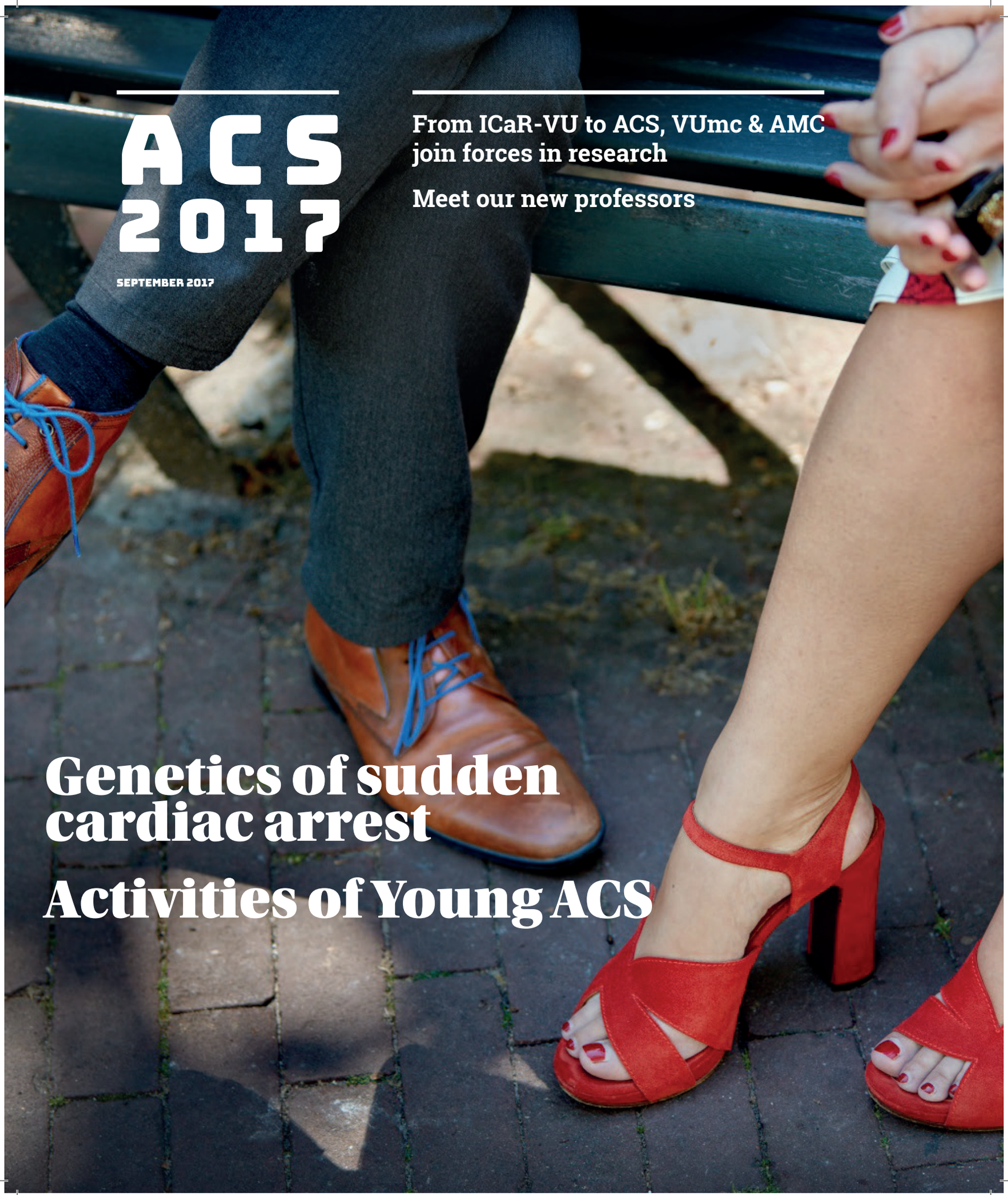


ACS 2017

SEPTEMBER 2017

From ICaR-VU to ACS, VUmc & AMC join forces in research

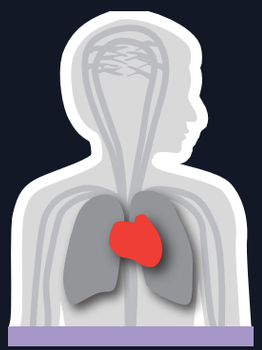
Meet our new professors

Genetics of sudden cardiac arrest

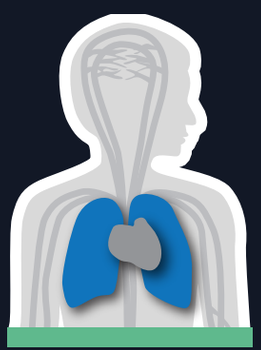
Activities of Young ACS

Mission To design knowledge-based treatment strategies to prevent and cure cardiovascular disease.

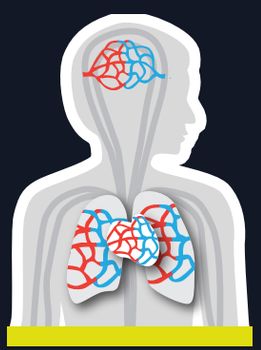
Vision To build one of the top European Cardiovascular Research Institutes by organizing education, research and clinical activities within 5 Research Themes to strengthen our position within Europe.



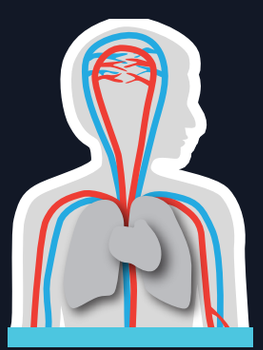
heart failure & arrhythmias



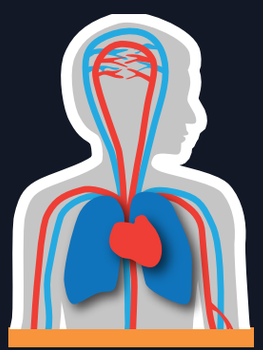
pulmonary hypertension & thrombosis



microcirculation



atherosclerosis & ischemic syndromes



diabetes & metabolism

TEAMED-UP cardiovascular research expertise in the Amsterdam arena

Mat Daemen & Jolanda van der Velden
Directors of the ACS

Due to changes in lifestyle, leading to obesity, hypertension and diabetes, cardiac and vascular problems are arising at a relatively young age. In spite of the significantly increased life expectancy, the ageing population is characterized by chronic cardiovascular disease such as heart failure, arrhythmias, diabetes and ischemic syndromes, which reduces quality of life and causes an excessive increase in healthcare costs. By combining our expertise within Amsterdam Cardiovascular Sciences, we strengthen and streamline our education, research and clinical activities and can build a common strategy to meet the current challenges in cardiovascular research. Amsterdam Cardiovascular Sciences brings together all cardiovascular research at AMC and VUmc and includes five major **research themes** (Heart Failure and Arrhythmia, Pulmonary Hypertension and Thrombosis, Atherosclerosis and Ischemic syndromes, Diabetes and Metabolism and a research cluster on Microcirculation). The research is translational by nature, encompassing basic and clinical research.Problems in patient care form the basis of novel experimental research concepts giving rise to a cycle of research from 'bedside to bench and back'. Our strategy enables us to to go from the patient care problem to experimental designs in the laboratory, and to subsequently test novel treatment strategies in selected patient groups.

