

Excellence in Cardiovascular Medicine and Research

Department of Cardiology
University Medical Center Mainz, Germany
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MAINZ



STIFTUNG
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Introduction to the Institution



The Department of Cardiology at the University Medical Center in Mainz has an internationally recognised leadership in the area of cardiac and vascular medicine

- The Department of Cardiology has currently approx. 400 staff members employed as physicians, nurses, technicians and administrators, who ensure that patients receive the highest quality of safe, professional and also highly innovative care in accordance with the latest treatment standards.
- We have 135 beds including an intensive and coronary care unit, a chest pain and atrial fibrillation unit, a heart valve unit and 6 heart catheterisation laboratories. Per

year we see 11,500 inpatients and 20,000 outpatients.

- The **Department of Cardiology** performs more than 750 heart valve procedures a year, 1,000 atrial fibrillation ablation procedures and implants around 700 devices (defibrillators and pacemakers). We perform 4,500 coronary diagnostic caths and almost 3,000 percutaneous coronary and peripheral interventions.
- In 2018, we opened the very first **Heart Valve Unit (HVV)** in **Europe**, thus contributing towards dealing with the drastic increase in incidence of heart valve disorders in this country.
- Together with the Department of Cardiovascular and Thoracic Surgery and Pediatric Cardiology, we are certified as a specialist

EMAH center for **adult congenital heart disease** and since 2019 we are certified as a **Cardiac Arrest Center** together with the Department of Anesthesia.

- Our **Chest Pain Unit** deals with more than 6,000 patients annually; 2,500-3,000 of these are hospitalised for further invasive diagnostic treatment. In this issue, we will be considering how this new patient care structure in Germany has evolved and whether all expectations have been fulfilled
- In our **Angiology Department** we offer all necessary diagnostic procedures with special focus on peripheral artery disease. We also perform around 500 peripheral interventions.
- In **Preventive Medicine** we offer comprehensive, state-of-the-art



check-up investigations for national and international patients in **primary, secondary and tertiary prevention**. The individually designed examination program over 2 (to max. 3) days covers interdisciplinary diagnostics. After completion, a detailed report and personal treatment recommendations are explained to the patient.

- With respect to research we initiated the **Gutenberg Health Study in 2007**, one of the world largest population-based, interdisciplinary cohort studies and we are member of **the German Center for Cardiovascular Research, DZHK**.
- We are continuing to place emphasis on research in the sector of **environment and health**. A major achievement here was the

identification of the molecular mechanisms by which aircraft noise can cause deterioration of vascular function and together with the Max Planck Institute at the Johannes Gutenberg University we published a new calculation of the cardiovascular burden of air pollution in Europe, which is meanwhile listed among the altmetric TOP 100 research articles worldwide in 2019.

- Our department has been responsible for more than 100 specialist publications on the subjects of vascular biology, blood coagulation and the environment besides articles relating to the Gutenberg Health Study, demonstrating our dedication to research.
- The **Mainz Heart Foundation**, which celebrated its **10th heart**

gala in 2019, raised €160,000 with this event. The foundation is supporting the clinic with about €500,000 per year. The **Mainz Heart Foundation** has extended its annual classes in prevention as part of the '**Children's Academy of Health**' project to a total capacity of 55 school classes (> 1,300 pupils). The purpose of this academy is to approach school pupils and young adolescents with a targeted prevention program.

In this excellence report we focus on minimally invasive, percutaneous heart valve therapy, on coronary diagnostics and interventions, on chest pain unit and on our preclinical and clinical research activities as well as on the Mainz Heart Foundation.

The Heart Valve Center: Transcatheter based minimally invasive Heart Valve therapy

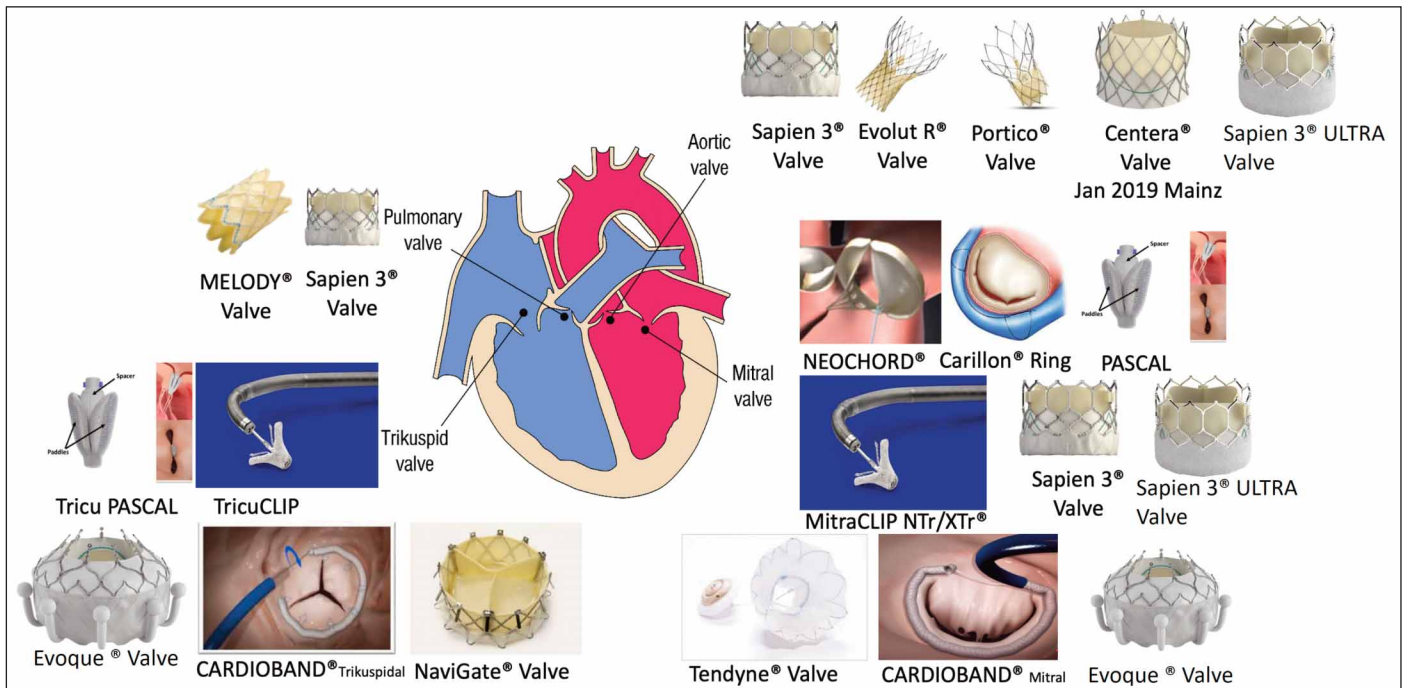


Fig. 1 Broad spectrum of interventional heart valve therapy in Mainz

The ageing populations in the western world with Japan and Germany being the countries with a high percentage of 65+ year old population induces an increase in the incidence of heart valve disease such as aortic valve stenosis or mitral as well as tricuspid regurgitation (incompetence) reaching epidemic proportions of disease prevalence. The main aetiology is a strict correlation of age to degenerative and secondary valve disease increasing from 1-2 per one 100 to 5-8 percent. In addition, we see a major increase in secondary atrioventricular valve regurgitation due to an increased incidence and survival of heart failure. All valve disorders interact with the chamber size and function of both the left and right heart and induce a vicious circle of pressure and volume load to the systolic function,

valve function and dilatation that leads to fatigue, symptoms of chest pain and dyspnoea.

A brief introduction into the physiology of the heart

The human heart consists of four chambers: The right and left ventricles, and the corresponding right and left atria. These chambers are sequentially separated from each other by four heart valves that direct the heart muscle contraction into a unidirectional blood flow through the heart chambers at each heartbeat. In the right heart, the tricuspid valve and the pulmonary valve ensure that the blood can only flow in the direction of the lungs to ensure oxygenation. On the left chamber side, the mitral valve and the aortic valve control the direction of blood flow.

Treatment options changed in 2002 when Cribier implanted the first human transcatheter based aortic

valve bioprosthesis which became a companion and later competitor to classical open chest valve replacement. Particularly in older patients or patients with relevant risk profiles - a **Transcatheter Aortic Valve Implantation, known as TAVI or TAVR for replacement** is principally used. Upcoming new generations of transcatheter systems and the increasing trial evidence in the PARTNER 1 to 3 randomised trials as well as the CoreValve study experience lead to an increase to more than 20,000 procedures annually in Germany alone, reaching approximately 125,000 procedures annually worldwide. Transcatheter based Mitral valve regurgitation treatment via implantation of a **MitraClip®** device started 2003 in humans and has reached a total implant experience of 100,000 patients (December 17 2019 at the Heart Valve Center Mainz,

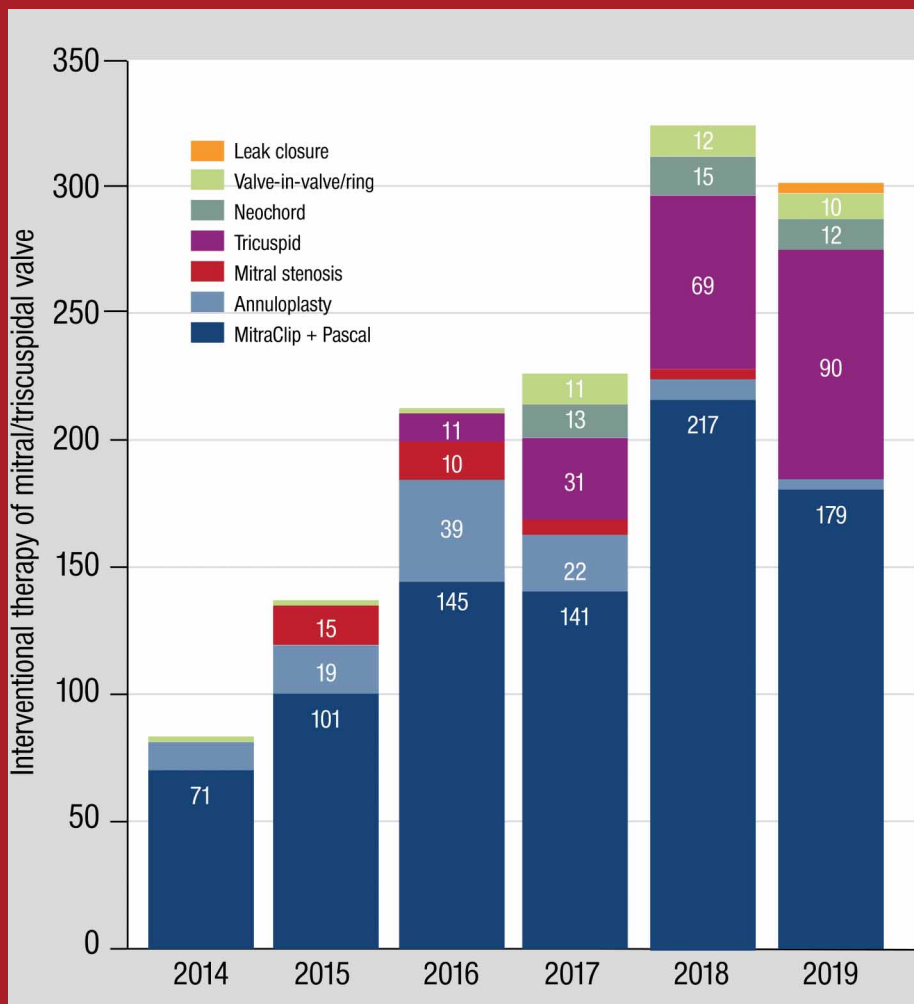


Fig. 2 Growth rates of transcatheter interventions concerning the mitral and tricuspid valves

