ACS 2021

JUNE 2021

PhD Thesis App

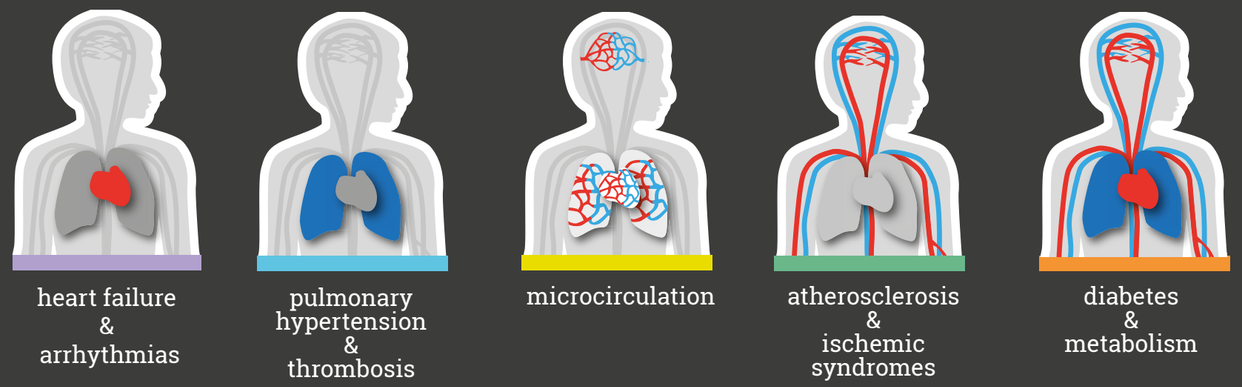
New research website

Patient involvement in ACS research

COVID-19 research within ACS

Mission To design novel treatment strategies to prevent and cure cardiovascular disease.

Vision To strengthen our top European Cardiovascular Research Institute by organizing education, research and clinical activities within the current 5 Research Programs.



Word from the directors

Jolanda van der Velden & Arthur Wilde
Directors of ACS

In your hands you have the 5th 'ACS glossy'. Unfortunately, 2020, and it now appears a big part of 2021, were and will be dominated by Corona (COVID-19) related challenges. We have all been confronted with COVID-19, some of us more personally affected with occasionally long-term negative effects. For others, PhD projects are delayed with the associated financial consequences and elective patient procedures, such as ablations, PCI and cardiac surgery, have been delayed. On the other hand, the Corona crisis has also provided opportunities, in particular in the research domain. At an unprecedented pace COVID-related research was launched within Amsterdam UMC. In August 2020, just six months after the first patient presented at Amsterdam UMC, 110 COVID-related studies had already been registered and at that time this number was still rapidly increasing. Numerous high impact papers have been published. Some of these studies are highlighted in this issue, including two randomized trials on targeting the complement system and vascular leakage in (severe) COVID-19 patients. There are high expectations for the artificial intelligence options coming from the massive amounts of COVID-19-related data obtained in the intensive care setting. These innovative approaches are also discussed in this issue.

Despite all the Corona-related issues the 'lateralization process' of Amsterdam UMC is continuing full speed ahead. We are now on the 3rd wave with a major impact on the Heart Center. Cardiac surgery and vascular surgery have now largely been moved to the AMC location and the department of Pulmonology to the VUmc location. These moves have also had a significant impact on the workflow within the Cardiology departments at both locations. New plans, including the construction of new catherization laboratories are about to be realized.

Another important topic covered in this issue is the active involvement of patients in ACS research. In the clinical domain patient-reported outcome measures (PROMs) have become daily practice in recent years. The patient's voice is also increasingly heard in basic and translational research. Every researcher who is actively involved in grant applications (Dutch Heart Foundation, ZonMw, EU) will have noticed that patient involvement has become a critical aspect. There is no grant without the patient's voice. This implies the patient involvement in the design of the application, as well as in the execution of the project, for example, by their participation on the user committee.

Finally, we will have a digital mid-term evaluation of ACS in June in preparation for our institute's audit in 2023. We are all longing for the post-Corona era and a time when in-person meetings will be the norm again. Nevertheless, and despite the relatively hectic times of 2020/2021, ACS scientists have performed extremely well. In fact, COVID-19 actually intensified collaboration between researchers at the AMC and VUmc locations. Facilitating collaboration is also one of the main aims of the new Amsterdam UMC research website. On this online platform, where ACS has its own pages, researchers can present themselves and their research via their own personal page. We encourage you to complete your personal page as it enhances the visibility of you, our ACS researchers.

Arthur Wilde & Jolanda van der Velden

CONTENTS

Colophon:

Design and layout: Karen Folkertsma
Photographs: DigiDaan
Drawings: Josine de Winter & Pleuni Hooijman (Sketch University)
English editing: Lisa Kohn

ACS Directors: Arthur Wilde & Jolanda van der Velden

Coordinators:
Anne-Lieke van Deijk
Isabelle Vergroesen
Jolanda van der Velden

Website: www.amsterdam-cardiovascular-sciences.org

ACS Thesis App

Harm Ebben

In January 2020, ACS created a PhD Thesis App portal for ACS PhD candidates who are graduating from Amsterdam UMC. All theses from ACS researchers will be bundled and freely available in the online ACS Thesis App. The app is linked to the monthly overview of PhD defenses that is sent to all ACS researchers. The ACS Thesis App makes your PhD thesis more interactive, accessible and sustainable, and replaces the former ACS grant for printing costs.

INCLUDE ONLINE NETWORKS AND A FORM FOR QUESTIONS

Enhance your PhD Thesis by incorporating online networks such as, ResearchGate, LinkedIn, Google Scholar, PubMed and Publons, and by adding a form for questions where people can ask questions about you or your PhD thesis. You can also include a map of the location of your PhD defense, reception and/or party that links to your mobile navigation App for directions.