Amsterdam Cardiovascular Sciences started in early 2016, stimulating and intensifying the collaboration between research groups at AMC and VUmc ever since. This is done by providing collaborative research grants, organizing network meetings, creating a website, sharing state-of-the-art expertise and infrastructure, and creating a platform for young researchers. Talented master students can follow a 2-year research master, and PhD students are part of the AMC or VUmc graduate school program. Amsterdam Cardiovascular Sciences has joint research programs with Amsterdam Public Health (for instance Helius), Amsterdam Neuroscience (for instance the neurovascular and the Heart-Brain programs) and Amsterdam Gastroenterology and Metabolism (for instance the Diabetes and Metabolism program).

In this first issue of the Amsterdam Cardiovascular Sciences magazine we highlight: several successful research lines, our cardiovascular imaging expertise in patients and animal models, and researchers at various stages of their research career.

CONTENTS

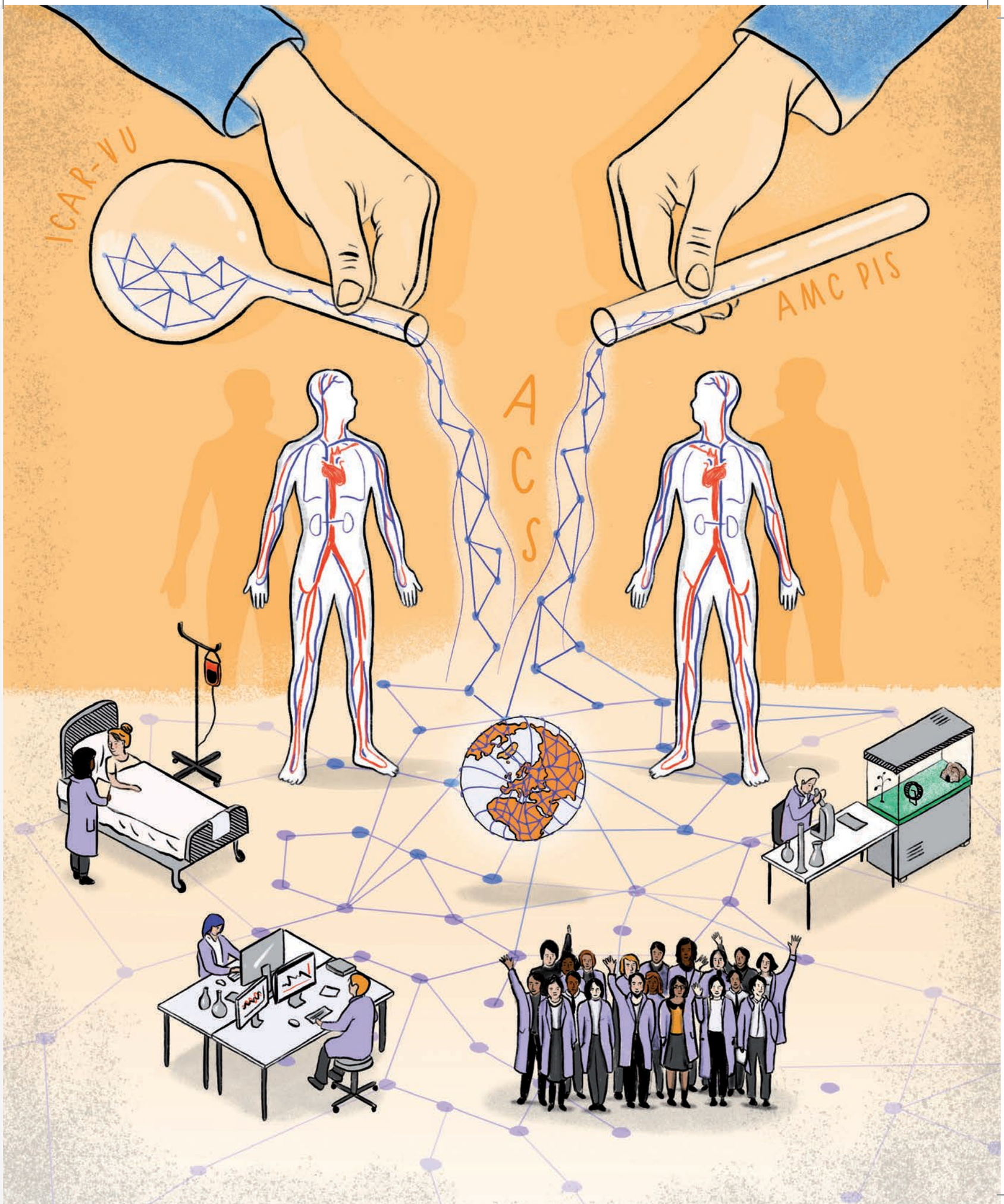
Colophon:

Design and lay-out: Karen Folkertsma
Photographs: Digidaan
Drawings: Gemma Illustraties
English correction: Lisa Kohn

Directors ACS: Mat Daemen and Jolanda van der Velden

Coordination:
Jolanda van der Velden
Isabelle Vergroesen

website: www.amsterdamresearch.org/web/cardio-vascular-sciences/home-4.htm


ICAR-VU
AMC PIS
ACS

Numbers & Facts

ACS Granted

- 1 PhD grant
- 5 MD 1day-a-week Postdocs
- 4 pre-clinical Postdocs
- 13 Out of the Box Grants
- 15 ACS symposia organized
- In 2017 food was served before the symposium, which may have increased attendance.

Members

- 600 PhD students
- 68 Postdocs
- 158 Principal Investigators
- 124 Staff members
- 22 Guests (senior and junior)

ACS Published

- 32 ACS Newsletters

3rd Annual Symposium

- 170 participants
- 70 Posters
- 6 Invited speakers
- 10 Selected presentations
- 1 Prize (500 Euro) for best presentation
- 2 Best Poster Prizes (200 Euro)
- 1 Best Publication of 2016 (200 Euro)
- 360 sandwiches for lunch, all finished at 5 pm
- 60 liters of coffee, 20 liters of tea, 7.5 liters of orange juice, 5 liters of milk, 1 liter of buttermilk