Fig. 3 Number of TAVI implantations 2011-2019. TA: transapical, TS: transsubclavia TF: transfemoral

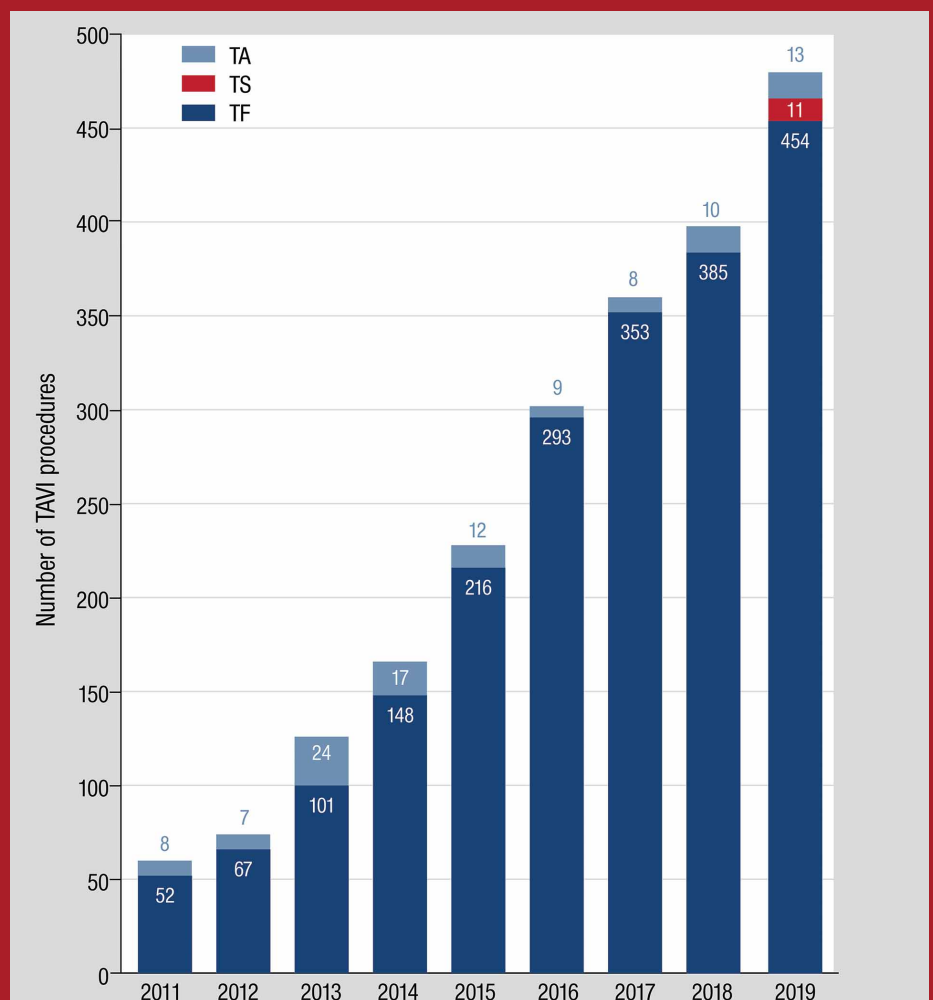




Fig. 4 Contemporary TAVI prostheses: Edwards Sapien 3 and Centera Heart Valve (left and mid position; © Edwards Lifesciences) and Medtronic Evolut Pro (right; © Medtronic)

Germany). The annual volume in Germany passed beyond more than 6,600 cases per year both in Germany and the United States.

Over a period of just 15 years in human implant experience and 11+ years of CE mark devices, transcatheter based therapy of heart valves has developed from a niche treatment used in otherwise inoperable patients to a significant and safe general therapeutic option with beginning evidence in low and non-risk patients.

Transcatheter valve procedures are now considered a routine medical procedure in this country - the safety of catheter-based intervention is excellent and the procedural survival rate is greater than 98-99% in experienced high-volume centers. Mainz is one of the few centers worldwide offering the complete spectrum of minimally invasive heart valve repair and replacement with small percutaneous access paths of only 3-10 mm ensuring fast postprocedural recovery and low infectious risk.

However, as in the case of all heart valve procedures, these minimally invasive interventions as well as surgical procedures do not guarantee indefinite durability because of the natural heart valve tissue (BioValve) being involved. Depending on the underlying disorder, follow-up intervention may be required after several - eight to 15 - years.

In addition to the TAVI and MitraClip procedure, other minimally invasive valve interventions include other

Edge-to-Spacer-to-Edge approaches as the PASCAL® (CE mark in 2019) and commercial annuloplasty procedures for the mitral and tricuspid valve such as Carillon® and the Cardioband® procedure as well as beating heart chordal replacement, the NeoChord® approach (Fig. 1).

Upcoming procedures in 2020 are devices to repair the tricuspid valve regurgitation via a leaflet repair approach with the TriClip® (CE mark pending) or PASCAL (early human experience only). In 2020 also mitral valve replacement via the Tendyne® Mitral Valve system with an apical left heart pad is expected to achieve routine use after CE mark and will further expand the alternative minimal invasive treatment options avoiding open chest surgical access.

In 2019, the Heart Valve Center in the Department of Cardiology implanted more than 200 MITRACLIP, PASCAL and Carillon repair devices among more than 300 atrioventricular valve interventions in total (Fig. 2).

TAVI has become a routine hospital procedure

Transcatheter aortic valve implantation (TAVI) is a procedure that represents one of the major innovations in cardiac medicine and its use has spread rapidly. As mentioned already, in Germany, patients with aortic valve stenosis are being treated more frequently with TAVI than with open-heart surgery supported by increasing wealth of study data. Dr Ralph Stephan von Bardeleben and Dr Alexander Tamm value this form of 'keyhole surgery' because subsequent recovery times

are substantially shorter. The Heart Valve Team has performed more than **1,800 TAVI procedures** - while the number of patients that require this type of intervention is still increasing. In the year 2019 we implanted more than 480 TAVI devices, an increase of more than 20% to 2018 (Fig. 3).

In the early TAVI experience only patients not suitable for conventional surgery were offered this minimally invasive procedure. In the meantime, TAVI has emerged as the standard approach for all patients with increased risk for open heart surgery and current data implicates in addition to published guidelines a selected elderly patient population with low risk scores to benefit both in mortality and stroke rate from this minimal invasive treatment option. The preferred access route is transfemoral, since latest study data shows a remarkably low complication and mortality rate and rapid recovery compared to more invasive options. Modern, third and fourth generation TAVI prostheses (Fig. 4) have nearly eliminated early problems encountered in the beginning of the TAVI era such as paravalvular leaks (PVL), permanent pacemaker needs, access site bleeding, annular rupture or device malpositioning leading to high 30 day and 1 year survival rates.

With a multidisciplinary team of highly specialised interventional cardiologists, heart surgeons, cardiac anaesthesiologists, valve nurses and technicians, TAVI procedures in Mainz are performed in a hybrid operating room offering high

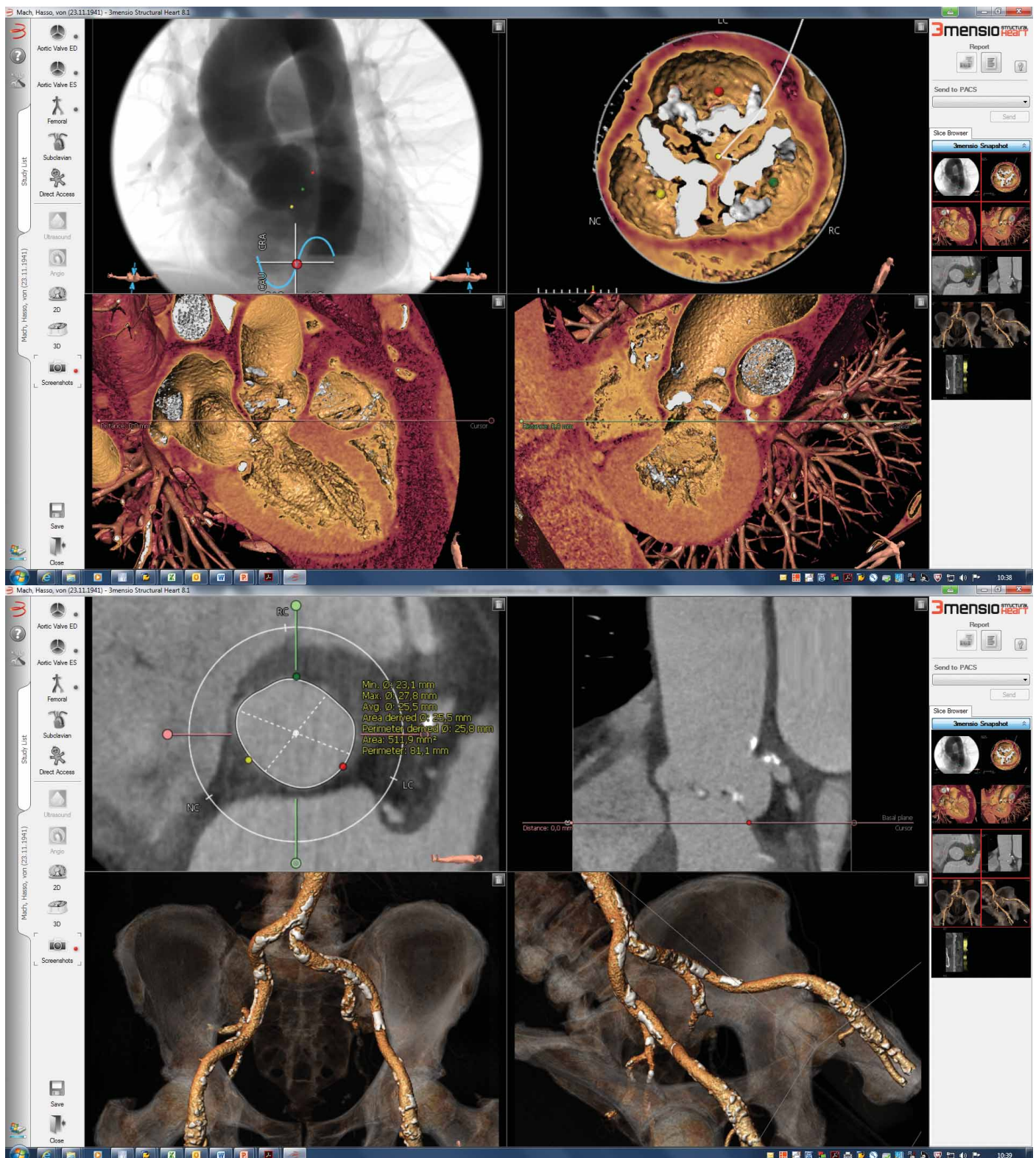


Fig. 5 3D Reconstruction of multislice CT scan for procedural planning using 3Mensio© software tools. Upper panel: Anatomy of the ascending aorta and aortic valve, annular plane, left ventricular size and distribution of calcifications. Lower panel: Annular plane sizing of the aortic valve, ostium of the left coronary artery, 3D-reconstruction of the iliac-femoral artery access routes.