SHOW VIDEOS AND LIVESTREAM TO YOUR ONLINE DEFENSE

Add videos or animations of your research experiments, flow-charts or visual abstracts. Include an online live-stream of your defense for people to follow live or on demand, at a later time. You can also share the slides of your presentation in your Thesis App.

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Save trees by sending a digital QR code or link to your PhD thesis via the ACS Thesis App portal. This will also save you expensive printing and shipping costs, leaving you more money for other expenses. These days it's even more important to be able to easily share your PhD thesis with all your colleagues, friends and family around the world. All chapters can be password protected, also the ones that are under embargo.

HOW TO GET ONTO THE ACS THESIS APP

You can access the ACS Thesis App and see all uploaded ACS PhD theses via app.thesisapps.com/acs/theses. If you want to apply for the ACS Thesis App, please visit www.amsterdamumc.org/acs-thesis-app for more information.

Patient involvement in ACS research

Dayenne Zwaagman & Patricia Vlasman

Patricia Vlasman and Dayenne Zwaagman go way back. Two heart patients who are passionately committed to the involvement of patients in cardiovascular research at Amsterdam UMC and beyond. Vlasman and Zwaagman joined the Dutch Heart Foundation and the 'Harteraad,' the Dutch patient federations for cardiovascular patients, to make sure that the patient's voice is heard. For a year and a half, they were both board members of the Hart4Onderzoek (Heart4Research), a patient charity foundation that raises money for scientific research on congenital heart and/or vascular diseases in young adults. At the end of their term, their paths separated. Nevertheless, they are both continuing their work to improve the connection between patients, care and research, albeit from a different angle.

PATIENT INVOLVEMENT

Zwaagman: 'I am currently working as a communication specialist at the Hartcentrum (Heart Center). I started with a blank sheet and have updated the website by removing jargon, thereby making it more comprehensible for patients. An important part of my work is to improve the information provided to patients, researchers and care staff. The COVID-19 pandemic worked as an accelerator of the digitalization, from outpatient visits to the introduction days for A(N)IOS. At the moment, I am digitalizing care pathways in which patients and their loved ones are being kept informed about the surgery they have to undergo. By using 3D and Virtual reality videos we try to prepare and comfort the patients as much as possible.'

Vlasman: 'Since 2014 I have been working as a patient representative within the several consortia of the Dutch Heart Foundation (CVON Dosis/Double Dose, Early HFpEF, AFFIP, SHE-PREDICTS HF and Cardio Moonshot). After my own successful heart transplantation, I started working again as a policy advisor at Patiëntenfederatie Nederland (Dutch Patient Federation) and in this role I approach the patient needs more from a public affairs and stakeholder management angle.

Together with Jolanda van der Velden, Diederik Kuster, Rudolf de Boer (UMCG) and Peter van Tintelen (UMCU) I recently started the international organization Cardiomyopathy Research The Netherlands (https://cardiomyopathie-onderzoek.nl). Together with other national and international research institutes, hospitals and other patient organizations, the foundation promotes the interests of all cardiac gene carriers and their families by: conducting scientific research of hereditary heart diseases, identifying predisposed relatives at an early stage and striving for better treatment to find a solution for the congenital and genetic heart (muscle) condition cardiomyopathy.'

It is important that the patient's voice is heard

Patricia Vlasman

Dayenne Zwaagman

Zwaagman: 'Recently Amsterdam UMC organized a Patient Day where representatives from cardiology patient federations were informed about the merger of the two academic hospitals and the implications for cardio(thoracic) patients. The representatives will forward this information on to the patients within the federation. But it is not just a one-way flow of information, it is also very important that the patients are heard. Doctors and nurses should be encouraged to include the patient story in their work, as well as in research. What does the patient need to know about participation in clinical trials? Most of the time it is about providing the patient with information they can understand.'

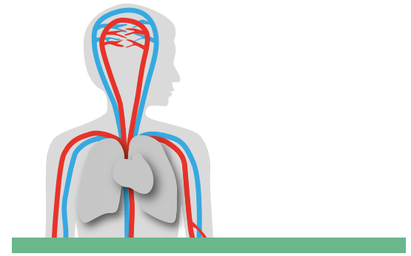
SOCIAL AWARENESS

Vlasman: 'In order to increase the societal impact of research, it is important to make research as accessible as possible. By including various perspectives, like the patient perspective in the research questions, the content of the research will improve and it will become more socially relevant. Citizens and patients demand more transparency and accountability when it comes to public funds, and to be more involved in discussions about usefulness and necessity. Research institutes must encourage their researchers to step outside. Only when scientific research functions in connection with society can it produce the fruits we need and the answers to the challenges we face together. Therefore, public and patient involvement in scientific research is fundamental.'

On June 1st, 2021 Patricia Vlasman started as staff advisor within ACS. Her focus is on the valorization of cardiovascular research, and the opportunities within public private partnerships.

Marfan Syndrome patient involvement in ACS research

VIVIAN DE WAARD, DEPT. MEDICAL BIOCHEMISTRY



What is Marfan syndrome?

Marfan syndrome is a rare genetic disease (3:10,000 incidence), where many different mutations in a structural protein, called fibrillin-1, causes variable pathology in different organs and organ systems, such as the eye, skeletal and cardiovascular system. Marfan syndrome is as rare as Cystic Fibrosis (CF), but unlike CF hardly anyone has heard of Marfan syndrome. Already, during adolescence patients with Marfan syndrome experience many symptoms and when not treated they often die of an aorta rupture before the age of 40. Currently, treatment options are limited to blood pressure lowering drugs and aorta surgery.

Support from a Marfan family

When we published that the food supplement resveratrol protected the aorta of our Marfan mice, one of our AMC patients asked why we could not perform a clinical study with resveratrol. This Marfan family provided the funding, via the AMC Foundation, of our RESVcue Marfan clinical study. PhD student Mitzi van Andel was hired to set up the study, which has enrolled 60 Marfan patients who are now on resveratrol. By the end of 2021 the study will end and we will analyze all data to see if there is cardiovascular improvement. Without this Marfan family our study would not have been possible, since funding for rare diseases is extremely difficult. The bonus of the involvement of this family has been to learn more about what they felt was important to measure or monitor. This led us to include psychological tests on wellbeing and fitness in the study.

