

# Excellence in Cardiovascular Medicine and Research

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MAINZ



STIFTUNG  
MAINZER HERZ

# Introduction to the Institution



## The Center for Cardiovascular Medicine at the University Medical Center in Mainz has an internationally recognized leadership in the area of cardiac and vascular medicine.

- The center has currently approximately 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 catheterization laboratories. Per year we see 11,500 inpatients and 20,000 outpatients.
- The Center for Cardiovascular Medicine performs more than 650 heart valve procedures a year, 1,000 atrial fibrillation ablation procedures and implants around 700 devices (defibrillators and pacemakers). We perform 4,200 coronary diagnostic caths and almost 3,000 percutaneous coronary and peripheral interventions.
- In spring 2018, we opened the very first Heart Valve Unit

(HVU) in Europe, thus contributing towards dealing with the drastic increase in incidence of heart valve disorders in Germany.

- 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 in 2017.
- Our Chest Pain Unit deals with more than 6,000 patients annually; 2,500-3,000 of these are hospitalized for further treatment. In this issue, we will be considering how this new patient care structure in Germany has evolved and whether all expectations were 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 the 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.

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

anniversary in 2017, is supporting the clinic with fundraising of about €500,000 per year. The Foundation Heart of Mainz has extended its annual courses in prevention as part of the 'Children's Academy Health' project to a total capacity of 55 school classes (> 1,300 pupils). The purpose of these is to encourage school pupils and young people not to smoke and to eat healthy food and to teach them how to resuscitate people with a sudden cardiac death.

In this center of excellence report we want to focus on the area of minimally invasive, percutaneous heart valve therapy, on Chest Pain Unit and on our preclinical and clinical research activities and on the foundation Heart of Mainz.