standards in clean air ventilation and emergency backup. Beside the interventional implant expertise, a detailed planning of the procedure is key to success and safety. Every patient receives a high resolution multislice CT before any replacement procedure in order to determine quality and size of access route, annular dimensions, calcification load to determinate the

optimal patient individual prosthesis type selection (Fig. 5).

In contrast to open chest and open-heart surgery, direct visualisation of cardiac structures is not intended and possible with catheter-based treatment options and therefore high-quality imaging is highly important and in any complex valve procedure mandatory. Thanks to a

longstanding imaging expertise in echocardiography and rotational cardiac 3D imaging modalities, the team has cooperations with the R&D units of the imaging and device industry and early access to innovate imaging techniques such as 3D virtual reality echocardiography, intracardiac imaging or fusion imaging (CT/fluoroscopy; echo/fluoroscopy) (Fig. 6 and 7).

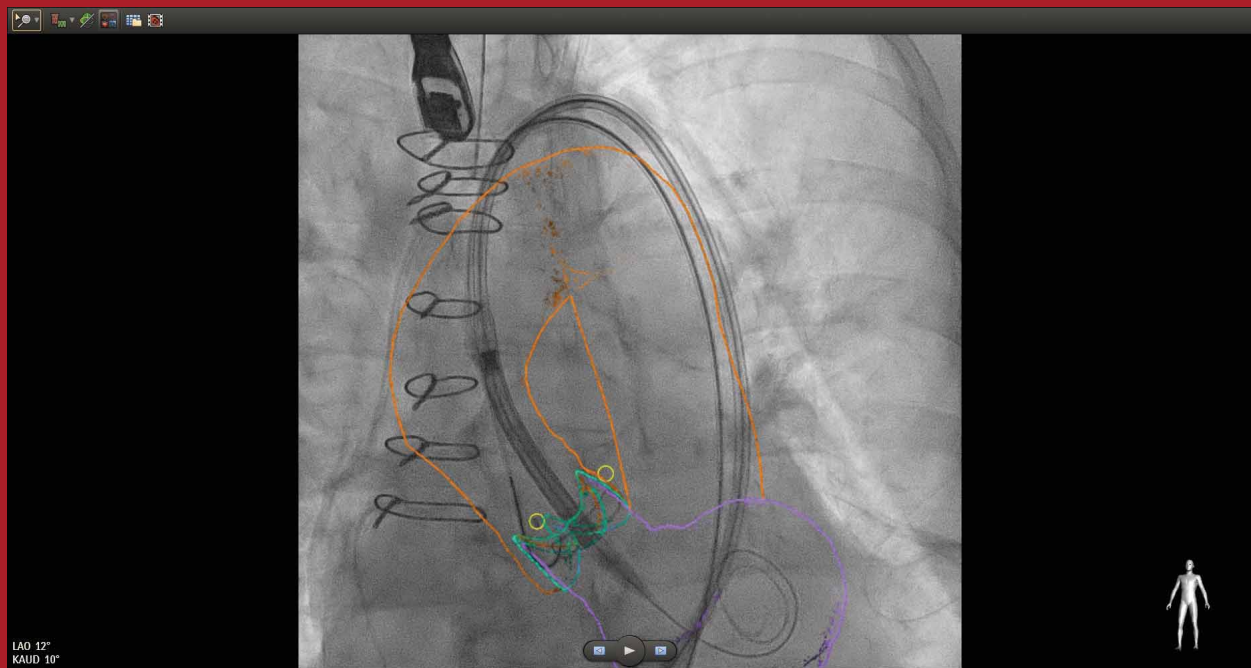


Fig. 6 Fusion imaging (CT/fluoroscopy) during a TAVI procedure ("valve-in-valve") With this high degree of innovation and increasing demand for catheter-based valve procedures, the Heart Valve Center Mainz at the University Medical Center is the leading institute among the University Cardiology Departments for interventional heart valve therapy in Germany.

Minimally invasive right heart valve procedures involving the tricuspid valve

The **Department of Cardiology** is also very successful in the treatment of **right-sided heart valve disease**. Few hospitals are able to offer **catheter-based treatments of the tricuspid valve with annular and leaflet repair options as well as first in human replacement**. In fact, only just over 1,600 such procedures have been performed for therapeutic reasons in early compassionate use experience (early devices with a notified approval by the Bundesamt für Arzneimittel und Medizinprodukte - BfArM in Bonn) or as part of clinical trials in recent years. Thus our department is one of the few centers worldwide able to offer this kind of treatment to overcome tricuspid regurgitation typically in a high risk cohort without surgical options.

In a patient with **tricuspid valve regurgitation**, one of the undesirable side effects is accumulation of fluids in the legs, pleural lung space and abdomen leading to a progressive deterioration of Quality of life (QoL) indices. The surgical methods used to date have not resulted in significant improvements overall and there is still a high mortality rate especially

in the weeks following surgery. Recent trial data on transcatheter therapy using TriClip as well as Cardioband Tricuspid with significant contribution from the Heart Valve Center Mainz team showed early feasibility and very low mortality in these procedures.^{1,2}

The team under **von Bardeleben** now employs two new techniques for the treatment of tricuspid valve regurgitation, the Cardioband® or a Triclip® (Fig. 7 and 8). These techniques have already been used in more than 190 patients to date, putting the Mainz University Medical Center at the top of the national and international leagues in this sector.

The Department of Cardiology of Mainz University Medical Center also offers a diverse range of information and training events in this area both for referring physicians, nurses and patients. The aim is to increase the awareness of the risk of problematic and life-threatening, untreated heart valve disease, to offer basic insights into the aetiology, diagnosis and treatment options and to ensure that effective therapy is provided over the long term. At the same time, medical staff and the patients in their care now have access to an innovative, less invasive catheter-based technique.

The first European Heart

Valve Unit (HVU)

Due to increasing life expectancy, an increasing percentage of the elderly population worldwide is suffering from valvular heart diseases. This includes in particular, aortic stenosis due to calcified aortic valve cusps or a regurgitation of the mitral or tricuspid valves. The annual growth rates of heart valve implantations by minimal invasive transcatheter procedures averages 10-15% nationally and internationally, while TAVI and Mitraclip implantations have both numerically outperformed open-heart valve surgery since 2016 in Germany. Importantly, the growth perspective to 2025 is about 10-20% per year as recently predicted in the Heart Valve Devices/Medtech 360/Market Analysis /Europe/2018 Report by the decision research group (<https://decisionresourcesgroup.com/report/549469-medtech-heart-valve-devices-medtech-360-market>). Coming from a noninferior perspective these transcatheter options are in selected patient subgroups even superior to conventional treatment.

Patients with these heart valve diseases can nowadays benefit tremendously from a minimally invasive heart valve intervention. The Mainz University Medical Center is one of the leading centers in



Fig. 7 The Valve Team (Dr Ralph Stephan von Bardeleben and Dr Ruf) during a case conference and in the hybrid operating theatre

Germany and worldwide³⁻⁶ for mitral and tricuspid valve interventions (including Sapien Ultra, MitraClip NTr/XTr, TriClip and Cardioband Mitral / Tricuspid). In 2019 we treated around 770 patients with left and right heart valve repair and replacement devices.

The increasing need for such interventions, the advanced age as well as complex and serious comorbidities of these patients, the rapid development and establishment of innovative heart valve devices and procedures and almost a daily change in the recommendations for medical treatment including recommendations for anticoagulation, have prompted the Department of Cardiology at the University Medical Center in Mainz to start with a new patient care structure for patients with Heart Valve Disease, The Heart Valve Unit (Fig. 9 and 10).

Currently, patients are admitted to a normal ward for preparation of the heart valve procedure. After the procedure they were typically transferred to the ICU and thereafter to an additional ward with monitoring facilities from which they are discharged.

What are the benefits of the new HVU to patients?

The new unit will combine all patient care in a single unit. The advantage of this new patient care structure is that all relevant steps of patient care during the hospital stay for heart valve implantation are conducted in one place including:

- patient admission and eventually recompensation
- complete planning of the procedure (including imaging modalities such as TTE, TEE, CT scans, coronary angiogram)
- monitoring on the intermediate care (IMC) part of the HVU directly after heart valve implantation after both conscious (no/low sedation) and general anaesthesia
- transfer within the HVU from IMC to monitor beds for heart rhythm documentation and initiation of optimal and in particular consistent medical therapy
- complete care and case management and discharge of patients is leading to faster and better patient information, optimal

patient diagnostic and treatment algorithms in order to improve the safety of the periprocedural setting and finally to improve patient satisfaction.

All measures now take place on one ward, thus avoiding frequent transfers of the elderly patients to different wards. The heart valve unit in Mainz has 25 beds, including 8 IMC beds and 17 normal beds equipped with cardiac monitoring capabilities. Six doctors and 15 nurses working in shifts are taking care of the heart valve patients. The establishment of the Heart Valve Unit (HVU) has led to a substantial reduction of the in-hospital stay period by almost 20% during the first few months.

