

CARIM MIDTERM

REVIEW

2019



2021



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Cardiovascular
Research Institute
Maastricht



Maastricht UMC+
Maastricht University

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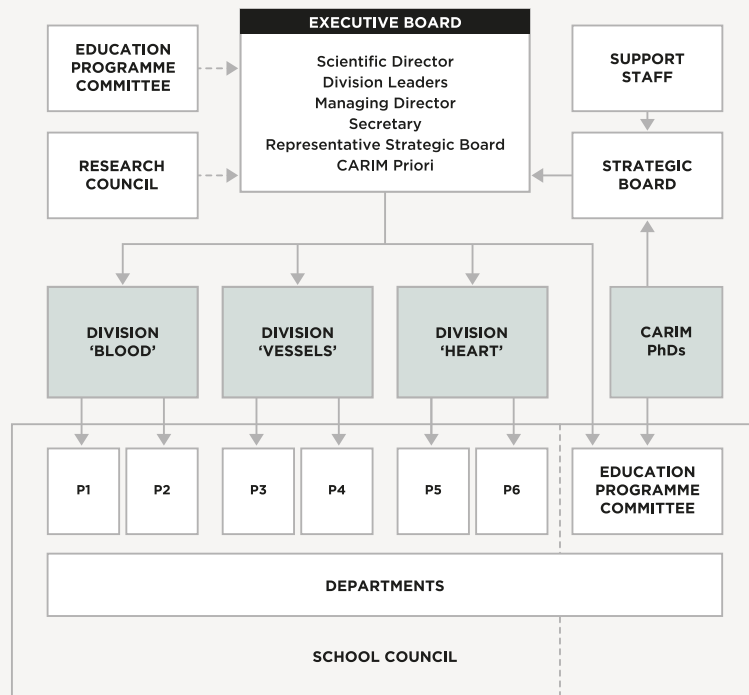
1 Introduction

CARIM, School for Cardiovascular Diseases, is one of the six research schools of the Faculty of Health, Medicine and Life Sciences of Maastricht University. CARIM was founded in 1988 and has established itself over the last decades as a leading research institute in the field of cardiovascular disease. At CARIM, basic mechanisms as well as early diagnosis and individual risk stratification of cardiovascular disease are studied, allowing faster translation of new research concepts to clinical practice. New findings, products and techniques which can be applied in healthcare are evaluated, often in collaboration with private partners, and the results of scientific research are disseminated through highly-cited international peer reviewed publications. Masters students, PhD candidates and MD students are trained to become independent researchers, and postdocs are trained to become leading scientists in the field of cardiovascular disease.

CARIM is built around three research divisions, 'Blood', 'Vessels' and 'Heart', comprising six programmes:

- | | | |
|---------|---|---|
| BLOOD | ■ | 1. Blood coagulation, venous thrombosis & bleeding; |
| | ■ | 2. Atherosclerosis, arterial thrombosis & stroke; |
| VESSELS | ■ | 3. Vascular complications of diabetes & hypertension; |
| | ■ | 4. Regenerative & reconstructive cardiovascular medicine; |
| HEART | ■ | 5. Structural heart failure and |
| | ■ | 6. Complex arrhythmias. |

These six programmes together host 21 Principal Investigator (PI) groups that represent independent research, infrastructural and financial units within CARIM.



To translate research into clinical practice, CARIM joined forces with the Heart+Vascular Center (HVC) of Maastricht UMC+, aiming to become a unique internationally recognised centre of excellence in cardiovascular medicine, including translational research and medical care.

Organisational changes at CARIM

Wouter Hankel succeeded Rob van der Zander as managing director in February 2019. Prof. Leon Schurgers took over the PI group of Prof. Chris Reutelingsperger in 2020. To improve both the integration of the research programmes within Division Vessels, as well as the integration of the Division into the HVC, the PI group of Profs Reutelingsperger/Schurgers (former Division Blood), became part of Division Vessels. The group focusses on the interaction between the blood and vascular smooth muscle cells (SMCs) and forms the link with the regenerative part of the Division, because of its close collaboration with the Department of Cardio-Thoracic Surgery. Herein, the collaboration with HVC for isolation of primary SMCs and differentiation of iSMCs from patients induced pluripotent stem cells (iPSCs) is anchored and integrates with RegMedXB and the University of California, Irvine, USA for investigating *ex vivo* vascularisation. Prof. Johan Heemskerk retired in 2020 and Dr Judith Cosemans took over his group and PI-ship. Prof. Harry Crijns, division leader Heart and PI within CARIM, retired in 2021. Prof. Kevin Vernooy became his successor. Prof. Frits Prinzen, PI in division Heart, retired in 2021 as well. Team members within his group have been placed in other PI groups. The group of PI Prof. Leon de Windt has partially been reallocated to the Faculty of Science and Engineering at the end of 2019.

2 Reaction on and follow-up of the recommendations of the previous assessment committee

In 2019, an external review committee evaluated CARIM as part of the six-year cycle of reviews conducted under the Standard Evaluation Protocol (SEP 2015-2021). That review covered the 2013-2018 evaluation period of CARIM. This chapter describes the recommendations of the last review committee and the follow-up of these recommendations by CARIM.

