order to study causative mechanisms of VC at the cellular and molecular level, an infrastructure was set up to isolate VSMC from patient vascular material, and to generate induced pluripotent stem cells (iPSCs) from patient and control blood cells. In the past year, three iPSC-lines were successfully obtained and deposited. Since VC is considered an active process regulated by VSMC and vitamin K-dependent proteins, vitamin K antagonists and vitamin K are being investigated *in vitro*, in pre-clinical models and in the clinic. Collaborations with the Departmenst of Internal medicine, Cardiology, and Vascular Surgery have led to clinical trials on vitamin K2 (VitaK-CAC and BASIK2) and joint publications, for example in the European Heart Journal. The groups of Dr Pieter van Paassen and Prof. Chris Reutelingsperger study another form of vascular impairment: endothelial damage caused by thrombotic microangiopathy (TMA), that occurs in association with diverse clinical conditions such as malignant hypertension. The development of a BioHybrid assay, that employs microvascular endothelial cells to report deficiencies of cell surface mediated complement regulation, has improved the understanding of complement-mediated TMA. Finally, Prof. Chris Reutelingsperger and Dr Gerry Nicolaes study organ failure – especially during sepsis - arising predominantly from dysfunction of endothelial cells of the microcirculation. In the search for causative it was discovered that low anticoagulant heparins protect endothelial cells by neutralising histones that are released into the circulation during the host response to fulminant infection. The low anticoagulant heparin is currently being developed as an Innovative Medical Product for the treatment of septic patients. The Clinical phase I/IIa study with low anticoagulant heparin will be conducted by Matisse Pharmaceuticals and is scheduled to start in the third quarter of 2019.

Ischemic stroke

Stroke, one of the leading causes of death and long lasting morbidity in the Western world, comprises different neurovascular diseases. These diseases are roughly divided into large vessel disease and small vessel disease. Stroke is therefore represented in two Divisions: Blood and Vessels. Within this programme, ischemic stroke due to large vessel disease is one of the major clinical entities that is being studied. It is one of the outcome measures of cardiovascular imaging (imaging vulnerable carotid artery plaque). The main area of research in the clinical setting is directed to the treatment of ischemic stroke due to large vessel occlusion. In a clinical setting, Programme 2 has greatly contributed to treatment of ischemic stroke. The research group of Prof. Wim van Zwam and Prof. Robert van Oostenbrugge as co-PIs of MR CLEAN (ISRCTN 10888758) represented a landmark trial in Vascular Neurology published in the New England Journal of Medicine, and is currently running MR CLEAN LATE (ISRCTN19922220). MR CLEAN was the first randomised controlled trial that showed safety and efficacy of endovascular treatment in acute ischemic stroke. The results of this study resulted in a paradigm shift in the acute treatment of acute ischemic stroke. The group also co-authored a highly referenced paper on the neuro-imaging standards for research into cerebral small vessel disease published in Lancet Neurology. MR CLEAN received the price of the Dutch Society of Medical Specialists (*Wetenschaps- en Innovatieprijs 2017*), which is awarded biannually.

Cardiovascular Imaging
The state of the art infrastructure of Maastricht UMC+, in combination with the research facilities which are branded as 'Imaging Valley Maastricht', offers a perfect basis for technically orientated and patient-centred research in all fields of radiology and nuclear medicine. As a special development within the Dutch setting, the Departments of Radiology and Nuclear Medicine have been merged in December 2017. This offers unique opportunities to combine anatomical and functional imaging for cardiovascular applications. The interdisciplinary platform of imaging connects imaging specialists from different other disciplines of Cardiology (Dr Simon Schalla, Dr Sebastiaan Bekkers, Dr Bas Streukens, Dr Bas Kietselaer; Dr Vincent van Ommen); Neurology (Prof. Robert van Oostenbrugge, Dr Julie Staals); Vascular Surgery (Prof. Willem Schurink; Prof. Cees Wittens), Biochemistry (Prof. Tilman Hackeng; Dr Ingrid Dijkgraaf); and Clinical Physics (Prof. Eline Kooi). A grant of the local Weijerhorst foundation (2.94 M€ for the period 2015-2019; Prof. Joachim Wildberger: 'cardiovascular imaging') has fuelled this translational interdepartmental clinical research line. Furthermore, integrative work has been performed between basic sciences (Dr Ingrid Dijkgraaf, Prof. Tilman Hackeng) and the nuclear medicine branch (Dr Jan Bucerius, Prof. Felix Mottaghy). The re-opening of a Hotlab facility enables in-house development of innovative radioactive tracers for diagnostics and therapy. Recently, Dr Hugo Aerts has been appointed as Professor of Artificial Intelligence within Imaging.
He will interact and include information from different diagnostic modalities (such as genetics, pathology, laboratory results, etc.) in an all –omics approach in close cooperation with his home base in Boston. Within Maastricht UMC+, researchers from the D- and M-Lab (Prof. Philippe Lambin, Dr Henry Woodruff, Dr Arthur Jochems) have part-time appointments for the optimisation of Radiomics in the clinical (cardiovascular) setting.

1.1.3 Specific targets of the past six years

Based on the observed **weaknesses** in the SWOT analysis by the former Theme I (limitations in the facilities for animal experimentation, lack of CARIM inter-Theme scientific meetings and exchange and underperformance in the national arena of organisation/committees of thrombosis and haemostasis), CARIM took several initiatives. This included efforts to accomplish the new animal facility (plans have now been approved and construction is planned), as well as addressing inter-division communication strategies. To do so, we utilised improved inter-programme communication, to initiate and strengthen translational research. From Division Blood two examples are highlighted to illustrate this: first, the studies by Prof. Leon Schurgers on the molecular basis and clinical consequences of (micro) vascular calcification; this collaboration between the current Divisions Blood and Vessels and Aachen further matured into the presently ongoing Horizon 2020 ITN INTRICARE, with CARIM as coordinating centre. A second example is the effective communication between the Divisions Blood and Heart that led to the present national CVON RACE V consortium including universities of Maastricht, Leiden and Groningen, in which CARIM is one of the leading centres, dealing with Hypercoagulability as a driver of atrial fibrillation, initiated by Dr Henri Spronk and Prof. Uli Schotten.

One of the observed **threats** ("The change in gravity towards arterial thrombotic disease research at the cost of venous thrombotic disease research due to societal needs and granting agencies poses a serious threat on the high level of venous thrombosis research that is maintained by Theme I"), was addressed by different approaches. First, studies on the genetic background were stimulated by Prof. Monika Stoll and her 'Genetic Epidemiology and Statistical Genetics group', embedded in CARIM since 2015, to close the void in complex disease genetics. Her group serves as one of the key partners in interdisciplinary research within CARIM, MaCSBio and the Maastricht UMC+. While her research programme is broader in scope, together with Dr Elisabetta Castoldi she stimulates further research on venous thrombosis, and recently on post-thrombotic syndrome (PTS; with Dr Arina ten Cate-Hoek). Meanwhile, Dr Elisabetta Castoldi's gene to function translational programme continues to also unravel novel determinants of venous thrombosis (and bleeding) after the very important discovery of factor V short in 2013, causing a paradigm shift in the understanding of TFPI biology, and explaining the large inter individual range of TFPI in plasma. With this, the programme on the role of TFPI in preventing venous thrombosis (Dr Elisabetta Castoldi, Prof. Tilman Hackeng) was revived. In 2020, Dr Kristien Winckers, specialised in Internal Medicine, will be appointed part-time at the Department of Biochemistry to continue her analysis on TFPI function in (recurrent) VTE.

As described in detail in the narrative on this topic (see CARIM website), several clinical studies on venous thrombosis and PTS were undertaken, two of which have recently been completed and published (IDEAL study) or submitted (CAVA reperfusion trial). These ZonMw funded studies resulted from close collaboration between researchers from former Theme I and former Theme III (Prof. Cees Wittens, venous surgery; Prof. M. de Haan, radiology) and with KEM-TA (Prof. Manuela Joore) on cost effectiveness analysis.

The **second threat**, related to a tendency towards consortium driven research over curiosity based research, remains a challenge to many. However, the acquired personal funding by talents (Dr Rory Koenen, Vidi; Dr Judith Cosemans, NHS, Vidi; Dr Ingrid Dijkgraaf, Vidi; Dr Paola van der Meijden EHA) illustrates the efforts and success of securing personal grants based on individual's ideas. We are confident that with CARIM's current talent track programmes this element will remain in focus.

In the ERC report's review and recommendations, one aspect that would need continuous strengthening was **translational research**. As noted by the committee, thrombosis and haemostasis is not a major theme within the Maastricht Study and for that reason, the relationship with centres with other large population based studies has been intensified. This has resulted in a deeper collaboration with the Center for Thrombosis and Haemostasis (CTH) from the Gutenberg University in Mainz, Germany. In particular the teams of Prof. Hugo ten Cate (awarded Gutenberg Fellowship and presently adjunct professor at CTH), Prof. Johan Heemskerk and Prof. Leon Schurgers are involved in this collaboration. In the recently funded TICARDIO Horizon 2020 ITN on thrombo-inflammation, lines of collaboration between even more researchers from CARIM's Division Blood and CTH Mainz are being established.

In addition, Prof. Leon Schurgers has strengthened the collaboration with Aachen, and together with Prof. Tilman Hackeng, he has initiated and currently coordinates the Horizon 2020 ITN INTRICARE that includes a number of translational and clinical studies with regards to mechanisms of calcification related to disease. A third Horizon 2020 ITN programme that started in 2018 is the TAPAS consortium, led by Prof. Johan Heemskerk from Division Blood, together with investigators from UK and Germany. The latter consortium also includes translational research using the Multichannel flow chamber, developed by the research group of Prof. Heemskerk, in conjunction with other state-of-the-art technology.

In line with the ERC recommendation, attention for **'big data'** use and analysis becomes essential, given that all aforementioned consortia produce substantial amounts of such 'big' data. Prof. Monika Stoll's team has introduced, at least for complex genomics and functional genomics, a fully operational IT infrastructure that provides extensive processing power and storage capabilities required for RNA sequencing data (and many other statistical analyses on the genome-wide scale). To facilitate these analyses, they purchased a Linux-based server, with twelve high-speed processors, extensive random-access memory to accommodate large datasets, and ten terabytes of storage capacity. This server is configured with the CentOS operating system and an RNA sequence analysis pipeline was installed, including reference genomes for Homo sapiens and Mus musculus, quality control protocols, and software for aligning, quantifying, analysing, and visualising transcriptome data. With rising interest in NGS approaches, and more researchers becoming interested in such approaches, in 2017, the infrastructure required extension of both the number of high-speed processors as well as the storage capacity, an investment that was supported by the CARIM strategic board and co-financed by a number of CARIM PIs. The new server with an extra 44 processing cores and 160 terabytes of storage should be sufficient to accommodate the needs at CARIM for the coming years.

For many other sources of big data (proteomics, biomarkers, imaging studies etc.) either agreements with other consortium partners are in place (e.g. for proteomics with Dortmund, Prof. Sickman; clinical data derived from Gutenberg Health Study at CTH Mainz etc.), or have been established at the Maastricht UMC+ (e.g. for Imaging, Prof. Joachim Wildberger) or within the Maastricht Study infrastructure. Underlying synchronisation of all these big data initiatives remains one of the major challenges for the near future in this respect. Regarding the final recommendation of the ERC: **limitations on funding by University** remains a concern (or threat). However, over the past years Division Blood has been successful in securing sufficient funding from other sources (EU, NWO Dutch

Heart Foundation, Interreg Euregio Meuse-Rhine, industry) to further expand its research activities. Consolidating partnerships within consortia and with industry, in conjunction with maintaining a keen eye for talent (track) and individual grant opportunities remains essential.

1.2 Description of the research programme's organisation, composition and financing

1.2.1 Organisation and embedding of the Research Programme

Division Blood is one of the three divisions within CARIM. Leader Prof. Hugo ten Cate represents Division Blood in the executive board of CARIM. Division Blood established shared leadership with staff members with excellent scientific standing taking into account and aiming for fair distribution of basic/clinical disciplines, diversity/gender, and various stages of career track. The board now consists of Prof. Hugo ten Cate, Prof. Leon Schurgers, Dr Judith Sluimer and Dr Julie Staals. The fact that Dr Staals falls under the PI-ship of Prof. Robert Oostenbrugge creates an opportunity for cross-activities between Division Blood and Division Vessels.

1.2.2 Composition

The number of staff in this Division has increased over the past six years, caused by an increase in scientific staff academic hospital and internal PhD candidates. The scientific staff FHML has decreased from 8.1 fte in 2013 to 7.0 fte in 2018, caused by the reduction in research labelling (direct funding) to 0.5 fte per researcher. The number of support staff has decreased from 18 to 10 (13.8 fte to 7.8 fte).

Table 1 Research staff at Division level

	2013		2014		2015		2016		2017		2018	
BLOOD	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**
Scientific staff FHML (1)	13	8.1	14	8.8	12	6.8	16	8.8	14	7.4	14	7.0
Scientific staff academic hospital	6	0.4	6	1.6	5	1.8	4	1.6	4	2.2	4	2.2
Post-docs (2)	15	10.5	9	6.6	8	6.8	8	7.3	6	5.8	7	7.0
Internal PhD candidates (3)	25	22.0	25	21.5	21	19.5	23	21.3	29	29.0	35	34.1
Total research staff	**59**	**41.0**	**54**	**38.5**	**46**	**34.9**	**51**	**38.9**	**53**	**44.4**	**60**	**50.3**
Support staff (research) (4)	18	13.8	17	9.6	17	7.8	10	7.8	11	8.8	10	7.8
Support staff (managerial) (5)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total staff incl academic hospital	**77.0**	**54.8**	**71.0**	**48.1**	**63.0**	**42.7**	**61.0**	**46.7**	**64.0**	**53.2**	**70.0**	**58.1**
Total staff excl academic hospital	**71.0**	**54.4**	**65.0**	**46.5**	**58.0**	**40.9**	**57.0**	**45.1**	**60.0**	**51.0**	**66.0**	**55.9**
External PhD candidates (6)	11		10		8		27		30		41	
Visiting fellows/professors (7)	7		6		9		7		7		10	

#: Number of persons active on the Research programme research activities on 31-dec of any year/average MJE (men year equivalents
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the Research programme research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the scientific director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Visiting fellows are researchers/professors who visit the Research programme for a period of typically one week up to three months to work with Research programme staff members.

1.2.3 *Financing*

The total labelling on research funding in Division Blood has increased from 40.56 fte to 48.80 fte, mainly caused by more contract research with for example Bayer and Nattopharma. The labelling on direct funding has remained relatively stable, but has decreased from 27% to 22%. The expenditures in Division Blood have remained stable over the years, with a dip in 2015 and 2016.

Table 2 Funding at Division level

BLOOD		**2013**		**2014**		**2015**		**2016**		**2017**		**2018**
Funding	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**
Direct funding (1)	11.06 (4)	27 (5)	10.75	29	8.30	25	8.40	23	7.80	18	10.80	22
Research grants (2)	4.00	10	6.00	16	7.50	23	4.70	13	6.10	14	4.10	8
Contract research (3)	25.50	62	10.10	54	17.30	53	24.20	65	29.04	68	33.90	69
Total funding	**40.56**	**100**	**36.85**	**100**	**33.10**	**100**	**37.30**	**100**	**42.94**	**100**	**48.80**	**100**
Expenditure:	K€	%	K€	%	K€	%	K€	%	K€	%	K€	%
Personnel costs	2,284	58	2,003	61	1,731	58	1,444	58	2,069	60	2,200	60
Other costs	1,638	42	1,296	39	1,236	42	1,066	42	1,373	40	1,441	40
Total expenditure	**3,922**	**100**	**3,299**	**100**	**2,967**	**100**	**2,509**	**100**	**3,441**	**100**	**3,641**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering'/lump sum budget).
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charity organisations
Note 4: Funds that do not fit the other categories.
Note 5: The funding in fte includes the total research staff but excludes the academic hospital-staff
Note 6: The funding in % in the research programme should be compared to the total within each research programme

1.3 Research quality

1.3.1 *Demonstrable research products for peers: a description of the research output*

The total number of refereed articles of Division Blood increased from 117 in 2013 to 168 in 2018 (highest number in 2016: 170). This was mainly due to a significant increase in refereed articles with IF (SCI/SSCI). The number of PhD theses is on average 10 per year and varies between six and 14.

Table 3 Main categories of research output at Division level (date: 7 June 2019)

	2013	2014	2015	2016	2017	2018
BLOOD						
Refereed articles (SCI/SSCI) (1)	93	104	115	141	108	140
Other refereed articles (2)	24	15	22	29	22	28
Total refereed articles (3)	**117**	**119**	**137**	**170**	**130**	**168**
Books	1	n.a.	2	n.a.	n.a.	n.a.
Book chapters	1	n.a.	4	n.a.	1	n.a.
PhD theses	7	10	11	14	6	13
Total publications	**126**	**129**	**154**	**184**	**137**	**181**

Note 1: Refereed articles ('wi-1') published in an international journal, which is mentioned in the (Social) Science Citation Index (SCI or SSCI) of Journal Citation Reports (JCR) ('wi-1')
Note 2: Refereed articles published in an international journal, not included in the SC/SSCI ('wi-2'), Editorial Materials, Letters to the editor and refereed articles in a national (Dutch) journal ('wn')
Note 3: Total refereed articles is the sum of the refereed articles (SCI/SSCI) and the other refereed articles

1.3.1.1 *Most important scientific publications*

The following publications have been selected because of their high impact and/or representation of the research foci of the Division.

Identification of platelet function defects by multi-parameter assessment of thrombus formation

de Witt SM, Swieringa F, Cavill R, **Lamers MM, van Kruchten R, Mastenbroek T, Baaten C**, Coort S, Pugh N, Schulz A, Scharrer I, Jurk K, Zieger B, Clemetson KJ, Farndale RW, **Heemskerk JW, Cosemans JM**. Identification of platelet function defects by multi-parameter assessment of thrombus formation. Nat Commun. 2014 Jul 16;5:4257 IF: 12.4

Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis

Amin EE, Bistervels IM, Meijer K, Tick LW, Middeldorp S, Mostard G, van de Poel M, Serné EH, Otten HM, Klappe EM, **Joore MA, Ten Cate H**, Ten Wolde M, **Ten Cate-Hoek AJ.** Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. Blood. 2018 Nov 22;132(21):2298-2304 IF: 15.1

Antisense-based RNA therapy of factor V deficiency: in vitro and ex vivo rescue of a F5 deep-intronic splicing mutation

Agten SM, Koenen RR, Ippel H, Eckardt V, von Hundelshausen P, **Mayo KH, Weber C, Hackeng TM.** Probing functional heteromeric chemokine protein-protein interactions through conformation-assisted Oxime Ligation. Angew Chem Int Ed Engl. 2016 Nov 21;55(48):14963-14966. IF: 12.1
Nuzzo F, Radu C, Baralle M, Spiezia L, **Hackeng TM**, Simioni P, **Castoldi E**. Antisense-based RNA therapy of factor V deficiency: in vitro and ex vivo rescue of a F5 deep-intronic splicing mutation. Blood. 2013 Nov 28;122(23):3825-3831 IF: 15.1

Vascular smooth muscle cell calcification is mediated by regulated exosome secretion

Kapustin AN, **Chatrou ML**, Drozdov I, Zheng Y, Davidson SM, Soong D, **Furmanik M**, Sanchis P, De Rosales RT, Alvarez-Hernandez D, Shroff R, Yin X, Muller K, Skepper JN, Mayr M, **Reutelingsperger CP**, Chester A, Bertazzo S, **Schurgers LJ**, Shanahan CM. Vascular smooth muscle cell calcification is mediated by regulated exosome secretion. Circ Res. 2015 Apr 10;116(8):1312-1323 IF: 15.2

Slower Progress of Aortic Valve Calcification With Vitamin K Supplementation: Results From a Prospective Interventional Proof-of-Concept Study

Brandenburg VM, Reinartz S, Kaesler N, Krüger T, Dirrichs T, Kramann R, **Peeters F**, Floege J, Keszei A, Marx N, **Schurgers LJ***, Koos R*. Slower Progress of Aortic Valve Calcification With Vitamin K Supplementation: Results From a Prospective Interventional Proof-of-Concept Study. Circulation. 2017 May 23;135(21):2081-2083 IF: 18.9 *equally contributing authors

Deficiency of the oxygen sensor prolyl hydroxylase 1 attenuates hypercholesterolaemia, atherosclerosis, and hyperglycaemia

Marsch E, Demandt JA, Theelen TL, Tullemans BM, Wouters K, Boon MR, van Dijk TH, **Gijbels MJ,** Dubois LJ**, Meex SJ**, Mazzone M, Hung G, Fisher EA, **Biessen EA**, Daemen MJ, Rensen PC, Carmeliet P, Groen AK, **Sluimer JC**. Deficiency of the oxygen sensor prolyl hydroxylase 1 attenuates hypercholesterolaemia, atherosclerosis, and hyperglycaemia. Eur Heart J. 2016 Oct 14; 37 (39): 2993-2997 IF: 23.4

High-Density Lipoproteins Exert Pro-inflammatory Effects on Macrophages via Passive Cholesterol Depletion and PKC-NF-κB/STAT1-IRF1 Signaling

van der Vorst EPC, Theodorou K, Wu Y, Hoeksema MA, Goossens P, Bursill CA, Aliyev T, Huitema LFA, Tas SW, Wolfs IMJ, **Kuijpers MJE**, **Gijbels MJ, Schalkwijk CG**, Koonen DPY, Abdollahi-Roodsaz S, McDaniels K, Wang CC, Leitges M, Lawrence T, Plat J, Van Eck M, Rye KA, Touqui L, de Winther MPJ, **Biessen EAL, Donners MMPC**. High-Density Lipoproteins Exert Pro-inflammatory Effects on Macrophages via Passive Cholesterol Depletion and PKC-NF-κB/STAT1-IRF1 Signaling. Cell Metabolism. 2017 Jan 10;25(1):197-207 IF: 20.7

1.3.2 *Demonstrable use of research products by peers*

Refereed publications (with and without IF) of Division Blood were cited 9,762 times in the period 2013-2018, as calculated by the University Library Maastricht. 1.39% of these publications appeared in Top 1% journals and 20.28% was published in Top 10% journals.

Table 4 provides an overview of the bibliometric statistics of Division Blood as calculated by the University Library Maastricht (based on refereed publications), including the number of articles (P); the average (mean) number of citations per paper (CI); the citation impact (citations per paper) normalised for subject, year and document type (CNCI); the citation impact (citations per paper) normalised for journal, year and document type (JNCI).