To our knowledge, the unit is the first of its kind and we are convinced that it will be a role model for Germany and the rest of the world since it provides an optimal answer to the rapidly growing challenges due to an increased need for transcatheter heart valve procedures. This model will go national and international soon, as happened when we installed the Chest Pain Unit Network in Germany years ago.⁷



Fig. 8 A human tricuspid valve procedure involving the TriClip leaflet approach.



Fig. 9 The new heart valve unit provides specialised, fast and efficient care for patients under highest quality standards

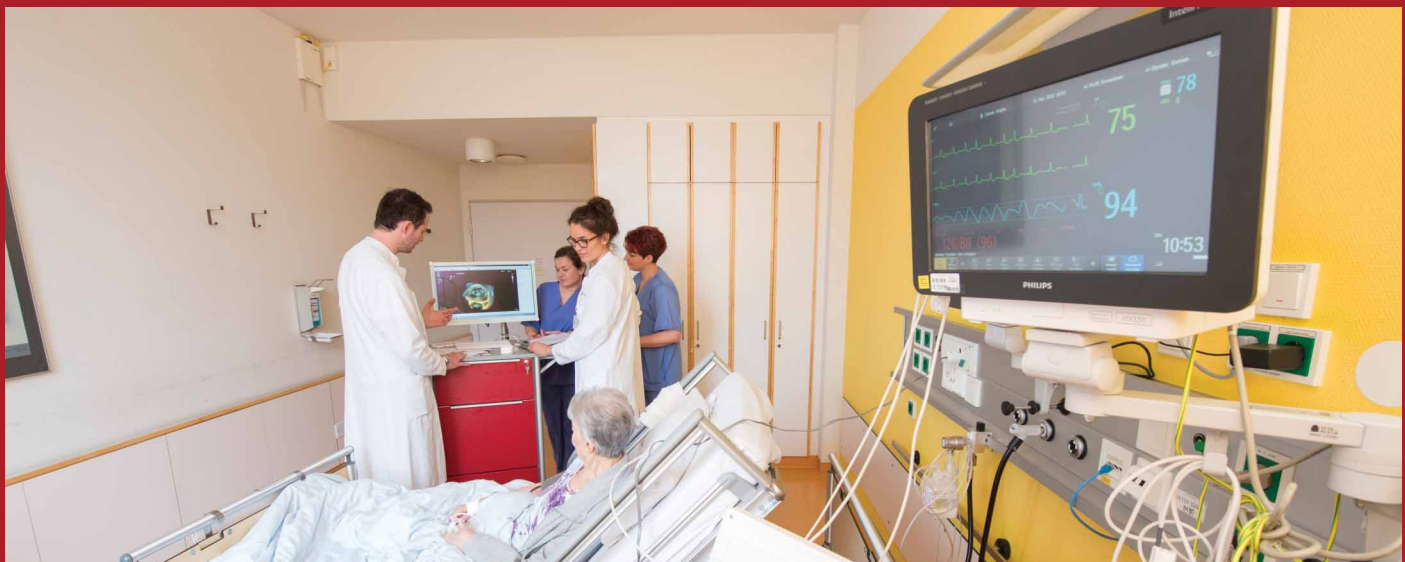


Fig. 10 Intermediate care room as part of our new heart valve unit (HVU)

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Coronary diagnostics, interventions and research

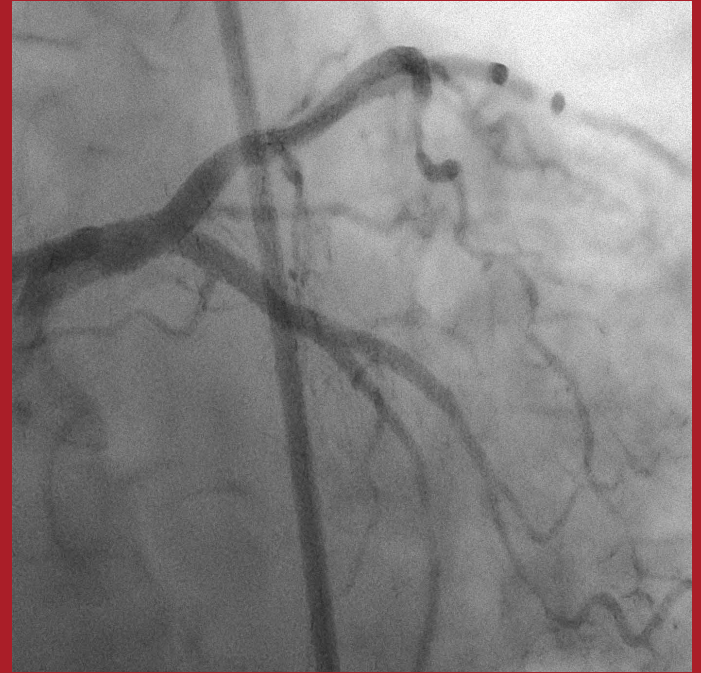
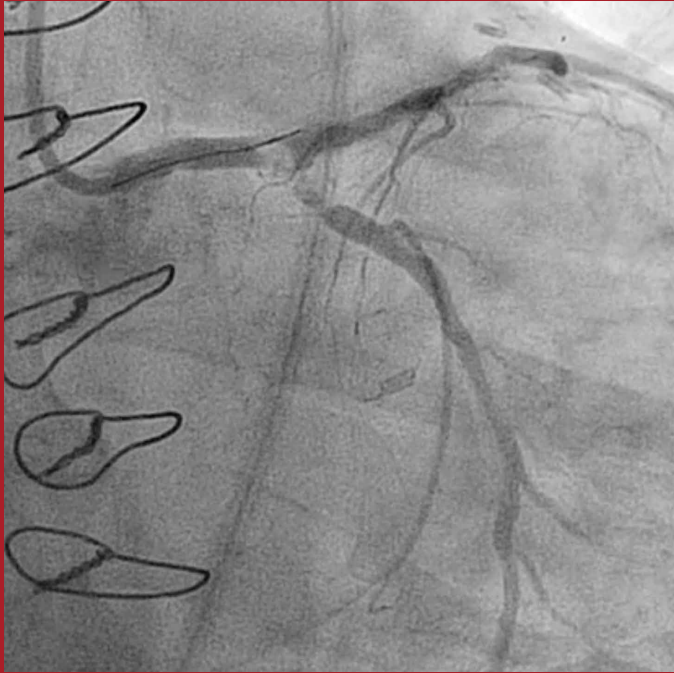


Fig. 11 Interventional therapy of a main stem bifurcation lesion with the reverse TAP technique

More than 5,000 patients undergo coronary angiography every year in our catheterisation laboratory and 2,500 receive a stent, among these more than 1,000 patients with an acute coronary syndrome. These figures make us one of the largest centers in Germany. We provide elective and emergency care 24 hours a day, each day of the year, within 30 minutes of the first call. Our door-to-balloon time (an index of quality that tells how much time it takes for a patient to be treated in the setting of a heart attack) is below 30 minutes and all indicators describing the incidence of complications are below the average of German third-care centers. The following paragraphs describe our spectrum of activities.

Coronary Intervention

Even though coronary interventions have been performed for more than 40 years, there is a large spectrum in the complexity of the patients that are treated. In our catheterisation laboratory, all types of coronary artery disease are treated, from the

simple to the most complex ones, including those requiring additional devices such as rotablation or coronary lithotripsy. Our clinic serves as referral center for several regional and over-regional cooperating hospitals, who refer their more difficult to treat cases to us. The cooperation with the Department of Heart and Thorax Surgery also allows a continuous interdisciplinary evaluation of the indication and method of treatment for our patients. We also conduct research in the field of coronary interventions: for instance, we are currently conducting two randomised trials comparing different types of treatment for bifurcation lesions (Fig. 11) and different methods for the assessment of coronary stenosis.

Imaging and hemodynamic techniques

Our laboratory is equipped with state-of-the-art tools for the assessment and the visualisation of coronary stenosis: these include imaging techniques such as optical

coherence tomography and intravascular ultrasound, as well as seven different methods to test the severity of a coronary stenosis and the presence of microvascular dysfunction (i.e., disease of the small vessels). This also includes methods that are not yet on the market or that are only rarely used in other centers, which makes us one of the centers with the largest portfolio of this types of devices in Europe (Fig. 12).

The coronary sinus reducer and lung embolism aspiration

Beyond treatment of heart blood vessels, our catheterisation laboratory performs a number of other procedures. As one of the few centers in Germany, we conduct implantations of the so-called coronary sinus reducer, a new device that is indicated for the treatment of refractory angina (i.e., chest pain that cannot be treated with standard therapies). Our experience with this device is extremely good: as many as 75% of the patients, who otherwise

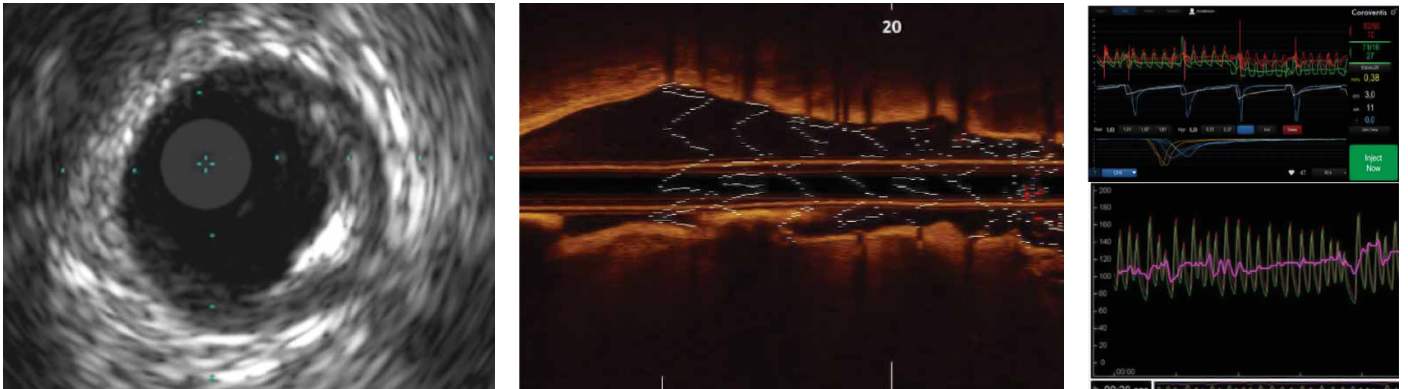


Fig. 12 Intravascular ultrasound, optical coherence tomography, and different hemodynamic methods for the assessment of coronary structure and function