Overall, CARIM was evaluated as ‘very good’ (2) in terms of research quality and viability and ‘excellent/world leading’ (1) in terms of relevance to society. At the division level, each division scored ‘excellent/world leading’ for relevance to society and viability and ‘very good’ for quality.

	QUALITY	RELEVANCE TO SOCIETY	VIABILITY
CARIM	2	1	2
 Blood	2	1	1
 Vessels	2	1	1
 Heart	2	1	1

In response to the recommendations of the ERC, CARIM has implemented several new strategies and visions and has refined several policies that were already under development.

Strategic Annual Wheel: To ensure that the follow-up of strategic plans and (financial) investments is guaranteed and goals are met, the board of CARIM evaluates the investment plans in the annual budget three times a year. Furthermore, the Strategic Board – as representative of the CARIM community – identifies strategic opportunities and advises the board of CARIM on the budget for the coming year(s). The managing director reports the progress of ongoing investments to the Strategic Board and School Council. If necessary, extra efforts or redirections to plans and investments will be made.

Diversity and Inclusivity: A transparent, hospitable and inclusive work environment is an essential prerequisite for creativity, productivity and well-being of UM employees and thus for the sustainability of long-term appointments of CARIM staff. CARIM is aware of the gender imbalance and is engaging in an active policy to improve this. An online survey has been developed by CARIM in collaboration with the Maastricht University Diversity Office and was distributed in 2020 to all CARIM staff members to get insights into the working experience and well-being of CARIM employees with respect to inclusivity and diversity, career opportunities, workload, Recognition and Rewards, communication and social safety.

Based on this survey and discussions with the Diversity Officer, steps have been taken to improve transparency and communication, inclusivity in CARIM decision making, social safety and Recognition and Rewards. In collaboration with FHML, CARIM has adjusted its style for recruitment through advertisements to make job descriptions more compliant to diversity and inclusivity policies. Positions in decision making bodies within CARIM, the university or national or international scientific organisations will be openly advertised. CARIM stimulates awareness and discussion about discrimination within CARIM and provides CARIM members with the tools necessary to engage in such conversations. In addition, a culture of addressing unwanted behaviour (regarding yourself or someone else) is promoted.

Grant acquisition: Although CARIM researchers have regularly been invited for European Research Council Starting and Consolidator grant interviews, acquisition of these grants has been largely unsuccessful. To improve this, CARIM, in collaboration with the Grants Office of FHML, has set up a programme to identify eligible researchers at an early stage and coach them during the whole applications process. This programme is in place for the ERC Starting and Consolidator grants and has resulted in five researchers to be invited for interviews so far. In addition, the CARIM Grants & Incentives team has been established to boost grant application activities by motivating researchers and research teams, keeping track of submitted, granted and rejected applications and discussing calls and opportunities. An overview of personal deadlines has been made for each researcher when to apply for internal, national, and European scholarships. In this way, CARIM aims at increasing both the number and the quality of grant applications. To improve awareness and provide information, CARIM distributes monthly funding alerts that contains abstracts, eligibility, and deadlines of upcoming funding opportunities.

Recruitment/leadership: Almost one third of first-generation CARIM PIs are expected to retire in the period 2020-2024. Therefore, in the coming period, there will be a strong focus on the follow-up of these leading researchers. To provide well-described and transparent career paths CARIM will follow the new guidelines that Maastricht University has formulated in the document 'New Career Development Regulations for Academic Staff' in 2019 in which the Assistant Professor-Associate Professor-Professor career ladder is described. For each open position, external and internal recruitment will be followed to ensure scientific exchange, quality and output of our research in that specific field of expertise. In order to improve transparency, policies on personnel planning (recruitment, promotion), will be actively communicated. Currently, Recognition & Rewards is being implemented leading to new career profiles for Assistant and Associated Professors. More attention will be paid to

horizontal development of academic staff. CARIM has pioneered in horizontal development even before R&R by appointing 'integrators', staff members who are unable to gain prestigious personal grants but are crucial for research continuity and viability. In the future, horizontal develop programmes will also be extended to OBP.

Infrastructure: In accordance with the ERC recommendations, CARIM has budgeted an investment of EUR 850k from 2021 to update and strengthen its technological infrastructure. CARIM Central has now made a total investment of approximately EUR 700k by acquiring the following equipment:

- Cytex spectral flow cytometer;
- 10-x Single-cell mRNA sequencing;
- Circular Dichroism spectroscopy.

Furthermore, funds have been reserved for improving the cardiovascular data science infrastructure within CARIM (EUR 50k). In addition to this equipment, investments have also been made in setting up a library of antibodies for the flow cytometer to allow low-cost use for CARIM researchers and in an internal 50% subsidy scheme for use of the 10-x with a budget of EUR 87k. CARIM encourages this research by providing a contribution of EUR 750 per sample when using the device, with a maximum of 10 samples per PI group. A procedure has been worked out and the 10-x project assessment committee has awarded contributions ('cash-back') to the first two researchers in December 2021.