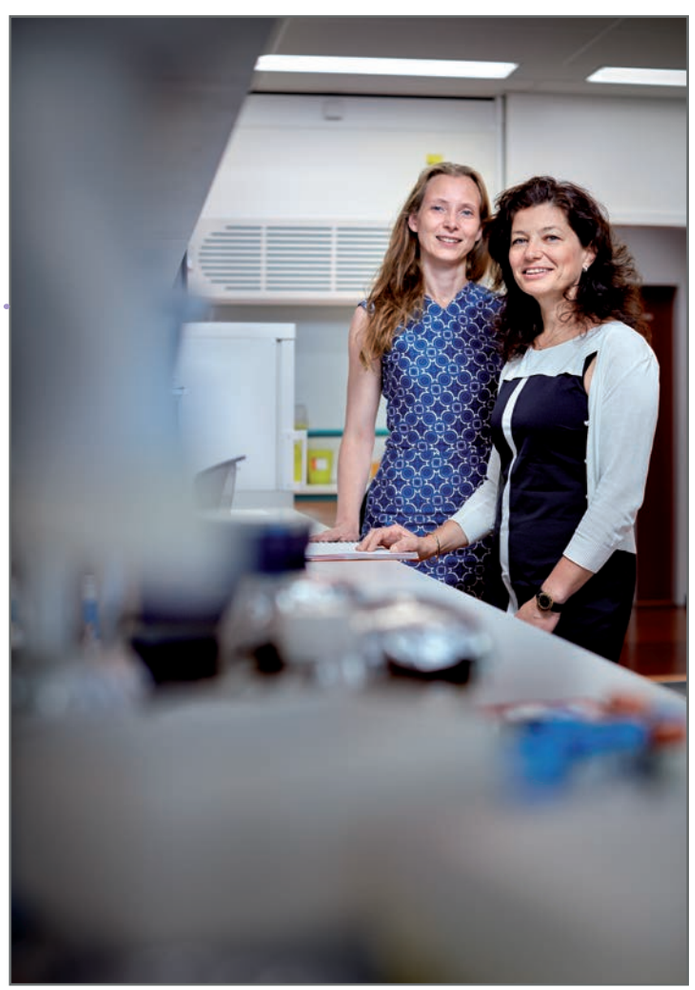
Genetics of sudden cardiac arrest

Connie Bezzina and Elisabeth Lodder have been working together to uncover the genetic causes that underlie cardiac arrhythmias leading to sudden cardiac arrest. Sudden cardiac arrest is a major contributor to mortality in the general population. In industrialized countries it accounts for almost 20% of deaths, which for the Netherlands translates to approximately 300 deaths per week. The most common arrhythmia causing sudden cardiac arrest is ventricular fibrillation. During this arrhythmia the heart muscle contracts in an uncoordinated manner and the heart is consequently unable to pump blood throughout the body. Although ventricular fibrillation mostly affects older individuals, it may also strike the young. In older individuals it typically occurs in the setting of cardiac pathologies that result from coronary artery disease, such as myocardial infarction. In the young it mostly occurs in the setting of familial cardiac disorders such as the Long QT Syndrome and Hypertrophic Cardiomyopathy.

Ventricular fibrillation, which presents as the first symptom of heart disease in a considerable proportion of patients, is fatal unless stopped within a few minutes by a defibrillatory shock. Unfortunately, medical help does not always reach victims on time. Thus, the identification of individuals who are at risk for sudden cardiac arrest and the timely implementation of preventive measures such as drug therapy or implantation of an ICD (implantable cardioverter defibrillator), are key in addressing the problem of sudden cardiac arrest.

Genetic factors play an important role in predisposition to ventricular fibrillation. The central goal of Connie's and Elisabeth's research is to identify genetic factors that underlie this arrhythmia such that these can be used to identify individuals at risk. In their studies they apply state-of-the-art genetic technologies including whole genome sequencing in affected families and large cohorts of patients collected in collaboration with colleagues from Clinical Cardiology and Clinical Genetics. Besides enabling genetic testing, the identification of new genes associated with sudden cardiac arrest also provides opportunities for understanding molecular and electrophysiological mechanisms underlying ventricular fibrillation. They therefore also conduct functional studies in collaboration with other researchers at the Department of Experimental Cardiology. This highly translational approach has resulted in the identification of several novel genes involved in predisposition to ventricular fibrillation. Current research is aimed at unraveling more complex genetic architectures.

300 deaths per week in the Netherlands caused by cardiac arrhythmias



Connie Bezzina (r.) &
Elisabeth Lodder (l.)
Experimental Cardiology, AMC

Joint efforts to reveal the role of the Adventitia in Remodeling of Resistance Arteries

Personal experience Anne de Leeuw

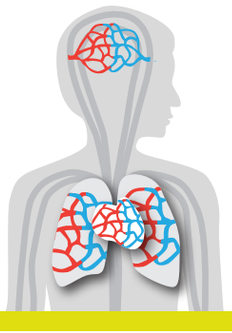
1ST PHD STUDENT ON JOINT AMC-VUMC PROJECT

I am honored to have been granted the opportunity to work in both the VUmc and AMC. I believe that the grant is helping the collaboration between the microcirculation groups in both centers, and that the ACS is doing a good job in promoting meetings and further collaboration between the cardiovascular groups. It is nice to see that the groups where I work, each has their own specialism and techniques, and are learning a lot from each other as a result of this collaboration.

Essential antihypertensive inward remodeling is a hallmark of hypertension, limits vascular reserve and is causally involved in the maintenance of high blood pressure. Moreover, inward remodeling is a strong independent risk factor for end organ events such as heart failure.

Resistance outward remodeling as a result of high shear stress is an adaptive response to, e.g., chronic exercise, and also occurs in collateral connections after main artery occlusion. The ability for outward remodeling and formation of collaterals is highly variable among the population, with large consequences for outcome in occlusive diseases.

Accordingly, there is a need for therapeutic interventions on resistance vessel structure and caliber. This requires a better understanding of the mechanisms of inward and outward remodeling. Most research on remodeling has been centered on the endothelial cells and smooth muscle cells.



Yet, the possible role of the adventitia in the regulation of remodeling is gaining interest. This layer is composed of a heterogeneous population of cells that are known to respond to stress, including induction of inflammatory responses and deposition of extracellular matrix proteins.

In our project we will study the role of adventitial cells in the resistance vessels. We will maintain resistance vessels pressurized and perfused in organoid culture, allowing the study of remodeling over the course of days. We will study adventitial cell differentiation and changes in key signaling pathways in response to the mechanical and biological stresses that are known to exist in cardiovascular pathologies.

Our results will provide a better understanding of the dysregulation of resistance vessel structure and function, and may lead to novel therapeutic choices for normalizing structure in hypertension and improving collateral caliber in occlusive diseases.

left to right: **Anne de Leeuw, Ed van Bavel, Erik Bakker, Peter Hordijk**
Biomedical Engineering and Physics, AMC & Physiology, VUmc

Imaging of the heart

Gustav Strijkers (l.) & Bram Coolen (r.)
Biomedical Engineering and Physics, AMC

The use of modern in vivo imaging techniques is considered of vital importance in translational research from animals to the patient and vice versa. The use of preclinical imaging has been increasing among biomedical and medical researchers as well as in the pharmaceutical industry, especially in the last ten years, due to the spectacular improvements in sensitivity, spatial resolution and speed. Most of the imaging modalities available not only allow detailed anatomical visualization, but can also provide functional, metabolic and even cellular or molecular information. Moreover, non-invasive imaging allows measurements in a living animal with minimal burden, thereby enabling longitudinal monitoring of disease progression. As such, preclinical studies can therefore unravel the interplay between different disease mechanisms and at the same time assess the long-term physiological impact of these diseases.

This year, the Amsterdam research arena has been strengthened by a new state-of-the-art preclinical magnetic resonance imaging (MRI) system as part of the new Preclinical and Translational MRI group led by Gustav Strijkers and Bram Coolen.

The new MRI facilitates in vivo studies in small animal models of various diseases, including brain-related disorders and cancer. A particular focus will lie on diseases involving the cardiovascular system, a research area that can strongly benefit from this advanced technology. Because of its excellent soft tissue contrast in combination with dynamic imaging at high spatial resolution (50-200 μm), MRI has become the gold standard technique for assessment of myocardial function in small animals. Furthermore, the use of MR contrast agents allows quantification of myocardial perfusion, as well as infarct size in models of myocardial infarction. Besides imaging, MR spectroscopy allows measurements of other nuclei, for instance 31P to study cardiac energy metabolism.