Marfan mysteries

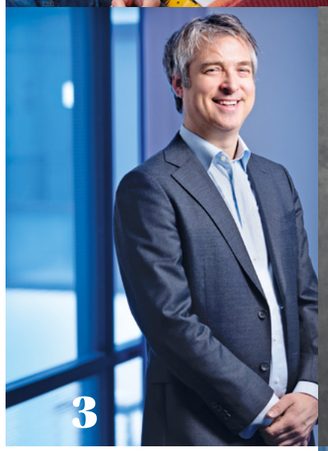
Even more rare is neonatal Marfan syndrome. Only very few mutations in fibrillin-1 cause this severe form, where it is not aorta problems, but heart failure that leads to mortality at around the age of 2, if not treated in time by surgical cardiac valve replacement. Interestingly and regrettably, it is a mystery why certain fibrillin-1 mutations cause a more severe form of Marfan Syndrome. That is exactly what we are looking into in two different studies. One study supported by ACS, is a collaboration of Dimitra Micha and Vivian de Waard, where PhD student Carmen Yap is growing cells of many different Marfan patients in order to identify various subtypes. By studying the cellular phenotype, we have observed that these different patient-derived skin fibroblasts are very informative. In the other study, supported by Stichting Steun Emma Kinderziekenhuis, pediatrician Leonie Menke is working with one of her patients named Sam. Sam has neonatal Marfan syndrome and his fibroblasts behave differently from most other Marfan cells. His mother recently published a book on her journey with her now 3-year-old son, entitled Een magisch getal (A magical number). A portion of the proceeds of her book is supporting our neonatal Marfan research at Amsterdam UMC. Via the internet, Sam's mother has been in contact with other mothers of children with the same condition from around the world, who share their knowledge and experiences.

Performing research on a rare disease is challenging. However, we have found a great willingness of Marfan patients and their families to help in various ways in finding novel ways to treat Marfan syndrome and its symptoms.

The Marfan family taught us more about what they felt was important to measure or monitor

left to right: **Dimitra Micha, Carmen Yap, Vivian de Waard, Mitzi van Andel**














Personal Grants

Jurjan Aman, Physiology, Veni 2020: *Preserving the small pulmonary arteries to treat pulmonary arterial hypertension*

Josine de Winter, Physiology, Veni 2020: *Energizing molecular dance in Dutch muscle disease*

Pim van Ooij, Radiology and Nuclear Medicine, Vidi 2019: *Less aortic motion in a diseased thoracic aorta*

Max Nieuwdorp, (Experimental) Vascular Medicine, Vici 2020: *Dietary fructose and its effect on microbiota and insulin resistance in obese subjects from different ethnic descent*

Stan van de Graaf, Tytgat Institute for Liver and Intestinal Research, Vici 2020: *Hepatic bile acid uptake as a target to halt the fatty liver epidemic*

Fleur Tjong, Cardiology, Rubicon 2019: *Deep learning for identification of ICD patients at risk of lethal cardiac arrhythmias*

Annette Neele, Medical Biochemistry, NHS Dekker Postdoc 2020: *The Polycomb Repressive Complex 2 (PRC2) in macrophages and atherosclerosis*

Harsha Devalla, Medical Biology, NHS Dekker Postdoc 2020: *Assembling pacemaker (BioPACE) and conduction (BioRELAY) tissues from hiPSC-derived cardiomyocytes*

Thijs van Mens, Vascular Medicine, NHS Dekker Clinical Scientist 2020: *Targets for treatment and prevention of autoimmune cardiovascular disease*

Monika Gladka, Medical Biology, NHS Dekker Senior Scientist 2020: *Investigating the protective role of ZEB2 and its downstream targets in oxidative stress response during cardiac repair*

Henk-Jan Mutsaerts, Radiology and Nuclear Medicine, NHS Dekker Senior Scientist 2020: *Developing arterial spin labeling (ASL) as vascular biomarker of cognitive decline*

Louis Handoko, Cardiology, NHS Dekker Senior Clinical Scientist 2020: *Targeting MItochondRiAl dysfunCtion and myocardial energy depLEtion in Heart Failure with Preserved Ejection Fraction (MIRACLE-HFPEF)*

Elena Rampanelli, Experimental Vascular Medicine, Dutch Kidney Foundation Innovation grant 2020: *A novel microbial metabolite to the rescue of diabetic kidney diseases*

Reinier Boon, Physiology, ERC Consolidator 2020: *Non-coding RNA and Intercellular Communication in Cardiac Ageing*

1 **Jurjan Aman**
2 **Josine de Winter**
3 **Pim van Ooij**
4 **Max Nieuwdorp**
5 **Stan van de Graaf**
6 **Fleur Tjong**
7 **Annette Neele**
8 **Harsha Devalla**
9 **Thijs van Mens**
10 **Monika Gladka**
(photo by Anna Zatica)
11 **Henk-Jan Mutsaerts**
12 **Louis Handoko**
(photo by Anita Edridge)
13 **Elena Rampanelli**
14 **Reinier Boon**

ACS SYMPOSIA AND EVENTS 2021 - 2022

Amsterdam Cardiovascular Sciences ACTIVITIES 2021

FEBRUARY 1	Atherosclerosis & Ischemic Syndromes
MARCH 1	Heart Failure & Arrhythmias
APRIL 12	Pulmonary Hypertension & Thrombosis
MAY 3	Diabetes & Metabolism
JUNE 7	Microcirculation
SEPTEMBER 2	6th Annual ACS conference
SEPTEMBER 6	Atherosclerosis & Ischemic Syndromes
OCTOBER 4	Heart Failure & Arrhythmias
NOVEMBER 1	Pulmonary Hypertension & Thrombosis
DECEMBER 6	Diabetes & Metabolism