PhD programme: CARIM improved the introduction of new PhD candidates in CARIM, in general, and in the PhD-TRACK monitoring system, in particular.

- PhD Guide: The CARIM's PhD-Guide to introduce PhD candidates to the organisational aspects of our institute as well as planning and logistics for PhD defence has been updated and reissued.
- Introduction meetings: To introduce new PhD candidates into CARIM and into the CARIM PhD programme, introduction meetings will be organised for PhD candidates that joined CARIM in the previous months.
- Buddy system: a junior buddy system has been set up, in which an experienced PhD candidate will be linked to a new PhD candidate (on a voluntary basis).
- Coaching system: Coaches will be assigned to new PhD candidates working at FHML/Maastricht UMC+. The coaching system is meant to allow PhD candidates to openly discuss non-scientific issues and professional relations with a senior CARIM staff member from a different CARIM division and not directly involved in the daily research activities of the PhD candidate.

External Advisory Board: Prof. Frits Rosendaal (LUMC) has been appointed as external scientific advisor to advise the institute on a yearly basis.

■ Division Blood

The recommendations of the external review committee for further improvement of Division Blood are well in line with CARIM's own aspirations to include genotype and transcriptome data in conjunction with deep phenotyping to improve disease prediction, clinical outcome and personalised medicine. The Maastricht Study will be more utilised as a resource for the population-genetic aspects of from thrombophilia and bleeding disorders. With regard to the specifically mentioned topics (venous thrombosis, acute stroke and atherosclerosis), a strong line in venous thrombosis and post-thrombotic syndrome (PTS) has been established. Translational atherosclerosis research has been strengthened by participation in the CONTRAST stroke CVON consortium and by the clinical and translational studies in collaboration with

the Department of Biochemistry. Currently, the scope of these studies from thrombophilia and bleeding disorders to diseases with hypercoagulability as a risk factor for disease outcomes is being expanded e.g. in stroke, myocardial infarction as a result of either atrial fibrillation or atherosclerosis, or even in the context of COVID-19. Deep phenotyping, mechanistic studies, and *ad hoc* genetic screening of patients with (unexplained) hyper- and hypocoagulability are available at the Department of Biochemistry. With respect to population-based studies, thrombin generation has been recently measured in ~9.000 participants of the Netherlands Twin Register (NTR) biobank in view of intersecting this coagulation phenotype with genotype and the life-style information and -OMICs data available at the NTR. The research line of translational cardiovascular chemistry, including the novel radio-biochemical cardiovascular imaging offers the possibility of a multidisciplinary approach between the Department of Biochemistry and the clinical care centers of Heart+Vascular Center and Imaging (see case study Dijkgraaf).

■ Division Vessels

To develop basic research in microcirculation and inflammation of its microenvironment, the vascular biology group of Prof. Leon Schurgers has been redirected from Division Blood to Division Vessels. This group includes a recent appointment of an expert (and Vidi laureate) on microcirculation from Amsterdam UMC-VU. Currently, the connection of microvascular research and the Maastricht Study is being established. In addition, the role of diabetes on the blood-brain-barrier is studied in a collaboration between internal medicine and neurology, supported by a CARIM strategic grant. With the addition of the Vascular Biology group, the clinical departments of Vascular Surgery and CTC are firmly integrated in Division Vessels allowing translation research on cell-matrix interaction, capitalising on the possibilities of using aTAA and aAAA-patient material for clinical as well as new imaging and model-based methods. To this end, these groups are establishing a unique infrastructure to build a database covering clinical data/imaging/genetics, OR-measurements, tissue-phenotyping, comprehensive cell-phenotyping, including patient-own iPSC-derived cells. Following up on the recommendation previously made by the ERC, researchers of the Division Vessels are currently successfully participating in several European consortia (EpiDemic, STAY, EvPro, MINDSHIFT).

■ Division Heart

The Division Heart acknowledges that the link with strong basic science in CARIM should be reinforced. In this respect, the protein-cell-to-bedside axis of the excellent research already present will be thematically embedded in coordinated activities in Experimental Cardiology (including the group of Prof. Leon de Windt and Prof. Paula da Costa Martins), Physiology, Biomedical Engineering and Biochemistry. Great progress has been made by the interaction through joint PhD candidates of Division Heart with the Department of Biochemistry that unveiled the causal relationship of enhanced procoagulant enzymatic activity and atrial fibrosis leading to increased AF and stroke. In addition, 'electrical heart failure' was defined being the bidirectional causal relationships between heart failure and complex atrial/ventricular arrhythmia and/or conduction disorders (e.g. HFpEF – AF, HFrEF – repolarisation disturbances – outcome after CRT, atrial myopathy). CARIM followed the recommendations of the external review committee and has appointed several excellent scientists with expertise in experimental electrophysiology (Dr Bas Boukens) and molecular mechanisms of heart failure (Dr Nazha Hamdani) to ensure sustainability in the translational research focus of electrical heart failure.