These data show that the CNCI (the crown indicator) of Division Blood has been between 1.5 and 1.7 during the last eight years, meaning that publications of Division Blood are cited about 1.5-1.7 times more frequent than the world

average. Furthermore, the JNCI > 1.0 indicates that the research unit publishes in journals with a relatively high impact. The H-indexes of the PIs in Division Blood can be found in Part A and range from 35 to 93.

Table 4 Bibliometric statistics Division Blood (excl. former Theme III) 2013-2018 (refereed articles)

	P	CI	CNCI	JNCI
2013 - 2016	452	18.84	1.53	1.10
2014 - 2017	473	14.74	1.66	1.10
2015 - 2018	534	10.26	1.65	1.08

1.3.3 Demonstrable marks of recognition from peers

Research grants awarded to individuals
Researchers in Division Blood have been successful in obtaining several prestigious personal grants, funded by for example the NHS Dr E. Dekker programme, the Innovational Research Incentives Scheme of NWO and the European Research Council (see Part A, page 20).

Most important scientific awards (see Annex 4 for a full overview)
Researchers in Division Blood have been successful in obtaining scientific awards. The most important awards that were received between 2013 and 2018 are listed below:

Prof. Tilman Hackeng received the ISTH Ratnoff MacFarlane Plenary Award from the International Society on Thrombosis and Haemostasis (ISTH) in 2013.

Dr Judith Cosemans was awarded the Dr Edmond Hustinx Prize for Science in 2014 for her research proposal on developing techniques to measure thrombosis tendency in small volumes of blood, which reduces the need for animal testing.

Prof. Christian Weber received the Alexander Schmidt Award from the Society of Thrombosis and Haemostasis Research (GTH).

Prof. Robert van Oostenbrugge and Prof. Wim van Zwam have received several prizes 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).

Dr Marjo Donners won the Marten Hofker Memorial Award during the ATVB congress that took place from May 4 until May 6, 2017 for her abstract entitled 'Endothelial Murine Atherosclerosis Development'.

Most important invited lectures (see Annex 5 for a full overview)
Researchers in Division Blood have been invited to present lectures at important international conferences such as meetings of the International Society on Thrombosis and Haemostasis (Prof. Tilman Hackeng, Dr Arina ten Cate-Hoek, Dr Elisabetta Castoldi, Dr Judith Cosemans, Prof. Johan Heemskerk, Dr Henri Spronk, Dr Paola van der Meijden, Dr Rory Koenen), the Gordon Research Conferences (Prof. Christian Weber, Dr Judith Cosemans), the Society of Thrombosis and Haemostasis Research (Prof. Hugo ten Cate, Prof. Tilman Hackeng, Prof. Johan Heemskerk, Prof. Christian Weber, Dr Judith Cosemans, Prof. Leon Schurgers, Prof. Monika Stoll) and the European Congress of Radiology (Prof. Joachim Wildberger, Prof. Wim van Zwam, Dr Casper Mihl)

Most important memberships of scientific committees (see Annex 6 for a full overview)

Name	Scientific Board	Character of membership (chair, board member)	Period
Christian Weber	ESC Working group on Atherosclerosis and Vascular Biology	Chair	2012-2014
Erik Biessen	NWO TOP grant committee	Member	2014-2015
Gerry Nicolaes	NWO Veni selection committee	Member	2012-2015
Ingrid Dijkgraaf	NWO ECHO committee Chemical Sciences/ENW	Member	2018
Ingrid Dijkgraaf	NWO Veni committee Chemical Sciences/ENW	Member	2016-present
Johan Heemskerk	Advisory Board Netherlands Thrombosis Foundation, The Hague	Member	2010-present
Robert van Oostenbrugge	Dutch Brain Foundation	Member	2015-present
Tilman Hackeng	Scientific Advisory Board Dutch Thrombosis Foundation	Chair	2015-present
Wim van Zwam	Stroke Task Force Cardiovascular and Interventional Radiological Society of Europe (CIRSE)	Chair	2018-present
Joachim Wildberger	Dutch Society for Radiology (NVvC), Cardiovascular section	Chair	2011-2017
Judith Sluimer	Grant panel Flanders Scientific organisation (FWO) PhD fellowships SBmed02	Member	2016-2017

* NWO: The Netherlands Organisation for Scientific Research; ESC: European Society of Cardiology

Most important memberships of editorial boards, editorships (see Annex 7 for a full overview)

Name	Journal	Character of membership (editor, member or guest editor	Period
Chris Reutelingsperger	JACC Cardiovascular Imaging	Guest editor	2014-2020
Christian Weber	Thrombosis Haemostasis	Editor	2010-present
Johan Heemskerk	Journal of Thrombosis Haemostasis	Associate editor	2011-2017
Leon Schurgers	Frontiers in Cardiovascular Medicine	Associate editor	2016-present
Rory Koenen	Thrombosis & Haemostasis	Associate editor	2017-present
Tilman Hackeng	Thrombosis and Haemostasis	Section editor	2015-present
Erik Biessen	Atherosclerosis	Editor	2016-present
Joachim Wildberger	Chair European Radiology - Section Computed Tomography	Editor	2014-2017
Wim van Zwam	Neuroradiology	Editorial board	2018-present

1.3.4 In conclusion: quality

Division Blood has a large number of publications on curiosity driven and clinically relevant cardiovascular research in high impact international scientific journals. Division Blood retains a broad international multidisciplinary network and the whole spectrum of cardiovascular research from molecule to patient and population, from basic to clinical, is covered. Researchers of Division Blood have been successful in attracting funding, PhD candidates and securing talent, thereby creating sustained quality and reliable partnerships.

1.4 Relevance to society

1.4.1 Demonstrable research products for societal target groups

Media exposure of Division Blood was centred around the following research: MR CLEAN (Prof. Wim van Zwam and Prof. Robert van Oostenbrugge, former Division Vessels), vascular calcification (Horizon 2020 project INTRICARE Prof. Leon Schurgers) and newly developed multiparameter tests (Prof. Johan Heemskerk). Articles and interviews appeared online and in national newspapers. The results of MR CLEAN have been presented during the World Stroke Day and at other national and international events. CARIM (mostly staff members in Division Blood) organises the World Thrombosis day, every year on 13 October, to inform citizens of southern Limburg on the signs and risks of cardiovascular disease. Furthermore, researchers in Division Blood give educational lectures at symposia (KNAW, European Platelet Summer School), schools (primary and secundary education), and other organisations (Sanquin Blood Bank).

1.4.1.1 Most important societal publications/outputs

Het vitamine K kookboek; gezond en lekker koken voor trombosedienstpatiënten

Leon Schurgers and Hugo ten Cate: Cookbook on vitamin K for patients of the oral anticoagulation clinic (*Het vitamine K kookboek; gezond en lekker koken voor trombosedienstpatiënten*). Trichis Publishing B.V. ISBN 9789490608460). This collaboration between the Dutch Thrombosis Foundation and scientists in the field of Biochemistry and Clinical Thrombosis and Haemostasis has yielded tried and tested recipes with known concentrations of vitamin K to create awareness amongst patients on oral anticoagulation with vitamin K antagonists.

Joachim Wildberger and Marco Das: Radiological diagnosis in pulmonary embolism. Handbook of Venous Thromboembolism. Thachil J, Bagot C, Hrsg: Wiley Blackwell, Oxford 2018 ISBN 978-1-119-09557-6 pp 55 – 59.
This chapter in a very practical handbook, puts emphasis on a disorder that remains an important contributor to death; pulmonary embolism. Prof. Joachim Wildberger and his team contribute substantially to state-of-the-art diagnostics in this field, which is an important means for all clinical management and studies in the field of venous thromboembolism.

Johan Heemskerk: Currently used clinical tests to diagnose recurrent bleeding in patients, unprovoked or due to medication, screen for either altered platelet function, abnormal von Willebrand factor, or defective plasma coagulation. With the newly developed multiparameter tests, applied to flowing whole-blood over micro patterned thrombogenic surfaces, it is now possible to check for platelet activation, von Willebrand factor activity and fibrin clot formation at the same time. The tests are currently validated using patient blood samples, for antithrombotic and prohaemophilic treatment, and for relation to genetic variance of platelet and coagulation factor genes.

Elisabetta Castoldi: As the recipient of two research grants from the Dutch Thrombosis Foundation (TSN), Dr Elisabetta Castoldi has provided yearly lay reports of her research for the Annual Bulletin of the TSN. Moreover, she gave a lay interview on FV-short that served as the basis for a fund-raising action among the contributors of the TSN. Another interview by the American journalist K. Grens about the original FV-short paper by Vincent et al. was published as Grens K. Bad Blood. The Scientist, 1 November 2013 (https://www.the-scientist.com/notebook/bad-blood-38465). Since 2017, Dr Elisabetta Castoldi has been a member of the Editorial Board of the ICTHIC Magazine, an online initiative meant to raise awareness on haemostasis and oncology among the medical and scientific communities, the media and the general public.

https://www.the-scientist.com/notebook/bad-blood-38465

1.4.2 *Demonstrable use of products by societal groups*

Patents

Patent	Application	Date	Scientist
Inhibitors of CD40-TRAF6 interaction	Treatment	27-08-2013	C. Weber; G. Nicolaes
New biomarkers to estimate the risk of allograft failure and patient mortality after organ transplantation	Biomarker	04-06-2013	C. Vermeer
Truncated Cystine-Knot Proteins	Diagnostics	14-04-2014 (granted)	T. Hackeng
Extendible stent	Device	30-12-2016	C. Wittens
Stent coupling device	Device	29-12-2016	C. Wittens
H4 peptides	Inflammation; treatment	22-12-2017	G. Nicolaes
Method for determining haemostasis under shear	Method	18-07-2018	J. Heemskerk; J. Cosemans
Annexin-1 BBB	Treatment	12-06-2018	C. Reutelingsperger

Spin-offs

The following spin-off companies were founded in the period of 2013-2018:

Cartesio Therapeutics Inc. The inflammatory paradigm for the pathogenesis of atherosclerosis has been validated by the CANTOS trial, providing proof-of-concept that anti-inflammatory therapy with anti-IL-1b cytokine antibody reduces cardiovascular event rates, but also featuring adverse effects. In this context, Cartesio Therapeutics Inc. It a Dutch start-up company, which aims to develop small molecule inhibitors more specifically targeting vascular inflammation without side effects, namely by interfering with TNF receptor-associated factors (TRAFs) in cytokine signalling, for late pre-clinical and early clinical trials and eventually for clinical application. Cartesio Therapeutics Inc. is based on intellectual property granted to LMU Munich and Maastricht University and has been founded by Dr Esther Lutgens, Dr Gerry Nicolaes, Prof. Christian Weber, Dr Dorothee Atzler and Dr Peter Ekhart.

Coagulation Profile BV offers a wide variety of assays to assess the 'Coagulation Profile' of a person. Assays range from classical methods, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), to chromogenic antigen and enzyme activity assays, as well as to tailor-made thrombin generation assessment and modifications thereof. Coagulation Profile BV is specialised in custom based coagulation assays and provides services for the modification of existing methods, as well as for the development of novel assays. Alterations in components of the coagulation system can result in either bleeding or thrombotic disorders. The 'Coagulation Profile' of an individual can therefore be defined as an overall potential or capacity to form a fibrin clot. Its facilities are ISO 9001 certified and Coagulation Profile BV has an extensive portfolio in performing analyses in a research setting and in support of phase I, II, and III clinical trials. Coagulation BV was founded by Prof. Hugo ten Cate, Prof. Leon Schurgers, Dr Henri Spronk, Rene van Oerle, Stella Thomassen and Prof. Tilman Hackeng.

FlowChamber (FLC) is a Maastricht UMC+ spin-off company and aims to rapidly assess haemostasis with high accuracy. FLC enables researchers to understand the origin of deficiencies in the blood clotting process. Clinicians are able to choose the most effective intervention in case a patient has a risk on blood loss. FLC's innovative flow chamber technology is developed by the Department of Biochemistry, and assesses blood platelet function and coagulation status at the same time, under physiological circumstances. FlowChamber was founded by Prof. Johan Heemskerk.

Matisse Pharmaceuticals

Matisse Pharmaceuticals is a biotechnology company dedicated to the development of pharmaceutical therapies to treat disorders that are associated with fulminant inflammation, such as sepsis. The most advanced product in the development is the heparin fraction M6229 for the treatment of severe sepsis and septic shock. Matisse Pharmaceuticals was founded By Dr Gerry Nicolaes, Prof. Chris Reutelingsperger and Prof. em Coen Hemker.

1.4.3 *Demonstrable marks of recognition by societal groups*

As demonstrated in Part A, researchers in Division Blood contribute extensively to (inter)national clinical guidelines and participate in committees responsible for (inter)national (health) policy reports. (See Annex 10 and 11)

1.4.4 *Narrative and anecdotal information*

For the narratives and anecdotal information, we refer to the overview of narratives collected from the four programmes, which are available at the CARIM website.

CARIM website

1.5 Research programme specific information on PhD programme, Talent Policy, scientific integrity and diversity

See Part A.

1.6 Trends, SWOT and strategic plans

1.6.1 *Trends*

Expanding technology: Technological developments in the area of genomics in the past six to eight years have been breath taking. Since the introduction of massive parallel sequencing (NGS) in 2010, there has not only been a sharp decline in price, but also an immense development of different sequencing protocols that now allow for the investigation of a myriad of transcripts or DNA changes (single nucleotide variants (SNVs), indels, deletions, or epigenetic marks (methylation or acetylation of DNA components) to the single cell level at reasonable cost. The same is true for the development of bioinformatics tools for the analysis of such complex data sets. CARIM has reacted to this development by recruiting Monika Stoll and Aaron Isaacs and by investing into an infrastructure, which benefits all researchers interested in NGS and functional genomics. In the coming years, traditional NGS methodologies will increasingly be replaced by single cell sequencing applications, which will be pivotal for future grant applications. This will require further investment into the infrastructure (DropSeq and or 10X or equivalent systems for barcoding single cells) and a specialised laboratory infrastructure for the library preparations, while we anticipate that the actual NGS runs can be outsourced to external providers.

A second technological 'revolution' takes place in the imaging facilities; thanks to timely investments and long lasting contracts with imaging companies, the hospital based radiology and nuclear medicine departments are up to date and prepared for all possible innovations in this field. ICT has to be optimised to support big data storage and handling, providing high-quality image information for physicians and scientists. In addition, tailor-made molecular imaging agents based on proteins and peptides are designed and synthesised by the Translational Cardiovascular Chemistry lab in the department of Biochemistry (Dr Ingrid Dijkgraaf, Dr Stijn Agten, Prof. Tilman Hackeng) that offers faculty broad services to imaging of angiogenesis, arteriogenesis, thrombus formation, and atherosclerosis on fluorescence, PET; SPECT; and MRI modalities. This facility will be incorporated in a CARIM-HVC overarching facility of Radiobiochemical vascular imaging in the immediate future.

Third, the availability of CRISPR/Cas, stem cell and 'organ on chip' expertise within Division Blood (Prof. Leon Schurgers, Prof. Johan Heemskerk) makes it of eminent importance to further develop this into a local facility, to support several lines of ongoing research.

Fourth, technology from CARIM becomes even more instrumental in structure function analyses from proteins/peptides, and in designing new therapeutic strategies (Prof. Tilman Hackeng, Dr Gerry Nicolaes, Dr Kanin Wichapong, Dr Ingrid Dijkgraaf) that will be embedded in international consortia (one current example is the recent Nature publication on histones and neutrophil trafficking in atherosclerosis in which Dr Kanin Wichapong, Prof. Hackeng and Dr Nicolaes are co-authors) on design and synthesis of a specific peptide-based Histone-4 inhibitor.

Consortia based research: An important trend is observed towards consortium driven and funded research, which has been and is an increasingly relevant source for funding to CARIM researchers. It is likely that this trend continues and may further expand across borders. The participation of several researchers in the ITN consortia INTRICARE, TAPAS and TICARDIO is an illustration of this development, as is the participation in the CVON funded consortium CONTRAST. Another, but related trend is that academy-industry partnerships are sought to strengthen translational CV research in a more efficient manner (for both parties). The CARIM-BAYER is a key example of this trend, and one that hopefully can be consolidated to establish a solid platform for translational science and drug development, based on the complementary skills, tools and expertise.

Personalised medicine: with advancing technology, more and more precision targeted options for diagnosis and in particular treatment of CVD become available. The associated options for geno- and phenotyping individuals (at risk of thrombosis, bleeding and/or atherosclerotic vascular disease will definitely create options for individualised management. Biomarker profiles in conjunction with clinical risk scores will provide a means for individual risk (thrombosis, bleeding, vascular complications like myocardial infarction and stroke) estimation, which will be more accurate than at present. Recent literature, e.g. on the ABC risk score for CVD, suggests that biomarker addition can make a difference here. Treatment options for atherosclerosis or thrombosis will inevitably be more precisely focused when individual risk factors lead to specific targets for intervention, and this is a development in which CARIM and Division Blood are at the forefront.

1.6.2 The SWOT analysis

STRENGTHS
- Strong publication record with a high percentage of papers in top 10% (high impact) journals. This results in citation scores that are substantially above world average;
- Strong track record in acquiring prestigious national and European grants, such as CVON, Horizon 2020 and Interreg Meuse Rhine; utilising CARIM-generated knowledge, in terms of patents and spin-offs and establishing long-lasting relationships with industrial partners (knowledge valorisation).

WEAKNESSES
- Slow progress of coordination activities around development of platform facilities such as stem cell, organoid and CRISPR/Cas facilities;
- Some increasingly important lines of clinical research, such as acute stroke management, receive insufficient staff support and are not structurally supported at the pre-clinical level;
- Given the capped ratio of scientific personnel to technical personnel of 0.7 (0.7 fte technical support staff per 1.0 fte scientific staff) and the FHML-enfored ceiling of research labelling of scientific staff paid for by direct funding to a maximum of 0.5 fte, it becomes a challenge to attract young and experienced technicians from outside the organisation. This affects the overall quality and sustainability of the laboratory research.

OPPORTUNITIES
- The presence of large cohorts and biobanks within CARIM offers many opportunties for studies into personalised treatment of cardiovascular disease;
- Utilise the potential of clinical and translational research to attract industrial partners;
- A new Biomedical Center containing a top-notch animal facility.

THREATS
- Losing CV research from the national and EU science agendas and lack of funding for curiosity driven research as well as for senior scientists;
- The increase of bureaucracy (e.g. GDPR, Animal Ethics Committee) will hamper scientists to operate/perform at the cutting edges.

1.6.3 *Strategic plans*

Division Blood spans a variety of expertise and backgrounds, jointly assembled under one arch, dealing with Blood related vascular disorders. Although the traditional backbone of thrombosis and haemostasis is maintained, the label Blood is overarching and non-exclusive. Interdivisional collaborations will be further exploited and collaborations with other universities, and non-academic partners including industry will be consolidated and extended (on a national and international level). Given these general objectives, a number of specific strategic plans can be distinguished:

1. **'Traditional' thrombosis and haemostasis in relation to inflammation**: since the foundation of the Department of Biochemistry, a main source of PIs to the former Theme and the current Division, a strong focus on venous thrombosis and bleeding disorders has been in place. '*Thrombophilia*' defined as congenital and acquired risk factors for thrombosis has been a strong line and this will not change substantially. GWAS studies yield new candidate genes; isoforms of known proteins and combinations of (mutant) proteins as well as novel miRNAs contribute to thrombosis and the functional, molecular, mechanisms still require exploration. The same holds for '*bleeding tendency*', although here the focus is more on cellular aspects and in particular on whole blood functional testing, using the Maastricht multichannel flow chamber. Using this tool, in conjunction with further genetic characterisation, bleeding as well as thrombosis tendencies will be explored to reveal targets for intervention. Here, the interaction with the CVC will be further strengthened. It is also the strong ambition to continue the recently started collaborations within the TAPAS and TICARDIO frameworks to intensify the international network of research in the area of bleeding and thrombophilia, also in relation to inflammation, while connecting the leading centres in this field in Europe.

2. **Optimised prevention and treatment of PTS**: CARIM research on venous thrombosis and PTS has gained wide recognition over the past few years and through several collaborations and new grant initiatives we expect this avenue to continue, combining non-invasive (new applications of old drugs, new agents) and invasive strategies (catheter guided clot removal and stenting), to diminish the burden of post thrombotic complaints. The active collaboration with KEMTA (Prof. Manuela Joore) will stay an essential element in establishing the cost-effectiveness of this and other interventions.

3. **Acute stroke** becomes an increasingly important research focus and from CARIM several investigators are in the lead, internationally, in large clinical studies addressing optimisation of (invasive) treatment of acute ischemic stroke. Within the CVON CONTRAST consortium, initiated by neurologists and radiologists from Maastricht UMC+/CARIM, a number of new therapeutic strategies are investigated. It is the intention of this consortium and also from us, to strengthen this line of research, including pre-clinical work, focused on thrombus characteristics and other biomarkers. There is ample interest from others within CARIM to participate. This involves not only ischemic but also an expanding programme on haemorrhagic stroke and microvascular cerebral disease (Dr Staals), optimising management of acute stroke (haemorrhagic and ischemic) through deep exploration of its pathophysiology, and improving imaging and therapeutic interventions. The intensive collaboration between the Departments of Neurology and Interventional Radiology, as well as with regional centres, referring patients, provided the basis for a strong clinical research programme, aimed at improving the outcomes of acute stroke. The success of the MR CLEAN study outcomes, including the CVON CONTRAST consortium provides a strong rationale for supporting this spearhead, with more emphasis on biomarker identification.