# Interventional, minimally invasive heart valve therapy

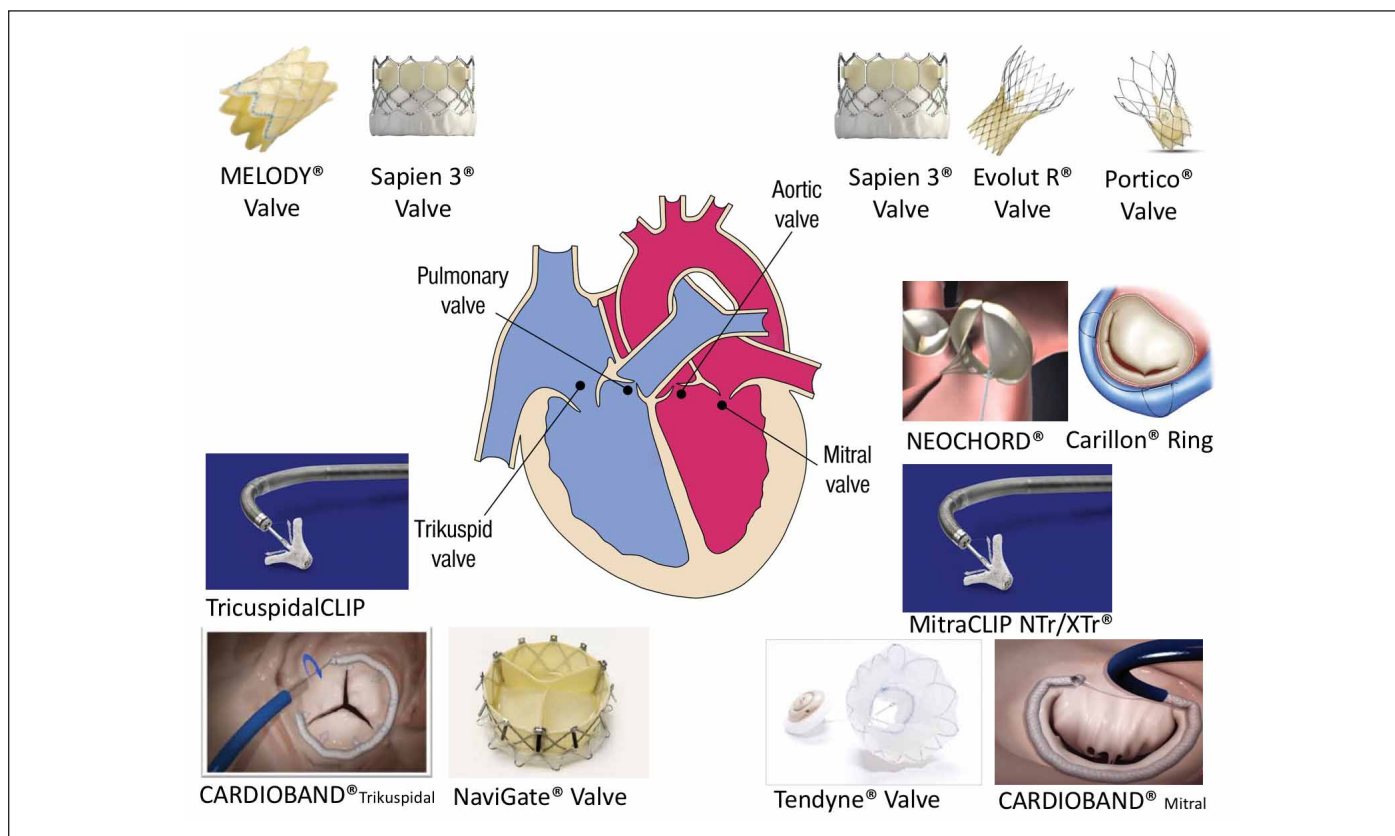


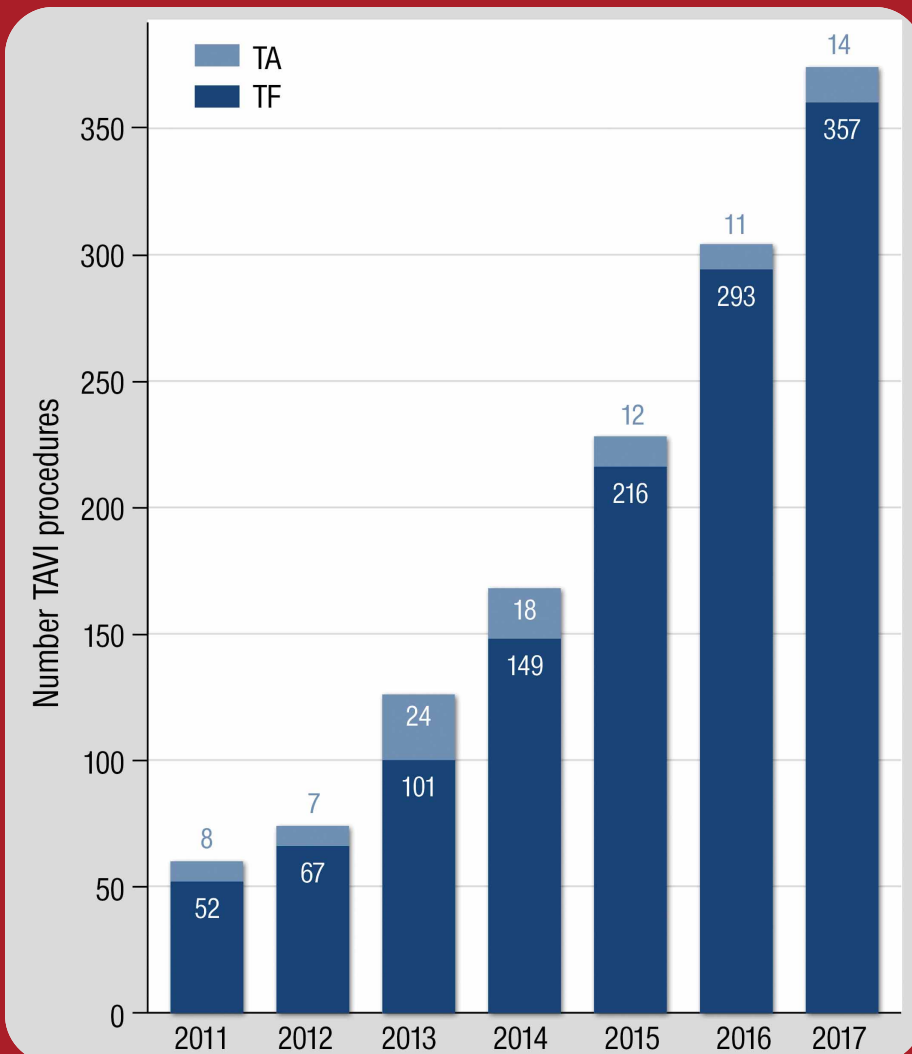
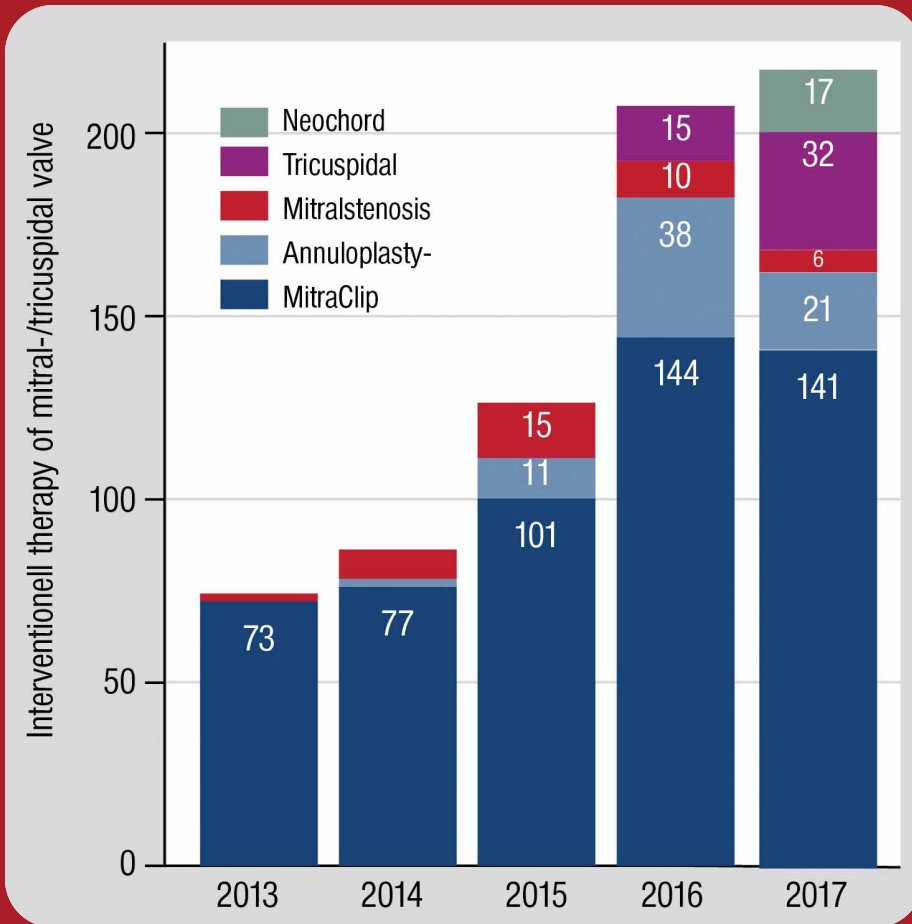
Fig. 1 Broad spectrum of interventional heart valve therapy in Mainz.

The increase in the incidence of heart valve disorders such as stenosis or regurgitation (incompetence) of the valves involving the left, but also the right side of the heart is currently reaching epidemic proportions. The main reason for this development is the progressive ageing of the population being associated with an increase in the incidence of aortic valve stenosis. In addition, we see a major increase in diseases of the atrioventricular valves (the mitral and tricuspid valve), mainly as the consequence of an increased incidence of heart failure.