Amsterdam Cardiovascular Sciences ACTIVITIES 2022

FEBRUARY 7	Microcirculation
MARCH 7	Atherosclerosis & Ischemic Syndromes
APRIL 4	Heart Failure & Arrhythmias
MAY 9	Pulmonary Hypertension & Thrombosis
JUNE 13	Diabetes & Metabolism
JULY 7	7th Annual ACS conference
SEPTEMBER 5	Microcirculation
OCTOBER 3	Atherosclerosis & Ischemic Syndromes
NOVEMBER 14	Heart Failure & Arrhythmias
DECEMBER 12	Pulmonary Hypertension & Thrombosis

Chapter 1 covers what is expected of individual research team members to achieve optimal cooperation

Chapter 5 covers the guidelines and tools needed for accurate research data management to allow for optimal transparency, reuse of data and scientific quality

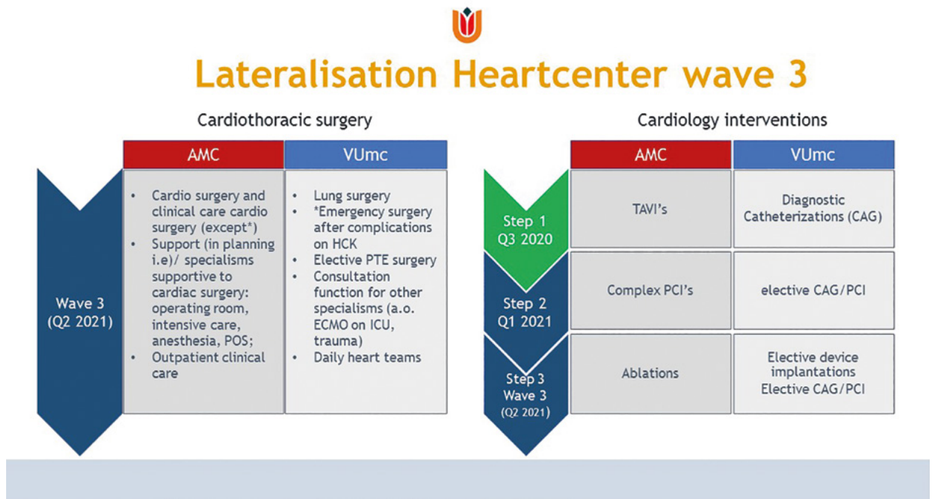
Chapter 6 covers the criteria and tools needed for assigning authorship fairly to ensure proper allocation of credit for research work

Amsterdam UMC
University Medical Centers

Visit https://www.amsterdamumc.org/research/integrity.htm for the complete Research Code

Lateralization Cardiology and Cardiothoracic surgery

Since AMC and VUmc merged in 2018 to become Amsterdam UMC, parts of the portfolio of care were located between the two institutions. In June 2021, Amsterdam UMC is taking another step towards completing this merger. As of May 31st 2021, cardiology and cardiothoracic surgery have redistributed their care.



Cardiothoracic surgery

As of April 1st 2021, all heart surgery will be performed at the AMC location, lung surgery will stay at the VUmc location. In the transition period until May 31st a team was available 24/7 at the VUmc for cardiothoracic surgery. After the transition period, there will be a cardiothoracic surgeon at the VUmc only during daytime.

Collaboration between Leiden and Amsterdam

The concentration of heart surgery at the AMC location is just one step in a bigger plan, in which Amsterdam UMC and Leiden University Medical Center (LUMC) are cooperating in order to form the largest cardiothoracic surgery center of the Netherlands.

'With our 25 heart-lung surgeons together with Leiden we now have knowledge for every (rare) heart disease. This will allow us to elevate the level of research and provide opportunities to educate the next generation of surgeons.'

Cardiology

'In 2024, the Amsterdam UMC Heart Center will be the knowledge center for cardiac care and innovative research, situated at location AMC (Meibergdreef), with state-of-the-art facilities and highly skilled employees.'

For Cardiology the redistribution of care in 2021 is a first step towards concentrating cardiac care at location AMC by 2023-2024. By that time the new Cardiology center will have been built at the AMC location, which will provide enough capacity for all clinical cardiac care and a Cath lab facility. At that time, certain specific patient groups, such as patients with cardio-oncologic disease or heart failure who need short out-patient treatments, will be concentrated at the VUmc location. In the meantime, we will do routine cardiac care and interventions at both locations. We look forward to the next step in this challenging process: the opening of the brand new and modern Cardiac Care Unit (CCU) department at F3 with 20 high-care beds, in June 2021.

Move in three steps

In 2021, Cardiology will redistribute the cardiac interventions in three steps as it is related to the presence of cardiothoracic surgery. Step 1, move TAVI-procedures to AMC location, this has already been completed. Step 2, moving high risk, high complex PCIs to AMC location, this is being carried out at the time of writing. The last step in 2021 is the concentration of ablations at the AMC location. Clinical research will follow the relocation of these patient groups.

Robert Klautz
Head of Cardiothoracic surgery

Steven Chamuleau
Head of Cardiology

CounterCOVID study

JURJAN AMAN & HARM JAN BOGAARD, DEPT. PULMONARY MEDICINE

The primary reason for ICU admissions and death in COVID-19 is hypoxemic respiratory failure. Infection with SARS-CoV-2 and the concomitant inflammatory response causes extensive endothelial damage and vascular leakage, leading to lung edema and hypoxia.