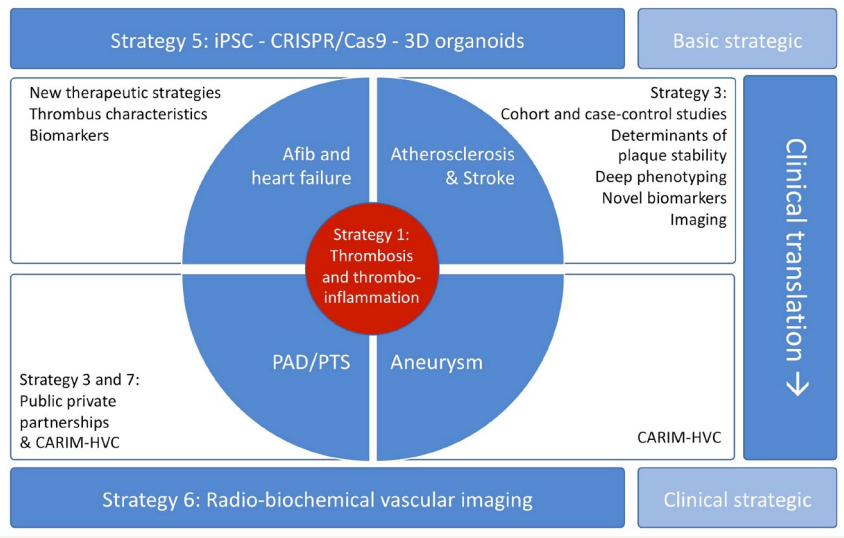
4. **Atherosclerosis** was and remains an extremely strong domain, which linked to atherothrombosis, spans a fair part of research within this Division. Collaborating with the Universities of Munich and Aachen, there are several lines of research that will be pursued. For translation and clinical studies a strengthened link with the Heart+Vascular Center at the Maastricth UMC+, as well as with other centres in the Netherlands and abroad, is essential. The input of state-of-the-art imaging techniques is one of the strongholds of CARIM research; combining different MRI and CT scanning techniques in conjunction with nuclear medicine technology is critically important to strengthen the CARIM position in this field. Atherosclerosis research has been a consistently strong and important theme for CARIM, spanning all Divisions in many aspects. Within Division Blood, atherosclerosis and atherothrombosis

research are closely coupled and link to many translational and clinical lines of research (and care). Dedicated studies in cohorts and case-control studies can be important in demonstrating determinants of plaque instability, critical lesion formation, and early fibrin formation. This should also include biomarker research, biochemical phenotyping of patients at different levels of risk, combining the available expertise within CARIM. Validating novel biomarkers within the Maastricht study, Gutenberg Health Study, or other large cohorts should be an important element of these translational studies. Combining this basic science with translational studies in patients at high risk of atherothrombotic complications (PAD, stroke, CAD, unprovoked VTE), in conjunction with new imaging modalities (MRI, firbin imaging, etc.), will maintain a strong line of research for the next decade. Thrombo-inflammation is an important concept in other areas, of which regenerative medicine is an area that will be focussed on; in the currently starting REGMED-XB consortium Division Blood participates in a programme on coagulation/anticoagulation and its impact on the preservation of the human heart under ex vivo conditions. This highly ambitious programme creates new opportunities to boost translational research in conjunction with the outstanding research and infrastructure of the REGMED XB partners.

5. **iPSC and CRISPR/Cas9 regenerative biology**: Recently, a laboratory was established for the generation of iSPC lines from patient material from HVC patients. We will generate cardiomyocyte (AF: WORM families) and SMC pathological phenotypes in the laboratory based on redifferentiation of iPSCs, and pursue repair of pathological mutations with CRISPR/Cas9 technologies. These technologies have been introduced through collaborations with the universities of Cambridge (Prof. Sanjay Sinha) and the University of California at Irvine (Prof. Chris Hughes). Early 2020, both collaborators will be appointed as visiting professors at CARIM. This novel strategy will go hand in hand with novel strategy 6: Radiobiochemical cardiovascular imaging.

6 Radiobiochemical Cardiovascular imaging: A novel programme will be initiated between the Departments of Biochemistry, Vascular Surgery and Radiology and Nuclear Medicine, which covers a multidisciplinary approach on research and imaging of vascular calcification of macro- and microvasculature. This new initiative sprouts from a previous joint CARIM and HVC request to the Maastricht UMC+ board to promote translational cardiovascular research through the programme 'Broad Achievements (*Pieken vanuit de breedte*): Bringing Mechanisms into the Clinic'. One of the four projects, Radio-Biochemistry, will now be incorporated in a larger initiative that comprises design and synthesis of calcification imaging agents, *in vitro* testing using primary smooth muscle cells and BioHybrid technologies, and then applies imaging technologies to pathological iPSCs derived from peripheral blood of HVC patients with impaired extracellular matrix and SMCs. Gene editing by CRISPR/Cas9 would then result in cell repair reflecting healthy SMC phenotypes in the lab. *In vivo* calcification models will be applied to novel imaging techniques with molecular imaging agents aiming at early detection of high risk microcalcification, that currently goes undetected by regular CT.

Figure 2 Strategy 5: iPSC – CRISPR/Cas9 – 3D organoids



7. **Collaborations with industry** including Bayer, 2M, and Nattopharma, requires attention as this type of joint research becomes more important, also for the industrial partners that seek clinically oriented research teams to provide the necessary materials and data for their lines of drug and diagnostic tool development. We aim to seek new grant opportunities (Horizon 2020 ITN, Interreg, PPS) to solidify current partnerships and to pursue new ones in a sustained way. Recently founded spin-off companies (Matisse Pharmaceuticals, Coagulation Profile) will be further exploited in the fields of therapeutic interventions (nonanticoagulant heparin and treatment of sepsis) and diagnostics, respectively.

8. **Deep geno- and phenotyping thrombophilia and bleeding tendency**, not confined to congenital deficiencies, but also including acquired haemorrhagic conditions, involving surgery and antithrombotic medication. Advance towards personalised geno- and phenotyping to provide reliable estimates of risks of thrombosis and bleeding, and to improve guidance of antithrombotic and pro-haemostatic management. CARIM basic science and its translational embedding remain unique and appealing for diagnostic and pharmaceutical companies as well; we seek to strengthen this process.

1.7 Viability

Division Blood, like the other Divisions, faces substantial challenges in the years ahead. Pressure concerning grant acquisition, performance (high quality output, volume of theses) and need for investments in talents and infrastructure, in order to remain competitive, provides a continuous burden to staff and students alike. Nevertheless, within this Division, several actions have been or are being taken to be 'future-proof', including:

1. Continue to strive for balanced talent track programmes, creating equal opportunities for males/females and support talents also in becoming role models for new generations of researchers; this includes active participation in programmes for dissemination, education, teaching at schools etc.;
2. Scout for (external) talents; stimulate internal talents;
3. Maintain focus on curiosity driven research, while pursuing the translation to the clinic and outpatient community;
4. Focus on research lines that remain key to CARIM and maintain to produce outstanding output and prestige. These include the substantial programmes on haemostasis (mechanisms of bleeding, individualised diagnostics), venous thromboembolism and PTS, atherosclerosis, vascular calcification and atherothrombosis;
5. Create room for new lines of interest, including e.g. acute stroke, personalised management of patients with thrombosis, and antithrombotic medication;
6. Invest in infrastructure to become competitive in the areas of gene repair (CRISPR/Cas), individualised blood phenotyping and risk prediction (organ on chip technology, flow chambers) in conjunction with investments in big data infrastructure (platforms, analytic support), modelling and clinical prediction (together with to be established Clinical Pharmacology and KEMTA) and drug development and target finding (strengthen protein core facilities; collaborations with industry, e.g. Bayer);
7. Optimise collaborations with clinical departments, i.e. Heart+Vascular Center, boosting translational research; optimise use of state of the art imaging facilities (Radiology and Nuclear Medicine) to support clinical and preclinical research;
8. Pursue international collaborations with academia and industry, and make optimal use of spin-off companies.

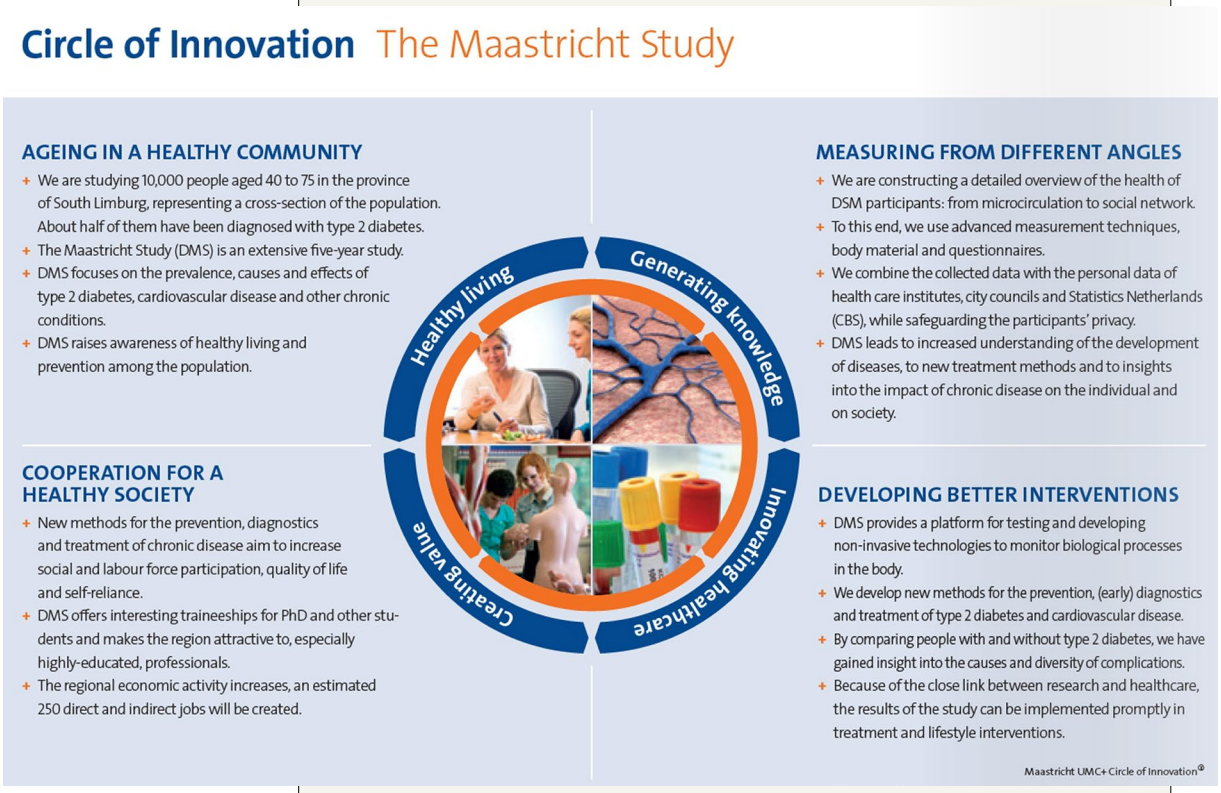
2 Division Vessels

2.1 Objectives and Research Area

2.1.1 *Vision, mission and objectives*

Research in Division Vessels (leader: Prof. Coen Stehouwer) focusses on translational research of micro- and macrovascular dysfunction in the context of specific cardiovascular diseases that are a major burden to an ageing society, namely 1) diabetes and the metabolic syndrome; 2) hypertension and chronic kidney disease; 3) cognitive impairment and depression in relation to diabetes and hypertension; 4) aortic aneurysm; and 5) venous disease. The mission of this Division is to decrease the health burden imposed by these diseases. Our research follows the 'Circle of Innovation©' (See Part A, page 11), in which basic research at CARIM including new technology boosts translational research within the HVC, supporting high-level academic health care. As a specific example of Division Vessels, the Circle of Innovation for The Maastricht Study is presented below:

Figure 1 Circle of Innovation 'The Maastricht Study'



From 2012 until 2018, research within what was then called 'Theme III: Vascular biology and medicine' was centred around eleven programmes led by PIs and eight key processes underlying cardiovascular disease: 1) microvascular dysfunction; 2) atherothrombosis; 3) arterial stiffening; 4) vascular smooth muscle cell plasticity; 5) endothelial dysfunction; 6) calcification; 7) advanced glycation; and 8) inflammation. In 2018, the research themes were restructured in order to reduce the number of programmes, and, the core of what had been Theme III continued as Division Vessels. This was accompanied by relatively large PI changes. Dr Leo Koole and Prof. Harald Schmidt left CARIM; Prof. Harry Struijker-Boudier retired; and Prof. Robert van Oostenbrugge, Prof. Erik Biessen, Prof. Christian Weber and Prof. Joachim Wildberger joined Division Blood. Prof. Coen Stehouwer continued as division leader (see Table below).

Two comprehensive programmes were created:
1. Vascular complications of diabetes and hypertension
2. Regenerative and reconstructive cardiovascular medicine

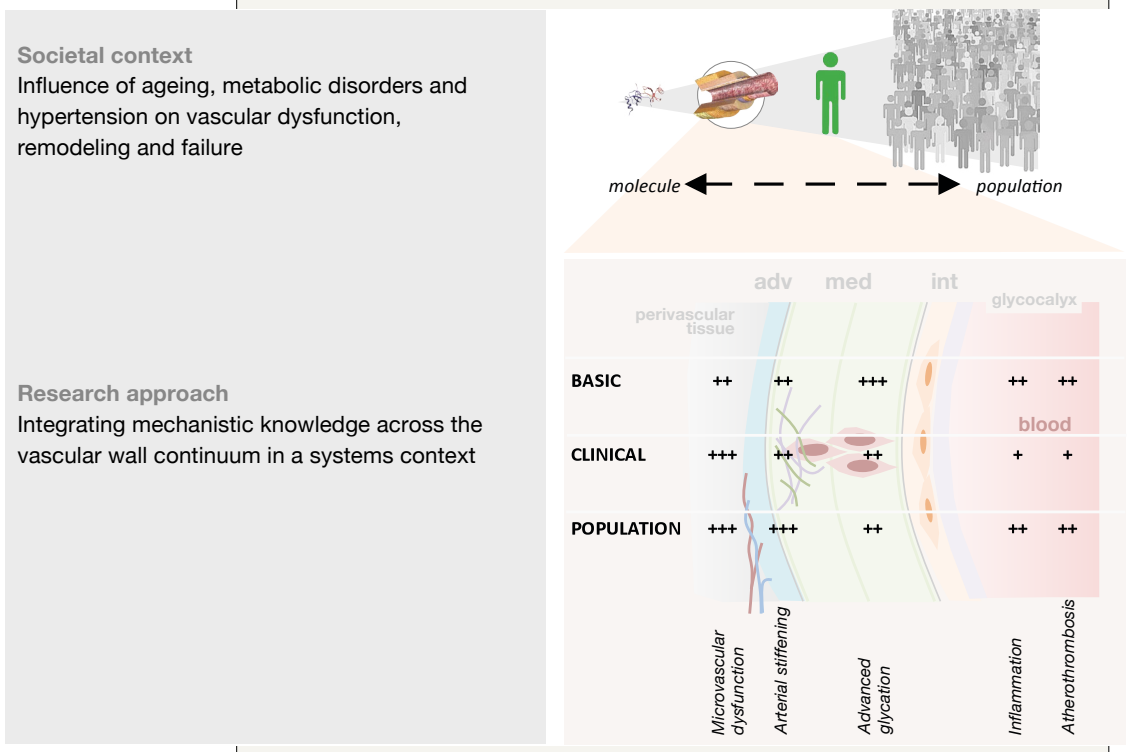
CARIM 2013-2018			CARIM 2019		
Theme III Vascular Biology			**Division VESSELS**		
19	Ilja Arts	Systems medicine of cardiometabolic disease	**3**	Vascular complications of diabetes & hypertension	Ilja Arts Bram Kroon **Coen Stehouwer**
20	Erik Biessen[1]	The vulnerable plaque: makers and markers			
21	Leo Koole[2]	Cardiovascular biomaterials			
22	Bram Kroon	Hypertension and target organ damage			
23	Mark Post	Regenerative and reconstructive medicine for vascular disease			
24	**Coen Stehouwer**	Vascular complications of diabetes and the metabolic syndrome			
25	Harald Schmidt[2]	Network pharmacology and cardiovascular drug discovery	**4**	Regenerative & reconstructive cardiovascular medicine	Jos Maessen[4] Mark Post
26	Harry Struijker-Boudier[3]	Vascular remodeling in cardiovascular disease			
27	Robert van Oostenbrugge[1]	Cerebral small vessel disease			
28	Hans Vink[2]	Macrovascular dysfunction and glycocalyx			
29	Joachim Wildberger[1]	Imaging			

Old and new Principal Investigator structure (left) and programme structure (right) of Division Vessels (formerly Theme III).
1: Prof. Erik Biessen, Prof. Joachim Wildberger and Prof. Robert van Oostenbrugge were transferred to Division Blood.
2: PI ships were revoked as a result of ERC recommendations 2013 and CARIM restructuring.
3: Prof. Harry Struijker-Boudier retired in 2018.
4: Prof. Jos Maessen came from former Theme II: Cardiac Function and Failure.

These major changes have stimulated an increased focus within the Division, which now centres around the following key processes: microvascular dysfunction, arterial stiffening, advanced glycation and inflammation. There is extensive collaboration with Division Blood, notably with regard to atherosclerosis, arterial thrombosis and stroke.

The interaction between the key processes studied in Division Vessels and specific cardiovascular diseases is depicted in Figure 2. The upper part of the figure illustrates the enormous societal impact (disease burden and economic burden) that vascular dysfunction imposes, i.e. remodelling and failure, in the context of ageing and highly prevalent disorders, such as the metabolic syndrome, type 2 diabetes and hypertension. The lower part of the figure shows, in a schematic and semi-quantitative manner, how the research approach in Division Vessels (left) is applied to specific vascular pathobiological processes (bottom) across the vascular wall (depicted schematically) in basic, clinical and population research. Abbreviations: adv, adventitia; med, media; int, intima. Symbols +, ++, +++: reasonably well-developed, well-developed, and very well-developed, respectively.

Figure 2 Interactions between key pathobiological processes and specific cardiovascular diseases studied in Division Vessels.



2.1.2 *Strategy and Research Area*

Division Vessels contains two major programmes involving five PIs. A brief perspective on PIs and their expertise is provided in Annex 9.

Programme 3 Vascular complications of diabetes and hypertension (PIs: Prof. Coen Stehouwer, Prof. Bram Kroon, Prof. Ilja Arts)

The programme 'Vascular complications of diabetes and hypertension' comprises the expertise of three PI groups and focusses around the following key processes; microvascular dysfunction, arterial stiffening, advanced glycation and inflammation.

Microvascular dysfunction and arterial stiffening
The research of the group of Prof. Coen Stehouwer, Dr Martijn Brouwers, Dr Simone Eussen, Dr Boy Houben, Dr Carla van der Kallen, Prof. Casper Schalkwijk, Dr Kristiaan Wouters, Dr Nordin Hanssen, Prof. Pieter Dagnelie, Dr Marleen van Greevenbroek, Dr Miranda Schram, Dr Ronald Henry and Dr Thomas van Sloten focusses on the elucidation of how metabolic changes, such as in pre-diabetes and diabetes, cause micro- and macrovascular disease. A key strength of the programme is the ability to combine epidemiology, clinical physiology and experimental approaches in the conviction that these approaches should complement and mutually inspire each other. An important development is the funding and start (2010) of The Maastricht Study, which combines very detailed, state-of-the-art phenotyping with an 'omics' approach in ~2000 individuals with, and ~7000 without type 2 diabetes. This serves to elucidate how diabetes leads not only to classic complications but also to so-called emerging complications, such as cognitive dysfunction, mood disorders, liver disease, musculoskeletal disease, pulmonary disease, sleep-disordered breathing, and infectious diseases.

Research within this programme has shown that microvascular endothelial dysfunction and arterial stiffening are early key processes in the development of cardiovascular and renal disease in diabetes. The pathophysiology of type 2 diabetes has been shown to be fundamentally bidirectional (microvascular <-> metabolic) rather than unidirectional (metabolic -> microvascular). Thus, microvascular endothelial dysfunction (1) precedes the occurrence of diabetes and is generalised even in prediabetes; (2) contributes to the onset of insulin

resistance, diabetes and hypertension in obesity; (3) is further enhanced when diabetes occurs; (4) is a major cause of cardiovascular disease in diabetes; (5) explains why albuminuria is strongly linked to cardiovascular disease; (6) may in part explain cognitive impairment and late-life depression in diabetes; and (7) explains in part why the key anti-diabetic drug, metformin, decreases cardiovascular disease risk. In addition, extensive arterial stiffening has been shown to occur very early in diabetes (in fact before its onset), causes microvascular dysfunction, and is a pathway leading to cardiovascular disease.

To probe these issues, the research group has developed novel methods of investigating; *in-vivo*, microvascular structure and function, and, *ex-vivo*, effects on arteriolar endothelium of insulin, adipokines and perivascular fat. Furthermore, the group has initiated 'The Maastricht Study' (cf. above). The Maastricht Study is unique when it comes to applying extremely extensive ('deep') phenotyping, particularly of the microcirculation, to understand the causes and consequences of microcirculatory dysfunction at the population level. With regard to diabetes, The Maastricht Study helps to understand why (cardiovascular and other) complications occur in some individuals but not in others; why diabetes is so often accompanied by other chronic diseases; and how microcirculatory dysfunction contributes to these issues (www.demaastrichtstudie.nl). Early results made international headlines, including CNN, when it was first announced that objectively measured sedentary behaviour (i.e. the daily time spent sitting) is a strong risk factor for diabetes and other cardiometabolic abnormalities, which is not mitigated by sports activities.

www.demaastrichtstudie.nl

Hypertension and target organ damage

Research activities on hypertension and target organ damage focus on a) vascular stiffness and calcifications in association with (microvascular) hypertension mediated organ damage, i.e. of the brain (in collaboration with MHeNs) and the kidneys, b) device-based treatment of resistant hypertension, i.e. renal denervation (RDN), (electrical) baroreflex activation therapy (BAT), and (mechanical) endovascular baroreflex amplification (EBA) treatment, and c) ambulatory 24-h and home blood pressure measurements. (Prof. Bram Kroon, Dr Boy Houben) To this aim, in collaboration with Prof. Leon Schurgers (Division Blood), a randomised placebo-controlled trial was started, investigating vitamin K2 supplementation on coronary artery calcifications (VitaK-CAC trial). Currently, the 2-years follow up study has almost been completed. Considering vascular stiffness, recently a meta-analysis was published, indicating that blood pressure lowering treatment per se did not significantly correlate to the proportion of reduction of left ventricular mass index, whereas reduction of aortic stiffness did, indicating the importance of therapeutic strategies reducing stiffness with regard to organ damage. We could also show with The Maastricht Study data, that the presence of (pre)diabetes independently increases regional carotid stiffness, but also that treatment with metformin is not associated with lower arterial stiffness.

With respect to the device-based treatment of resistant hypertension we participated in the publication of two important papers. Firstly, the proof-of-principle CALM-FIM study with EBA indicating the safety and potential efficacy of the MobiusHD carotis stent, and secondly, a position paper of the ESH Working Group of Interventional Treatment of Hypertension, showing new data fuelling renewed studies in the blood pressure lowering effect of renal denervation. In addition and related to the latter topic of blood pressure measurements, blood pressure variability (BPV) was studied in more detail. It became clear that while very short-term to mid-term BPV is a substantial and important determinant of cardiovascular risk in individuals with and without diabetes in patients with (pre) diabetes BPV only explains a small part of this increased risk. Moreover, BPV explained greater aortic stiffness and maladaptive carotid remodelling, but not carotid stiffness. These findings may explain, at least partially, the increased BPV-associated cardiovascular disease risk, in particular stroke.