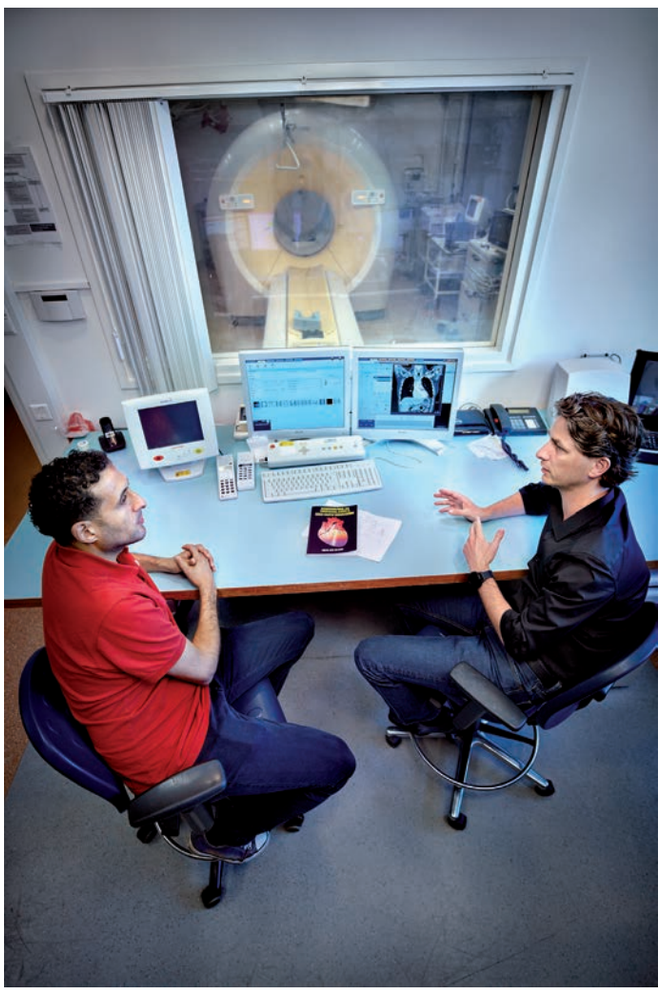
An ongoing AMC-VUmc collaboration (with Jolanda van der Velden & Diederik Kuster, Physiology VUmc) investigates the etiology of hypertrophic cardiomyopathy (HCM), which is characterized by unexplained hypertrophy, diastolic and microvascular dysfunction, fibrosis and impaired energetic efficiency. This project was initiated with an ACS Out of the Box grant. All these parameters can be assessed using preclinical MRI measurements. The goal of this project is to elucidate the sequence of pathomechanisms underlying disease progression of HCM by using a genetic mouse model of HCM and performing MRI measurements during cardiac development. This allows us to differentiate between primary disease drivers and secondary effects, and ultimately develop targeted preventive therapies.

The preclinical MRI scanner is part of APRIL (Amsterdam Preclinical Imaging Laboratories), which also includes other imaging modalities, such as SPECT, PET, Ultrasound and a Fluorescence Imaging Cryomicrotome system. The availability of these preclinical techniques will not only strengthen basic fundamental research, but will undoubtedly facilitate translation of these results to a clinical setting.

From bench to bedside

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in Western civilized countries. Early detection of CAD allows optimal therapeutic management in order to decrease morbidity and mortality. In the Netherlands 80.000 invasive coronary angiographies are performed each year. Invasive coronary angiography (ICA), particularly in conjunction with fractional flow reserve (FFR) measurements, is considered the gold standard in diagnosing and evaluating the severity of CAD in the current era. However, ICA is an invasive procedure which is associated with a low, though significant, complication rate including bleeding, coronary artery dissections, cerebral embolism, cardiac arrhythmias, myocardial infarction and death.

Therefore, there is a need for non-invasive imaging techniques for diagnosing and evaluating the hemodynamic significance of CAD. Non-invasive techniques can serve as a gatekeeper for ICAs in order to decrease the number of purely diagnostic invasive angiographies and associated morbidity and mortality. By more accurately identifying patients who are eligible for coronary revascularization with the use of non-invasive imaging, the number of unnecessary invasive diagnostic coronary angiographies can be decreased. Noninvasive cardiac imaging plays a central role in the diagnosis, management and risk stratification of patients with suspected CAD. An array of noninvasive tests is available for diagnosis of CAD, including single photon emission computed tomography (SPECT), positron emission tomography (PET) and coronary computed tomography angiography (CCTA). These imaging methods allow for assessment of myocardial perfusion, absolute myocardial perfusion and coronary stenosis severity, respectively. At present, European and US guidelines do not advocate for any non-invasive imaging modality over another.



Ibrahim Danad (l.) & Paul Knaapen (r.)
Cardiology, VUmc

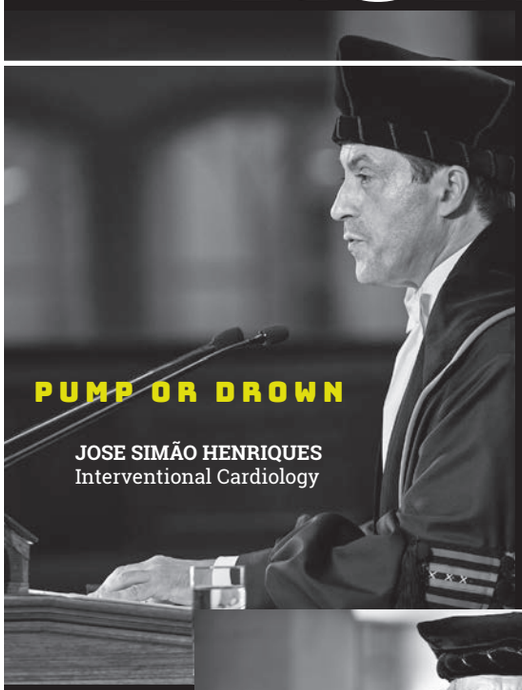
Current professional societal guidelines advocate for non-invasive imaging to be used for intermediate CAD risk patients, given the higher reclassification rates for these patients based upon imaging findings. In the Prospective compArison of CardIac PET/CT, SPECT/CT perFusion imaging and CT coronary angiography with Invasive Coronary angiography (PACIFIC) trial we found that 15O-water PET imaging exhibits the highest diagnostic accuracy for assessment of hemodynamics significant CAD as defined by FFR measurements compared with SPECT and CCTA imaging. Nevertheless, CCTA has high sensitivity and negative predictive value allowing the exclusion of obstructive CAD with near to absolute certainty. However CCTA is, by its nature, limited when evaluating the functional aspects of coronary stenoses. Surprisingly, the PACIFIC-trial taught us that hybrid cardiac imaging combining CCTA with SPECT or PET has no additional diagnostic value compared to standalone imaging. Indeed, the addition of functional techniques to CCTA comes at a cost of sensitivity and guides clinical decision-making in an unsalutary fashion.