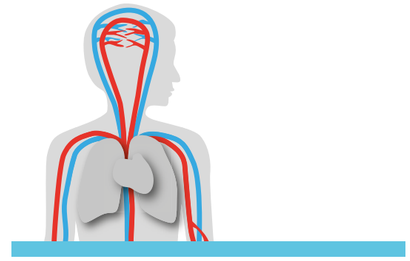
Several years ago, as an ICaR-VU PhD student, Jurjan Aman showed that the kinase inhibitor imatinib improves the endothelial barrier when jeopardized by inflammation. In a collaboration with Harm Jan Bogaard and his team of pulmonary vascular researchers, Aman applied his observations to clinical challenges posed by COVID-19. With a start-up grant from the Amsterdam Foundation, Aman and Bogaard designed a randomized clinical trial, the CounterCOVID study, to test the hypothesis that imatinib reduces vascular leakage in COVID-19 and thereby enables patients to recover more quickly from respiratory support (mechanical ventilation and supplemental oxygen). The trial was quickly approved by the Medical Ethics Review Committee and within a few weeks 13 hospitals had been recruited to participate in the study. Additional funding was obtained from ZonMw and the EU Innovative Medicines Initiative (IMI). To conduct the study, a large team of young cardiovascular investigators, who were temporarily unable to perform their own research due to the Corona lockdown, was assembled. Between March 2020 and January 2021 four hundred patients were treated with imatinib or placebo. The results of the study are currently under peer review, but because of the clear indications of clinical benefit from imatinib, follow-up trials are currently being conducted and planned. These follow-up studies include a study using an intravenous imatinib formulation in the ICU (INVENT-COVID) and incorporation of imatinib as a treatment arm in the international, WHO sponsored, SOLIDARITY platform.

Aman and Bogaard consider the CounterCOVID study an extraordinary journey of translational research that has led to clinical application with the potential of a global impact. Making this journey together with a group of cardiovascular researchers who were not particularly invested in clinical trials and infectious diseases made it all the more special. Now we can only hope that the use of imatinib will quickly be implemented in daily practice. It is likely that the advantages of imatinib treatment, a relatively cheap and safe drug, will probably be greatest in low-income countries with limited resources, access to vaccines and expensive immune modulators.

An extraordinary journey of translational research that has led to clinical application with the potential of a global impact

Harm Jan Bogaard (l) and **Jurjan Aman** (r), Pulmonary Medicine

Thrombosis and COVID-19



Shortly after the first wave of the COVID-19 pandemic hit the Netherlands, we observed that many patients developed venous thromboembolism: the formation of blood clots in leg veins that can break away and lead to clots in the lungs.

First report on venous thromboembolism in COVID-19

We immediately felt the need to determine how often this complication occurs, both in the most severe cases admitted to the intensive care unit and in patients admitted to the ward. Fueled by the unprecedentedly high number of admissions, we were swiftly able to publish one of the first reports on the risk of venous thromboembolism (VTE) in COVID-19, in a collaboration with many colleagues from the departments of internal medicine, pulmonology, radiology and intensive care. This paper was published on a preprint server before peer-review, where it was downloaded over 800 times in the first 12 days. The final peer-reviewed paper in the Journal of Thrombosis and Haemostasis was cited 340 times in just the first year. It was a unique time in which we continued to gain further insights that could be applied in clinical care almost immediately. And in fact, it is not over yet. We are still not sure which prophylactic dose of anticoagulants optimally balances the risks of thrombosis and bleeding in COVID-19 patients.

We immediately felt the need to determine how often venous thromboembolism in COVID-19 occurs

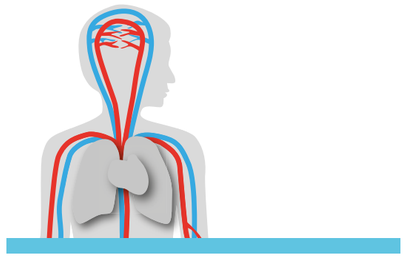
Addressing thrombosis-specific questions in COVID-19 patients

With the early understanding that COVID-19 could be with us for a longer time than initially expected, the CovidPredict cohort study was quickly initiated during the first wave, by Martijn Beudel (neurologist location AMC), to facilitate research on COVID-19. This study has currently enrolled more than 2,500 COVID-19 patients and serves as a basis for further studies addressing thrombosis-specific questions in different patient groups with COVID-19. On a national level, we are participating in the Dutch COVID and Thrombosis Coalition (DCTC), a platform supported by grants from ZonMw and the Netherlands Thrombosis Foundation and coordinated by Marieke Kruip, hematologist in the Erasmus MC.

Finally, in collaboration with Andries van der Meer from the Technical University Twente, supported by a grant from ZonMw, we are working on an in vitro model called “Blood vessel-on-a-chip” in order to further investigate which specific factors in COVID-19 induce the highly prothrombotic state. With these studies, we aim to increase our understanding of the pathophysiology of COVID-19 related thrombosis and to find the optimal way of preventing these potentially fatal clots.

left to right: **Michiel Coppens, Thijs van Haaps, Nick van Es,** Vascular Medicine

Breath-taking discoveries: the relationship between COVID-19 and the diaphragm



Heder de Vries (l) and **Coen Ottenheijm** (r), Intensive Care Medicine & Physiology

The COVID-pandemic has led to many patients being admitted to the Intensive Care unit to receive mechanical ventilation. Many of these patients require a significant amount of time before they can breathe without the assistance of a mechanical ventilator, even after their primary symptoms have lessened. We theorized that this could be due to diaphragm weakness. The diaphragm, a dome-shaped muscle that lies between the thorax and abdomen, is the most important muscle for generating the movements of breathing. As such, weakness of the diaphragm can contribute to difficulties in weaning from the ventilator. Whether COVID-19 had a specific effect on diaphragm function in ventilated patients was unknown and required further study.

Teamwork and a strong connection between the laboratory and the clinic allowed us to generate these fascinating data in a shorter timespan than we had thought possible

What we did

Historically, Amsterdam UMC has had a strong connection between pre-clinical and clinical researchers interested in diaphragm function. In the past, this allowed us to collect diaphragm biopsies from relatively healthy patients and ICU patients, and has led to new insights in diaphragm weakness. As the pandemic developed, we quickly set up a research team to collect diaphragm biopsies from patients that had died from COVID-19. These samples were transferred to the Physiology laboratory in the O2 building, where a vast array of structural and functional tests were conducted. These data were correlated with several clinical characteristics including duration of ventilation, compliance of the lungs and levels of steroids or inflammatory markers that were collected in the clinic.