With respect to research activities on hypertension and target organ damage, one of the main target end organs for hypertension is the brain. Cerebral small vessel disease (cSVD) is an umbrella term that covers all pathologies of the small vessels of the brain. The most prevalent one is age- and cardiovascular risk factor associated (cSVD). In collaboration with researchers from MHeNs, our group studies the relation between blood-brain barrier permeability and cerebral microperfusion in the development of clinical and radiological features of cSVD. We were among the first to show the relation between increase of blood brain barrier permeability and cSVD, and to show that lower cognitive performance is associated with lower microvascular perfusion in the normal appearing white matter and cortical grey matter. These findings support recent findings that both

cortical grey matter and normal appearing white matter perfusion may play a role in the pathophysiology of cognitive dysfunction in cSVD.

Mathematical and computational modelling and complex data-analysis
Research activities on mathematical and computational modelling and complex data-analysis is used to increase our understanding of the molecular biology and physiology underlying cardiometabolic diseases. (Prof. Ilja Arts). Rapid technological advances in the measurement of biomarkers and their use in human studies now enable us to study cardiometabolic disease from a systems biology perspective. Mathematical and computational modelling and complex data-analysis is important to get a quantitative understanding of the human metabolism at a systems level, to predict individual responses in target tissues, to get better insight into disease heterogeneity, and to identify subgroups that have a desirable response to a particular intervention. This enables a biology-based approach to personalised health (P4 Medicine) for cardiometabolic diseases.

MaCSBio

The work in this programme is conducted in close collaboration with the Maastricht Centre for Systems Biology (MaCSBio), of which Prof. Ilja Arts is the Scientific Director. MaCSBio was established in 2015 as an interfaculty research institute (now 24 researchers, 23 associate members, and four support staff). MaCSBio is part of the Faculty of Science and Engineering, the Faculty of Health, Medicine and Life Sciences, and the Faculty of Psychology and Neurosciences. At MaCSBio mathematical and computational models and approaches to modelling are (further) developed and applied. The focus is on the integration of multi-scale data (genomics, transcriptomics, metabolomics, microbiome, clinical, lifestyle) from deep-phenotyped humans (healthy and diseased) at the whole body, organ, and intracellular level, using genome scale metabolic and dynamical models, and pathway and network models. After the initial start-up phase, substantial output is now being generated, with 111 PubMed publications linked to the Centre so far. An example of the close collaboration with other CARIM groups is the Maastricht UMC+ funded patient stratification project focussing on the identification of subgroups of people with obesity who are at increased risk of developing type 2 diabetes or cardiovascular diseases (e.g. van der Kolk et al. Int J Obes (Lond), (Sep 21 2018), https://doi.org/10.1038/s41366-018-0189-8).

https://doi.org/10.1038/s41366-018-0189-8

Programme 4 Regenerative and reconstructive cardiovascular (PIs: Prof. Mark Post, Prof. Jos Maessen)

The programme 'Regenerative and reconstructive cardiovascular medicine' comprises the expertise of two PI groups and focusses the following research areas: regenerative medicine and tissue engineering, and reconstructive cardiovascular medicine.

Regenerative medicine and tissue engineering
Research activities in this programme focus on regenerative medicine and tissue engineering for vascular tissues, and encompass the creation of tissue engineered constructs that are prevascularised, and graft solutions for specific surgical applications, such as the arteria-venous shunt as a dialysis conduit. In addition, molecular pathways of collateralisation are being studied. Using computational fluid dynamics, ideal graft configurations are determined for optimal graft-vessel haemodynamics. These grafts are subsequently characterised *in vitro* and *in vivo* in animal models. Vascular biology of aneurysm formation is studied focusing on the role of vascular smooth muscle cells, using *in vitro* techniques, animal models and biobank with human tissue and blood samples. (Prof. Mark Post, Prof. Michael Jacobs, Dr Barend Mees, Prof. Geert Willem Schurink, Dr Maarten Snoeijs, Dr Nynke van den Akker, Dr Daniel Molin).

Collateral formation as a response to complete vascular occlusion of a major conduit is a target for pharmacological intervention. The chemokine CXCL1 appears to play a role in the initiation of collateral formation and exogenous administration of CXCL1 indeed improves collateral formation in a rat model of hindlimb ischemia. We also found that anti-inflammatory M2 macrophages rather than M1s improve arteriogenesis and angiogenesis. Molecular Imaging of collateral formation may be a more sensitive method to monitor therapeutic efficacy. Using SPECT imaging of labelled NGR or EVASIN effectively allowed molecular imaging of collateralisation (Hendrikx, 2016, 2016, 2016).

Short term thrombotic occlusion is a complication arising with small diameter tissue engineered vascular grafts (TEVG). It is considered a prerequisite that the TEVG's inner lumen surface should be antithrombotic. The first-choice

solution is seeding with autologous endothelial cells (EC). Analyses of patient derived vascular endothelium showed that venous endothelial cells exhibit the lowest thrombogenicity and, therefore, are the preferred source for ex-vivo endothelialisation of TEVG. We showed in a chronic kidney disease (CDK) rat model that autologous arteriovenous (AV) fistulas for vascular access are at high risk to non-maturate due to hampered nitric oxide related vascular maladaptation. Our data showed that CKD induces oxidative stress and, subsequently, NO resistance and hampered AV fistula maturation. Moreover, sGC activators such as BAY 60-2770 were shown to be therapeutically valid to increase AV fistula maturatio. Proof of concept data on electro-responsive smart polymer/fibrin hydrogels and TEVG coated with these hydrogels have proven to be superior *in vitro* and *in vivo* as compared to non-coated grafts. Electrostimulation of the vascular hydrogels enhanced smooth muscle cell proliferation and provided excellent collagen 3D alignment with higher extracellular deposition as well as superior cellular distribution in the hydrogels. Also *in vivo* electrostimulation resulted in faster and highly cellularised hydrogel grafts that morphologically and in function outperformed bare TEVGs that were implanted in a rat *in vivo* vascular interposition model (Thesis Rahimi 2014). Furthermore, novel PDLLA-based biodegradable drug-eluting microspheres for transarterial chemoembolisation were successfully designed, created and tested *in vitro* and in an *in vivo* Renca tumour mouse model.

In a consortium with TU/e, DSM and InSciTe the optimal arteriovenous graft for dialysis access has been developed using electrospinning. With computational fluid dynamics (CFD) and fluid structure interaction (FSI) modelling the optimal graft configuration was determined. Different graft materials and geometries were analysed, as well as the influence of the dialysis needle on AV graft haemodynamics. *In vitro* experiments have shown the optimal fibre size and electrospinning conditions for the new XS-graft and these were confirmed in *in vivo* experiments in a rat aortic interposition model. The subsequent step in the development of the new AV graft is a preclinical porcine model.

The aneurysm research line is a collaboration between the Ddepartments of Vascular Surgery (Prof. Michael Jacobs, Prof. Geert Willem Schurink, Dr Barend Mees), Cardiothoracic Surgery (Dr Eshan Natour, Dr Elham Bidar), Biochemistry (Prof. Leon Schurgers, Prof. Chris Reutelingsperger, Prof. Tilman Hackeng) and Biomedial Engineering (Dr Koen Reesink, Dr Wouter Huberts, Prof. Tammo Delhaas). The pathogenesis of aneurysm formation is being studied with the vascular smooth muscle cell (VSMC) as main cell of interest. The research platform is built on two pillars: a biobank containing aneurysm patient tissue and blood samples, and *in vivo* aneurysm animal models. From aortic tissue VSMC are isolated, cultured and characterised. Comparative studies between VSMC from thoracic versus abdominal aneurysms, from aneurysm versus healthy aorta and from degenerative aneurysms versus connective tissue disease induced aneurysms are performed. We have shown that aneurysm VSMC demonstrate phenotypic switching from a contractile state to a synthetic state. The molecular mechanisms of this phenotypic switching are further unravelled, including the influence of nicotine and vitamin K (Petsophonsakul, 2019 ATVB accepted for publication). In parallel, we have isolated pluripotent stem cells (iPSC) from plasma of aneurysm patients. These iPSC are differentiated into VSMC and characterization of these VSMC will reveal the role of genetic factors on aneurysm formation compared to local environmental factors. Using both techniques, we are able to generate patient-specific VSMC cell lines and perform patient-specific aneurysm biology research. In 2018, a high-throughput camera-based method was conceived to determine ascending aortic aneurysm wall properties (dynamic stress and strain; BME). The current approach will be developed to sustain such tissue characterisation in sync with the biobanking. This will allow studies into cell-matrix interactions (e.g. mechanobiology, stiffness homeostasis) to identify the key drivers of aneurysm formation, explaining the patient-to-patient variance in pathological presentation.

The *in vivo* research line encompasses a collaboration with the University of Cambridge. The first aneurysm mouse model in place is a Diphtheria Toxin (DT) mouse model that allows selective erosion of VSMC from aortic media at predetermined times. The DT mouse model opens research avenues to study in depth the role of VSMC in remodelling of the aortic wall. The Dynamice methodology under development at the Department of Biomedical Engineering in collaboration with the Humphrey lab at Yale University (Dr Bart Spronck) will enhance the studies by considering the mechanobiological and biomechanical context of VSMC phenotype and function. The aneurysm research line has been

re-established two years ago and exciting results are to be expected in the coming months.

Reconstructive cardiovascular medicine
Another part of this programme focusses on how concepts from basic sciences can be applied clinically to improve or enhance the regenerative and reconstructive potential of a surgical intervention on the one hand and how surgical interventions can offer an experimental model for testing hypotheses emerging in basic sciences, on the other. (Prof. Roberto Lorusso, Prof. Sandro Gelsomino, Dr Peyman Sardari Nia, Prof. Jos Maessen). To achieve this, all PhD candidates in the programme have to combine their clinical appointment with an appointment at a basic science department. As a result, most of the PhD candidates continued their research activities after registration as a medical specialist and were able to develop their own, mostly translational line of interest. Preliminary studies on extracorporeal circulation have been initiated and carried out in collaboration with the Department of Biomedical Engineering (Dr Wouter Huberts, UM) and externally with the Department of Biomedical Engineering at the TU/e (Prof. Frans van der Vosse).

Research has led to the development of a new and highly successful treatment to restore atrial function by applying fundamental electrophysiological concepts in a minimally invasive, surgical context. Clinical data on the effects of this treatment in turn were used for modelling physiological processes. In reconstructive surgery of the aorta and mitral valve, modelling, virtual reality and experimental imaging processing were successful in improving outcome, whereas the results raised new hypotheses in vascular biology. At the same time, these examples illustrate growing and successful interdisciplinary collaborations.

2.1.3 *Specific targets of the past six years*

The most important change has been the conversion of Theme III into Division Vessels, which has reduced heterogeneity and allowed for more focus. Like Theme III, Division Vessels has maintained a strong societal focus (cf. Figure 1). Interdisciplinary collaboration, especially with MaCSBio and MHeNs, has increased, notably with regard to systems medicine and vascular aspects of cognition and depression; but also with regard to genomics, microcirculation, and brain imaging. The Vascular Network Group has continued its work to increase collaboration across Divisions and Schools. To enhance the work on diabetes and the metabolic syndrome in the context of The Maastricht Study, and thus following the ERC's advice, CARIM had attracted two talented senior clinical scientists (Dr Martijn Brouwers and Dr Bastiaan de Galan, who will be appointed in 2019 as Professor of Endocrinology and Professor of Diabetology, respectively). The Maastricht UMC+ Board of Directors has shown strong support for The Maastricht Study, by providing additional transitional funding (3 M€, 2018) while regional support is being sought to finance a second, 5-y (2020-2024) round of deep phenotyping (projected budget, 14-18 M€). Regardless, The Maastricht Study, which started in 2011, has now accumulated sufficient follow-up to start longitudinal analyses, which will enhance its impact.

The ERC's advice to invest in basic microcirculatory research is being actively pursued; its advice to appoint a chair in immunology has not been followed due to budgetary restraints. Translational research projects between cardiovascular surgeons and basic scientists have been stimulated among others through shared PhD trajectories in clinical and basic science. Overall relevant developments also for Division Vessels have been described in Part A, 1.3, and have not been repeated here.

2.2 Description of the Research programme's organisation, composition and financing

2.2.1 *Organisation and embedding of the Research programme*

Division Vessels is one of the three Divisions within CARIM. Leader Prof. Coen Stehouwer represents Division Vessels in the Executive Board. Division Vessels established shared leadership with staff members with excellent scientific standing, taking into account and aiming for fair distribution of basic and clinical disciplines, diversity/gender, and various stages of career development. The Board now consists of Prof. Coen Stehouwer, Dr Koen Reesink, Dr Vanessa van Empel, Dr Marleen van Greevenbroek and Prof. Casper Schalkwijk. Close collaboration exists with the other Divisions within CARIM, the University Hospital and other research Schools.

2.2.2 *Composition*

The number of staff in this Division has decreased over the past six years. At the end of 2013, 104 research staff members (64.6 fte) were employed within Division Vessels, while at the end of 2018 this number was significantly lower (50.6 fte). The number and fte of support staff decreased even more, both in absolute numbers as relatively from 39.9 fte to 17.8 fte. These trends are in line with the general trends in CARIM.

Table 1 Research staff at Division level

	2013		2014		2015		2016		2017		2018	
VESSELS	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**
Scientific staff FHML (1)	36	15.5	32	12.8	36	13.5	28	8.9	30	11.1	29	10.8
Scientific staff academic hospital	16	4.5	10	3.4	11	5.2	15	5.4	14	5.2	12	4.9
Post-docs (2)	19	14.1	18	13.7	15	10.2	15	10.6	14	10.1	20	12.7
Internal PhD candidates (3)	33	30.5	28	26.3	31	28.3	24	23.0	23	22.2	23	22.2
Total research staff	**104**	**64.6**	**88**	**56.2**	**93**	**57.2**	**82**	**47.9**	**81**	**48.5**	**84**	**50.6**
Support staff (research) (4)	59	39.9	46	33.3	40	29.4	27	20.3	23	16.2	26	17.8
Support staff (managerial) (5)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total staff incl academic hospital	**163**	**104.5**	**134**	**89.5**	**133**	**86.6**	**109**	**68.1**	**104**	**64.7**	**110**	**68.3**
Total staff excl academic hospital	**147**	**100.0**	**124**	**86.0**	**122**	**81.4**	**94**	**62.7**	**90**	**59.5**	**106**	**63.4**
External PhD candidates (6)	26		24		30		45		46		46	
Visiting fellows/professors (7)	9		8		3		6		5		4	

#: Number of persons active on the Research programme research activities on 31-dec of any year/average MJE (men year equivalents
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the Research programme research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the scientific director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Visiting fellows are researchers/professors who visit the Research programme for a period of typically one week up to three months to work with Research programme staff members.

2.2.3 *Financing*

The total labelling on research funding in this Division has decreased from 60.1 to 45.7 fte due to a substantial reduction of direct funding (11.9 fte in 2018 compared to 23.0 fte in 2013). The amount of research grants and contract research together has fluctuated between 30 and 37 fte over the last six years, but is becoming an increasing proportion of the Division's funding (62% in 2013 to 74% in 2018). The total expenditure has decreased by almost 40% from 2013 to 2018.

Table 2 Funding at Division level

VESSELS		**2013**		**2014**		**2015**		**2016**		**2017**		**2018**
Funding	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**
Direct funding (1)	23.00 (4)	38	16.78	31	16.52	32	11.71	28	13.17	30	11.87	26
Research grants (2)	2.85	5	7.35	14	7.35	14	3.80	9	3.80	9	4.70	10
Contract research (3)	34.22	57	29.60	55	28.10	54	26.94	63	26.34	61	29.08	64
Total funding	**60.07**	**100**	**53.73**	**100**	**51.97**	**100**	**42.45**	**100**	**43.31**	**100**	**45.65**	**100**
Expenditure:	K€	%	K€	%	K€	%	K€	%	K€	%	K€	%
Personnel costs	4,623	55	3,880	60	3,037	55	2,592	50	2,231	50	2,811	55
Other costs	3,773	45	2,631	40	2,442	45	2,547	50	2,205	50	2,283	45
Total expenditure	**8,396**	**100**	**6,511**	**100**	**5,478**	**100**	**5,138**	**100**	**4,436**	**100**	**5,093**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering'/lump sum budget)
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charity organisations
Note 4: The funding in fte includes the total research staff but excludes the academic hospital-staff

2.3 Research Quality

2.3.1 *Demonstrable research products for peers: a description of the research output*

The number of refereed articles within this Division has decreased from 349 in 2013 to 289 in 2018, of which 253 were refereed articles with an impact factor according to SCI/SSCI. The number of PhD theses deriving from Division Vessels was between 14 and 22 per year.

Table 3 Main categories of research output at division level (date: 7 June 2019)

	2013	2014	2015	2016	2017	2018
VESSELS						
Refereed articles (SCI/SSCI) (1)	281	280	281	255	244	253
Other refereed articles (2)	68	36	50	41	40	36
Total refereed articles (3)	**349**	**316**	**331**	**296**	**284**	**289**
Books	1	n.a.	8	n.a.	n.a.	n.a.
Book chapters	3	5	1	n.a.	3	n.a.
PhD theses	14	19	14	22	20	13
Total publications	**367**	**340**	**354**	**318**	**307**	**305**

Note 1: Refereed articles ('wi-1') published in an international journal, which is mentioned in the (Social) Science Citation Index (SCI or SSCI) of Journal Citation Reports (JCR) ('wi-1')
Note 2: Refereed articles published in an international journal, not included in the SCI-SSCI ('wi-2'), Editorial Materials, Letters to the editor and refereed articles in a national (Dutch) journal ('wn')
Note 3: Total refereed articles is the sum of the refereed articles (SCI/SSCI) and the other refereed articles

2.3.1.1 *Most important scientific publications*

The following publications have been selected because of their high impact and/or representation of the research foci of the Division. The most important scientific publication related to The Maastricht Study is mentioned in Part A.

Higher levels of advanced glycation endproducts in human carotid atherosclerotic plaques are associated with a rupture-prone phenotype

Hanssen NM, **Wouters K**, Huijberts MS, **Gijbels MJ**, **Sluimer JC**, **Scheijen JL**, **Heeneman S, Biessen EA**, Daemen MJ, Brownlee M, de Kleijn DP, **Stehouwer CD**, Pasterkamp G, **Schalkwijk CG**. Higher levels of advanced glycation endproducts in human carotid atherosclerotic plaques are associated with a rupture-prone phenotype. Eur Heart J 2014;35(17):1137-46 IF 14.72

Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle cohort study

Spiering W, Williams B, van der Heyden J, van Kleef M, Lo R, Versmissen J, Moelker A, **Kroon A**, Reuter H, Ansel G, Stone GW, Bates M. Endovascular baroreflex amplification for resistant hypertension: a safety and proof-of-principle cohort study. Lancet 2017;390:2655-61 IF 47.83

Carotid stiffness is associated with incident stroke: a systematic review and individual participant data meta-analysis

Van Sloten TT, Sedaghat S, Laurent S, London GM, Pannier B, Ikram MA, Kavousi M, Mattace-Raso F, Franco OH, Boutouyrie P, **Stehouwer CDA**. Carotid stiffness is associated with incident stroke: a systematic review and individual participant data meta-analysis. J Am Coll Cardiol. 2015;66(19):2116-2125 IF 16.50

Higher levels of advanced glycation endproducts in human carotid atherosclerotic plaques are associated with a rupture-prone phenotype

Van Sloten TT, Tafflet M, Périer MC, Dugravot A, Climie RED, Singh-Manoux A, Empana JP. Association of Change in Cardiovascular Risk Factors With Incident Cardiovascular Events. JAMA 2018;320(17):1793-1804 IF 47.66

Cxcl1 promotes arteriogenesis through enhanced monocyte recruitment into the peri-collateral space. Angiogenesis

Vries MH, Wagenaar A, Verbruggen SE, **Molin DG**, **Dijkgraaf I**, **Hackeng TM**, **Post MJ**. Cxcl1 promotes arteriogenesis through enhanced monocyte recruitment into the peri-collateral space. Angiogenesis. 2015;18:163-171 IF 4.876

2.3.2 *Demonstrable use of research products by peers*

Publications (refereed articles with and without IF) of Division Vessels were cited 32,128 times in the period 2013-2018, as calculated by the University Library Maastricht. 2.64% of these publications appeared in Top 1% journals and 20.7% was published in Top 10% journals.

Table 4 provides an overview of bibliometric statistics of Division Vessels as calculated by the University Library Maastricht (based on refereed articles) including the number of articles (P); the average (mean) number of citations per paper (CI); the citation impact (citations per paper) normalised for subject, year and document type (CNCI); the citation impact (citations per paper) normalised for journal, year and document type (JNCI).

These data show that publications of Division Vessels are cited almost two times more frequent than the world average (CNCI). Furthermore, the JNCI is around 1.1-1.2, showing that the research unit publishes in journals with a relatively high impact. The H-indexes of the PIs in Division Vessels can be found in Part A and range from 29 to 110.

Table 4 Bibliometric statistics Division Vessels (incl. former Theme III) 2013-2018

	P	CI	CNCI	JNCI
2013 - 2016	1,068	27.76	2.11	1.15
2014 - 2017	1,061	18.23	1.98	1.12
2015 - 2018	1,063	12.77	1.94	1.22

2.3.3 *Demonstrable marks of recognition from peers*

Research grants awarded to individuals
Researchers in Division Vessels have been successful in obtaining several prestigious personal grants offered by, for instance, the NHS Dr E. Dekker programme and the Innovational Research Incentives Scheme of NWO (see Part A, page 20).

Most important scientific awards (see Annex 4 for a full overview)
Researchers in Division Vessels have been successful in receiving scientific awards for their researchers of which the most important ones are listed below:

Dr Kristiaan Wouters received the Prof. dr. J. Terpstra Award (2015) from the Dutch Association for Diabetes Research (NVDO) for his research on how circulating immune cells in the blood behave in people who are overweight and which cell types contribute to the increased risk of developing type 2 diabetes.

Prof. Coen Stehouwer received the McDonald Award from the Artery Society in 2017.

Prof. Nicolaas Schaper received a Lifelong Achievement Award from the Diabetic Foot Study Group of the European Association of the Study of Diabetes (EASD) in 2014.