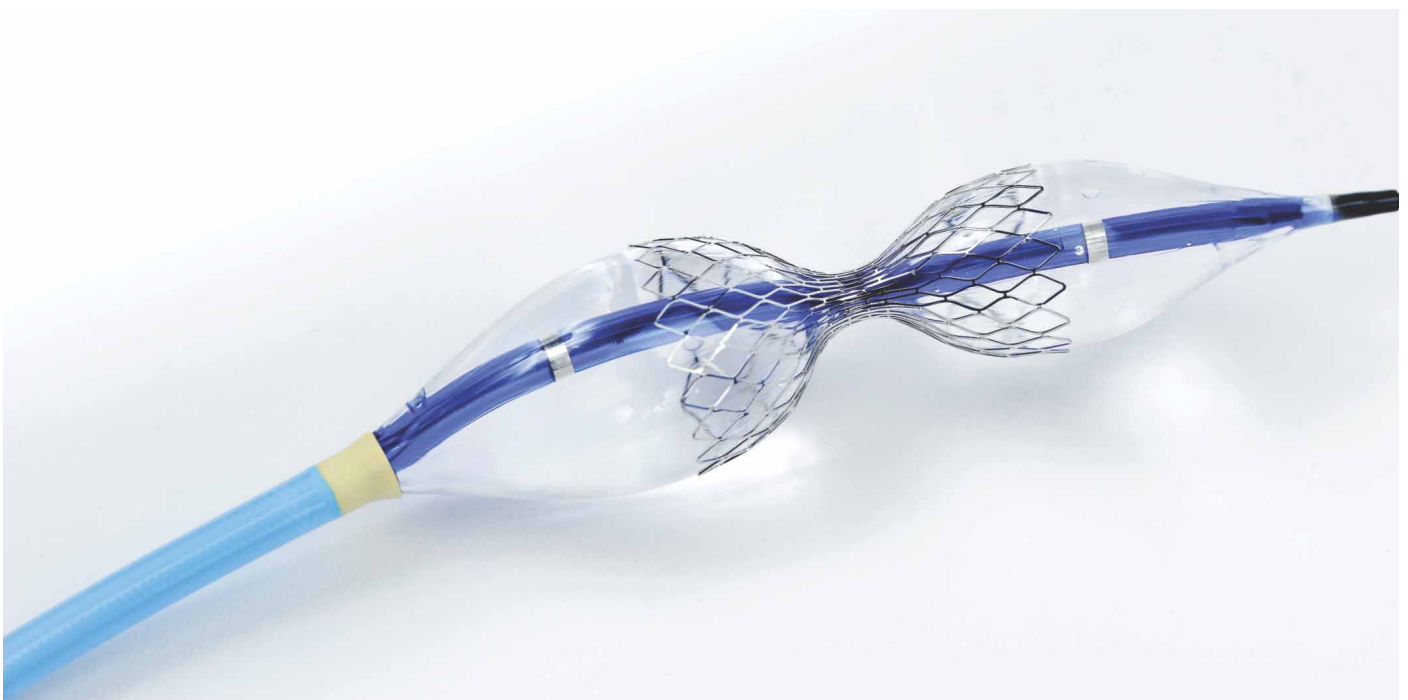


Fig. 13 Coronary sinus reducer



Fig. 14 Left is a CT angiogram before thrombus aspiration, in the middle the thrombus, and right the same CT after aspiration. Gori T, Eurointervention 2019

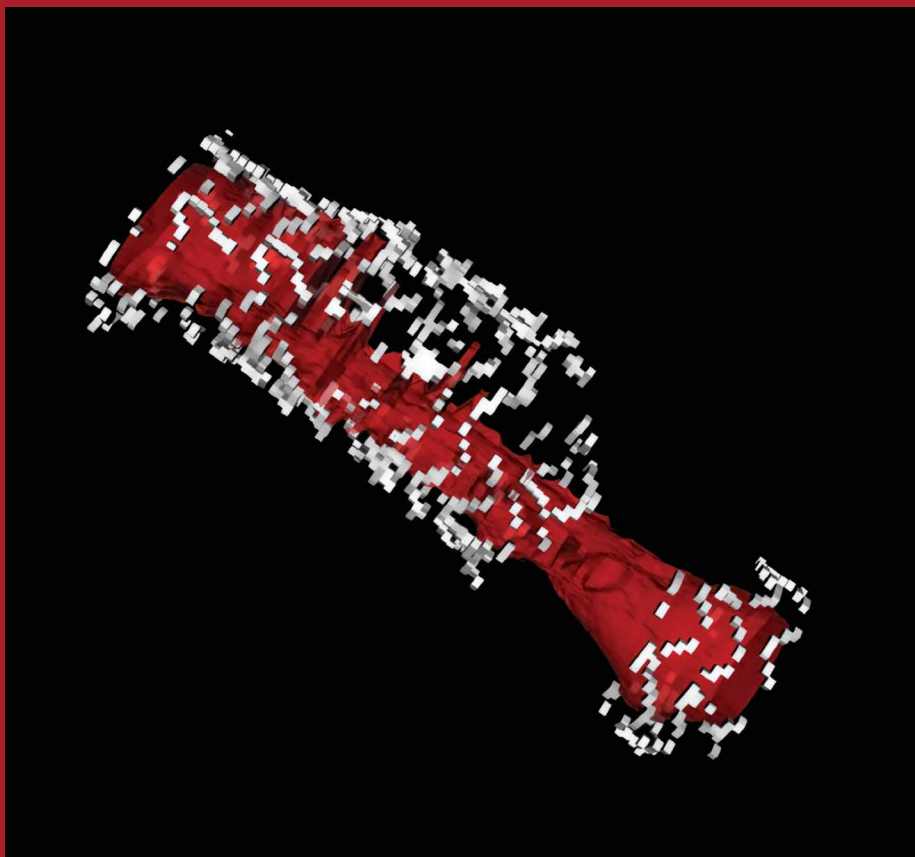


Fig. 15 A stent fracture. The stent is white, the stent is broken and a whole segment is missing from the middle. The blood flow (in red) is limited in the ruptured segment

were unable to conduct a normal life due to their chest pain, report a significant increase in their symptoms. An example of sinus reducer is presented in Fig. 13.

Additionally, Mainz has established one of the first PERT (pulmonary embolism response team) in Germany, a group of physicians specialised in the treatment of acute lung embolism. Pulmonary embolism is one of the most frequent causes of death. Employing an innovative technique, we can now extract the blood clots using catheters, thus helping those patients at extreme risk. The picture shows one of these cases (Fig. 14).

Finally, we regularly perform complex procedures such as **alcohol septum ablation for patients with hypertrophic cardiomyopathy**, or **chronic total occlusions** (using these techniques we are now able to open blood vessels that have been occluded for more than ten years). In all these fields, our laboratory is well integrated and visible in national and international working groups.

Research in interventional cardiology

Beyond patient care, our mission is also the investigation of the

mechanisms of coronary artery disease, as well as the effects and efficacy of drugs and devices like stents. In the last years, our research has focused particularly on different fields: the first is the use of the intravascular imaging techniques in the diagnosis of complex diseases of the coronary arteries. Our most recent contribution is a study to classify stent fractures and investigate their impact on the outcome after implantation of stents (Fig. 15).

As well, we also take the safety of our staff very seriously: another study ongoing in our laboratory at the present time deals with ways to reduce the exposition of medical and nursing staff to potentially harmful X-Rays (Fig 16).

Our Core Labs also provides support for external cooperation partners who ask us to analyse their data in a standardised, certified way. Finally, our center focuses on the study of coronary and peripheral endothelial function, an important parameter that determines the function of blood vessels and the prognosis of patients. Although basic, this research is important as it might one day lead to the development of novel therapies and improves our understanding of

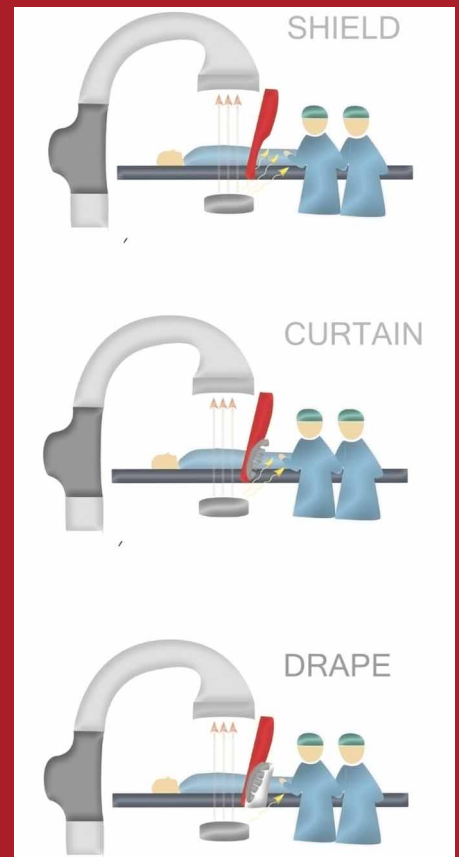


Fig. 16 schematic representation of different methods to protect the staff from radiations

the effects of drugs on the heart's blood vessel system.

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Interventional therapy of chronic coronary occlusions (CTO)

The term **Chronic Total Occlusion (CTO)** refers to a complete closure of a coronary artery, at least for more than three months. The duration of closure is usually estimated according to the best possible clinical assessment, based on appropriate changes in ECGs, angiographic findings or a new positive stress test.

CTOs are found in approximately 15-20% of all patients in the cardiac catheterisation laboratory. A complete occlusion may occasionally occur as a clinically silent event without signs for an acute myocardial

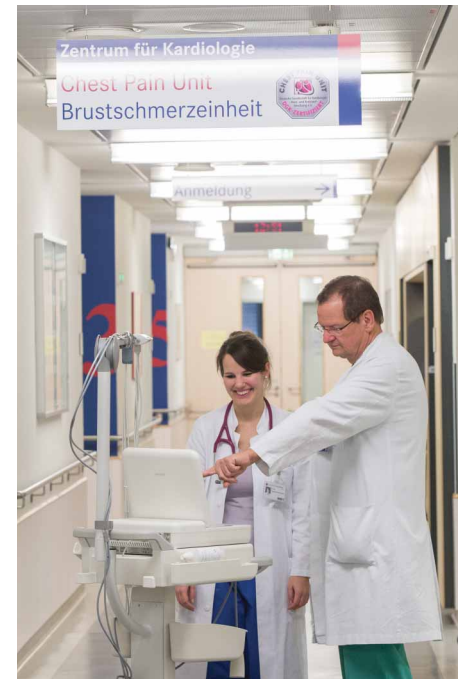
infarction. With respect to the pathophysiology it is postulated that a continuous tightening of the vessel (stenosis) often leads to the formation of so-called collaterals. The heart muscle behind a CTO can survive through these collaterals arising from the ipsilateral or contralateral coronary system. Characteristic for the patients is that they have no symptoms at rest but become symptomatic under physical exertion thus getting angina pectoris symptoms. In these cases, reopening the native vessel may improve symptoms and even survival.