The following paragraph provides a brief introduction into the physiology of the heart. The human heart consists of four chambers: The right and left ventricles, and the right and left atria. These chambers are separated from each other by four heart valves. Their task is to ensure that blood is pumped in the correct direction through the heart chambers each time the heart beats. In the right heart, the tricuspid valve and the pulmonary valve ensure that the blood can only flow in one direction of the lungs. In the heart's left side, the mitral valve and the aortic valve control the direction of blood flow.

When it comes to catheter-based minimally invasive treatments of disorders of the left heart valves - particularly in older patients or patients with relevant risk profiles - a **Transcatheter Aortic Valve Implantation or TAVI** is principally used and there are up to 19,000 procedures of this kind annually in Germany alone, while a cure of mitral valve regurgitation via implantation of a **MitraClip®** is undertaken in more than 5,600 cases a year.

Importantly, over a period of just ten years, catheter-based therapy of heart valves has developed from a niche



treatment used in otherwise inoperable patients to a significant and safe general therapeutic option. These procedures are now considered routine in this country - the safety of catheter-based intervention is very good and the survival rate is greater than 98%. Importantly, Mainz is one of the few centers worldwide offering the complete spectrum of minimally invasive heart valve repair.

However, as in the case of all heart valve procedures, these minimally invasive interventions 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 - up to ten - years.

In addition to the TAVI and Mitraclip® procedure, other minimally invasive valve interventions include annuloplasty procedures for the mitral and tricuspid valve such as CARILLON® and the NEOCHORD® approach (Fig. 1).

This year, the Cardiology Department will do for the first time more than 200 MitraClips® and more than 300 interventions with respect to atrioventricular valves (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 remarkably rapidly. As mentioned already, in Germany, patients with aortic valve stenosis are being treated more frequently with TAVI than with open-heart surgery. Prof. Eberhard Schulz, Director of the Interventional Heart Valve Therapy Unit at Mainz University Medical Center, values this form of 'keyhole surgery' because subsequent recovery times are shorter. He and his team have performed more than 1,500 TAVI procedures - while the number of patients that require this type of intervention is still increasing. In the year 2018 we will implant more than 400 TAVIs (Fig. 3)



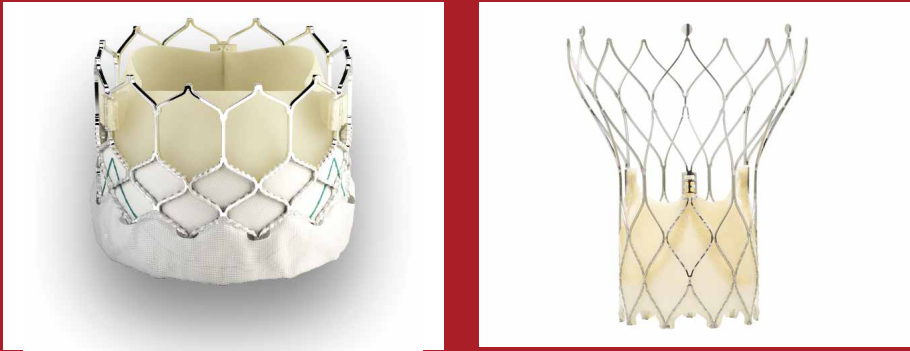


Fig. 4 Contemporary TAVI prostheses: Edwards Sapien 3 (Left; © Edwards Lifesciences) and Medtronic Evolut Pro (Right; © Medtronic)