Dr Peyman Sardari Nia has received the Techno-college innovation award 2014 from the European Association For Cardio-Thoracic Surgery for his invention of the High-Fidelity Endoscopic Mitral Valve Surgery Simulator.

Prof. Mark Post received the World Technology Award in 2013 from the World Technology Network. The World Technology Awards bring together the most innovative people and organisations in science and technology from around the world, exploring what is imminent, possible, and important in and around emerging technologies.

Most important invited lectures (see Annex 5 for a full overview)
Researchers in Division Vessels have been invited to present lectures at important international conferences, such as meetings of the European Society of Hypertension (Prof. Bram Kroon, Prof. Coen Stehouwer), the European Society for Clinical Investigation (Prof. Bram Kroon, Prof. Casper Schalkwijk), the ESC (Prof. Mark Post), and annual meetings of the European Association for Cardio-Thoracic Surgery (Prof. Jos Maessen, Dr Peyman Sardari Nia).

Most important memberships of scientific committees (see Annex 6 for a full overview)

Name	Scientific Board	Character of membership (chair, board member)	Period
Coen Stehouwer	NWO TOP grant committee	Member	2011-present
Coen Stehouwer	Selection Committee member Dutch Heart Foundation Dr. Dekker stipend Clinical Established Investigator	Member	2012-2015
Ilja Arts	Research Foundation Flanders (FWO), panel Health Sciences	Member	2015-2016
Ilja Arts	*Diabetes Doorbraakprojecten* committee member (collaboration between ZonMw and Dutch Diabetes Research Foundation)	Member	2018-present
Mark Post	Expert group World Economic Forum	Member	2018
Joachim Wildberger	Executive Committee European Society of Cardiac Imaging (ESCR)	Member	2014-2017
Casper Schalkwijk	Member of the Scientific Board of the Dutch Diabetes Research Foundation	Board member	2015-present

Most important memberships of editorial boards, editorships (see Annex 7 for a full overview)

Name	Journal	Character of membership (editor, member or guest editor	Period
Ilja Arts	BMC Systems Biology	Guest editor	2017-present
Casper Schalkwijk	Diabetologia	Member advisory board	2015-present
Coen Stehouwer	Hypertension	Editorial board	2004-2016
Coen Stehouwer	Lancet Diabetes Endocrinology	Editorial board	2015-present
Roberto Lorusso	Atherosclerosis	Associate editor	2006-present
Mark Post	Cardiovascular Research	Guest editor	2007-2018
Michael Jacobs	Aorta	Editor	2013-present

2.3.4 *In conclusion: Quality*

Division Vessels has a large number of publications about clinical and preclinical aspects of vascular biology and medicine in high impact scientific international journals, which are cited almost two times more frequent than the world average. Researchers have been successful in attracting funding and the number of PhD candidates is stable. One of the strengths of this Division is The Maastricht Study, which is nationally and internationally a unique large cohort study. Researchers in this Division have a high international academic reputation, which is demonstrated by the high number of invited lectures, awards and prizes, memberships of scientific committees and editorial boards and editorships.

2.4 Relevance to society

2.4.1 *Demonstrable research products for societal target groups*

Media exposure of Division Vessels was mostly centred around the research of Prof. Mark Post (cultured meat), AGEs (Prof. Casper Schalkwijk), and social isolation associated with type 2 diabetes. It consisted of documentaries, and interviews in national and international papers (Trouw, Der Spiegel), on television (ZDF, L1, ABC Australia) and radio. Scientific results of The Maastricht Study have been presented to participants of the study during annual symposia.

2.4.1.1 *Most important societal publications/outputs*

Mark Post: Principles of Tissue Engineering for Food (2014)
Prof. Mark Post's efforts with regard to tissue engineering for food constitute an important effort to enhance sustainability of meat consumption.

Michael Jacobs: European Vascular Course Book (yearly)
Prof. Michael Jacobs's European Vascular Course is held yearly. Attracting vascular surgeons from the entire world, it has increased standards and innovation in vascular surgery and thus affects the lives of countless patients suffering from vascular insufficiency or degeneration.

Casper Schalkwijk: Prof. Casper Schalkwijk recently published the first database on Advanced Glycation End products (AGEs) in 240 food items, as measured with state-of-the art UPLC-MSMS. He found that dietary AGEs are associated with AGEs in the body.

Maastricht Study: Annual symposia of The Maastricht Study to inform participants, the general public and the press on the scientific results.
This involves for instance television articles on the cardiometabolic health consequences of sedentary behaviour (CNN; Daily Mail UK; Dutch press) and of social isolation (Dutch press), as well as on the concept that women's health may deteriorate more rapidly than that of men prior to the onset of type 2 diabetes (Dutch press). These are just examples; many more are shown on the website (https://www.demaastrichtstudie.nl/actueel/nieuws).

2.4.2 *Demonstrable use of products by societal groups*

Patents

Patent	Application	Date	Scientist
A transapical heart port for insertion into a heart of a human or an animal subject	Surgery; device	13-03-2018	P. Sardari Nia
Echo imaging	Cardiology; surgery	22-11-2018	P. Sardari Nia
Venous canula	Cardiology; surgery	20-11-2018	R. Lorusso
Ablation Catheter	Cardiology; device	19-11-2018	S. Gelsomino

Spin-offs

The following spin-off companies were founded in the period of 2013-2018:

Cell2Tissue B.V. is an UM startup that develops technological platforms based on tissue engineering principles. Applications vary from food to regenerative medicine products. CEO is Prof. Mark Post.

Mosa Meat, B.V.

Mosa Meat, B.V. is a Maastricht University start-up aiming to commercialise cultured meat. CEO is Peter Verstrate and CSO is Prof. Mark Post. The company currently has 24 employees and had series A funding (7.5 M€) to improve and scale up production of cultured meat. Cultured meat is essentially tissue engineering but for food purposes. Bovine satellite cells are harvested through a biopsy, expanded and through self-assembly turned into muscle fibres. Adipose tissue derived stem cells are derived in the same way and differentiated into fat tissue. In a hamburger the two are combined. Research and development include maximising muscle protein expression and fat expression, optimising serum-free media for proliferation and differentiation of muscle and fat stem cells, scaling up cell production, increasing the stemness of satellite cells, and automation of tissue production. The aim is to culture meat in a serum-free and antibiotics-free condition, without any animal components except for the cells.

Qorium B.V. is a Maastricht University startup aiming to commercialise cultured leather. CEOs are Rutger Ploem and Stef Kranendijk, CSO is Prof. Mark Post. The company has four employees and has seed funding (250 K€). Cultured leather is cultured from bovine skin fibroblast to generate sheets of collagen that are cross-linked into leather. The skin cells are harvested from cows, expanded and cultured in sheets or on a biodegradable scaffold. Research and development is focussed on large scale cell production and maximizing and patterning collagen production. Avoiding some of the harsh chemical processes during tanning, cultured leather is a sustainable alternative to livestock skin.

2.4.3 *Demonstrable marks of recognition by societal groups*

As demonstrated in Part A, researchers in Division Vessels contribute extensively to (inter)national clinical guidelines and take place in committees responsible for (inter)national (health) policy reports. (See Annex 10 and 11)

2.4.4 *Narrative and anecdotal information*

For the narratives and anecdotal information, we refer to the overview of narratives collected from the four programmes, which are available at the CARIM website.

2.5 Research programme specific information on PhD programme, Talent Policy, scientific integrity and diversity

See Part A.

2.6 Trends, SWOT and strategic plans

2.6.1 *Trends*

The trends that are described in Part A of this report also apply to Division Vessels: more emphasis on translational research, big data, and regenerative medicine.

Consortium-based research: The recent developments with regards to -omics research (such as genomics, transcriptomics and metabolomics) have increased the trend towards larger national and international consortia. Participation of, among others, The Maastricht Study and the Cohort on Diabetes and Atherosclerosis Maastricht in the Dutch Biobanking and Biomolecular Recources Research Infrastructure The Netherlands (BBMRI-NL) illustrates this. The trend for the coming years is to develop towards better synchronisation and harmonisation of the available data and phenotypes, and hence to more precise biological information and better opportunity for group-level and/ or personalised data and opportunities for intervention.

Personalised medicine: With advancing technology, more and more precision-targeted options for diagnosis and treatment of CVD become available. The associated options for geno- and phenotyping individuals (at risk of micro- and macrovascular dysfunction, atherosclerotic vascular, cardiometabolic and heart disease will definitely create options for individualised management. Biomarker profiles in conjunction with clinical risk scores will provide a means for individual risk (for vascular complications such as myocardial infarction, heart failure and stroke) estimation, more accurately than at present. Treatment options for cardiovascular diseases will inevitably be more precisely focussed when individual risk factors lead to specific targets for intervention and prevention. With more (e.g. from repositories, wearables), more diverse (e.g. multi-omics, imaging), and more time-dependent (e.g. continuous glucose monitoring, challenge tests) data becoming available at an increasing pace, it is essential to have in-house expertise and complex data-analysis and modelling. Deep learning is a very promising development of machine learning techniques, which will boost the identification of new (individual) risk factors in the coming years. Recently, a specific deep learning technique, called deep convolutional neural networks, has been developed for analyses of (clinical) images. These techniques enable very accurate diagnoses of diseases. In addition, these techniques can be trained not only to recognise specified (known) features, but also to learn new (unknown) features with high predictive value. Besides improving (individual) risk profiling and diagnosis, this will fuel future research in new pathophysiological mechanisms of cardiovascular/metabolic diseases. These methods complement more biology-based modelling approaches, such as dynamical differential equation-based models and pathway and network models. The development of hybrid models that combine the strengths of both data-driven and biology-based approaches will boost the development of powerful predictive models that will be useful in personalised medicine and at the same time increase our understanding of diseases.

The ageing society: The overall higher age of the population puts a strain on the Dutch healthcare system. Moreover, the larger part of current knowledge is based on non-aged individuals, and detailed (patho)physiological information on the ageing body is currently lagging behind. Ageing does not affect everybody at the same pace - the perceived "biological age" (physiological age) of an individual often deviates from the 'chronological age' (calendar age). Methods to asses an individual's biological age (e.g. DNA methylation) are developing rapidly and will contribute to better insight in how (enhanced) progression of biological age affects (patho)physiology in different organs. Particularly important in the ageing body are the small and large blood vessels. Identification of factors that contribute to the development of pathological vascular ageing will provide valuable tools for the clinician to improve early recognition and diagnosis of CVD. They will contribute to better prevention and treatment of CVD related to pathological vascular ageing, and prevention of premature mortality. Identification of relevant subpopulations with advanced (vascular) ageing in e.g. The Maastricht Study, combined with follow-up information on morbidity and mortality and the anticipated second wave of phenotyping, puts this study at the forefront of research into (healthy) vascular ageing.

2.6.2 *The SWOT analysis*

STRENGTHS
- Combination of epidemiology, clinical physiology and experimental approaches, which complement and mutually inspire each other;
- High societal relevance, as the key processes, which constitute the research programme, are studied in the context of cardiovascular diseases that are major burdens to an ageing society;
- The Maastricht Study (strongly supported by Maastricht UMC+ and UM);
- Excellent clinical and research infrastructure, such as the clinical imaging facility, The Maastricht Study, Maastricht UMC+ biobank, CARIM Muroidean Facility, MaCSBio computational biology facilities, and clinical research infrastructure;
- Close collaboration with MaCSBio, MHeNs, and other institutes; e.g. Brightlands Maastricht Health Campus and Chemelot Campus, MaCSBio, MERLN, M4I, Imaging Valley, RegMed XB, Eindhoven University of Technology (TU/e), and the Central Bureau for Statistic.

WEAKNESSES
- Limited expertise in immunology, pharmacology and ageing;
- Limited gender diversity, notwithstanding recent local, national and global initiatives;
- Limited experimental microcirculatory research expertise;
- Missing standards and/or fragmentation of data storage and post-processing;
- Insufficient critical mass with regard to analysis of complex data and systems biology;
- Insufficient alignment with HVC, resulting in a) absence of laboratory for experimental surgery; b) insufficient HVC support for vascular neurology, vascular medicine, vascular surgery (in part), and cardiology (in part).

OPPORTUNITIES
- Alignment of expertise in basic and clinical pharmacology is actively pursued;
- Center of Integrated Diagnostics within the academic hospital offers opportunities for advanced decision support and optimisation of therapy;
- Alignment of joint data storage and access ('vendor neutral archive' within the academic hospital);
- Appointment of professor in Artificial Intelligence (Dr Hugo Aerts, Boston from January 2019 onwards) with opportunities with regard to cardiovascular –omics approaches;
- Participation in new (inter) national consortia (eg, *Nationale Wetenschapsagenda*; Aachen cardiorenal centre);
- More focus by reduction of number of PIs and research programmes;
- Appointment of two talented mid-career scientists (in 2018 and 2019) to enhance the work on diabetes and the metabolic syndrome in the context of The Maastricht Study;
- Extensive participation in (inter)national consortia: long-lasting relationships with private partners (e.g. ESAOTE Europe, Microlife Corp.).

THREATS
Insufficient opportunities for academic advancement of clinicians due to extra engagement in - and underrecognition of - patient care and residency training programmes;
Possible lack of continued funding for The Maastricht Study;
Reduction of research staff as a result of a changing research grant landscape.

2.6.3 *Strategic plans*

The Division has key strengths with regard to output, funding and research infrastructure. Maintenance of the latter is an important strategic goal; funding of The Maastricht Study, especially, requires continuous effort. Additional strategic goals to complement existing infrastructure and research include investments in experimental microvascular research; the biology of ageing; and cardiovascular pharmacology. From the point of view of translational and cross-disciplinary research, the much-appreciated intensified collaboration with MHeNs (i.e. neuroscience) will be expanded. For example, CARIM will start a closer collaboration with MHeNs regarding research into the complex interaction between vascular and neural function. Furthermore, the alignment with the HVC, which currently is insufficient, will be reinvigorated. A UHF-MRI study into the relation between vascular stiffness of small penetrating arteries of the brain and neurovascular coupling has recently been started (Prof Bram Kroon, Prof. Walter Backes and Dr J. Staals).

2.7 Viability

Based on current output and strategic considerations alluded to above, viability of this Division is deemed high. Division Vessels, as CARIM in general, houses high quality research and highly motivated researchers. The number of PhD candidates, the earning power and the number of high impact papers of Division Vessels is high and has been stable over the years. This trend is expected to continue. Not only is the research quality high, so is the societal relevance of the research in this Division, as the key processes which constitute the research programme are studied in the context of cardiovascular diseases that are major burdens to an ageing society, now and in the future. The research facilities of Division Vessels are excellent, securing both continuity and potential growth. Our governance structure promotes a shared responsibility for the development of the Division. CARIM's team-rather-champion organisation stimulates senior and junior researchers to develop their expertise in collaboration with each other.

Programme 3 'Vascular complications of diabetes and hypertension' (three PI groups) is extremely strong. An important asset of the programme is the combination of basic, clinical, epidemiological and computational modelling science, and the right infrastructure to make this work. The Maastricht Study in particular is a key asset; given its strong institutional support, the likelihood of financing a second round of deep phenotyping from 2020 onwards is high. Moreover, it should be stressed that even if such second round is postponed, the longitudinal follow-up in terms of morbidity and mortality outcomes is already in place and will yield important insights, based on the first round of deep phenotyping. The Maastricht Study also serves as a hub to increase collaboration with MHeNs with regard to the vascular causes of depression and cognitive impairment. The programme will be further strengthened by the appointment (2019) of two new chairs, of Endocrinology and Clinical Diabetology, respectively, after the retirement of Prof. Nicolaas Schaper. In addition, investments in microvascular biology and the biology of (vascular) ageing are being actively pursued. This would increase the viability of the programme even further. Within this programme, only Prof. Ilja Arts' group at MaCSBio (i.e., analysis of complex data and systems biology) has quite limited direct CARIM funding, and this needs reassessment and strengthening.

Programme 4 'Regenerative and reconstructive cardiovascular medicine', with two PI groups, has a strong collaboration with vascular surgery centring around tissue engineering of vascular grafts for arteriovenous shunts or bypass surgery. This part of the programme is embedded in a regional collaboration between CARIM, TU/e and DSM. In addition, prevascularisation or vascular mimicking in tissue engineered muscle constructs has a strong relationship with UM spin-off/start-up companies generating these engineered tissues (muscle, fat tissue and skin). Another part of this programme focusses on the interaction between basic sciences and the regenerative and reconstructive potential of surgical interventions. Translational potential is enhanced by all PhD candidates who are supervised by both clinicians and basic scientists. The recent appointment of Prof Roberto Lorusso will significantly strengthen these interactions. In conclusion, viability of Programme 4 is considered to be high based on its translational and innovative potential.

3 Division Heart

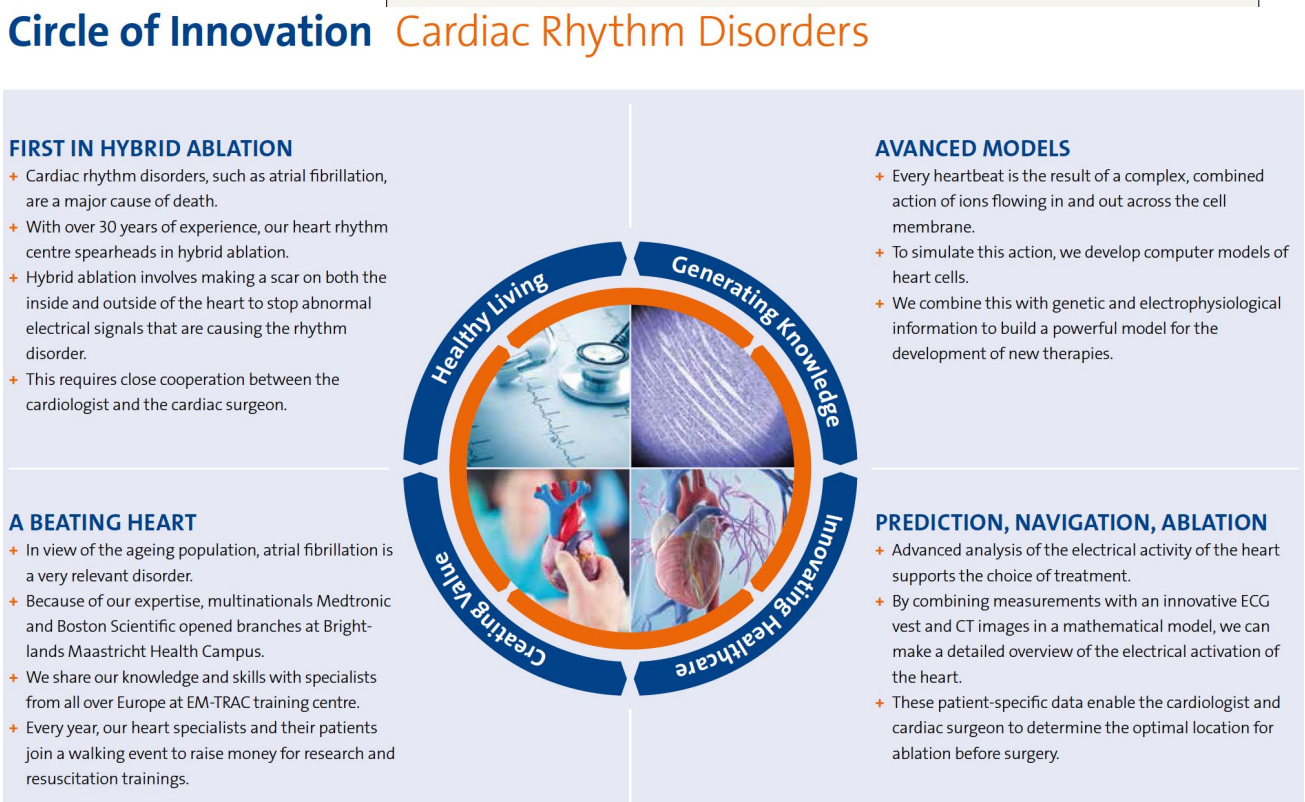
3.1 Objectives and Research Area

3.1.1 Vision, mission and objectives

The mission of Division Heart is to improve individuals' lives by reducing the burden of heart failure (HF), arrhythmias and sudden cardiac death (SCD).

Division Heart (leader: Prof. Harry Crijns) includes two programmes – 'Structural heart failure' and 'Complex arrhythmias' – the former includes cardiomyopathies with thick heart HF (HF preserved ejection fraction, HFpEF and hypertrophic cardiomyopathy) and thin heart HF (HFrEF and dilated cardiomyopathy), and the latter atrial fibrillation (AF) and sudden cardiac death (SCD). In heart failure research, both the *thick* and the *thin* heart are studied to unravel basic and clinical heart failure mechanisms with the aim of enhancing diagnosis and treatment. Complex arrhythmias encompasses diagnosing and treating patients in whom arrhythmias or conduction disturbances lead to, or enhance, HF and/or result from underlying (cardio)myopathy and HF). Cutting-edge translational cell-to-bedside discoveries on arrhythmia and heart failure mechanisms have led to innovative diagnostic and therapeutic concepts and strategies. These form a firm steppingstone for patient management and above all for early extensive and comprehensive diagnosis. Modelling, complex genetics, and advanced imaging are essential research areas to strengthen the matrix. Our research follows the 'Circle of Innovation©' (See Part A, page 11) in which basic research at CARIM, including new technology, boosts translational research within HVC, thereby supporting high-level academic health care. Below, we present the Circle of Innovation for Cardiac Rhythm Disorders as a relevant example for Division Heart:

Figure 1 Circle of Innovation 'Cardiac Rhythm Disorders'



Division Heart was restructured following the advice of the External Review Committee (ERC) in 2014 to reduce the number of programmes within Theme II (now Division Heart) in order to improve the alignment and cohesion between the programmes within the Division and to promote PIs who score high on impact and visibility. In addition, we followed the advice to broaden governance, make

space for young talents and stimulate cooperation between scientists. Three programmes (PI groups) were terminated for underperformance: clinical heart failure, mitochondrial disease and intermediate cardiac metabolism. The previous Theme II programme 'Surgical intervention' is now incorporated in Division Vessels under the title 'Regenerative and reconstructive cardiovascular medicine'.