amc

MEET OUR NEW PROFESSORS

AN MRI FOR EVERYONE

GUSTAV STRIJKERS
Biomedical Engineering and Physics

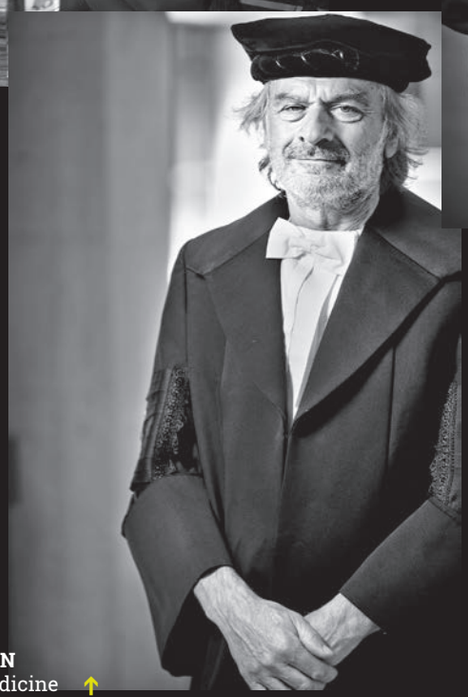


PUMP OR DROWN

JOSE SIMÃO HENRIQUES
Interventional Cardiology

THE CURIOUS CASE OF LIPIDS

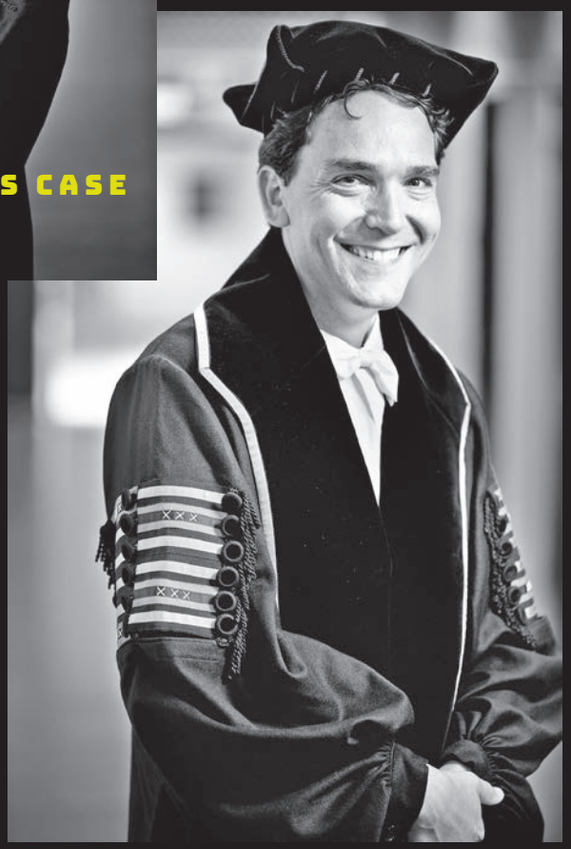
NOAM ZELCER
Biochemistry



BERT GROEN
Internal medicine ↑

SUGAR ON THE MOVE: FROM GROUP TO INDIVIDUAL →

MAX NIEUWDORP
Internal Medicine



THE DIAPHRAGM: A BREATH-TAKING MUSCLE

COEN OTTENHEIJM
Physiology

RESTART YOUR HEART

BIANCA BRUNDEL
Physiology

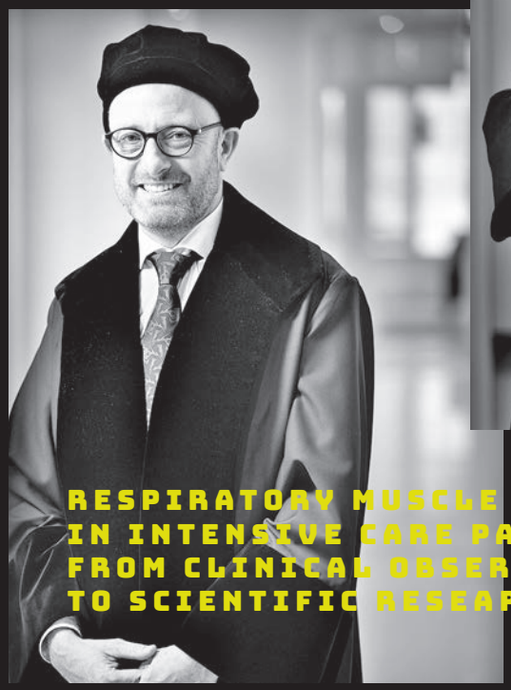
ALUS AEGROTI SUPREMA LEX

FRANS VAN ITTERSUM
Nephrology

JUDITH HUIRNE
Gynaecology

BE SURPRIZED

CHRISTA BOER
Anesthesiology

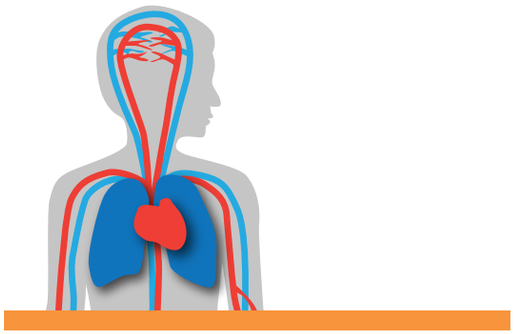


RESPIRATORY MUSCLE WEAKNESS IN INTENSIVE CARE PATIENTS: FROM CLINICAL OBSERVATION TO SCIENTIFIC RESEARCH

LEO HEUNKS
Intensive Care

RHEUMATIC DISAESES: HEART FOR YOUR HEART

MIKE NURMOHAMMED
Rheumatology



The kidney-heart connection

Marc Vervloet (l.) & Ed Eringa (r.)
Nephrology and Physiology, VUmc

Chronic kidney disease greatly increases risk of cardiovascular disease. Earlier research identified the FGF23 – klotho – vitamin D axis as a potential mediator of this risk. The hormone fibroblast growth factor 23 (FGF23) controls phosphate levels in the blood by stimulating its secretion in the urine. When phosphate levels rise due to kidney failure, FGF23 levels in the blood balloon. Importantly, this rise in FGF23 levels predicts who will suffer from cardiovascular disease such as a myocardial infarction or heart failure.

FGF23 qualifies as a clinical target of therapy

However, the predictive value of a protein does not mean that it will cause a disease, and therefore we (Marc Vervloet and Ed Eringa) teamed up to test whether FGF23 causes cardiovascular disease in a mouse model of chronic kidney disease. In these mice, surgical removal of one whole kidney and two-thirds of the other increases FGF23 levels and impairs endothelial function, one of the earliest steps in atherosclerosis. When we mimicked the rise in FGF23 by giving it to healthy mice, the impairment of endothelial function was similar, and blocking FGF23 in mice with failing kidneys restored endothelial function. In other words, a rise in FGF23 is necessary and sufficient for impairment of endothelial function in this model of chronic kidney disease. We discovered that FGF23 impairs endothelium-dependent vasodilatation by increasing the concentration of an endogenous inhibitor of NO synthase, asymmetric dimethyl arginine (ADMA). These findings, combined with the relationship between FGF23 and cardiovascular disease shown in chronic kidney disease patients, suggest that FGF23 has potential as a therapeutic target for delaying cardiovascular disease in patients with failing kidneys.

After characterizing the role of FGF23 in interactions between the kidneys and vasculature, we worked with heart failure experts Diederik Kuster and Jolanda van der Velden to determine its role in regulation of myocardial contraction. In isolated cardiomyocytes, we discovered that both kidney failure and chronically increased FGF23 activity impair calcium fluxes within the cardiomyocytes, an early step in the development of diastolic cardiac dysfunction.

Collectively, these studies support the concept that FGF23 qualifies as a clinical target of therapy, since this may prevent heart failure and disturbed microvascular disturbances. The combination of clinical and biological expertise and cardiac and vascular function specialists was critical to these discoveries

YOUNG ACS

YoungACS is an internal advisory board (think tank) of upcoming ACS researchers. **YoungACS** enhances the interaction between the young generation of ACS researchers and the ACS directorate. Each Center of Excellence is represented in **YoungACS** by a member from the AMC and another from the VUmc, in anticipation of the AMC-VUmc merger and thus accelerating the building of bridges between these two Amsterdam medical centers.

YoungACS advises the ACS directorate on issues including Branding & Communication and research strategies. The goal of this endeavor is to attract and stimulate talented researchers and boost collaborative initiatives between the ACS' Themes within the AMC-VUmc alliance. By participating in **YoungACS**, members further develop their organisational and collaborative skills alongside their work as medical professionals and researchers. In addition, **YoungACS** proposes the scientific content for the Annual ACS Symposium and the monthly ACS Colloquia. The Masterclasses that are organized during the ACS Colloquia offer a platform for young researchers to present their work to a top-notch (international) cardiovascular researcher.