The procedure of reopening the vessel may last several hours and therefore markedly longer as compared to the normal treatment of a coronary vessel e.g. with a stent. Thus, a careful planning of the treatment strategy is of enormous importance. The opening of such chronic occlusions is carried out with various wires of different hardness and coating. These may vary from very soft flexible wires that can probe very small non-visible channels to pass through the closure (so called microchannels) up to very hard, stiff wires that can penetrate the occlusion site directly. Quite common, the use of multiple wires with different features (both soft and hard wires) is necessary in the same catheterisation procedure. Often, we try to pass the closure from the "front" side also called antegrade approach. If this does not work, we will try to open up the closure via a retrograde approach coming from vessels feeding the collaterals to the occluded vessel. In case we can successfully pass the occlusion, a dilatation of the vessel will be carried out by means of a balloon followed by a stent implantation (see Fig. 17). Since 2018 our clinic has been a member of the European CTO Club. In the same year, we reached the second place in the "Associated Members" of the CTO Club with more than 100 CTO cases and a very high success rate of about 90%, thus a great development with benefits of course for our patients and our department.



Fig. 17 Top left: Part of an occluded right coronary artery. Top right: The blue rectangle shows the left coronary and the red one parts of an occluded right coronary artery, which are connected with the left coronary artery via collaterals and supplied with blood from it. Bottom left: Retrograde reopening of the right coronary artery through the collaterals from the left coronary artery. This approach is called "reverse CART". Bottom right: Final result with opened right coronary artery

The German Chest Pain Unit (CPU) Network of the German Cardiac Society (DGK) attracts international attention



Now that our Chest Pain Unit (CPU) is 14 years old, it seems timely to provide a summary of our experience to date with this relatively new form of patient care facility. The university hospital in Mainz was one of the first in Germany (2005) to put in place this unit for patients with chest pain.

An article on the German CPU Network by Professor Thomas Münzel and Professor Gerd Heusch was recently published in the Journal of the American College of Cardiology 2017.¹

The authors point out that there have been significant improvements in the quality of diagnosis and treatment of patients with chest pain following the creation of the CPU Network in Germany. Associated with this are prognoses for patients with acute coronary syndrome that are better than those of patients treated in

standard emergency departments. This is because the time from onset of symptoms to initiation of targeted measures is much shorter in a CPU than in a normal emergency department. In addition, it is possible to undertake effective intervention in a directly associated cardiac catheterisation lab. It is essential that a chest pain unit has immediate access to a cardiac catheterisation lab.

"I am of course proud that I am able to steer the development of a CPU network in Germany from here in Mainz," explains Münzel. "We set up one of the first university hospital-based CPUs here in 2005 and the German CPU Network that we have helped build is - together with the network in the US - quite unparalleled elsewhere."

It is the intention of the German Cardiac Society (DGK) to disseminate this CPU concept

throughout Europe. Accredited CPUs have already been established in other German-speaking countries - Switzerland (Zurich and Lucerne) and Austria (Vienna). The requirements for the certification of CPUs have been translated into English, making it possible for CPUs in other countries to apply for accreditation (<http://cpu-international.dgk.org>).

Motivated by the implementation of the CPU network in Germany and the publication of certification criteria, the **European Acute Cardiovascular Care Association** has produced its own guidelines for the realisation of this concept throughout Europe.

Every minute counts. Time is heart muscle

Reference

- 1 Münzel T, Heusch G. Chest Pain Unit Network in Germany: Its Effect on Patients With Acute Coronary Syndromes. J Am Coll Cardiol 2017;69:2459-2460

Department for Preventive Medicine Mainz

"Prevention is the best medicine" – this age-old adage is still proving itself to be true and worthy. Nowadays health protection is considered an important prerequisite for a powerful, balanced, independent, and self-determined life. The Department of Cardiology has recognised the importance of preventive medicine and has developed the concept for a profile center "University Center for Preventive Medicine Mainz" integrated in the University Medical Center Mainz. The work in this center starts where current research ends and therapy has not even begun: Newest research achievements are translated into diagnostics and therapy by including them directly into preventive, but also therapeutic recommendations. The Center aims at improving patient care in primary, secondary and tertiary prevention by using an interdisciplinary approach. The available expertise in various medical fields is bundled for providing latest

medical knowledge and therapy in disease prevention, early disease diagnostics and prognostics after an acute disease.

The interdisciplinary teamwork of various clinics and institutions of the University Medical Center Mainz results in the opportunity to create a comprehensive health check covering all medical fields. The examination program has an age- and sex-dependent design and is adapted according to the individual needs and requests.

A full investigation is conducted in the following departments:

- General Medicine and Cardiovascular Medicine
- Interventional Cardiology
- Urology
- Gynaecology
- Gastroenterology
- Endocrinology



Fig. 20 Our expertise for your health

- Dermatology
- Ophthalmology
- Otolaryngology (ENT)
- Psychosomatic Medicine and Psychotherapy
- Radiology

This check-up examination is predominantly used by international patients with a high percentage of country representatives and leading personalities.

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sprechstunde@praeventive-kardiologie.de

Epidemiological research at the Center for Cardiovascular Medicine

The research program in the Department of Cardiology has a special focus on translational research and splits up into basic science, epidemiological science and clinical trials. A focus is put on the development of large-scale databases with the observation of diseased patients, but also the population over long-term periods. These large databases help to:

- translate new findings from basic science into the clinical setting;
- return clinically observed associations back to the laboratory bench (reverse translation) for further investigations;

- understand the variability of disease in humans; and
- improve patient care.

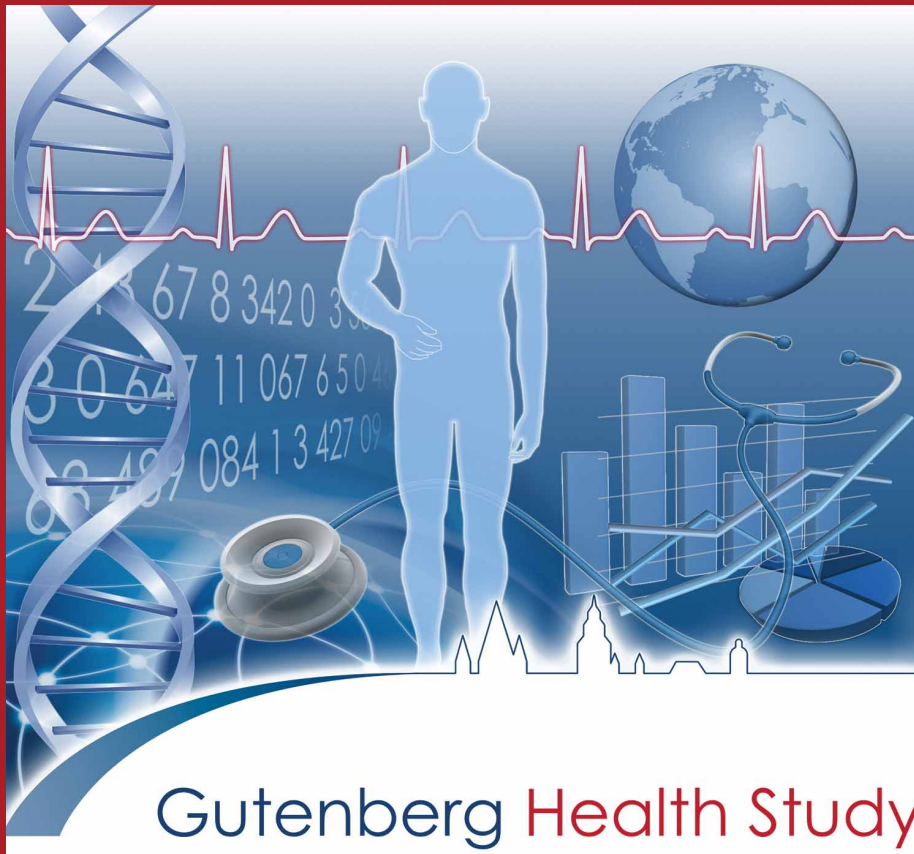
The hypothesis is that bioprofiles of individuals including various information levels from the molecular profile to the subclinical and clinical disease, environment, lifestyle and personality will help to understand the development and course of diseases.

A valuable resource is a centralised repository of biomaterials with approx. seven million biospecimens of various sources and qualities.



Fig. 21 Medical data are recorded in a centralised electronic file, which allows for monitoring health development over sequential visits over years. The findings are explained by specialists and summarised in a comprehensive concluding review with a prevention specialist. A comprehensive check-up is usually performed within two to a maximum of three days, as there are no long distances between specialists and waiting times are reduced to a minimum.

The Gutenberg Health Study: A population-based science with a large-scale, state-of-the-art cohort study with a multidimensional biodataBASE



GHS is part of a broad national and international research network.

The second examination in the study center after five-years was completed in April 2017. Over 90% of the 15,000 subjects initially included remained in the Gutenberg Health Study. The second phase of the Gutenberg Health Study was kicked off in 2017. Although the successful concept of the first phase (2007-2017) was retained, the examination program underwent significant expansion and development in light of the multicausality of common diseases, and now takes between five and six hours to complete. In addition, a broader age range and data collection on an even wider range of biomaterials enable the generation of new data levels, which will ultimately enhance the unique features of the Gutenberg Health Study in translational research. This makes the GHS an all the more unique translational research platform and a distinguishing attribute of UMCM. Over 100 employees work on data recording, processing and analysis at the study site, in laboratories and affiliated departments.

The high participation reflects the strong willingness of the local population to actively contribute to the advancement of medical research.

Several cohorts of diseased individuals have been established to enable clinical research on clinically overt cardiovascular disease and the daily applied clinical care (Fig. 21). The cohorts include institutionalised

BY the time the fourth round of follow-up examinations was conducted in 2017, it had been ten years since the First Patient First Visit (FPFV) for the Gutenberg Health Study (GHS). The Gutenberg Health Study is a flagship project in the research landscape of the University Medical Center Mainz. The GHS aims to improve the prediction of the individual risk for the development and progression of various common diseases. Its findings will hopefully contribute to improving medical prevention, diagnosis and treatment. The interdisciplinary design of GHS

makes it ideally suited for this purpose.

The GHS is a population-based cohort study conducted by University Medical Center Mainz (UMCM), in which a population sample of over 15,000 men and women from the City of Mainz and the District of Mainz-Bingen undergo regular and highly standardised health examinations at fixed intervals.