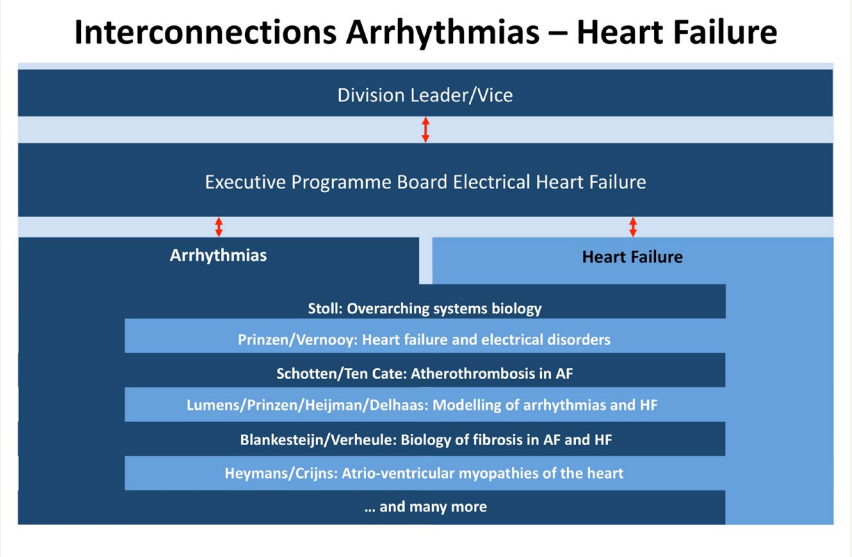
To facilitate cooperation and alignment in the overarching theme of electrical heart failure, two large programmes were formed; 'Complex arrhythmias' and 'Structural heart failure'. In addition, governance was reshaped into a structure in which six PIs take shared responsibility for the division's development, as well as for organisational and operational issues.

CARIM 2013-2018			CARIM 2019	
Theme II Cardiac Function and Failure			**Division HEART**	
7	Hans Peter Brunner-La Rocca[1]	Clinical heart failure	**5** Structural heart failure	Matthijs Blankesteijn
8	**Harry Crijns**	Clinical atrial fibrillation		Stephane Heymans
9	Matthijs Blankesteijn	ECM + Wnt signalling		Leon de Windt
10	Leon de Windt	Gene regulation		
11	Tammo Delhaas	Cardiovascular system dynamics		
12	Jan Glatz[1]	Intermediate cardiac metabolism	**6** Complex arrhythmias	**Harry Crijns**
13	Stephane Heymans	Cardiomyopathy		Tammo Delhaas
14	Jos Maessen[2]	Surgical intervention		Frits Prinzen
15	Frits Prinzen	Electro mechanics		Uli Schotten
16	Uli Schotten	Experimental atrial fibrillation		Paul Volders
17	Bert Smeets[1 0]	Mitochondrial disease		
18	Paul Volders	Arrhythmogenesis and cardiogenetics		

Old and new programme and Principal Investigator structure of Division Heart (formerly Theme II).
1: PI ships were revoked as a result of ERC recommendations 2013 and CARIM restructuring.
2: Prof. Jos Maessen was transferred to Division Vessels.

The interconnections between the two programmes – also outside the Division - are illustrated in Figure 2. These 'interconnections' are dynamic and adapt as research and collaborations evolve.

Figure 2 Interconnections between programmes in Division Heart



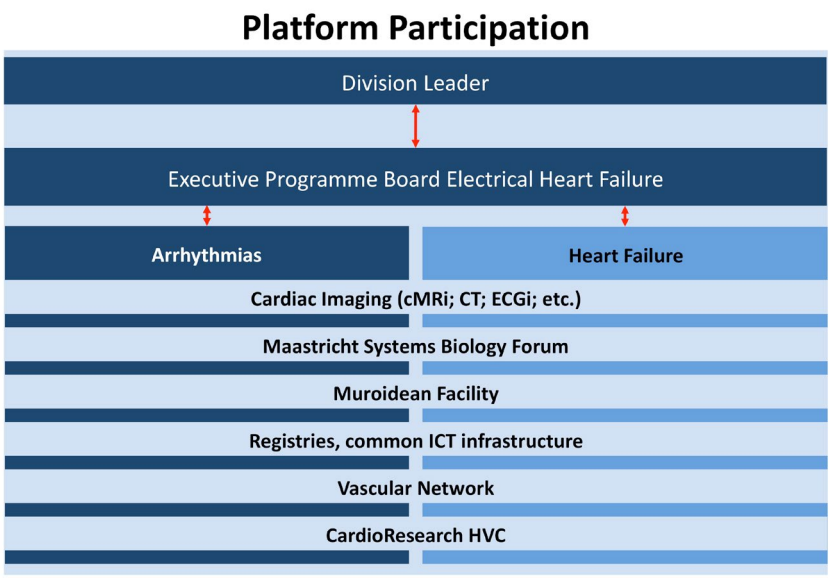
Interconnections in infrastructure, including the experimental lab (*'Groot Lab Cardiologie'*) were maintained after the last ERC and incorporate researchers across divisions and programmes. To enhance translational research within HVC, two clinical research officers have been appointed, Dr Kevin Vernooy and Prof. Hans-Peter Brunner-La Rocca, who head up the clinical divisions of arrhythmias and structural heart disease in HVC, respectively. They see to it that translational cell-to-bedside research finds its way easily to the clinical workspace. It should be noted that the clinical workspace for translational research is organised within

HVC's outpatient and inpatient clinics to serve all three Divisions: Blood, Vessels and Heart alike. The CardioResearch-HVC unit also continues to coordinate clinical research following GCP principles (good clinical practice), facilitating and performing patient registries and randomised clinical trials, all supported by the Clinical Trial Centre Maastricht (CTCM).

Integrators and talents
CARIM recognises that a research area thrives because of teams rather than chiefs. Therefore, much attention is given to the role and perspective of essential 'integrators' in Division Heart: co-PIs who are essential to continuity and quality of research standards and implementing research strategies, and who often have excellent teaching capabilities as well. In addition, focus is set on young talents, i.e. junior postdocs who may flow into a talent programme and eventually continue as Vidi laureates in a tenure track. Finally, career paths for junior talents are prepared, i.e. to get them ready to fly in 5-10 years. Junior talents are mainly found among excellent young (clinical) PhD graduates, who often combine a residency in cardiovascular medicine with postdoc grant activities.

Structured Brainstorm Meetings
Brainstorm Meetings are typically organised twice a year by the representatives of the individual programmes. These meetings are essential to promote cross-division and programme-overarching activities and collaborations in a so-called platform participation model (see figure 3), including joint publications and grant applications. For 'Complex Arrhythmias', process owners and session leaders are Dr Jordi Heijman, Dr Joost Lumens and Prof. Paul Volders; for 'Structural Heart Failure', process owners and session leaders are Dr Paula da Costa Martins, Dr Vanessa van Empel, and Prof. Stephane Heymans.

Figure 3 Platform participation of Division Heart

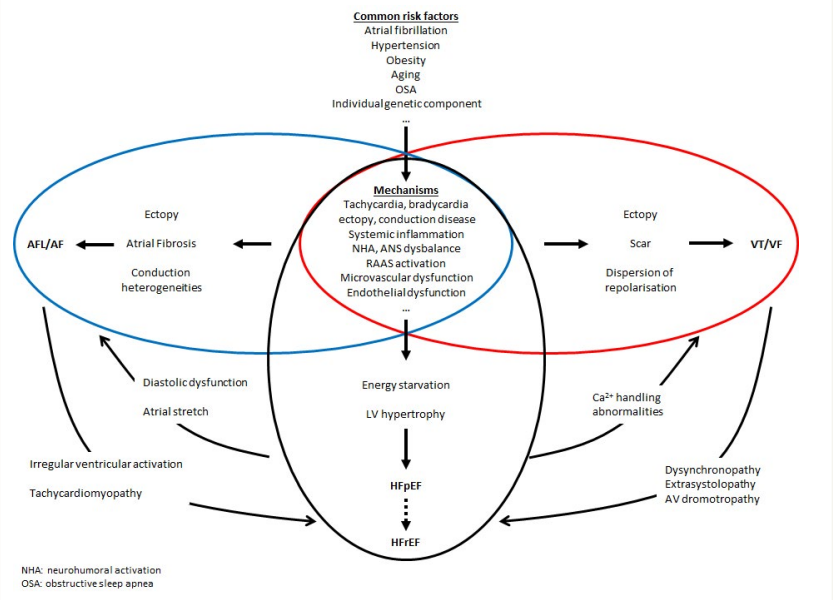


In summary, the restructuring of Theme II, now Division Heart, as described above, has yielded an integrated research environment, facilitating alignment and cooperation within and across divisions and programmes. Within Division Heart it has created a common identity shared by the individual programmes, and, it has stimulated content-driven interaction around the notion of 'electrical heart failure', supported by input from CARIM's Strategic Board, and fed by regular informative research meetings. Above all, our structure is flexible and supports opportunities for young talents to a maximum.

3.1.2 *Strategy and Research Area*

As mentioned above, Division Heart contains two major programmes, and involves eight PIs and several integrators. A brief perspective on PIs and their expertise is provided in Annex 9. To illustrate the overarching connections between arrhythmias and heart failure, Figure 4 indicates the various areas in which Division Heart researchers are active.

Figure 4 Research areas within Division Heart showing the interactions between arrhythmias, sudden death and heart failure.



Programme 5 Structural heart failure (PIs: Prof. Leon de Windt, Prof. Stephane Heymans, Dr Matthijs Blankesteijn, Prof. Tammo Delhaas)

The programme 'Structural heart failure' comprises the expertise of three groups.

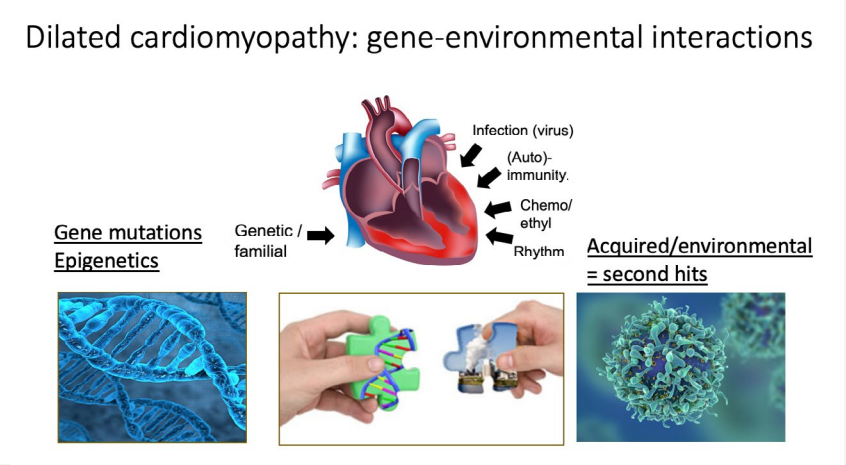
Non-coding RNAs and regenerative approaches in heart failure
The research in the group of Prof. Blanche Schoen, Dr Martina Calore, Dr Paula da Costa Martins and Prof. Leon de Windt is focussed on cardiac gene regulatory mechanisms by various classes of non-coding RNAs that control pathological cardiac remodelling, an early step towards heart failure. Chronic heart failure is a progressive disorder of the heart muscle that affects all vital organs, ultimately resulting in reduced quality of life. We study how non-coding RNAs (microRNAs, long non-coding RNAs) affect cardiac muscle cells and endothelial cells to understand how programmes of cellular differentiation and morphogenesis are affected in the processes leading to severe heart disease. The processes we study are evolutionarily conserved across diverse organisms. This conservation allows us to take a cross-species approach to dissect the precise workings of single genes in simple cellular systems, perform gain and loss-of-function experiments *in vivo* using mouse models of disease, and study the relevance of disease mechanisms in human heart disease. Our recent work focusses on stimulating the proliferation of already existing cardiomyocytes, suppressing pathological hypertrophy, and enhancing neoangiogenesis to achieve endogenous cardiac regeneration in the setting of ischaemic heart disease. Our ultimate goal is to dissect genetic pathways for the function of each of these cell types in distinct subtypes of heart failure, and to use this information to devise new RNA-based pharmacologic and genetic therapies, and translate this knowledge towards inherited and acquired heart diseases in humans.

The positioning of our research team between the Faculty of Sciences and Engineering (FSE) - that harbours expertise in technology-driven Regenerative Medicine - and the FHML allows us to create translational opportunities for discipline-focussed clinician-scientists within the Heart and Vessels research programmes 'Structural heart failure' and 'Regenerative and reconstructive cardiovascular medicine'. Several position papers of the European Society of Cardiology (ESC) and Heart Failure Association (HFA) on those topics were led by Prof. Leon de Windt.

Cardiomyopathies

One of the activities in this programme is the development of a clinical care programme and associated cohort of non-ischaemic cardiomyopathies, including dilated cardiomyopathy (DCM), myocarditis and HFpEF patients at HVC (> 1100 DCM with > 15 yrs FU, and > 200 HFpEF with 2 yrs FU). The research group of Prof. Stephane Heymans, Prof. Blanche Schroen, Dr Vanessa van Empel, Prof. Hans-Peter Brunner-La Rocca, Dr Marc van Bilsen, Dr Matthijs Blankesteijn and Dr Sander Verheule, in collaboration with Dr Mark Hazebroek and Dr Christian Knackstedt, brings together immunologists, microbiologists, geneticists and molecular cardiologists, clinical cardiologists and imagers to study the role of genetics, viruses, auto-immunity, and environmental factors in cardiomyopathies. Together with the Department of Genetics and Cell Biology (Prof. Han Brunner and Prof. Jan Glatz), the prognostic relevance of specific gene mutations, gene-environment interactions, molecular profiling of cardiac samples, and imaging for both outcome and reverse remodelling was uncovered. The clinical research within cardiomyopathies allows for a continuous translation between bench and bedside. Experimental studies within the programme address the role of secreted matrix proteins, non-coding RNAs, and metabolic pathways in non-ischaemic cardiomyopathies and myocarditis. Several position papers of the ESC and HFA on those topics were led by Prof. Stephane Heymans. With his team he has been work package (WP) leader in different clinical research projects related to cardiomyopathies and heart failure, chemotherapy induced cardiomyopathies (FP7 Hecatos), and biomarkers in heart failure (FP7-Homage). Furthermore, in 2018 the team was WP leader in the IMI project-CARDIA TEAM on cardiomyopathy diabetes mellitus, a consortium of international industry (Sanofi, Bayer and Lilly) and academic partners.

Figure 5 Representation of the translational research on acute myocarditis and dilated cardiomyopathy. Both result of the interaction between gene mutations, epigenetics (such as non-coding RNAs) and second hits (acquired diseases including chemotherapy, viral infection and auto-immunity)



Next to HFrEF and DCM, heart failure with preserved ejection fraction (HFpEF) and diastolic dysfunction is one of the main research topics by Prof. Blanche Schroen, Prof. Stephane Heymans, Dr Vanessa van Empel, Dr Marc van Bilsen, Prof. Hans-Peter Brunner-La Rocca, Prof. Arnoud van 't Hof and Dr Sander Verheule. This team has a broad scientific interest in cellular and molecular mechanisms in the diseased heart, including the role of immune cells, fibroblasts and the microvasculature in the progression towards HFpEF, the latter in collaboration with Dr Boy Houben and Dr Sébastien Foulquier (Vessels). In addition, the team

has expertise in metabolic determinants of cardiomyocyte function. These cellular aspects of heart failure development are investigated predominantly by focussing on the role of immune mechanisms, matrix proteins and non-coding RNAs within the different cell types. As a basis for the research conducted within the group, the impact of systemic diseases such as hypertension, diabetes and obesity on the heart is considered central to the progression towards heart failure and HFpEF.

Personalised approach to heart failure
Overarching endeavours to achieve individualised care of HF patients are reflected in HF research activities. On the one hand, this is reflected in various projects on biomarker research in the different areas of HF (Dr Sandra Sanders-van Wijk, Dr Vanessa van Empel, Prof. Stephane Heymans, Prof. Hans-Peter Brunner-La Rocca) with the ultimate aim to impact prevention, early detection and long-term treatment of HF on an individualised level, rather than merely predict outcome. On the other hand, these activities include the development of eHealth to individualise treatment and to enable patients to perform self-care including prescription of medication (Prof. Hans-Peter Brunner-La Rocca, Dr Christian Knackstedt). The collection of data accompanied by these activities additionally support the translational focus of Division Heart and electrical heart failure.

Intermezzo I – Electro-mechanical modelling as a bridge between Arrhythmia and Heart Failure programmes in 'Heart' (Dr Jordi Heijman, Dr Joost Lumens)
Several research areas within Division Heart are connected through state-of-the-art experimental and computational modelling to study the fundamental mechanisms of cardiac arrhythmias. In recent years, Dr Jordi Heijman's team (1 MSc, 3 PhDs) has focussed on the diverse pathophysiological roles of abnormal calcium handling in cardiomyocytes, for example identifying important atrial calcium-handling abnormalities in patients with atrial fibrillation or heart failure, and elucidating the distinct underlying molecular mechanisms in each subgroup. In addition, his work has revealed how calcium-dependent regulation of various ion channels has altered in disease and may promote arrhythmogenesis. At present, Dr Jordi Heijman aims to translate these insights into improved tailored risk prediction and treatment of patients through mechanistic models operating at different temporal (from microsecond to years) and spatial (from ion channel to patient) scales and through machine learning approaches. In addition, cutting-edge electromechanical computer models are being developed in close collaboration with the team of Dr Joost Lumens, enabling novel investigations into the link between arrhythmias and heart failure.

Pharmacology of Heart Failure
Another research focus is pharmacology of heart failure (Dr Matthijs Blankesteijn), i.e. signalling mechanisms controlling the remodelling of the heart in response to a pathological stimulus, such as pressure overload or ischaemia. In this context, we discovered the role of WNT signalling in processes associated with cardiac remodelling such as fibrosis and angiogenesis. We have developed a collection of peptide fragments of WNT to act as inhibitors of the signalling pathway. Studies from my group and others have shown that pharmacological inhibition of WNT signalling has a beneficial effect on infarct healing in case of smaller infarcts and a better preservation of cardiac function. The activation of cardiomyocyte regeneration in the border zone has recently been proposed as a potential mechanism, which is in line with the well-established role for WNT signalling in the control of stem cell differentiation. In the meantime, it has become evident that WNT signalling is also involved in other cardiovascular conditions, such as atherosclerosis and vascular calcification. These findings support the development of interventions in WNT signalling towards clinical application.

Programme 6 Complex arrhythmias (PIs: Prof. Uli Schotten, Prof. Harry Crijns, Prof. Paul Volders, Prof. Frits Prinzen, Prof. Tammo Delhaas)

The programme 'Complex arrhythmias' comprises the expertise of five groups.

Translational electrophysiology of atrial fibrillation
One of the research activities in the programme 'Complex arrhythmias' focusses on pathophysiological mechanisms of AF, ranging from changes in signalling pathways and structural alterations on the molecular and cellular level to electrophysiological mechanisms determined by high-density mapping in large animal models as well as in patients. (Prof. Uli Schotten, Prof. Monika Stoll, Dr Gudrun Antoons, Dr Sander Verheule, Dr Stef Zeemering, Dr Frans van Nieuwenhoven). Invasive and non-invasive characterisation of AF is being performed together with the Departments of Cardiology (Prof. Harry Crijns)

and Cardiothoracic Surgery (Prof. Jos Maessen) in order to identify targets for AF ablation and the development of better patient selection for rhythm control strategies. In collaboration with Dr Jordi Heijman individualised computer models of AF are developed to better understand and predict the efficacy of antiarrhythmic drugs (see Intermezzo I). In the large national CVON network RACE V the interaction between hypercoagulability and AF is explored in collaboration with the Departments of Biochemistry (Division Blood; Prof. Hugo ten Cate, Dr Henri Spronk), Cardio-thoracic Surgery (Division Vessels; Prof. Jos Maessen) and of Cardiology (Prof. Harry Crijns). Finally, a project on complex genetics of AF (Division Blood; Prof. Monika Stoll), investigating the role of gene expression alterations in several large cardiac tissue banks of clinically well characterised patients (Prof. Harry Crijns, Prof. Jos Maessen), has been added to the programme in order to link leading molecular mechanisms of AF to the clinical presentation of the patients, potentially enabling mechanism-based therapy of AF in the future.

Clinical atrial fibrillation
Clinical atrial fibrillation evaluates innovative concepts for the diagnosis and treatment of atrial fibrillation through focus on arrhythmogenic mechanisms and vascular risks of patients with AF (Prof. Harry Crijns, Prof. Uli Schotten, Prof. Hugo ten Cate, Dr Henri Spronk, Dr Jordi Heijman, Dr Bart Maesen, Prof. Jos Maessen, Dr Bas Bekkers). Studies using these concepts intend to personalise rhythm control interventions, including electrical cardioversion, catheter ablation and antiarrhythmic drug therapy (RACE 1-7 trials). Research now focuses on vascular mechanisms of arrhythmia progression (CVON RACE V network) and collaboration with Prof. Hugo ten Cate, Prof. Uli Schotten and Prof. Jos Maessen. In addition, studies currently focus on improving rhythm control strategies in recent-onset atrial fibrillation (RACE 7 ACWAS) within the national RACE 7 ACWAS network.

Sudden cardiac death
Cardiogenetic care of patients with inherited cardiomyopathies, including those with inherited arrhythmias, is a key focus at Maastricht UMC+ (HVC-CARIM, Department of Genetics and Cell Biology). Within this clinical-experimental environment, the active research projects focus on novel pathogenetic insights and improved management of ventricular arrhythmias and sudden cardiac arrest. Traditionally, the team consisting of Prof. Paul Volders, Dr Rachel ter Bekke, Dr Jordi Heijman and Prof. Monika Stoll has focussed on the electrophysiological characterisation of arrhythmia substrates in inherited cardiomyopathies and in acquired cardiac overload, compensated hypertrophy and failure. While these studies continue at the cellular, intact-animal and patient level, increasing research activities are directed to: (1) intracellular signalling pathways determining ion-channel function; (2) the genetic and genomic basis of cardiac arrhythmias; and (3) systems biology to integrate the basic molecular and functional determinants of arrhythmia syndromes with the clinical characteristics of individual patients, in order to provide better risk management and treatment.

Electromechanics of the heart
Research in electromechanics focusses on the prediction of the response to cardiac synchronisation therapy (CRT) in heart failure and the improvement of the application of CRT. (Prof. Frits Prinzen, Dr Kevin Vernooy, Dr Joost Lumens, Prof. Tammo Delhaas) Specific projects relate to vectorcardiographic predictors of CRT response; ECG-imaging for better analysis of substrate for resynchronisation and arrhythmias; His-bundle and LV septum pacing for resynchronisation; Resynchronisation for patients with dyssynchronous right ventricle: evidence from computer simulations and patients; Importance of biventricular resynchronisation: *in silico* and *in vivo* studies; Use of mechano-sensors in pacing leads and laser diffraction measurement of skin motion for optimisation of pacemaker therapy; Pacing-induced treatment of AV dromotropathy for treatment of heart failure; and intermittent pacing as a potential novel treatment of heart failure.