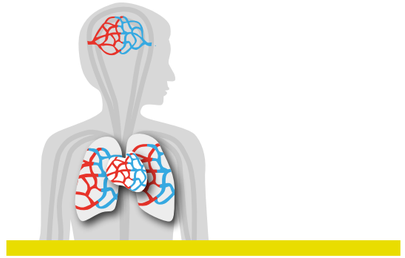
What we have learned

We were the first in the world to show that diaphragm muscle fibers possess the required receptors for the corona virus to enter the muscle fibers. Additionally, we were the first to observe that virus particles had indeed invaded the diaphragm muscle fibers. Interestingly, some patients with COVID-19 had extensive fibrosis of the diaphragm, which can make the muscle stiff. This might explain why some patients required such a long time to be weaned from the mechanical ventilator.

How patients benefit

Extra care can be taken to ensure that patients with COVID-19 train their respiratory muscles to recover. Future studies should identify the specific pathways that lead to diaphragm stiffening, and might provide targets for preventing this process altogether.

Severe COVID-19 Is complement the way out?



Severe COVID-19 is characterized by a strong inflammatory response and a high incidence of thromboembolic complications. Complement activation may form the common pathway in severe COVID-19, leading to the observed inflammation and coagulopathy.

Complement activation in patients with severe COVID-19

Autopsies of patients with severe COVID-19 showed widespread complement activation in lung and kidney. The complement system is a part of our immune system that enhances the ability of antibodies and other immune cells to clear pathogens, promote inflammation and attack the pathogens by the membrane attack complex (MAC) formation. The complement system consists of small proteins produced by the liver which circulate in an inactive form and can become active after several stimuli. COVID-19 studies showed binding of the SARS-CoV-2 virus N-protein to the complement activating mannose-associated serine protease 2 (MASP2), ultimately leading to downstream complement pathway activation and generation of C5a. The potent anaphylatoxin C5a attracts neutrophils and monocytes to the infection site and strongly activates these cells, causing tissue damage by oxidative radical formation and enzyme release. This also induces the release of tissue factor from endothelial cells and neutrophils thereby activating the coagulation system. High concentrations of C5a have been reported in patients with severe COVID-19, and the C5a-C5aR1 signaling axis has been suggested to be crucial in COVID-19-associated inflammation. The complement system is normally a very useful part of our immune system for attacking pathogens. However, in COVID-19 the balance between attacking the virus and collateral damage to the target organs goes wrong. By blocking C5a in severe COVID-19 this balance may be restored and the inflammatory and coagulation cascade slowed down.

Treating severe COVID-19 by restoring the balance of the immune system

Alexander Vlaar, Intensive Care Medicine

International phase III trial

Until recently, only upstream blockade of complement was possible which resulted in potential side effects due to blocking of C5b-9, and thereby the MAC formation. The MAC formation plays a crucial role in host defense through cell lysis. The pharmaceutical company InflaRx has developed a specific anti-C5a antibody which leaves the MAC formation intact while blocking the potent anaphylatoxin C5a. Vilobelimab is a chimeric monoclonal IgG4 antibody that specifically binds with high affinity to the soluble form of human complement component C5a. InflaRx initiated and funded the current adaptive phase II/III trial, to investigate the effect of anti-C5a treatment in severe COVID-19. Prof. Alexander Vlaar is the international principal investigator of this trial, and recently published the first part of the adaptive phase II/III PANAMO trial exploring potential benefit and safety of selectively blocking C5a with the monoclonal antibody vilobelimab in patients with severe COVID-19 [Vlaar et al. Lancet Rheum]. The results showed that C5a inhibition with vilobelimab was safe and secondary outcomes were in favor of vilobelimab. There were consistent signals of benefit in the treatment-group including a lower 28-day all-cause mortality rate, lower rate in impaired kidney function, faster normalization in lymphocyte counts and greater reduction in LDH. This warranted investigating C5a inhibition with vilobelimab within a phase III trial. The phase III trial is currently being conducted in several medical centers, world-wide, including Amsterdam UMC.

Numbers & Facts

Symposia organized in 2020*

1 Annual meeting: 11th Rembrandt Symposium
9 Monthly ACS symposia
30 Educational lectures and discussions at these symposia

ACS grants awarded in 2020

2 ACS Postdoc grants of €70,000
1 ACS MD/PhD grant of €25,000
5 ACS Out of the Box grants of €25,000

ACS published in 2020

1 ACS glossy
20 ACS newsletters
10 ACS PhD thesis defenses announcement letters

ACS PhD defenses and inaugural lectures in 2020

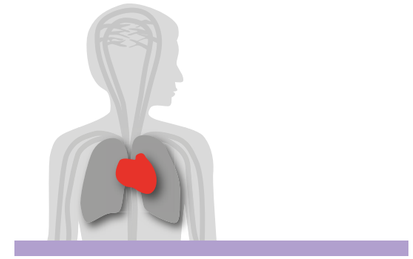
109 PhD defenses
2 Inaugural lectures

ACS members in 2021

372 PhD students
71 Postdocs
32 Specialists in training
160 Principal Investigators
106 Staff members

* Due to the COVID-19 measures, our annual ACS meeting and PhD retreat had to be cancelled.

Safer open heart surgery by preventing unnecessary and life-threatening complications



On the 18th of November 2020, a ZonMw Pearl was awarded to cardiothoracic surgeon Dave Koolbergen and his team. They received the award for their research into reducing complications after open heart surgery by using an innovative pericardial flushing system. ZonMw Pearl projects stand out as each year only a select few are awarded.

Every year, 1.45 million open heart surgeries are performed worldwide. During the recovery phase, postoperative blood loss is drained from the internal wound through two or more chest tubes that are placed at the end of the surgery, and stay in place until the patient has recovered. However, 17% of the patients suffer from postoperative complications caused by the drainage system's failure to adequately evacuate blood after open heart surgery. This leads to accumulation of blood and clots around the heart in the pericardial space. Frequently, it requires immediate reopening of the chest wound and evacuation of blood and clots.