3 Mission, ambitions, strategic aims and the strategy compared to the previous assessment

CARIM aims at defining and addressing key cardiovascular questions and clinical needs through interdisciplinary basic, translational and clinical research in an optimal team science setting by combining expertise, track, translation and innovation. Results are disseminated to scientific journals, communities and society in general to contribute to early recognition and prevention of cardiovascular disease and improved cardiovascular care.

The strategy in the past years has been in line with the recommendations of the last external review (see Chapter 2). The vision of CARIM 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. This strategy has now been aligned by Maastricht UMC+/FHML's strategy to couple newly organised care centers to their relevant research schools and institutes. To support these initiatives, CARIM has successfully positioned clinical researchers in basic research departments and vice versa, facilitating the interaction between disciplines on a daily basis. In addition, to stimulate CARIM-Heart+Vascular Center interaction and strategy, joint monthly board (MT) meetings are installed.

In addition to the actions described in chapter two, the following initiatives are worth mentioning divided per topic/specific aspect:

COVID-19: The COVID-19 pandemic had a large impact on research activities of CARIM, as it affected all research and clinical activities of the divisions Blood, Vessels, and Heart, and has led to > 80 (clinical) research publications that have been cited > 750 times. Pioneering work from CARIM researchers has contributed to better understanding and treatment of COVID-19.

Infrastructure: A central iPSC research facility 'SCRUM' (Stem Cell Research Unit Maastricht) was initiated by CARIM and supported by FHML and has been realised in the years 2019-2021. Run by CARIM, SCRUM consists of two laboratories, one closed facility in which SCRUM personnel establishes healthy and diseased iPSC lines from peripheral blood mononuclear cells, and one open facility in which researchers under guidance of technical CARIM personnel can differentiate iPSC lines in their cells/tissues of choice. Based on iPSC technology, CARIM together with MERLN has participated in the National Growth Fund (NGF) initiative in which a EUR 16 M grant for large scale cell production was obtained. With (part of) this grant, CARIM will engage in iPSC-based revascularised (cardiac) tissue, for therapy testing and transplantation purposes. The appointment of Prof. Chris Hughes on the CARIM-HVC chair is of particular importance for this initiative as he is a world leader on tissue revascularisation and has offered his full support to CARIM's endeavours.

Collaboration: The Aachen-Maastricht Institute for Cardiorenal REsearch (AMICARE) has been initiated, focusing on the collaboration between the Universities of Aachen and Maastricht in the field of heart and kidney disease. AMICARE is located on the Melaten campus of RWTH Aachen, and will have a Dutch branch within CARIM.

Talent policy/human research policy: A major focus within CARIM is the identification and mentoring of young talent for which programmes are in place to identify, train and coach talented Bachelor and Masters students, future PhD candidates, and PhD candidates to become independent researchers, and postdocs to become leading scientists in the field of cardiovascular disease. Personal grants for young talents in the aforementioned career stage are provided by CARIM via the so-called HS-BAFTA programme. CARIM's talent development programme will be adjusted according to UM's Recognition & Rewards policy. Because future UM's Recognition & Rewards individual Development Boards will be performed at the level of departments, CARIM is

considering additional School level Development Boards for talents who are crucial for School strategies.

Open science policy: CARIM's involvement in European networks and the obligation to implement an open science policy in its data management plans has improved the accessibility of research output (see Annex 1, Figure 1). Maastricht UMC+ actively promotes the implementation and practice of Open Science in academia. Maastricht UMC+ supports the principle of Open Access publications: full and immediate Open Access to publications from publicly funded research. The Maastricht UMC+ follows the ambition of the National Plan Open Science. The leading principle in this regard is that publicly funded research results should also be freely accessible to the public. 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 (see case study Schram and Van der Kallen).

Academic culture/scientific integrity: Every new researcher (including PhD candidates) who receives a contract from the Human Resources Department of the Maastricht UMC+/FHML is informed about the contents 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. 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. At the University level a Counsellor for Scientific Integrity and a Committee for Scientific Integrity are installed, who advise the Um Executive Board on complaints filed regarding scientific integrity.

In 2018, FHML/MUMC+ has setup a FHML/MUMC+ Platform Scientific Integrity (PSI) to increase awareness on scientific integrity among students and staff by further stimulating discussion on relevant topics in a constructive and positive manner. Prof. Tammo Delhaas (PI within CARIM) is a member of this FHML/Maastricht UMC+ Platform Scientific Integrity. In 2022, this platform has developed an online course on scientific integrity for PhD candidates, which will be adjusted into a course for all scientific staff in 2023. Moreover, the platform stimulates the Schools and departments to play the dilemma game (via the app) on scientific integrity (developed by Erasmus University Rotterdam), in small groups of PhD candidates or researchers within the Schools, including CARIM.

PhD policy and training: The ongoing activities regarding PhD policy and training are described in Chapter 2. CARIM has actively involved its PhD candidate organisation 'I'M CARIM' to improve policy and training from the bottom-up, based on experiences and needs of the PhD community. This has led to a completely renewed PhD guide and a recruitment movie found on CARIM's website.