CardioVascular Systems Dynamics
The CardioVascular System Dynamics Research Group (CVSDRG), consisting of Prof. Tammo Delhaas, Dr Joost Lumens and Dr Jordi Heijman focusses on asynchronous electrical activation, vascular and myocardial structure-function relation, myocardial adaptation, and computer model-assisted diagnosis and treatment of cardiac failure, pulmonary hypertension and congenital heart diseases. Besides standard expertise, the CVSDRG uses the following techniques/models: 1) CircAdapt, a lumped parameter mathematical model of the human heart and circulation that enables real-time simulation of cardiovascular system dynamics in a wide variety of physiological and pathophysiological situations; 2) The CircAdapt model has been extended with submodels describing

CircAdapt

electromechanics on cellular, fibre, and organ level; and 3) Finite Element Model of the heart with left and right ventricle, simulating local stress and strain as a function of time.

Intermezzo II - Mechano-electrical modelling as a connector between Heart Failure and Arrhythmias programmes (Dr Joost Lumens, Dr Jordi Heijman)
Dr Joost Lumens' research team (2 MSc students, 5 PhD candidates and 1 postdoc) focusses on cardiac electro-mechanics and haemodynamics at different scales (cell-tissue-organ-system). Their translational research approach typically combines integrative computational modelling/simulation techniques with experimental and/or clinical data to gain mechanistic insight in various cardiac diseases and their treatments. This approach has been successfully applied to clinical and fundamental research questions in the fields of 1) complex arrhythmia (arrhythmogenic cardiomyopathy), 2) dyssynchronous heart failure and its treatment with cardiac resynchronisation therapy, 3) diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF), and 4) right ventricular failure due to pulmonary hypertension and/or valvulopathies. An overarching theme is patient-specific modelling, i.e. the integration of patient-specific diagnostic information into a personalised model of a patient's heart. This virtual patient simulation technology can be seen as a layer of artificial intelligence on top of conventional diagnostic data, facilitating personalised medicine by providing insight in the disease substrate of a patient, and by enabling *in silico* therapy optimisation and outcome prediction. Our medical engineering skills and philosophy enables us to bridge the different yet complementary disciplines of Computer Science and Engineering, Physiology, and Clinical Cardiology. Our line of research typically connects the two programmes in this division.

3.1.3 Specific targets of the past six years

Overall developments that are relevant for Division Heart have been described in Part A, 1.3, and are not repeated here. In general, the Division shows a stable picture with high visibility and impact of its research and teaching activities.

The research area of Division Heart has changed, due to focussing on complex arrhythmias and cardiomyopathies, in particular thick and thin heart HF. This change went hand in hand with important steps in the alignment of HVC and CARIM, and the restructuring of cardiology and cardiothoracic surgery in HVC, including formation of the clinical divisions of arrhythmias and structural heart disease, the latter incorporating cardiomyopathies, in particular HFpEF and idiopathic dilated cardiomyopathy.

To enhance focus and stimulate collaborations, several multidisciplinary meetings under the title 'Informative and Brainstorming Meeting on Current and Future Projects' were held at Division Heart, organised by Prof. Stephane Heymans. These meetings also involved the other CARIM Divisions, as well as groups outside CARIM. They were very fruitful, yielding important new internal collaborations and scientific projects, and at the same time formed the basis for new external collaborations in CVON as well as European. Specific topics included 'Cardiomyopathy and HFpEF Unit' in 2016, 'Translational Cardiomyopathy Meeting' in 2018 and 'Experimental microcirculation' in 2018.

Since the last ERC, Division Heart contracted several talented senior translational scientists, such as Dr Joost Lumens, Dr Jordi Heijman and Dr Stef Zeemering. Interdisciplinary collaborations are numerous and have increased substantially since the External Review in 2014, see Figure 4.

3.2 Description of the Research programme's organisation, composition and financing

3.2.1 Organisation and embedding of the Research programme

Division Heart is one of three Divisions within CARIM. Leader Prof. Harry Crijns represents Division Heart in the Executive Board of CARIM. Division Heart established shared leadership with staff members with excellent scientific standing taking into account and aiming for fair distribution of basic/clinical disciplines, diversity/gender, and various stages of career track. The board now consists of Prof. Harry Crijns, Prof. Frits Prinzen, Prof. Blanche Schroen, Prof. Stephane Heymans, Prof. Paul Volders and Prof. Uli Schotten. Close collaboration exists with the other Divisions within CARIM, Maastricht UMC+ and other research Schools.

3.2.2 Composition

The number of staff in Division Heart has decreased over the past six years. In 2013, Division Heart employed 101 researchers (88.8 fte, including Maastricht UMC+ staff), of which 33 PhD candidates. Furthermore, the Division employed 17.7 fte support staff in 2013. At the end of 2018, the numbers were significantly lower, as a result of a decrease in direct funding; 86 researchers (50.0 fte), of which 44 PhD candidates; and 13.2 fte support staff. The scientific staff paid for by the academic hospital however, has increased from 1.0 fte in 2013 to 5.0 fte in 2018 (in 2016: 6.8 fte).

Table 1 Research staff at Division level

	2013		2014		2015		2016		2017		2018	
HEART	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**	**#**	**fte**
Scientific staff FHML (1)	31	16.8	32	17.4	28	14.2	28	11.7	29	11.0	26	10.7
Scientific staff academic hospital	12	1.0	16	4.2	13	5.3	17	6.8	15	6.0	14	5.0
Post-docs (2)	25	22.1	16	15.0	15	13.4	23	17.4	18	13.8	10	8.3
Internal PhD candidates (3)	33	31.3	36	33.3	30	29.5	43	39.9	45	43.2	45	45.0
Total research staff	**101**	**71.2**	**100**	**69.9**	**86**	**62.4**	**111**	**75.8**	**107**	**74.0**	**95**	**69.0**
Support staff (research) (4)	27	17.7	20	14.6	21	14.5	18	15.6	17	15.1	13	81.6
Support staff (managerial) (5)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Total staff incl academic hospital	**128**	**88.9**	**120**	**84.5**	**107**	**76.9**	**129**	**91.4**	**124**	**89.1**	**108**	**81.6**
Total staff excl academic hospital	**116**	**87.9**	**104**	**80.3**	**94**	**71.6**	**112**	**84.6**	**109**	**83.1**	**94**	**76.6**
External PhD candidates (6)	19		16		30		42		45		46	
Visiting fellows/professors (7)	8		11		7		9		8		12	

#: Number of persons active on the Research programme research activities on 31-dec of any year/average MJE (men year equivalents
fte: Sum of actual fte-factors (in fulltime equivalents) labelled on the Research programme research activities on 31-dec on any year/average
Note 1: Comparable with WOPI-categories HGL, UHD and UD; tenured and non-tenured staff appointed at the FHML
Note 2: Comparable with WOPI-category 'Onderzoeker' (1, 2, 3, 4), with completed PhD, not belonging to scientific staff (with WOPI-categories HGL, UHD and UD)
Note 3: Standard PhD (employed)
Note 4: All support staff working on research (research assistants, lab technicians, and other support staff not working at the management office)
Note 5: Support staff working at the School's management office including the scientific director
Note 6: External PhD (externally or internally funded but not employed)
Note 7: Visiting fellows are researchers/professors who visit the Research programme for a period of typically one week up to three months to work with Research programme staff members.

3.2.3 *Financing*

The total labelling on research funding in Division Heart has decreased from 70.15 fte to 63.95 fte mainly due to a decrease in direct funding (11.40 fte in 2018 compared to 22.80 fte in 2013). The amount of contract research however, has increased over the last six years (34.95 fte in 2013 compared to 42.55 fte in 2018). It is clear that an increasing proportion of Division Heart's funding (68% in 2013 to 77% in 2018) depends on external sources (research grants and contract research together constituted 68% of funding in 2013 and 77% in 2018), which may be considered a natural development in our times. The total expenditure remained relatively stable over the last six years.

Table 2 Funding at Division level

HEART		**2013**		**2014**		**2015**		**2016**		**2017**		**2018**
Funding	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**	**fte**	**%**
Direct funding (1)	22.80 (4)	33	24.40	37	16.20	28	15.50	22	12.60	19	11.40	18
Research grants (2)	12.40	18	8.30	13	10.00	17	11.00	16	12.50	18	10.00	16
Contract research (3)	34.95	50	33.15	50	31.85	55	42.48	62	42.90	63	42.55	67
Total funding	**70.15**	**100**	**65.85**	**100**	**58.05**	**100**	**68.98**	**100**	**68.00**	**100**	**63.95**	**100**
Expenditure	K€	%	K€	%	K€	%	K€	%	K€	%	K€	%
Personnel costs	3,356	58	3,302	62	2,753	61	3,188	59	3,425	59	2,931	64
Other costs	2,480	42	1,982	38	1,728	39	2,228	41	2,349	41	1,661	36
Total expenditure	**5,836**	**100**	**5,284**	**100**	**4,481**	**100**	**5,416**	**100**	**5,774**	**100**	**4,592**	**100**

Note 1: Direct funding by FHML/ Maastricht University ('basis financiering'/lump sum budget).
Note 2: Research grants obtained in national scientific competition (e.g. grants from NWO, ZonMw and KNAW)
Note 3: Research contracts for specific research projects obtained from external organisations, such as industry, governmental ministries, European organisations, including ERC, and charity organisations
Note 4: The funding in fte includes the total research staff but excludes the academic hospital-staff

3.3 Research Quality

3.3.1 *Demonstrable research products for peers: a description of the research output*

The number of publications within this Division shows a natural fluctuation throughout the last six years, with a steady production of refereed articles with IF (SCI/SSCI), generally regarded as the most important type of publications. The Division's policy is to reduce the number of 'other refereed articles' for lack of robust impact compared to 'refereed articles with IF (SCI/SSCI)'. The number of PhD theses varies largely between 15 and 20, with a low of eight in 2014, and a high of 23 theses, two years later. The ratio between the average yearly number of active internal PhD candidates (Table 1) and the average number of theses per year is a reassuring 2.29 (37.3/16.3).

Table 3 Main categories of research output at Division level (date: 7 June 2019)

	2013	2014	2015	2016	2017	2018
HEART						
Refereed articles (SCI/SSCI) (1)	209	214	236	203	185	227
Other refereed articles (2)	41	43	54	42	96	62
Total refereed articles (3)	**250**	**257**	**290**	**245**	**254**	**289**
Books	n.a.	1	9	1	1	n.a.
Book chapters	1	5	2	4	7	1
PhD theses	14	8	21	23	14	18
Total publications	**265**	**271**	**322**	**273**	**276**	**308**

Note 1: Refereed articles ('wi-1') published in an international journal, which is mentioned in the (Social) Science Citation Index (SCI or SSCI) of Journal Citation Reports (JCR) ('wi-1')
Note 2: Refereed articles published in an international journal, not included in the SSI/SSCI ('wi-2'), Editorial Materials, Letters to the editor and refereed articles in a national (Dutch) journal ('wn')
Note 3: Total refereed articles is the sum of the refereed articles (SSI/SSCI) and the other refereed articles

3.3.1.1 Most important scientific publications

The following publications have been selected because of their high impact and/or representation of the research foci of the Division. The three most important papers published by Division Heart, by Hazebroek et al., Spronk et al. and Lumens et al., are not included in this list; they can be found in Part A.

Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk

ter Bekke RMA, Haugaa KH, **van den Wijngaard A**, Bos JM, Ackerman MJ, Edvardsen T, **Volders PGA**. Electromechanical window negativity in genotyped long-QT syndrome patients: relation to arrhythmia risk. Eur Heart J. 2015;36:179-186 IF 15.20

Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure

Lumens J, Ploux S, **Strik M**, Gorcsan III J, Cochet H, Derval N, Strom M, Ramanathan C, Ritter P, Haïssaguerre M, Jaïs P, **Arts T**, **Delhaas T**, **Prinzen FW**, Bordachar P. Comparative electromechanical and hemodynamic effects of left ventricular and biventricular pacing in dyssynchronous heart failure. JACC 2013; 62: 2395-403 IF 14.09

MicroRNA-221/222 Family Counteracts Myocardial Fibrosis in Pressure Overload-Induced Heart Failure

Verjans R, Peters T, Beaumont FJ, **van Leeuwen R**, van Herwaarden T, **Verhesen W**, **Munts C**, **Bijnen M**, Henkens M, Diez J, **de Windt LJ**, **van Nieuwenhoven FA**, **van Bilsen M**, Goumans MJ, **Heymans S**, González A, **Schroen B**. MicroRNA-221/222 Family Counteracts Myocardial Fibrosis in Pressure Overload-Induced Heart Failure. Hypertension. 2018 Feb;71(2):280-288. doi: 10.1161/HYPERTENSIONAHA.117.10094. Epub 2017 Dec 18. PMID: 29255073 IF 6.86

Nfat and miR-25 cooperate to reactivate the transcription factor Hand2 in heart failure

Dirkx E, Gladka MM, Philippen LE, Armand AS, Kinet V, Leptidis S, El Azzouzi H, Salic K, Bourajjaj M, da Silva GJ, Olieslagers S, van der Nagel R, de Weger R, Bitsch N, Kisters N, Seyen S, Morikawa Y, Chanoine C, **Heymans S**, **Volders PG**, Thum T, Dimmeler S, Cserjesi P, Eschenhagen T, **da Costa Martins PA**, **De Windt LJ**. Nfat and miR-25 cooperate to reactivate the transcription factor Hand2 in heart failure. Nat Cell Biol. 2013 Nov;15(11):1282-93. IF 20.06

Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias

Verdonschot JAJ, **Hazebroek MR**, Derks KWJ, Barandiarán Aizpurua A, Merken JJ, Wang P, Bierau J, **van den Wijngaard A**, Schalla SM, Abdul Hamid MA, **van Bilsen M**, **van Empel VPM**, **Knackstedt C**, **Brunner-La Rocca HP**, **Brunner HG**, Krapels IPC, **Heymans SRB**. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J. 2018 Mar 7;39(10):864-873 IF 23.43

WNT Signaling in Cardiac and Vascular Disease

Foulquier S, Daskalopoulos EP, Lluri G, Hermans KCM, Deb A, **Blankesteijn WM**. WNT Signaling in Cardiac and Vascular Disease. Pharmacol Rev. 2018; 70:68-141 IF 18.97

3.3.2 *Demonstrable use of research products by peers*

Refereed articles of Division Heart were cited 21,776 times in the period 2013-2018, as calculated by the University Library Maastricht. 1.78% of these publications appeared in Top 1% journals and 18.84% was published in Top 10% journals.

Table 4 provides an overview of the bibliometric statistics of Division Heart, as calculated by the University Library Maastricht (based on refereed articles), including the number of articles (P); the average (mean) number of citations per paper (CI); the citation impact (citations per paper) normalised for subject, year and document type (CNCI); the citation impact (citations per paper) normalised for journal, year and document type (JNCI).

These data show that the CNCI (the crown indicator) of Division Heart has been around 1.9 during the last 8 years, meaning that publications of Division Heart are cited about 1.9 times more frequent than the world average. Furthermore, the JNCI is between 1.2 and 1.5 showing that the research unit publishes in journals with a relatively high impact. The H-index of the PIs in Division Heart can be found in Part A and ranges from 28 to 100.

Table 4 Bibliometric statistics of Division Heart 2013-2018 (refereed articles)

	P	CI	CNCI	JNCI
2013 - 2016	857	23.32	1.84	1.22
2014 - 2017	845	18.11	1.84	1.25
2015 - 2018	881	11.47	1.92	1.45

3.3.3 *Demonstrable marks of recognition from peers*

Research grants awarded to individuals
Researchers in Division Heart have been successful in obtaining several prestigious personal grants funded by for example the NHS Dr E. Dekker programme and the Innovational Research Incentives Scheme of NWO (see Part A, page 20).

Most important scientific awards (see Annex 4 for a full overview)
Researchers in Division Heart have been successful in obtaining scientific awards for their research. The most important awards that were received between 2013 and 2018 are listed below:

Prof. Leon de Windt received the Outstanding Achievement Award of the ESC Council for Basic Cardiovascular Science and the Galenus Research Prize.

Prof. Uli Schotten was awarded the Albert Frankel Award of the German Society of Cardiology in 2016. He received the Award for the discovery of cellular mechanisms underlying atrial fibrillation and the development of diagnostic methods and new therapeutic approaches for this arrhythmia.

Dr Sébastien Foulquier received a Young Investigator Award from the European Council for Cardiovascular Research for his presentation entitled 'Hypertension-induced vascular cognitive impairment: the microglial culprit?' in 2017.

Stephane Heymans was awarded the Outstanding Achievement Award of the European Society of Cardiology for Basic Cardiovascular Research in 2015, and the Doctor Léon Dumont Prize from the Belgian Society of Cardiology in 2013.

Bart Spronck was the Winner of the Maastricht University Valorization Award 2016 awarded by Maastricht University; and received an Artery Career Development Award from the Artery Society in 2017

Harry Crijns received the Wenckebach Lecture Award in 2015.

Mark Hazebroek received a Young Investigator Award Clinical Research during the annual meeting of the European Heart Failure Association of the ESC. He presented his work on the 'Prognostic relevance of gen-environmental interactions in dilated cardiomyopathy patients: applying the MOGES classification'. His PhD thesis was awarded as the best at CARIM in 2017.

Most important invited lectures (see Annex 5 for a full overview)
Researchers in Division Heart have been invited to present lectures at important international conferences such as meetings of the European Society of Cardiology (Prof. Leon de Windt, Prof. Harry Crijns, Prof. Stephane Heymans, Dr Paula da Costa Martins, Prof. Blanche Schroen, Prof. Hans-Peter Brunner-La Rocca, Dr Vanessa van Empel, Dr Jordi Heijman, Prof. Paul Volders), the ECCR (Dr Matthijs Blankesteijn), the Gordon Research Conferences (Prof. Uli Schotten, Prof. Paula da Costa Martins, Dr Sander Verheule), Keystone conference (Prof. Leon de Windt, Prof. Stephane Heymans, Dr Paula da Costa Martins) and EHRA-EUROPACE (Dr Joost Lumens, Prof. Frits Prinzen, Dr Jordi Heijman, Prof. Paul Volders).

Most important memberships of scientific committees (see Annex 6 for a full overview)

Name	Scientific Board	Character of membership (chair, board member)	Period
Harry Crijns	Dutch Heart Foundation	Chair	2014-present
Harry Crijns	Supervisory Board of the Netherlands Heart Institute	Chair	2001-present
Leon de Windt	Selection Committee member Dutch Heart Foundation Dr. Dekker stipend Medical Doctor in training to specialist	Member	2012-2018
Leon de Windt	Working group of Myocardial Function of European Society of Cardiology	Nucleus member	2012-2016
Paula da Costa Martins	NWO Rubicon grant Committee	Member	2015-present
Joost Lumens	ESC working group on eCardiology	Chair	2018-2020
Marc van Bilsen	NWO Veni Committee	Member	2012-2016
Blanche Schroen	NHS Dekker committee junior post-doc and Physician in specialty training	Member	2013-present
Uli Schotten	Steering committee of the German Network of Competence Atrial Fibrillation (AFNET)	Member	2011-present
Frits Prinzen	EHRA Scientific Initiatives Committee	Member	2017-present
Stephane Heymans	NWO Vidi committee	Member	2016-present
Stephane Heymans	European Heart Failure Association	Board Member	2014-present
Stephane Heymans	European Heart Failure Association, basic science section	Chair	2018-present
Jordi Heijman	Working group 'Cellular Electrophysiology', German Cardiac Society	Nucleus member	2016-present
Paul Volders	European Heart Rhythm Association	Board Member	2011-2018
Hans-Peter Brunner-La Rocca	Working group heart failure of the Dutch Society of Cardiology	Board Member	2014-present

* NWO: The Netherlands Organisation for Scientific Research; EHRA: European Heart Rhythm Association; NHS: Dutch Heart Foundation

Most important memberships of editorial boards, editorships (see Annex 7 for a full overview)

Name	Journal	Character of membership (editor, member or guest editor	Period
Paula da Costa Martins	PLoS ONE	Editor	2012-present
Joost Lumens	Netherlands Heart Journal	Associate Editor	2017-present
Stephane Heymans	Circulation	Guest editor	2017-present
Harry Crijns	European Heart Journal	Member	2010-present
Jordi Heijman	International Journal of Cardiology - Heart & Vasculature	Associate Editor	2017-present
Leon de Windt	Cardiovascular Research; European Journal of Heart Failure, Journal of Molecular Cellular Cardiology; International Journal of Cardiology – Heart & Vasculature; Biochemical Pharmacology	Editorial board member	2006-present
Leon de Windt	Non-coding RNA Research	Associate Editor	2017-present
Tammo Delhaas	Pediatric Cardiology	Member	2012-present
Hans-Peter Brunner-La Rocca	European Heart Journal	Editorial board member	2010-present

3.3.4 *In conclusion: Quality*

Division Heart has a large number of publications on clinical and preclinical arrhythmias and heart failure, most with a strong translational character. Researchers have been successful in attracting funding as well as PhD candidates. All researchers have a robust international reputation within strong networks.

3.4 Relevance to society

3.4.1 *Demonstrable research products for societal target groups*

Media exposure of Division Heart was mostly centred around the research of Prof. Paul Volders and Dr Rachel ter Bekke (Worm Study), Prof. Leon de Windt (microRNAs), Prof. Stephane Heymans (myocarditis) and Dr Guido Haenen (antioxidants) and consisted of interviews and articles in newspapers and television interviews. Furthermore, Prof. Uli Schotten has contributed to several opinion papers about atrial fibrillation management.

3.4.1.1 Most important societal publications/outputs

MyAF
AF manager

Uli Schotten and Harry Crijns: CATCH ME applications MyAF and AF manager, providing guidance for patients with atrial fibrillation and a platform for interaction with their care providers; in addition, the platform provides a repository for big data analyses. These apps are the official European Society of Cardiology apps for health care professionals and AF patients. They have been designed as part of the CATCH ME projects and the ESC has decided to further maintain and develop these apps in the context of future projects.

Harry Crijns and Vanessa van Empel: '*Hartsvrienden*' *('bosom friends'*), an interactive patient journal, 3 times per year.

https://kids.frontiersin.org/article/10.3389/frym.2019.00065

Henry Sutanto and Jordi Heijman: 'The role of calcium in the human heart: With great power comes great responsibility' on heart rhythm disturbances in 'Frontiers for Young Minds', a journal aiming to educate children and teenagers about science (https://kids.frontiersin.org/article/10.3389/frym.2019.00065).