We welcome any suggestions and comments you might have to further improve Amsterdam Cardiovascular Sciences! Please contact us at: **h.j.herrema@amc.nl**

left to right: Stephan Huveneers (Biochemistry, AMC), Raphael van Duivenvoorden (Internal Medicine, AMC), Michiel Coppens (Vascular Medicine, AMC), Frances de Man (Pulmonology, VUmc), Rick Meijer (Internal Medicine, Vumc), Diederik Kuster (Physiology, Vumc), Anke Tijsen (Experimental Cardiology, AMC), Hilde Herrema (Internal Medicine, AMC), Paul Krijnen (Pathology, VUmc) (not in the picture: Kakkhee Yeung (Vascular Surgery, VUmc))

Personal Grants

Several investigators received prestigious grants from the Netherlands Organisation for Sciences (NWO; VENI-VIDI-VICI innovation grants) and the Netherlands Heart Foundation (NHS Dekker program)

AMC

Bram Coolen, Radiology Veni 2015: Risky blood vessels - MRI sees what we can't see

Esther Lutgens, Biochemistry, ERC Consolidator grant 2015: CD40 goes innate: defining and targeting CD40 signaling intermediates in the macrophage to treat atherosclerosis

Anke Tijsen, Experimental Cardiology, VENI 2015: Fewer cases of severe congenital cardiac arrhythmia?

Anke Loregger, Biochemistry, NHS Junior Postdoc Dekker grant 2016: Which genes determine the Blood Cholesterol

Ot Bakermans, Radiodiagnostics, VENI 2016: Exercise magnetic resonance imaging and spectroscopy of the long-chain fatty acid beta-oxidation deficient heart

Bas Boukens, Anatomy, Embryology and Physiology, NHS Dekker senior Postdoc: Rol van genen bij prikkeloverdracht

Geert Boink, Cardiology, ERC Starting grant: Repair of junctional Atrioventricular conduction and impuls formation

VUMC

Reinier Boon, Physiology, Vidi 2016: 'Junk' RNA and heart ageing

Nicole Dekker, Anesthesiology, NHS Dekker grant for Medical doctor before the start of specialisation 2016: Preservation of renal microcirculatory perfusion during cardiac surgery with cardiopulmonary bypass to prevent acute kidney injury

Anton Vonk Noordegraaf, Pulmonology, VICI 2016: "Saving the right"

Deli Zhang, Physiology, NHS Junior Dekker postdoc grant 2017: BEAT Atrial Fibrillation: prevention of microtubule-SR-mitochondria disruption

Photo top, left to right: **Anke Tijsen, Anke Loregger, Ot Bakermans, Bram Coolen, Bas Boukens and Esther Lutgens.**
Photo bottom: **Anton Vonk Noordegraaf and Deli Zhang**
(Photo's by Digidaan)

Photo top: **Reinier Boon**
Photo middle: **Nicole Dekker** (Photo by Marieke Wijntjes)
Photo bottom: **Geert Boink** (Photo NN)

INTERNATIONAL PROGRAM

Master Cardiovascular Research

The Master Cardiovascular Research offers students a challenging program with a high degree of freedom to choose among several specialized Master courses and a number of outstanding research groups for research projects. It is a two-year international program of 120 ECTS with all tuition in English.

MIRIAM VAN STRIEN 'MOTIVATED STUDENTS'

What I particulary like about the master Cardiovascular Research is that it is a small-scale international master. The level of education is high and the students that are currently enrolled in the program are very motivated. I think that this master program is a good preparation for the future careers of our students. At the beginning of this year, the midterm review of our master program was very positive. On top of that, the master Cardiovascular Research reached the 3rd place of all biomedical masters in the Netherlands in the Dutch Student Survey. Already a great result but there is always room for improvement.

CHRISTA BOER 'PROUD TO BE PART OF THE SUCCESS'

It is very rewarding to know that our students feel and take on the passion of their teachers, which is reflected by the extensive discussions during the lectures. Moreover, it is during the graduation ceremonies that I am reminded that we should be proud to be part of the success of our students in their internships and future careers. In particular, most of our students are currently working as scientists in the cardiovascular field. This is the reason why I am motivated to improve our master program every day, as we provide a future for all students who decide to contribute to the prevention and treatment of cardiovascular disease.

Full text of the interviews see website: **http://www.amsterdamresearch.org/web/cardiovascular-sciences/education.htm**

FUTURE SCIENTISTS

Margot Venhuizen
Student 2016

Margot Venhuizen, student 2016

What did you like the most about your first year?

The first thing that comes to mind is the study trip to Florence, to attend a symposium about cardiomyopathies. We rented a house for two nights and got to know each other on a different level. Our group grew very close over the course of last year. With our new coordinator Miriam van Strien, we were recently able to get funding for a study trip at the end of September to Belgrade in order to attend a symposium on diabetes, coronary artery disease and heart failure. This time, because of the financial help of ACS, the whole group will be to attend the symposium.

Luuk Hopman, student 2016

What do you like the most about our master program?

The diversity in pre-clinical and clinical education. I noticed that I am not the type of person who is fascinated by hard-core lab research. The clinical approach of this master program gives me the possibility to do clinical research as well. And thus, I am able to get the vision and knowledge of someone with a biomedical background. Therefore, I am able to understand most parts of pre-clinical research. This makes it attainable for me to make a meaningful connection between the lab and the clinic.

Luuk Hopman
Student 2016

Rocio Muniz, student 2015

When did you know that you wanted to do the master cardiovascular research and why?

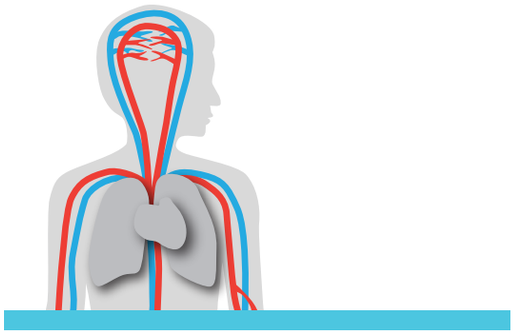
I realized that I wanted to do the CVR Master during my Bachelor Internship at the Physiology department at the VUmc. I was working at the Angiogenesis Research group under the supervision of Pieter Koolwijk and Rob Wust. I was enjoying the internship and the cardiovascular topic greatly so I decided that I wanted to have a deeper insight by doing a Master in this field.

Laween Uthman
Alumnus master program
PhD student at AMC

Laween Uthman, Alumnus master program & PhD student at AMC

Was it easy for you to find a job?

Yes and no. As there are not many academic positions in research, I think we as researchers have quite a difficult path to walk towards a scientific career. But I really felt that doing a research master that is concentrated on cardiovascular research per se gave that extra push for me to be more confident on my job interviews, which eventually got me my current job.