4 Accomplishments/results during the last 3 years, supported by factual evidence

4.1 Research quality

Research products for peers

CARIM has published over 2,700 refereed articles in the period of 2019-2021 and 136 PhD theses were produced (see Annex 1, Table 1). The number of published refereed articles strongly increases over time with a peak in 2021 (see Annex 1, Figure 1). The percentage of publications published Open Access has increased at CARIM, with 19.1% of the total output being available under an Open Access license in 2014, and 60.9% in 2021. When taking green Open Access into account, 71.7% of CARIM's publications of 2021 is Open Access (see Annex 1, Figure 2).

Use of research products by peers

Impact indicators measure the effect of scholarly work on the research community and society. The Category Normalized Citation Impact (CNCI) for CARIM 2013-2019¹ is above world average (1.9 times the expected citations) and has one peak in 2016 due to three highly cited papers (see Annex 1, Figure 3). 2.4% of CARIM's total output (93 publications) has a CNCI higher than 8 and more than half of CARIM's output (51%) receives more citations than expected based on the age, document type and subject area.

The three items with the overall highest CNCI are:

- Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials (2016) (see case study MR CLEAN)
- A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke (2015)
- 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS (2016) (see case study Crijns and Schotten)

3.6% of CARIM's output belongs to the top percentile in terms of citation impact, and 22.6% of publications belongs to the top 10%. This shows that 1/5th of CARIM's publications is leading in their respective fields. 33 publications are the highest cited publications in their field (Annex 1, Figure 4).

To get insight in the citation impact of the different research lines of CARIM, the number of publications and citation impact indicators are listed per research line in Table 2. This is done for 2019 only, since the research lines were established in that year and citation impact for the years 2020 and 2021 cannot be reliably calculated yet. Table 2 shows that 'Blood' has 233 publications. Those publications have a mean CNCI of 1.9 and 8 publications (3.4%) are in the top 1% of the world – regarding citation impact and compared to publications of the same age, document type and subject area. 'Vessels' has 206 publications with an average CNCI of 2.0, which is also due to a relatively high share of publications in the top 1%. There are no major differences between the research lines. 'Heart' has the least publications (174), but the average CNCI of all publication is the highest (2.4). This is due to a high (relative) amount of publications in the top 1%, since it has a slightly smaller share of publications in the top 10% compared to 'Blood' that has the highest share of publications in the top 10%.

¹ The period for citation impact analyses differs from the evaluation period, because citations need time to accumulate and normalized citation counts can therefore only be reliably calculated until 2020.

Marks of recognition from peers

Research grants awarded to individuals

CARIM researchers have been consistent in obtaining personal grants from large national research institutions such as NWO, Dutch Heart Foundations, Dutch Thrombosis Foundation and Dutch Diabetes Research Foundation. See Annex 1, Table 3 for an overview of the personal grants obtained in 2019-2021. However, as already mentioned in Chapter 2, acquisition of personal European grants has been largely unsuccessful.

Grants awarded to major collaborative research projects

In contrast to ERC personal grant acquisition, CARIM has a great track record of participating in collaborative European projects (see Annex 1, Table 4). Especially within Division Vessels this has improved after the previous external evaluation. CARIM has particularly been successful in the Innovative Training Networks (ITNs) of the European Commission, both as Coordinator (see case study INTRICARE) as well as Beneficiary. This track record is the result of the long-lasting collaborations of our researchers with partner institutes. The collaborations are being formalised by setting up joint or double doctorate structures between several universities, e.g. with Aachen, Leuven, Stockholm and Hasselt, and is also clear from the publication analysis (see Annex 1, figure 5). At the moment, about 45 double PhD theses are expected in the upcoming years.

Other marks of recognition

CARIM scientists have received prestigious scientific awards and prizes (see Annex 1, Table 5), for example the *Dr. Saal van Zwanenberg Ereprijs* by Prof. Harry Struijker-Boudier, the Winkler Medal by the MR CLEAN investigators or the Jordan Prize by Prof. Hugo ten Cate. CARIM researchers represent six out of 30 members of the Dutch Cardiovascular Alliance future leaders programme. In addition, there is a strong representation of CARIM members in guideline and steering committees. Finally, CARIM scientists have been invited for numerous plenary presentations at international conferences (Annex 1, Table 6) and are (inter)nationally very well represented as members of scientific reviewing boards of funding agencies (Annex 1, Table 7) and editorial boards (Annex, Table 8).

4.2 Relevance to society

Cardiovascular diseases are the leading cause of death globally. An estimated 17.9 million people died from cardiovascular diseases in 2019, representing 32% of all global deaths. CARIM researchers contribute to the prevention, diagnosis, treatment, valorisation and knowledge dissemination of cardiovascular disease. 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 members of our society about early warning signs of cardiovascular disease. CARIM's PhD programme contributes to the development of a growing group of cardiovascular experts with a state-of-the-art scientific knowledge base who contribute, each in their own way, both locally and globally to societal challenges in cardiovascular diseases to improve patient care. International training is provided by all three divisions leading to three excellent and much acclaimed courses: the Certificate of Advanced Studies in Antithrombotic Management (CAS-AM: Division Blood);

The European Vascular Course (EVC: Division Vessels), and the Diploma of Advanced Studies in Cardiac Arrhythmia Management (DAS-CAM: Division Heart).