As an interdisciplinary research consortium, the GHS is financially, scientifically and structurally supported by various central and partner institutions of UMCM and external partner organisations. The



Fig. 22 Cohorts on various indications in the field of cardiovascular medicine are available for research

samples from the UMC Mainz and the established networks of hospitals, but also patients from ambulatory health care. They comprise 16 cohorts in the fields of acute coronary syndrome, myocardial infarction at younger age, heart failure, venous thromboembolism, cardiovascular sequelae in childhood cancer survivors or psoriasis, interventional valve implantations (mitral, tricuspid and aortic position), and drug interventions (arterial hypertension, diabetes mellitus, dyslipidaemia).

Data from diseased individuals can be compared to the population by making use of the GHS, as cohorts have been harmonised with regard to data assessment and biobanking

(Fig. 22). The German Centers for Health Research strive to create optimal research conditions to combat common diseases.

The **German Center for Cardiovascular Research (DZHK)** is one of six health research centers funded by the German Federal Ministry of Education and Research (BMBF). The goals of the center are to improve the prevention, diagnosis and treatment of cardiovascular diseases. UMCM belongs to the Rhein-Main site of the DZHK (together with Johann Wolfgang Goethe University Hospital Frankfurt, Max Planck Institute Bad Nauheim and Kerckhoff Hospital Bad Nauheim).

As part of this national network of excellence, UMCM focuses on patient centered research in heart failure, coronary heart disease, acute coronary syndrome and myocardial infarction. The Mainz site of the DZHK supports national cooperation projects in the network through the exchange of scientific expertise and methods. Various cooperative projects were launched within the framework of the 'Shared Expertise' funding scheme and six scientific platforms for research partnerships in national and international networks are offered. In addition, the careers of junior scientists are fostered by a dedicated program and long-term support within the framework of the DZHK.

Research on the impact of environmental stressors on cardiovascular health

One of the main focuses in the area of vascular biology is the impact of environmental stressors such as transportation noise on vascular function. We believe that noise represents a novel and important cardiovascular risk factor. It has been known now for many years that noise can cause cardiovascular disease but the mechanisms underlying noise induced vascular dysfunction have remained obscure. In 2013 we demonstrated for the first time that night-time aircraft noise causes endothelial dysfunction in healthy volunteers.¹ Importantly, endothelial dysfunction was markedly improved by the oral administration antioxidant vitamin C indicating that most of endothelial dysfunction was secondary to increased production of reactive

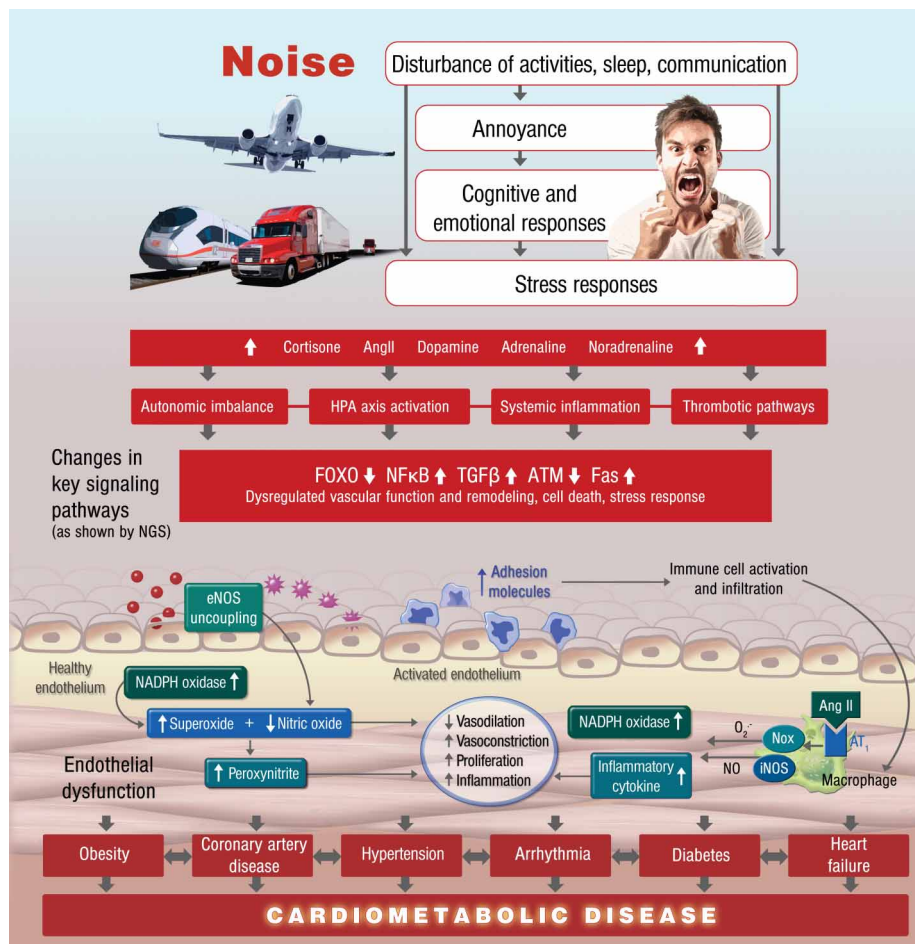
oxygen species. We also established increased stress hormone levels of adrenaline in noise-exposed subjects. Over a couple of years we extended this observation by demonstrating that in subjects with coronary artery disease, night-time noise caused an increase in blood pressure, an even stronger degree of endothelial dysfunction that was interestingly not explained by the noise annoyance reaction. The underlying molecular mechanisms of these phenomena remained unclear. Using a newly developed animal model, our research team was able to establish vascular dysfunction and increased oxidative stress within the vasculature. As superoxide sources an NADPH oxidase (phagocytic Nox2) and an uncoupled nitric oxide synthase were identified.² More recent studies

demonstrate that night time aircraft noise is responsible for vessel and brain damage and that a Nox2 knockout completely prevents aircraft induced adverse effects.³ In addition, we have demonstrated that the disturbance of sleep and of the circadian rhythm causes vascular and brain damage,³ suggesting that stress due to too short sleep and/or fragmentation of sleep is responsible for this phenomenon. These findings have provided, for the first time, a molecular insight into noise-induced vascular and brain damage. All results that were published in the European Heart Journal, the world's most prestigious cardiovascular journal, may represent indeed a breakthrough in (aircraft) noise research helping to develop mitigation and treatment strategies in order to avoid these noise-induced side effects. Based on these findings in our recent translational patient and animal studies we developed a scheme with a pathophysiological concept of how noise causes vascular damage.

Due to a review published in the Journal of the American College of Cardiology,⁴ TIME made a brilliant movie summarising our review www.youtube.com/watch?v=fkraKdJXsY.

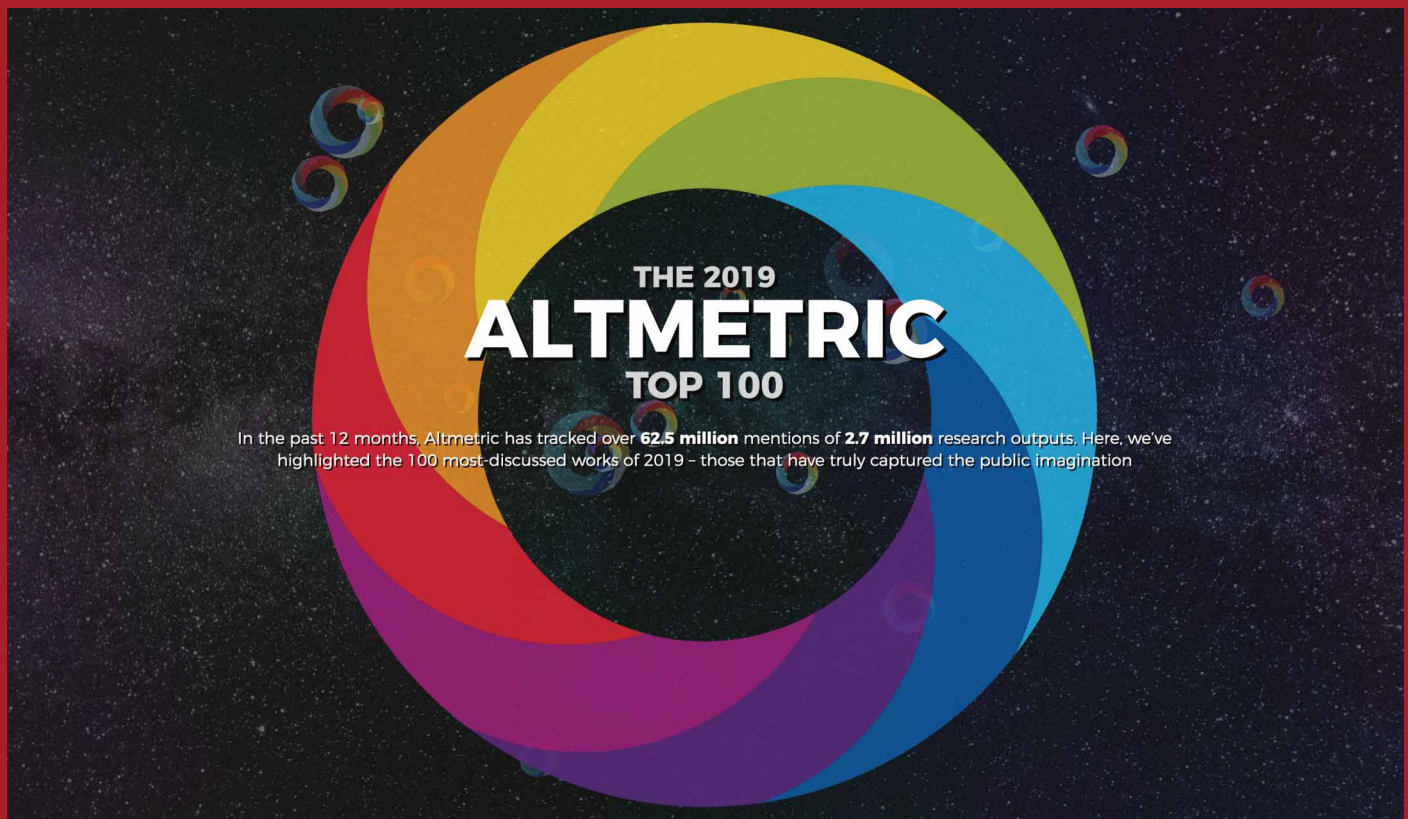
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HOT SCIENCE: Air pollution, the underestimated cardiovascular risk factor

The original manuscript published in EHJ from Jos Lelieveld and Thomas Münzel came in position 72 of the top 100 of the Altmetric Top 100 score for 2019. The Altmetric worldwide ranking was the result of tracking 62.5 million mentions of 2.7 million research outputs. The result highlights the popularity of the Lelieveld/Münzel article



#72 of 100

Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions



Air pollution is putting a strain on our hearts, especially in Europe, where it could cut life expectancy by 2 years. This research shows that about 120 people for every 100,000 people in a population die early due to air pollution globally – and that figure is even higher in Europe, at 133.