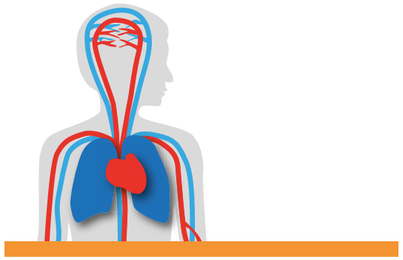
Continuous postoperative pericardial flushing after open heart surgery decreases blood loss and unnecessary reoperations

Dave Koolbergen, Cardiothoracic surgery (Fred van Diem Photography)

During his career as congenital cardiothoracic surgeon, Dave Koolbergen invented the innovative flushing method that has led to the Haermonics Flush system. The system proactively and continuously flushes the pericardial space with a warm saline solution at the end of an open heart procedure and is continued postoperatively. The saline flush completely cleans the wound from activated blood and toxic remnants allowing for normal clotting to take place and the bleeding to stop. Two randomized clinical trials have proven that the Haermonics Flush system prevents 60% of postoperative blood loss, unnecessary reoperations and tamponades. In addition to that, the system supports the surgeon and medical staff in the decision-making process as it measures blood loss and sets off alarms when this blood loss increases.

From innovative idea to medical device

In order to develop a medical device that allows for autonomous and safe flushing, Haermonics was founded as an AMC spinoff in 2015. Haermonics has patented its flushing device and disposables, and is now building its investigational device. Haermonics aims to save 10,000 lives in 2030.



Sharing is caring: how COVID-19 led to large-scale collaboration for icudata.nl

PAUL ELBERS, PATRICK THORAL, TARIQ DAM, LUCAS FLEUREN
ON BEHALF OF THE DUTCH ICU DATA WAREHOUSE COLLABORATORS

LABORATORY FOR CRITICAL CARE COMPUTATIONAL INTELLIGENCE, DEPARTMENT OF INTENSIVE CARE MEDICINE, AMSTERDAM MEDICAL DATA SCIENCE

Source: The Netherlands Journal of Critical Care, volume 29, no. 2 – March 2021

For many people worldwide, the COVID-19 pandemic will have created long-lasting memories. For the Laboratory for Critical Care Computational Intelligence at Amsterdam UMC, the pandemic proved to be nothing short of a rollercoaster ride. And despite the many challenges imposed upon our profession by the pandemic, this ride was largely fueled by excitement, in particular the rapidly expanding enthusiasm for large-scale data sharing and collaboration between Dutch intensive care units (ICUs).

Uniting clinical and data science expertise

Obviously, our story started long before the COVID-19 crisis began. Intensive care medicine is a natural habitat for data science as large amounts of data are routinely collected during intensive care treatment, such as those from devices for monitoring and life support. Our laboratory was created with the primary focus of uniting clinical and data science expertise in order to use these data to improve the care and treatment of future critically ill patients. We do so by developing and validating models, integrating these into clinical decision support tools to be used at the bedside, and evaluating their effect on outcomes relevant for critically ill patients.

Three of the most prominent results from our philosophy are the: first freely available European ICU database under the European Society of Intensive Care Medicine and Society of Critical Care Medicine joint data sharing initiative (AmsterdamUMCdb); bedside decision support for personalized antibiotic dosing and bedside decision support for preventing untimely patient discharge from ICUs. Because of these contributions to the field, our lab already had the infrastructure and knowledge base to readily facilitate large-scale data sharing when the pandemic hit the Netherlands. Specifically, our expertise could facilitate sharing of high-frequency device data and most other clinical information from the electronic health record (EHR), with the goal of generating insights from ICU patient data as the pandemic was unfolding. Covering entire ICU admissions with highly granular data, the Dutch Data Warehouse is the largest COVID-19 dataset to date. It is a natural habitat for advanced statistics and machine learning, effectively extending the opportunities for high-frequency big data analysis provided by large ICU datasets such as MIMIC and AmsterdamUMCdb to the COVID-19 domain.

left to right: **Martin Haan, Tariq Dam, Lucas Fleuren,** Intensive Care Medicine

The ICU data initiative icudata.nl is supported with two million euros for the next five years

Two million euros for the icudata.nl initiative

We are excited that the Dutch Association for Intensive Care (NVIC), strongly supported by the Research Collaboration Critical Care the Netherlands (RCCnet), has now initiated a similarly large-scale collaboration amongst Dutch ICUs to engage in large-scale data sharing on all critically ill patients. This should enhance the understanding of the timing and combination of treatments that may lead to better outcomes for a specific ICU patient. This collaboration is coordinated by our laboratory at Amsterdam UMC. There are strong ties with the National Intensive Care Evaluation foundation (NICE), known for their experience in analyzing data for ICU benchmarking. Machine learning partner Pacmed will use their expertise to combine and analyze the data. Zorgverzekeraars Nederland (Dutch Health insurers), uniting all major health insurance companies in the Netherlands, will support the initiative with two million euros for the next five years. This new collaboration between Dutch ICUs is called icudata.nl and is expected to give rise to the Dutch ICU Data Warehouse. We are thrilled that it was immediately received with great enthusiasm among a large majority of ICUs. Their enthusiasm could make the Dutch Data Warehouse the largest of its kind in the world.

This is our story on how a severe crisis can give rise to a unique opportunity. Let's keep up the momentum and join us if you have not done so already!

Want to read more?

www.amsterdammedicaldatascience.nl

www.icudata.nl

‘HEART’: Hogeschool van Amsterdam En Amsterdam UMC Research Team

The Amsterdam UMC Heart Center has developed a successful research collaboration with the Amsterdam University of Applied Science, Faculty of Health (AUAS), and two professors as frontrunners. Located on the same campus the institutions collaborate intensively on education and interdisciplinary research. The interdisciplinary research group ‘HEART’ is comprised of nurses, physicians and paramedics, led by Prof. Ron Peters, chair of division 3 Heart Center.