Research products for societal target groups

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, and to create awareness on the importance of research on prevention of cardiovascular disease, which is to a large extent supported by public (governmental) funding. In addition, CARIM-HVC organises a number of annual events, such as 'Walk (and cycle) with your Doctor' (see case-study Van Empel) 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 cure 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 have financially supported. Basic and clinical researchers of CARIM give lectures for patient associations and at elementary and high schools.

Marks of recognition from societal target groups

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, e.g. Rogier Veltrop in Op1, Dr Chahinda Ghossein-Doha in Jinek (see case study Ghossein-Doha) and Prof. Martijn Brouwers (see case study Brouwers) and Dr Rob Holtackers (see case study Holtackers and Bijvoet) in national and regional newspapers. CARIM clinicians are involved in major guideline and position papers (see highest-cited papers above), both as authors as well as reviewers, with the aim to improve health care in general and prevention and treatment of cardiovascular disease in particular.

Use of research products by societal target groups

Several groups within CARIM (based in all three divisions) have been successful in filing patents on results emerging from their studies (see Annex 1, Table 9). 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 for an overview and description of the CARIM spin-off companies (see Annex 1, Table 10).

CARIM researchers have been involved in developing health services and information delivered or enhanced through the Internet and related technologies (eHealth/mHealth), such as FibrCheck, an application on smartphone to measure the patient's heart rhythm and heart rate for 7 days before a scheduled teleconsultation, which has been implemented in the TeleCheck-AF project established during the COVID-19 pandemic (see case study Linz and Hermans).

4.3 Case studies

The following case studies can be found in Annex 3:

1. MR CLEAN: The endovascular treatment of acute ischemic stroke – Julie Staals, Robert van Oostenbrugge and Wim van Zwam
2. A tale of the RACE trials – Harry Crijns and Uli Schotten
3. INTRICARE – Tilman Hackeng and Leon Schurgers
4. Heart Failure with preserved Ejection Fraction (HFpEF) – Vanessa van Empel
5. Queen of Hearts – Chahinda Ghossein-Doha
6. The TeleCheck-AF project – Dominik Linz and Astrid Hermans
7. The Maastricht Study – Carla van der Kallen and Miranda Schram
8. The Digital Twin – Joost Lumens, Jordi Heijman, Uyen Nguyen and Matthijs Cluitmans
9. Determinants and cardiometabolic consequences of non-alcoholic fatty liver disease – Martijn Brouwers
10. Cardiac Magnetic Resonance-Guided Electrophysiological Intervention (iCMR) – Miranda Bijvoet and Rob Holtackers
11. Ticknology: bio-inspired diagnostics and therapeutics – Ingrid Dijkgraaf

4.4 Trends regarding research staff, funding and the duration/success rates of the PhD programme

The number of CARIM staff and total FTEs has remained largely stable over the years, see Table 1 in Annex 2. This is true for both the research staff as well as the total staff. Within the research staff, there is a slight shift towards more PhD candidates and fewer postdocs. This has been identified as one of CARIM's threats and a challenge for the future (see SWOT and viability).

An overview of the total funding of research staff at the level of the School is provided in Annex 2, Table 2. CARIM's budget consists for about 20-25% out of direct funding by Maastricht University and 75-80% of research grants and contract research. CARIM's funding fluctuates from 150 FTE in 2016 to 158 FTE in 2018 and 2019 and back to 150 FTE in 2021. This fluctuation is related to the obtained grants and contracts prior to this period and effectuates with a 1-2 years delay. This trend is also visible on a faculty level. In 2016 and 2017, CARIM researchers were very successful in obtaining new grants, resulting in newly appointed staff in 2018 and 2019. As from then, funding has decreased, which led to less staff on research grants in the years after. One of CARIM's major challenges for the upcoming years is to secure new funding.

Annex 2, Table 3 shows an overview of the number of regular (internal) PhD candidates who started between 2011 and 2017. About 30 PhD candidates are appointed at CARIM yearly on a standard contract, over half of these are women. About 20% of CARIM's PhD candidates graduates within four years, while 50% graduates within 5 years. The average total drop-out is 14%.

5 SWOT analysis

Below we describe the SWOT analysis for CARIM based on input from the Executive Board, the Strategic Board and the Education Programme Committee.