Published in *European Heart Journal*

Date March 2019

Subject area Medical and Health Sciences

A team of scientists headed by Professor Jos Lelieveld of the Max Planck Institute for Chemistry and Münzel of Mainz University Medical Center has revealed that air pollution shortens the average life expectancy of Europeans by about two years. According to the study,

around 120 people per 100,000 population die prematurely from the effects of air pollution on a global scale. The corresponding figure for Europe stands at 133 per 100,000 population, which thus exceeds the global average. Cardiovascular diseases are the cause of death in at least half the incidents.

Poor air quality, especially by fine particulates, can lead to respiratory and cardiovascular diseases, and are associated with a remarkable high mortality risk. In the study, published in the *European Heart Journal*,¹ the researchers adjusted the most recent calculations of the Global Burden of

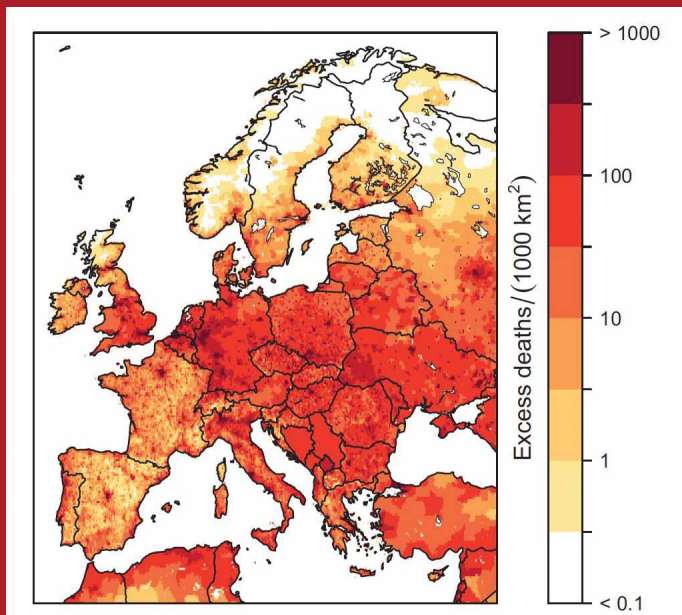


Fig. 24 Regional distribution of estimated annual excess mortality rates from cardiovascular diseases (CVD = IHD + CEV; IHD: ischemic heart disease, CEV: cerebrovascular disease) attributed to air pollution. These rates are lower limits as other non-communicable diseases are not included

Disease (GBD), a global health study, as well as their own values² substantially upward: Until recently, it had been assumed that the global mortality rate due to air pollution was around 4.5 million people a year. The recalculated value puts that figure at 8.8 million per year. In Europe alone, nearly 800,000 people die prematurely every year as a result of air pollution.

It became necessary to update the calculations, as a recently published study³ placed the disease-specific hazard rates well above the GBD values. Because this study incorporated 41 large-scale case-group investigations from 16 countries, including China, it provides the best data base currently available, says Jos Lelieveld, director at the Max Planck Institute for Chemistry.

Polluted air claims at least as many lives as smoking

According to the new calculations by the Mainz researchers, poor air quality now ranks among the most serious health risks, including hypertension, diabetes, obesity and smoking. By comparison, the World Health Organization (WHO) estimates the premature mortality rate from smoking tobacco – including passive smoking – to be 7.2 million people per year. Consequently, ambient air pollution poses a risk that is at least similar to smoking. Tobacco smoking, however, is a personal decision, whereas exposure to ambient air pollution is not.

The researchers emphasise that particulate matter with a diameter less than 2.5 micrometres (PM_{2.5}) is the main cause of respiratory and cardiovascular diseases, which explains the high mortality rates attributed to poor air quality. "The results of our study show that the European limit value for particulate matter – 25 micrograms per cubic meter of air averaged over a year – is much too high", says Münzel, director of Cardiology Center at the University Medical Center in Mainz. This limit is well above the WHO guideline of 10 micrograms per cubic meter.

For their calculations, the team first determined the regional exposure to pollutants such as particulate matter and ozone using an established, data-driven atmospheric chemistry model. They then linked the exposure values to disease-specific hazard functions from epidemiological data as well as population densities and causes of death in all European countries.

Particulate matter levels should be reduced: "Our results show a much higher disease burden from air pollution than previously assumed", says Münzel, who also initiated the Mainz Heart Foundation. "It has become more urgent than ever to reduce exposure to particulate matter and to adjust the limit values accordingly. In addition, fine particulate matter as a cause of cardiovascular diseases should be featured more prominently in the

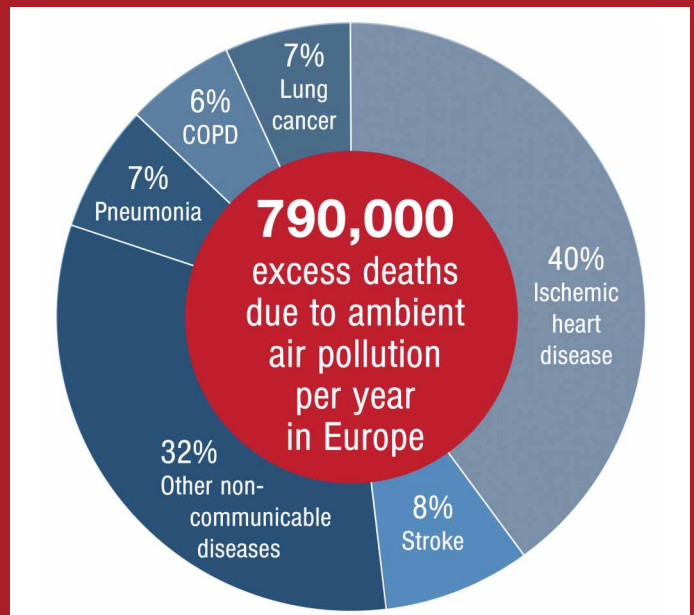


Fig. 25 Estimated excess mortality attributed to air pollution in Europe, and the contributing disease categories. At least 48% are due to cardiovascular disease (ischemic heart disease and stroke). A fraction of other non-communicable diseases should also be counted to cardiovascular diseases related mortality, with an upper limit of 32%. COPD, chronic obstructive pulmonary disease

guidelines of the European Society of Cardiology."

Replacing fossil fuels with clean energy sources could reduce the mortality rate by more than half

Since much of the fine particulate matter and other airborne pollutants result from the burning fossil fuels, scientists advocate replacing fossil fuels with sustainable sources of energy. "When we shift to clean, renewable energy, we could comply with the Paris agreements to mitigate the effects of climate change", explains Jos Lelieveld who is a professor at Johannes Gutenberg University in Mainz and at the Cyprus Institute in Nicosia. **"We can then also reduce air pollution-related mortality rates in Europe by up to 55%."**

- 1 Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Lelieveld J, Klingmüller K, Pozzer A, Pöschl U, Fnais M, Daiber A, Münzel T, *Eur Heart J*. 2019 May 21;40(20):1590-1596. doi: 10.1093/eurheartj/ehz135
- 2 Age-dependent health risk from ambient air pollution: a modelling study of childhood mortality in middle and low-income countries. Jos Lelieveld, Andy Haines, Andrea Pozzer *The Lancet Planetary Health*, 2. Juli 2018; pre-publication 29 June 2018
- 3 Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter Burnett et al.: *Proceedings of the National Academy U S A*. 115(38):9592-9597, doi: 10.1073/pnas.1803222115, 2018

Foundation Heart of Mainz



The Mainz Heart Foundation was founded in 2007 with the aim of promoting:

- Research and education
- Improvement in patient care and
- Prevention.

The Mainz Heart Foundation has therefore set itself the task of approaching children and adolescents early on with a targeted prevention program, the Children's Academy of Health. This year we celebrate the 10th anniversary of the Academy. A total of more than 6,500 school children from the Rhineland Palatinate, Hessen and Saarland regions have since participated in the program. The main topics of this education program are to explain the children the function of the heart and the circulatory system, to educate on the dangers of cigarettes, E-cigarettes and Shishas, to inform about healthy food habits and to teach why to exercise regularly (Fig. 26).

The children also learn how to resuscitate patients with a sudden cardiac arrest (Fig. 27).

It is exciting that the Prime Minister of Rhineland Palatinate, Malu Dreyer, has always loved being the chairman of our academy

Per year the foundation raises around €500,000 to support research with a focus on health and on the environment. The Children's Academy of Health and the Gutenberg Health Study receive considerable funding as well. The most important fundraising event is the **Heart Gala** in the **Mainz Castle**, which celebrated its 10th anniversary in November 2019 (Fig. 28).

The highlight this year was that three scientific awards were given for outstanding scientific achievement: To Professor Philipp Wild for the Gutenberg Health Study (€200,000), to Dr. Ralph Stephan von Bardeleben for research on heart valve replacement (€50,000) and to



Fig. 26 Children in our walkable heart leaning how the heart functions and how to listen to heart sounds.



Fig. 27 Children during resuscitation training



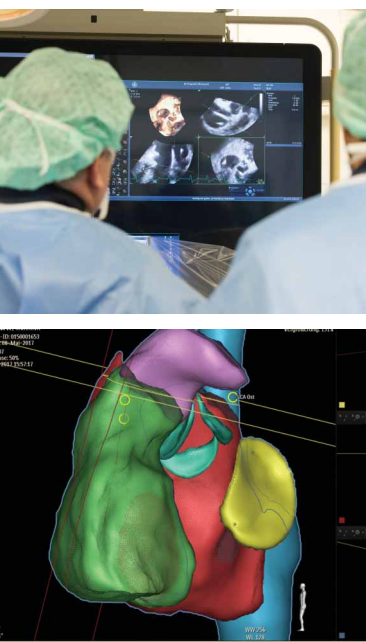
Fig. 28 Heart Gala in the Mainz Castle November 2019.



Fig. 29 From the left: Professor U. Förstermann, Scientific Head of the UCMC; Professor Tommaso Gori, Professor Philipp Wild, Gabi Maas, Dr Ralph Stephan von Bardeleben, Professor Thomas Münzel

Professor Tommaso Gori for research on coronary interventions (€50,000). The lifelong performance of Gabriele Maas, responsible for Nurse

Management at the Department of Cardiology, was also awarded. This was for the first time that a prize for Nurse Management was awarded.



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