Over the past decade, the Heart Center has initiated a support program of scientific academic development for selected Bachelor and Master educated nurses. During their development as investigators, the nurses are embedded in a research group, currently led by Marjolein Snaterse. She is a Postdoc researcher, nurse and senior lecturer at the Amsterdam University of Applied Science.

The interdisciplinary research collaboration has resulted in the completion of several randomised controlled trials: RESPONSE 1, RESPONSE 2 and the Cardiac Care Bridge. These studies explored a multidisciplinary nurse-coordinated approach to prevention in patients with coronary heart disease and in older cardiac patients. RESPONSE 2, for example, found that nurse-coordinated referral to existing community-based lifestyle programs is effective in achieving lifestyle improvements, and the participation of the patient’s partner increases the rates of success. The interdisciplinary partnership is successfully running ongoing PhD programs and has already successfully completed several PhD programs in several professions including nursing, general practice, physiotherapy and pharmacy.

Combining science with patient care in the nursing research program.

Conducting scientific research represents an important step in career development for Master educated nurses. Combining science with patient care creates an appealing perspective for talented nurses, and stimulates the recruitment of junior nursing talents for Amsterdam UMC. In addition, nursing research programs lead to new leadership in patient care, supporting the development of evidence-based nursing. As an example, a journal club has been created for nurses in the department of cardiology where recent and important publications are discussed. Another offspring of these programs is the development of patient-oriented outcomes that are responsive to nursing care.

The programs now enjoy multi-level support from the Amsterdam UMC Board of Directors, the Heart Center Division Board and the Amsterdam Research Board. With this support nursing research is now and integral part of the Heart Center. The financial support from scientific institutes, such as ACS, is welcomed and is a great stimulus for the nursing research projects. These developments in cardiovascular sciences will lead the way for all clinical divisions of Amsterdam UMC.

Marjolein Snaterse

ACS Nursing Research grant

In March 2021, ACS initiated a funding scheme to stimulate research by nurses. The ACS Nursing Research grant is aimed at Amsterdam UMC nurses with a Master’s degree, who are interested in preparing a PhD trajectory in the cardiovascular field in combination with clinical duties as a nurse.

Ron Peters

The new Amsterdam UMC research website: aiming to connect

Caroline Arps & Anne-Lieke van Deijk

Last December the new research website of Amsterdam UMC was launched. It is an online platform where the eight research institutes of Amsterdam UMC, including ACS, present their researchers, research programs and highlighted projects. The website facilitates collaboration and interaction between researchers and other interested parties.

www.amsterdamumc.org/research

AMSTERDAM UMC RESEARCH WEBSITE

The new Amsterdam UMC research website is intended for our own research community and for visibility outside of Amsterdam UMC. It highlights: researchers' profiles in a searchable database; which themes Amsterdam UMC is working on, and the latest news on current projects. The research website provides an online platform that enables internal and external researchers to connect with each other based on content and interests. In addition, the website can further stimulate interdisciplinary research. Researchers and research groups are easily identified based on expertise and program.

PRIDE

Amsterdamumc.org/research will also appeal to new target groups. By linking vacancies to research content, it aims to attract talented researchers to Amsterdam UMC. Patients will find it interesting to discover what Amsterdam UMC is doing in terms of research, for example, what is currently happening in the field of COVID-19. Such a platform presents Amsterdam UMC as an important player in the field of research. And last but not least, colleagues may feel a personal sense of pride when they see what we have to offer as a scientific organization.

ACS PAGES

On this new website, ACS has its own pages where we have our community for cardiovascular research in Amsterdam: www.amsterdamumc.org/acs. On this platform, you can find all ACS researchers, detailed information about our five ACS research programs with illustrated infographics, internal ACS grants you can apply for, information for PhD students within ACS and internships for master students interested in cardiovascular research.

BETTER PRESENTATION AS A RESEARCHER

Researchers have their own personal page on this website where they can highlight their specialization, focus of research, key publications and upload a headshot. An up-to-date personal page provides clear visibility of you as an Amsterdam UMC researcher and makes it easier for others to find you. Therefore, we would like to invite you to complete your personal page via Pure the output registry system of Amsterdam UMC.

ACS awards 2020-2021

ACS awarded: Postdoc grants (€70,000), MD/PhD grants (€25,000) and Out of the Box grants (€25,000) to stimulate innovative collaborative research

2021 SPRING

Alwin Zweerink	Conduction System Pacing - MECHanical ANd electrICal Study (CSP-MECHANICS)	MD/PhD
Laura Bosmans	Targeting Glucocorticoid-Induced TNF Family-Related Protein (GITR) in macrophages to combat atherosclerosis: Identification of GITR-TRAF Small Molecule Inhibitors	Postdoc
Arnout Mieremet	UnHiDe Marfan: Uncovering Haploinsufficient and Dominant Negative iPSC phenotypes in Marfan Syndrome	Postdoc
Reinier Boon & Monika Gladka	Single nuclei RNA sequencing to study the human diseased heart	OOTB
Bianca Brundel & Anke Tijsen	Culturing of LMNA hiPSC-derived atrial cardiomyocytes to dissect mechanism underlying atrial fibrillation	OOTB
Vivian de Waard & Kakkhee Yeung & Connie Jimenez	What drives the engine of the aortic aneurysm: identifying (phospho)proteins at the center of vascular smooth muscle cell contractile dysfunction	OOTB
Esther Lutgens & Ed Eringa & Reinier Zandbergen	SARS-CoV2 infection of perivascular adipose tissue and hyperinflammation in COVID-19	OOTB
Max Nieuwdorp & Elena Rampanelli & Barbara Verhaar & Daniel van Raalte	The role of gut microbiota and its metabolites in blood pressure regulation	OOTB

Amsterdam UMC
University Medical Centers

Amsterdam Cardiovascular Sciences