STRENGTHS

- The entire cardiovascular spectrum - blood, vessels and heart- is covered by CARIM, which is unique for a cardiovascular institute
- Close collaboration with the clinical departments results in high quality translational research, including strong connection between CARIM and HVC
- Multidisciplinary and team science approach of research groups
- Strong publication record with a high percentage of papers in top 10% (high citation) journals. This results in citation scores that are almost two-fold world average
- CARIM HS-BAFTA young talent programme for Bachelors, Masters, (pre-) PhDs and PDs
- High quality PhD candidate training and supervision programme including a dedicated organisation for CARIM PhD candidates
- Strong international public and private scientific partnerships
- Strong representation of CARIM members in guidelines and steering committees, as well as funding agencies
- Excellent state of the art research infrastructure
- Dedicated support for funding acquisition through a Research Council, Grants & Incentives team, incentives, monthly funding alert
- Strong track record in long term involvement and coordination of European collaborative projects

WEAKNESSES

- Accessibility of clinical data for research purposes is limited
- Scattered expertise in cardiovascular data science, hampering participation in large data-driven projects
- Limited success in obtaining personal European Grants (ERC)
- The academie hospital and FHML are still separate entities creating differences at the administrative and cultural level
- Underrepresentation of females as PIs and in decision-making bodies
- Lack of mass and expertise in experimental pharmacology and clinical pharmacy

OPPORTUNITIES

- Shaping the new Electronic Patient File system to research opportunities
- Implementation of Recognition & Rewards in multidisciplinary team science setting
- Investing in better guidance of PhD candidates and in the monitoring of their well-being
- Growing priority and recent advances in data sciences at the national and faculty level, supported by a CARIM specific data science working group, are expected to facilitate findability and accessibility of cardiovascular data for research purposes
- Strengthening of translation research and improvement of clinical care by the integration of research programmes and clinical care pathways
- Expanding personalised medicine approaches
- Implementation of measures to improve diversity in higher positions and decisionmaking bodies
- Initiatives on knowledge utilisation and impact of research through public private partnerships
- Development of a translational Department of Clinical Pharmacology

THREATS

- Cardiovascular research does not have a prime position on national and international research agendas
- Increasing teaching work load because of under-compensation of educational activities
- New faculty labeling for clinical researchers is not matched anymore to the medical specialist salary by Maastricht UMC+, jeopardizing translational research
- Lack of funding programmes for mid-career researchers leading to less postdocs
- Loss of focus on basic (curiosity-driven) science in a successful translational institute
- Differences in interpretation of Recognition & Rewards between national and international research communities (H-index, Journal Impact Factor)
- Decreasing new contracts and grants
- Focus on PhD candidates (due to grant systems and direct funding), threatening the continuity in research lines (lack of permanent mid-career researchers)
- Uncertainty animal facility
- Restrictive knowledge utilization and spin-off policies of the university
- European funding for PhD projects of three years is not compatible with Dutch PhD system

6 Strategic plans

CARIM will continue to implement the strategic plans as set-out in the Self Evaluation report 2013-2018 and in chapter 2 of this midterm report.

Data Science: There has been a growing prominence of data science in the field of cardiovascular research. Modern data science, including data management, sharing, integration and artificial intelligence (AI)/machine learning (ML)-based analyses, offers opportunities to expand the effective use of data for better understanding, prevention and treatment of cardiovascular diseases. An inventory within the divisions and a subsequent SWOT analysis by the CARIM Strategic Board revealed an urgent and growing need to strengthen data science support within all three divisions of CARIM.

In response to this analysis, dedicated budget was made available and a working group with representatives of all three divisions and tight links with the CARIM Strategic Board and Executive Board was recently established to support data science initiatives within CARIM. Based on initial discussions, the working group decided to focus on three components: promoting data sharing (including accessibility to clinical data) and data reuse, supporting research design and data analyses, and training of CARIM scientists and support staff in data science-related topics. For all of these it should be noted that significant expertise and/or resources are often already in place, either within CARIM, within the University at large, or within the region. Therefore, an important task of the working group will be to make CARIM researchers aware of the available resources. Finally, members of the working group also represent CARIM in the faculty-wide initiatives on data science for optimal alignment with larger initiatives such as the access to patient data.

Animal-restricting innovation: By increasing research activities that directly use human data, exemplary for the epidemiologic approach in the Maastricht Study, modeling of human hearts as of Digital Twins (see case study The Digital Twin), and iPSC technology to create human tissue in the lab, CARIM is currently shifting research more to human models and less to animal experimenting. With this, CARIM creates a laboratory animal restricted environment to limit animal experimenting to the absolute necessity. In this way, CARIM is less dependent on the CPV (animal facility). In addition, large scale mechanistic studies in patients are increasingly undertaken to explore the complexity of individual disease mechanisms resulting from the large diversity of comorbidities associated with cardiovascular diseases (see case studie Crijns and Schotten). Animal experiments will always be needed, especially when multi-organ systems are studied, but many can be replaced with modeling and by using human material and tissues for therapy testing and mechanistic studies, which at the same time offer better models for studying human disease.

Infrastructure: Research at CARIM can only flourish when state of the art technological infrastructure lies at its basis. CARIM has already invested EUR 1M in the past years in infrastructure, and has centralised its equipment plan: proposed equipment > EUR 25k that is supported in a broad sense by CARIM divisions and of which 50% of the cost is contributed by PI groups (signed statements with budget numbers) will be financed for the additional 50% by CARIM.