Treasure trove in lipidology

Familial Hypercholesterolemia (FH) is a prevalent (1:250) disease, characterized by extremely elevated plasma levels of Low Density Lipoprotein- cholesterol (LDL-C) and severely increased cardiovascular disease risk. Mutations in LDLR, APOB and PCSK9 underlie FH1, FH2 and FH3, respectively. Our understanding of cholesterol metabolism is largely derived from studies in patients with extreme lipid phenotypes such as FH and current lipid lowering therapies are targeted against the proteins encoded by the causative genes. These therapies all have their specific limitations and additional targets are therefore to be identified.

left to right: Rens Reeskamp, Merel Hartgers, Kees Hovingh
Internal Medicine, AMC

Implementation of an integrative study model to quantify the impact of Familial Hypercholesterolemia 4 on atherosclerosis

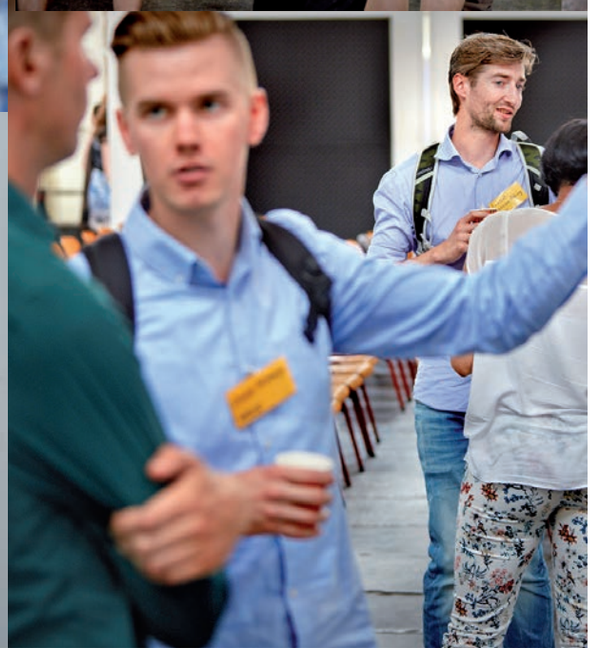
Approximately 5-10% of the FH patients suffer from FH4, a form of FH where no mutation is identified in the three FH genes. Unravelling the cause of FH4 is widely acknowledged to be the treasure trove in lipidology, since it may lead to the identification of a target that is druggable by an oral agent, which will have an impact for every patient at risk for cardiovascular disease. Despite considerable efforts little progress has been made in elucidating the aetiology of FH4, which has resulted in the present stand still in target identification.

We will overcome this barrier by implementation of an integrative study model where data derived from cellular, proteomic, transcriptomic, kinetic and genomic studies are analysed conjointly using state of the art systems medicine tools in an unique cohort of FH4 families. Whereas previous studies have focused solely on the genetic origin of dyslipidemia, we will perform a root cause analysis by investigating all crucial steps that ultimately lead to the plasma LDL-C concentration, including LDL formation, modification and degradation. The studies performed will not only focus on the cause, but also on the clinical consequence of FH4, in order to quantify the impact of FH4 on atherosclerosis, the ultimate phenotype to be addressed.

ACS SYMPOSIA

Monthly meetings & yearly symposium to discuss advances in CV research

Meet and greet with colleagues *from* **both sides** *of the* **Amstel**



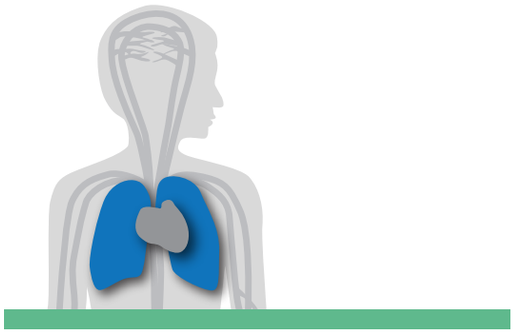
ACS SYMPOSIA AND CONFERENCES

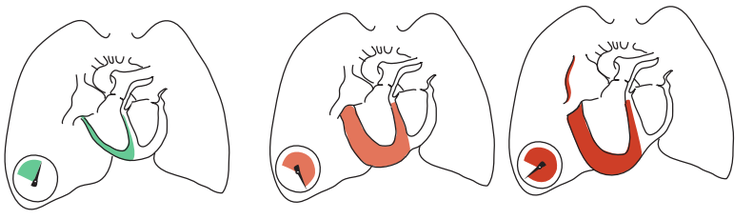
Amsterdam Cardiovascular Sciences Activities 2017

MARCH 6	Atherosclerosis & Ischemic syndromes
MARCH 9	Defense of Personal Research Proposals (VUmc)
APRIL 3	Heart Failure & Arrhythmias
MAY 8	Microcirculation
JUNE 12	Pulmonary Hypertension & Thrombosis
JULY 6	**3rd ACS conference (Oosterkerk)**
SEPTEMBER 4	Diabetes & Metabolism
OCTOBER 2	Atherosclerosis & Ischemic syndromes
NOVEMBER 6	Heart Failure & Arrhythmias
DECEMEBR 4	Pulmonary Hypertension & Thrombosis

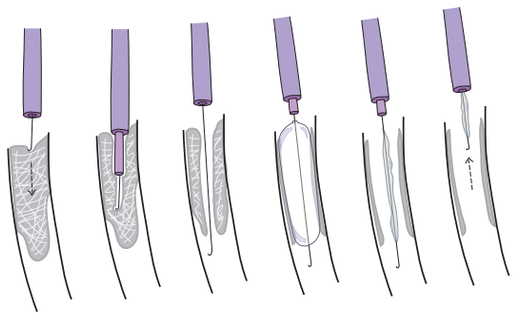
Amsterdam Cardiovascular Sciences Activities 2018

FEBRUARY 5	Microcirculation
MARCH 5	Diabetes and Metabolism
APRIL 9	Heart Failure & Arrhythmias
MAY 7	Atherosclerosis & Ischemic syndromes
JUNE 4	Pulmonary Hypertension & Thrombosis
JULY 5	**4th ACS conference**
SEPTEMBER 3	Diabetes & Metabolism
OCTOBER 1	Microcirculation
NOVEMBER 5	Heart Failure & Arrhythmias
DECEMBER 3	Atherosclerosis & Ischemic syndromes

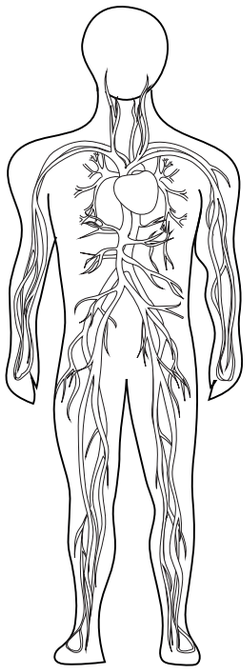


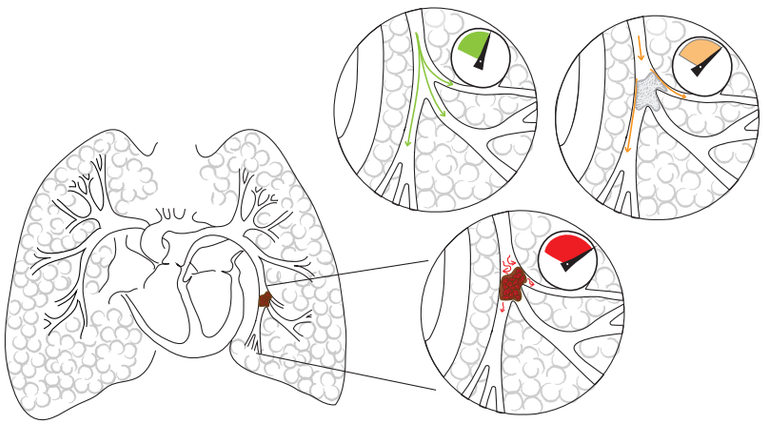


Development of right heart failure in patients with chronic thrombo-embolic pulmonary hypertension (CTEPH): from RV hypertrophy to excessive dilatation.