Jordi Heijman: Lecture to educate primary school children about heart rhythm disorders at two different primary schools in Maastricht (60 participants each), as part of the Maastricht University KidzCollege series.

CircAdapt

Joost Lumens and Tammo Delhaas: The educational version of the CircAdapt model of the human heart and circulation (freely downloadable) is an example of educational valorisation. The model is used for teaching cardiovascular physiology and pathophysiology to >1000 medical students of Maastricht University per year, but also in Medical School Curricula at Radboud University Nijmegen, Utrecht University, University of Utah, Stellenbosch University, University of Cali, Duke University, University of Copenhagen, and more (>6000 external downloads between 2013-2018). In addition, the open-source research version of the CircAdapt model is being used for basic cardiovascular science projects at several renowned international universities, such as Bordeaux University, University of Graz, King's College, University of Utah, Washington University in St Louis, and more.

Frits Prinzen: Corelab ECG and vectorcardiography for clinical studies on CRT (Abbott: 40.000 ECGs; and Biotronik: 500 ECGs).

Kevin Vernooy and Frits Prinzen: organisation of Congress on Electrical Management of Heart Failure (Maastricht, 2018).

Matthijs Blankesteijn: editor of 'Medicines', a popular scientific magazine on drug research in the Netherlands, until 2016.

3.4.2 *Demonstrable use of products by societal groups*

Patents

Patent	Application	Date	Scientist
Method and apparatus for optimisation of cardiac resynchronisation therapy using vectorcardio-grams derived from implanted electrodes	Method and apparatus	11-9-2013	F. Prinzen, K. Vernooy
Electrogram-based control of cardiac resynchronisation therapy	Method	31-05-2017	F. Prinzen, K. Vernooy
Integrated assessment of electrical activation and myocardial strain	Method	04-06-2018	F. Prinzen, A. Auricchio
Biomarkers in the selection of therapy of heart failure	Markers	04-12-2013	H-P. Brunner- La Rocca
Methods for the treatment or prevention of eating disorders, overweight or obesity	Method	09-03-2016	L. de Windt
Marker for statin treatment stratification in heart failure	Marker	26-02-2016	H-P. Brunner-La Rocca
MicroRNAs for the treatment of heart diseases	Treatment	18-08-2016	L. de Windt; P. da Costa Martins
Circulating ESM-1 (Endocan) in the assessment of atrial fibrillation	Biomarker	04-08-2018	U. Schotten
Circulating Spon-1 in the assessment of atrial fibrillation	Biomarker	22-08-2018	U. Schotten
Circulating FGFBP-1 in the assessment of atrial fibrillation and the prediction of stroke	Biomarker	24-08-2018	U. Schotten
Circulating TFPI-2 in the assessment of atrial fibrillation and anticoagulant therapy	Biomarker	16-08-2018	U. Schotten

Spin-offs

The following spin-off companies were founded between 2013 and 2018:

Mirabilis Therapeutics

Mirabilis Therapeutics (Prof. Leon de Windt) is a drug development company, dedicated to the discovery and development of innovative products in the field of cardiovascular diseases. Our front runner product is an antisense oligonucleotide indicated against heart failure. Mirabilis Therapeutics has established *in vivo* proof of concept for its three most advanced antisense oligonucleotides and multiple follow-on products under evaluation. All this is based on a strong technology and IP position. Mirabilis Therapeutics focusses on developing microRNA therapeutics, drugs that target aberrantly expressed microRNAs in disease areas of high-unmet medical need. By regulating microRNA function, the use of antisense oligonucleotides as microRNA inhibitors for the treatment of cardiovascular diseases produces therapeutically beneficial results by restoring proper target gene regulation. Since current heart failure pharmacotherapy only has a marginal impact on long-term prognosis of the disease, there is both room and need for the development of innovative bio-therapeutics. Development of microRNA-modulating drugs also requires optimisation of their chemical and pharmacological properties. Mirabilis Therapeutics' scientists have vast experience in pharmacologically modulating microRNAs using oligonucleotides, pre-clinical and clinical development, formulation and regulatory affairs.

YourRhythmics BV

In 2016, the spin-off YourRhythmics BV was founded by Prof. Uli Schotten. YourRhythmics develops hardware and software solutions for non-invasive characterisation of cardiac electrical activity, particularly atrial fibrillation. The vision of the company (CEO Patric Machiels) is to contribute to individualised therapy of cardiac arrhythmias by improving non-invasive identification of ablation targets and improvement in patient selection.

3.4.3 Demonstrable marks of recognition by societal groups

As demonstrated in Part A, researchers in Division Heart contribute extensively to (inter)national clinical guidelines and participate in committees responsible for (inter)national (health) policy reports. (See Annex 10 and 11)

3.4.4 Narrative and anecdotal information

CARIM website

For the narratives and anecdotal information, we refer to the overview of narratives collected from the four programmes, which are available at the CARIM website.

3.5 Research programme specific information on PhD programme, Talent Policy, scientific integrity and diversity

See Part A.

3.6 Trends, SWOT and strategic plans

3.6.1 Trends

Division Heart has good earning power and a large number of high impact papers, and this is expected to continue since we invest in young talent, in collaborations across programmes and Divisions, and in collaborations within our national and international networks. Adaptation to the FHML policy of emphasis on the number of PhD candidates as a funding criterion has been successful, as has been our strategy of interdisciplinary collaboration. Infrastructure (e.g. connections between CARIM Departments of Physiology, Biochemistry and Haematology with HVC) is excellent, and a new animal facility is being built. CARIM has taken up the implementation of IPS technology and recognises the impact of CRISPR-Cas based research and interventions. Investing time and money in large externally based databases (e.g. UK biobank, sleep apnea databases including MrOs, SAVE, SERVE-HF) is recognised as an important trend. There are continuing weaknesses (see SWOT below), but most of these are being addressed by Division Heart and CARIM.

Further strengthening of translation and integration: Translational research with impact on people and patients is considered very important by patient associations, funding organisations and society as a whole. A central ambition of recent research projects in Division Heart is therefore to identify the relative contribution of individual disease mechanisms to the clinical presentation of patients. In this respect, a shift from mono-level, small-scale studies to multidisciplinary approaches that span various scales, all the way from molecule to population, is an important development, also pursued by Division Heart. Integration of the different information modalities seems critical for bridging the translational gap between the individual molecular mechanisms and the manifestation of a disease at the organ level or the clinical presentation of a patient. This is particularly relevant for diseases with diverse aetiologies and mechanisms but a relatively uniform symptomatology, such as heart failure and complex arrhythmias. For this reason, all research projects (see e.g. the projects outlined in section 1.2) show a strong element of multidisciplinary collaboration and combine non-invasive diagnostics, advanced imaging, or computer models with insights into molecular and cellular mechanisms of the disease.

Reducing animal experimentation: An important trend is the reduction of animal experiments, especially in the Western world. Following that trend, Division Heart has committed itself to further reducing the number of animal experiments. Although animal experimentation still is a major source of new pathophysiological insights and offers irreplaceable opportunity to test new therapeutic interventions, viable alternative approaches have to be implemented. Firstly, while shifting from generalised functional concepts to studying individual physiological responses and disease mechanisms, functional assays need to be individualized. By definition, the inter-individual variability needs to be addressed in human subjects or patients rather than in standardsed animal models. Secondly, our society increasingly demands stricter regulations in animal experimentation and the Dutch government has expressed its ambition to reinforce the Netherlands' role as world leader in animal-free innovation. The main pillars of CARIM's strategy to work towards more animal-free experimentation are to focus more on patient-oriented research, application of computer models where applicable, and the development of novel isolated cell and organ functional assays (e.g. organoids). Particularly focussing more on patient-oriented research with man as the ultimate model to study is well supported by the strong focus of Division Heart on translational research and also implies involvement of basic scientists in clinical studies and clinicians in basic research programmes as part of a multidisciplinary research continuum.

Education: Professional societies such as the European Society of Cardiology (ESC) recognise the importance of training future leaders in respective areas of cardiological expertise, thus bridging a generation gap. In addition, the ESC expects the gender and geographical gaps to be closed in the foreseeable future. In addition, clinicians will be highly sought after for leading positions in hospital or governmental environments. The Maastricht based 'Diploma of Advanced Studies in Cardiac Arrhythmia Management' (DAS-CAM) is an illustrative example of this development, providing an integrated training opportunity in the field of cardiac arrhythmias. DAS-CAM is a collaboration between Maastricht University, the European Heart Academy (EHA) and the European Heart Rhythm Association (EHRA) and integrates state-of-the-art knowledge of cardiac arrhythmia management, with leadership skills, biostatistics and health technology assessment. Researchers from Division Heart already play a major role in the DAS-CAM programme, with four CARIM principal investigators serving as anchorpersons and several CARIM researchers involved as members of the Scientific Programme Committee. In addition, a number of participants from the first DAS-CAM cohort will continue their affiliation with CARIM by means of a PhD research project.

Imaging: The field of cardiovascular imaging experiences an exponential growth in terms of new modalities, new applications, technological advancements and complexity. As a result, investments in dedicated and well trained cardiovascular imagers and physicists are needed to guarantee enforceability. Advanced cardiovascular imaging is essential for 1) clinical cardiovascular medicine and 2) obtaining a better understanding of the pathophysiology and mechanisms of cardiovascular disease.

Cooperation with device industry: The cooperation with industry - including companies like Philips and Medtronic - is becoming increasingly important for research institutes and investigators. In projects in the area of technology development, Division Heart in CARIM covers the biological part, i.e. from cell to technology at the bedside whilst companies provide the technical infrastructure. An important example is the development of a left ventricular assist device programme (LVAD) in which Division Heart will provide the biological know-how. There are many more examples not listed here.

Machine learning, big data: Statistical models already play a central role in the clinical management of arrhythmias and heart failure, for example to assess stroke/bleeding risks. The significant increase in data availability, including technological advances in wearables, home-monitoring systems, and non- or minimally-invasive diagnostics, as well as advances in machine-learning techniques to derive models has promoted a strong interest in big data. Division Heart can take advantage of this trend through ongoing collaborations within the HVC Business Information Management unit and the Department of Data Science and Knowledge Engineering (see 'opportunities', below). In these databases, machine learning will be used to identify prediction models for cardiovascular events, success rates of interventions and outcomes.

3.6.2 The SWOT analysis

STRENGTHS

- Division Heart is tightly embedded in a network of multiple strong research collaborations within the Division, between CARIM Divisions, within the University, nationally, and internationally. This is achieved by scientific excellence, communicative skills and the ability of the current PIs to preserve and further develop the scientific heritage of the founder generation (Wellens, van der Vusse, Reneman, Allessie);
- Functional integration of physiology, biomedical engineering, cardiothoracic surgery and cardiology provides innovative translational research;
- Excellent connection of the Departments of Physiology, Biomedical Engineering and Biochemistry to the Departments of Cardiology and Cardiothoracic Surgery at HVC, through alignment of HVC plans to the needs of CARIM Division Heart and Blood 2020, thus robustly accommodating translational cell-to-bedside research;
- Very good representation in DCVA and CVON projects (active CVON projects, representation in Scientific Advisory Board and committees of the Dutch Heart Foundation, representation in the Supervisory Board of the Netherlands Heart Institute, formerly known as ICIN);
- Very strong representation in the European scientific community on multiple levels (EU funds, ESC guideline committees, ESC organisation teams of consensus conferences, European educational programmes, multiple international conferences with CARIM as local host);
- The Division is renowned for its expertise in cardiac arrhythmias, electrical management of heart failure, molecular basis of heart failure, cardiogenetics, imaging and modelling of cardiovascular diseases;
- Prompt implementation of emerging research trends (AF-HF link, AF and dementia, pleiotropic effect of coagulation factors, ILR monitoring to characterise atrial fibrillation);
- Collaborations across Divisions and Departments, in particular with Division Blood (haematology/biochemistry, complex genetics) and Division Vessels (Internal Medicine, Radiology); and the Department of Genetics at Maastricht UMC+;
- Excellent connection to patient communities (through Health Foundation Limburg and other national patient initiatives).

WEAKNESSES

Limited resources to implement newest research protocols and procedures into clinical workflow on a routine basis;
Expertise in electrophysiology could be better integrated in imaging modalities such as CT, echo or results from navigation systems.

OPPORTUNITIES

- Increasing collaboration between computer modellers in the field of cardiac mechanics and electrophysiology;
- Expansion of Physiology research in the area of microcirculation;
- Expand ties with The Maastricht Study;
- Broadening research towards Division Vessels for HFpEF research with focus on microcirculation;
- Broadening of the scope of cardiac research programmes towards neurosciences, e.g. on cognitive decline in HF and AF;
- Boost of molecular sciences by the establishment of the Faculty of Science and Engineering;
- BIM and Datahub building up infrastructure for automated data collection for clinical epidemiological and translational research, including machine-learning and deep-learning approaches;
- Increasing awareness of funding bodies for the need of patient-tailored and mechanism-based therapeutic approaches. This matches well with basic science projects addressing individual pathophysiological mechanisms, based on detailed patient phenotyping using genetic, circulating biomarker, and functional markers (in line with the Dutch Heart Foundation and DCVA strategy of early recognition).

THREATS

- Upcoming retirement of the head of Cardiology;
- Upcoming retirement of the head of electrical heart failure within Physiology.

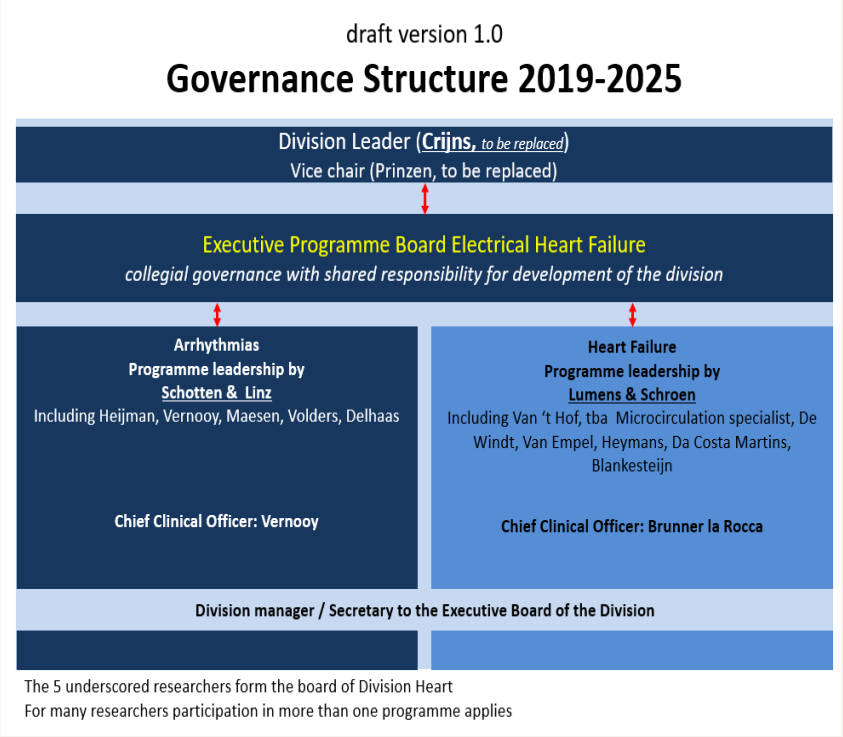
3.6.3 Strategic plans

Division Heart recognises the increasing need for the understanding and early detection of individual disease mechanisms as one of the central challenges in biomedical research in the years to come. This holds true for both programmes within Division Heart. Several actions will be undertaken to address this objective:

The succession of leaders within the Department of Physiology and the Department of Cardiology is in progress. In this respect, the development of Division Heart towards the common topic of Electrical Heart Failure is a major push forward, since it offers a clear focus to attract potential new leaders to Division Heart. Furthermore, the recent appointment of Prof. Uli Schotten as head of Physiology, is important in this respect.

The governance structure of Division Heart will be revised to rejuvenate collegial leadership, see draft version 1.0.

Figure 6 Draft governance structure Division Heart 2019-2025



The connection between CARIM departments will be tightened by mutual in-line appointments. The integration of the Departments of Physiology and Biomedical Engineering will be explored to enhance cardiac modelling expertise, to optimise synergism in signal processing, and to ensure sustainable software management including software development, testing, documentation, and maintenance.

We will continue to invest in upcoming talents at the crossroads of Physiology and Cardiology by investing in a translational arrhythmologist (Dr Dominik Linz) and positioning an early career biomedical engineer (Dr Stef Zeemering). Co-financed by Philips (increasingly important partner for the Division Heart), Matthijs Cluitmans has been appointed in both institutions and has been granted a tenure track in CARIM just recently. For the development of the cardiomyopathy programme, cooperation with genetics and bio-informatics will be expanded for multilevel omics in cardiac biopsies and DNA, and to study novel genetic mutations, modifiers and markers of dilated cardiomyopathies and HFPEF. Furthermore, international collaborations on genetics, imaging and biomarkers of dilated cardiomyopathies are needed and a strong interactions with European partners like Imperial College London, Barts Hospital and Harvard Boston are needed and will be explored.

Developing and implementing new non-invasive or minimally invasive diagnostic technology to quantitatively describe disease mechanisms is an essential step. Such diagnostics can be used in large patient cohorts and advances in analysis algorithms and miniaturisation have tremendously increased usability and interpretability of such technologies. Examples include using non-invasive and semi-invasive electrograms for arrhythmia classification (one spin-off founded in 2016), combining body surface potentials with Imaging (in close collaboration with Philips and EP solutions), use of implantable loop recorders to analyse patterns of AF with functional implications of its mechanism and use of non-invasive measurements of microvascular function in HFpEF patients and the automated analysis of echocardiography (collaboration with Philips, Dr Christian Knackstedt). Similarly, continuous pulmonary pressure measurements using implantable devices will be used in heart failure patients.

Interventional cardiovascular magnetic resonance (iCMR) promises to enable radiation-free catheterisation procedures and to enhance contemporary image guidance for structural heart and electrophysiological interventions. Additionally, iCMR will enhance interdisciplinary collaboration thereby facilitating the use of advanced cardiovascular imaging techniques in experimental and clinical research. CARIM-HVC will invest in this initiative.

The Division Heart will also focus more on creating databases that link insights into molecular mechanisms of CVD derived from biomarkers or tissue analysis to detailed phenotyping of patients. For example, extended biosampling is performed in various cohorts of patients with atrial fibrillation (Multi-AF, RACE V, AF ablation registry) and heart failure (HFpEF and HFrEF). Advanced workflow for large-scale analysis of biosamples using transcriptomics (collaboration Prof. Monika Stoll), spectrometry imaging (Prof. Ron Heeren), and biomarker development (collaboration with Roche Diagnostics, Rotkreutz, CH) was implemented recently. Another example yet to implement is the ISOLATION registry, a prospective registry of patients undergoing AF ablation, will be set up to prospectively collect patient characteristics, and to build a biobank to determine biomarkers and electrophysiological measures to further develop prediction models to identify patients at risk for ablation failure. The long-term vision of these projects is to develop individualized mechanism-based therapies for complex arrhythmias and heart failure.

Several PIs and scientists of the Division Heart are currently working on improvement of workflow and infrastructure for data collection and management. For several patient populations specialised diagnostic workflows are currently installed allowing for more extended and standardised patient phenotyping with the aim to routinely collect data of all patients being seen in Cardiology. This will increasingly be linked to innovative Business Information Management (BIM) strategies, enabling more direct usage of clinical databases for research purposes, implementation of operational excellence strategies, and teaching.

Additionally, investigators invested in several large data servers allowing secured and standardized access to research data and the analysis of large and complex data sets requiring strong computational power (e.g. for bioinformatical analysis and running individualized computer models for CVD).

A large part of the required analysis software is custom-made and developed at the Departments of Physiology, Biomedical Engineering, and Cardiology and collaboration with external partners. These Departments are currently developing joint strategies for programming, testing, maintaining, and archiving custom-made software solutions.

Further to the above, the Division Heart and the HVC invest heavily in computer models, which increasingly show clinical relevance. Also, extensive infrastructure to perform non-invasive measurements, including all imaging techniques (MRI, echocardiography, CT, ECG imaging and advanced ECG analysis such as VCG, is available and will be further developed. To further enhance our strategy, the Division Heart and HVC work on implementation on registry-based clinical trial methodologies.

3.7 Viability

Current PIs and staff in Division Heart cover various stages of career development so that smooth transition to future leaderships is secured. All PI groups have managed to establish a solid scientific and financial basis for their groups for the coming years. Furthermore, the tight embedding of their groups in national and international networks will contribute to the excellent future perspective of the Division Heart.

CARIM's Division Heart and HVC have aligned their plans such that HVC accommodates CARIM's research within the outpatient department and cardiac catheterisation laboratory, and *vice versa*, CARIM departments provide lab space for clinical departments. Our governance structure promotes a shared responsibility for the development of the Division. The team-rather-than-champion organisation stimulates senior and junior researchers to develop their expertise in collaboration with each other. Functional integration of Physiology, Biomedical Engineering, Cardiothoracic Surgery and Cardiology provides innovative translational research feeding the future developments, projects and collaborations. We have seen collaborations start to grow, with young researchers initiating new programmes. Mid-career researchers connect various departments on important topics including electrical management of heart failure (Dr Kevin Vernooy, Dr Dominik Linz), HFpEF (Dr Vanessa van Empel, Prof. Blanche Schroen), microcirculation (Prof. Arnoud van 't Hof, new appointment at Physiology), electromechanical modelling and data science (Dr Stef Zeemering) and they will all strengthen the collaborations.

The potential for innovation is large. One important example is the future collaboration on microcirculation between Physiology and Cardiology in the area of HFpEF and intracoronary hemodynamics. Coupling of Biomedical Technology to Physiology will enhance translational and integrative research, as well as optimise workforce. CARIM's Division Heart will also continue its strong link between the Dept. of Cardiology, Dept. of Radiology and Dept. of Internal Medicine (the Maastricht Study) to develop imaging for early detection of cardiovascular disease as well as interventional treatments of arrhythmias.

Ongoing national and international projects and novel grant applications that reinforce the strength and viability of CARIM's Division Heart and include PASSION-HF, RACE 8, RACE 9, CATCHME, SUMMA, AFib-TrainNet, TRAIN-HEART, PERSONALIZE AF.

Post-graduate education activities are able to grow independently. These include among others DAS-CAM and a continuous stream of ITN grants.