Diversity and Inclusivity: CARIM formed a working group on diversity, inclusivity and social safety to further implement this policy. CARIM will continue its platforms and theme sessions to enable and feed discussion on this topic. Currently, plenary session have been organised to increase awareness on D&I and maintaining the dialogue in our CARIM community on this important topic. There is still a underrepresentation of female PIs and female membership in decision making bodies. CARIM is engaging in an active policy to improve this.

Grant acquisition: CARIM will more actively invest in guidance and hiring external grant writers to stimulate national and international (personal) grant acquisition. CARIM has improved its infrastructure with the Research Council for research plan and objective guidance, but for the increasingly complex application parts on data management and societal impact external support will be more intensively sought. Cardiovascular research does not have a prime position on national and international research agendas. Therefore, CARIM researchers have to collaborate with other (less obvious) disciplines to obtain grants.

PhD programme: CARIM has shifted the well-being and guidance of our PhD candidates to a central position (see Chapter 2). As a first institute within FHML, buddies and senior coaches have been assigned to new PhD candidates as from 2021. This new tool will be evaluated before the upcoming External Review. In addition, a detailed reference guide has been developed to introduce and guide PhD candidates through their track.

Regenerative cardiovascular medicine: CARIM will invest strongly in vessel and heart regeneration through continuation of REGMED XB Cardiovascular Moonshot consortium, which is a cross-border collaboration between universities (KU Leuven, LUMC, UMCU, Tu/E and Maastricht UMC+) and National Growth Fund acquisition (CARIM, MERLN) allowing large scale iPSC derived cells and tissue production. All three divisions of CARIM and HVC are involved, clinical as well as preclinical, stimulating basic-clinical interaction to a large extent. Our successful CARIM-UC Irvine alliance will enable revascularisation of iPSC derived heart tissue as model to assess therapeutic options for in vivo repair of hereditary heart disease.

Social media: As the use of social media has become indispensable in a scientific institute, CARIM will structurally incorporate this medium in its communication strategy. CARIM members are encouraged to participate and sharing of professional content within their own social media networks.

Open Science policy: CARIM will continue to encourage researchers to publish their results in open access journals.

7 Viability

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 flourishes in strongly embedded and 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 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-ranked journals and apply economic and societal knowledge utilisation as a main responsibility. Creating awareness

on effects of lifestyle and social economic status on cardiovascular disease will be further embedded in CARIM's responsibilities.

The current focus on funding of PhD projects and lack of funding for mid-career scientists jeopardizes the continuity in research lines and infrastructure. Therefore, CARIM has invested in fixed positions for mid-career researchers, the so-called integrators, who are essential and indispensable for CARIM research but have not been successful in obtaining personal research grants allowing them to develop horizontally in a safe environment. In addition, CARIM will invest in three extra postdoc positions to expand the mid-career layer of CARIM and to stimulate interaction within the division on a strategic level. Finally, the backbone of CARIM research represented by our research support staff has been strengthened by giving fixed positions to nine support staff members with an appointment with expiration date.

One of the challenges for the upcoming years is to ensure that new research funding will be acquired. While the number of PhD candidates enrolled in the last years and the number of PhD theses finalised have been stable in the last years, obtaining new contracts and grants is necessary to keep CARIM viable in the future. CARIM has made this a top priority for the upcoming years. A lot of PhD candidates within CARIM are part of ITN programmes of the European Commission. Funding within these programmes is for three year PhD trajectories, which is less than the Dutch PhD system. Until 2020, CARIM accommodated the fourth year by deploying the SEO (*Stimulerend Europees Onderzoek*) resources, together with the promotion team incentive and the remaining budget from CARIM central. As of 2020, the SEO resources have not been allocated to CARIM, which puts pressure on the budget of CARIM. In addition, CARIM can no longer guarantee the 4th year for EC PhD candidates.

CARIM has several concerns related to teaching. The workload of researchers increases due to intensifying teaching activities, inhibiting people from performing research on a competitive level. In addition, new teaching activities are not reasonably compensated. Finally, there are concerns about the new curriculum of the bachelor of medicine, especially about the lack of smaller educational roles, often executed by PhD candidates or postdocs. The result is that the workload of senior researchers increases even more and young researchers can no longer perform teaching roles, which may have consequences for their future academic careers. Attracting external candidates is as important as fostering internal talent in order for CARIM to maintain its excellence. To meet this need, several external researchers have been attracted to CARIM in the last few years: Prof. Andrew Baker, Dr Elizabeth Jones, Dr Ed Eringa, Prof. Bastiaan de Galan, Prof. Marc Hemmelder, Dr Bastiaan Boukens, Dr Martijn Hoes, and Dr Nazha Hamdani. In addition, a fully covered CARIM assistant professorship programme to attract external talent is being prepared.

Follow-up for retiring PIs has been taken care of (Prof. Harry Crijns, Prof. Frits Prinzen, Prof. Chris Reutelingsperger) or is being actively explored (Prof. Hugo ten Cate, Prof. Bram Kroon).



Cardiovascular
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