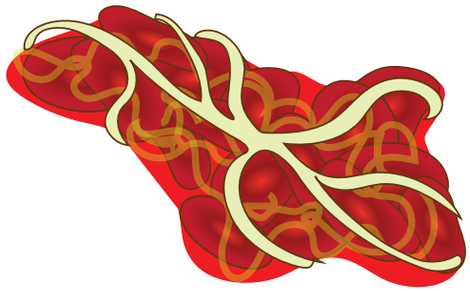
Novel procedure to treat patients with inoperable CTEPH: Balloon pulmonary angioplasty (BPA).
A wire with balloon is inserted in the lung vessel with obstruction, by inflating the balloon the pulmonary blood flow is restored.

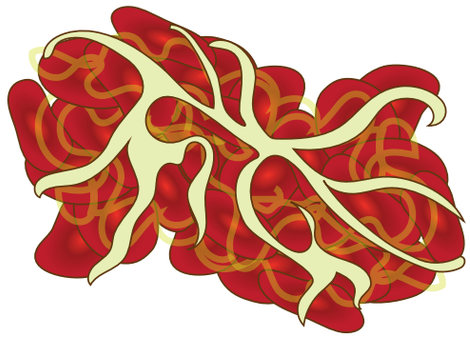


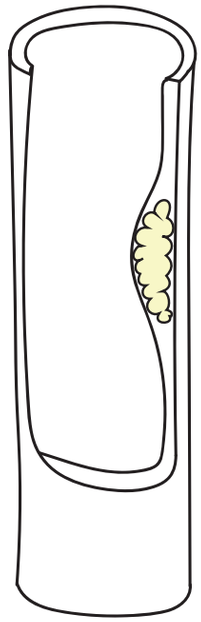


CTEPH is caused by a thrombotic lesion in the small pulmonary arteries. BPA is a new therapeutic approach to restore the pulmonary blood flow.

Thrombo-embolic clot







Awards for
Best Presentation
Best Publication
Best Poster

Best Presentation
Anna Huis in 't Veld, The effect of upfront combination therapy on right ventricular volumes in patients with pulmonary arterial hypertension

Best Publication
Bernadette S. de Bakker, Kees H. de Jong, Jaco Hagoort, Karel de Bree, Clara T. Besselink, Froukje E.C. de Kanter, Tyas Veldhuis, Babette Bais, Reggie Schildmeijer, Jan M. Ruijter, Roelof-Jan Oostra, Vincent M. Christoffels & Antoon F.M. Moorman.

An interactive three-dimensional digital atlas and quantitative database of human development. Science. 2016 Nov 25;354(6315).

Best Posters
Maike Schuldt: Mutation location determines disease severity in Hypertrophic Cardiomyopathy

Denielli Da Silva Goncalves Bos (price was accepted by Xiaoqing Sun): Contribution of impaired parasympathetic activity to right ventricular dysfunction and pulmonary vascular remodeling in pulmonary arterial hypertension

ACS awards 2015-2017

ACS awarded: a PhD project (€ 200,000), postdoc projects (€ 70,000), MD/PhD projects (€ 25,000) and out of the box grants (OOTB) (€ 25,000) to stimulate innovative collaborative research.

2015

Lutgens/van Royen	In vivodetection of high-inflammatory plaques by tracking CD40 with molecular PET/CT	OOTB
Muller/van Lieshout	Hypertensive treatment in frail elderly: should we SPRINT faster?	OOTB
Scheffer/Stiedl	Establishment of a computerized home cage-based cognitive test in a murine Alzheimer's disease model	OOTB
Kuster/Strijkers	I can see clearly now: Small animal imaging to distinguish cause and effect in early HCM disease pathology	OOTB
Wust/Houtkooper	The inconvenient truth about antibiotic toxicity in heart failure	OOTB
Hordijk/ Zelcer	The Ubiquitin ligase MARCH6 links cholesterol metabolism and RhoGTPase signaling to the control of endothelial integrity	OOTB

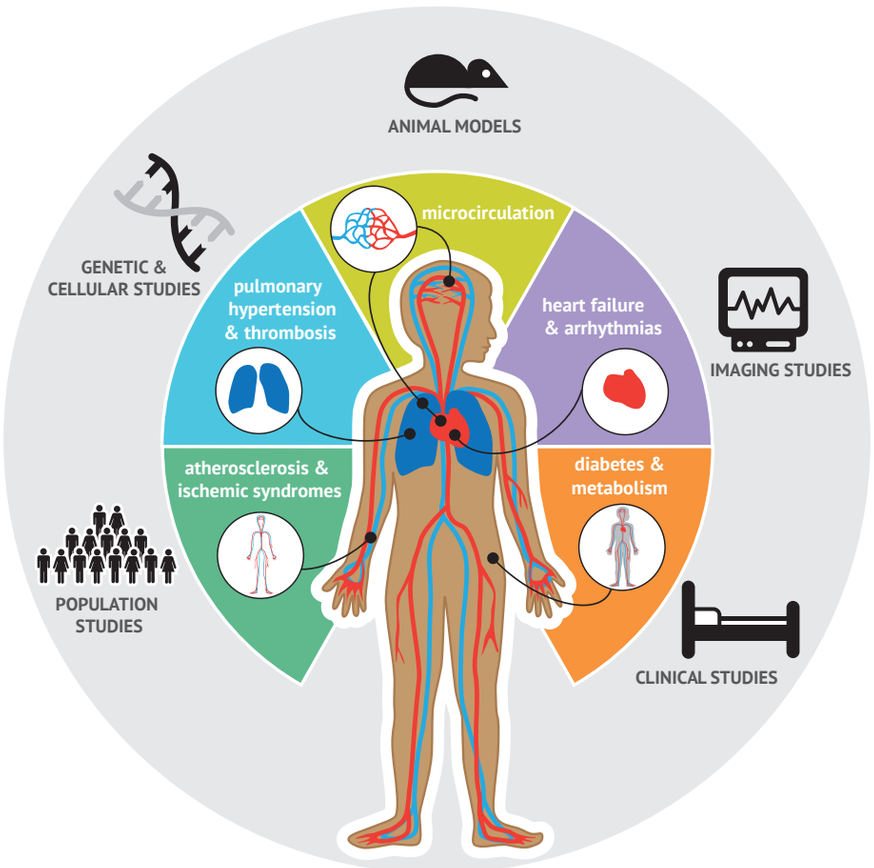
2016

de Leeuw	Role of the adventitia in resistance vessel remodeling	PhD
Seijkens	Costimulation-mediated regulation of hematopoieticA critical pathway in atherosclerosis	MD/PhD
Yeung	The key role of smooth muscle cell contractility in development	MD/PhD
Delewi	Improving cerebral hypoperfusion after implantation	MD/PhD
Meijer	Sweet Memories: Getting Insulin into the Brain	MD/PhD
Lauw	Venous and arterial complications ...MD/PhD	
Hoeksema	Mapping macrophage enhancers to identify central atherosclerotic disease	Postdoc
Sequeira	Impaired energy homeostasis as a cause of acute hypertrophic cardiomyopathy	PD

2017

de Winter	KBTBD13: a novel gene implicated in cardiomyopathy	Postdoc
Kroon	Targeting inflammation and leukocyte migration	Postdoc
Heunks/Ottenheijm	Partial diaphragm ventilation	OOTB
Eringa/Groen and Turaihi	The silent whisperer: the after bariatric surgery OOTB 25.000	
Huveneers/Hordijk	Visualizing endothelial dynamics in zebra fish blood vessels	OOTB
Houweling/Creemers	Myocardin mutationsheart and smooth muscle	OOTB
Hermkens/de Vries	Intracranial endothelial cognitive impairments	OOTB
Brundel/de Waard	Transcription factor nur77 is a genetic modifier for cardiac arrhythmia	OOTB
vd Hoff/Houweling	Integrating cardiovascular human development	OOTB

Amsterdam Cardiovascular Sciences



amc

VUmc