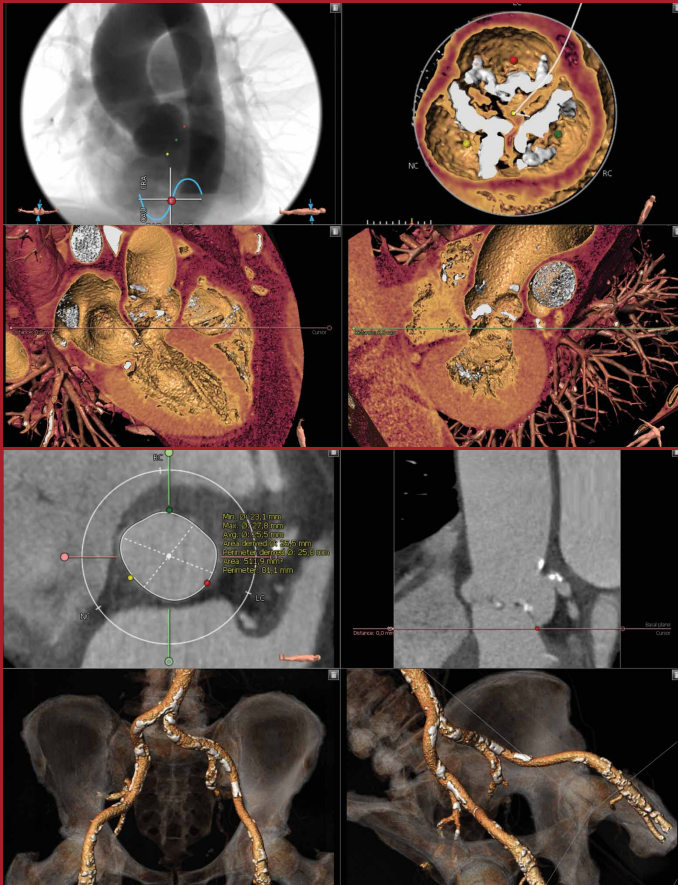


Fig. 5 Reconstruction of multislice CT Scan for procedural planning. Upper panel: anatomy of the aortic valve, left ventricle and aorta. Lower panel: annular plane of the aortic valve, ostium of the left coronary artery, 3D reconstruction of the iliac-femoral arteries

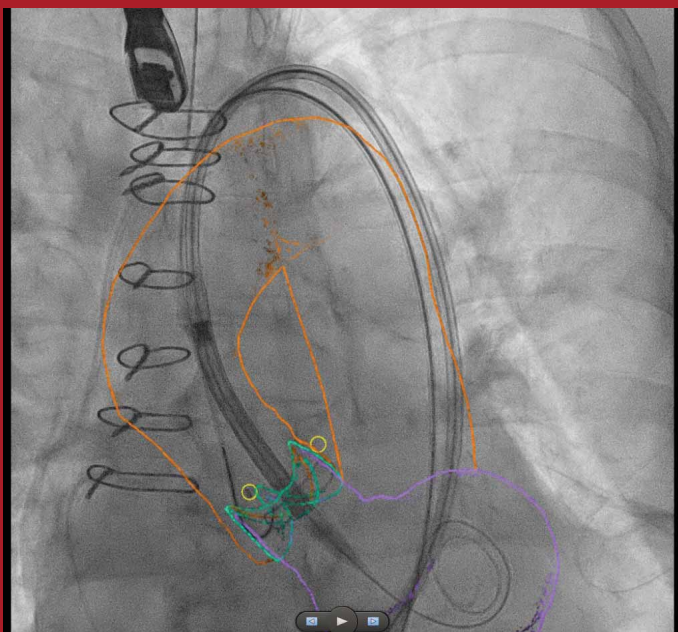


Fig. 6 Fusion imaging (CT/fluoroscopy) during a TAVI procedure (valve-in-valve) With this high degree of innovation and increasing demand for catheter-based valve procedures, the Mainz University Medical Center is among the 10 largest centers for interventional heart valve therapy in Germany.

In the beginning, only patients who were not suitable for conventional surgery were offered a TAVI procedure, in the meantime TAVI has emerged as the standard approach for all patients with increased risk for open heart surgery. The preferred access route is transfemoral, since latest study data show the lowest complication rates and rapid recovery. Modern, third generation TAVI prostheses (Fig. 4) have nearly eliminated early problems in the beginning of the TAVI era such as relevant paravalvular leakage, frequent need for a permanent pacemaker, access site bleeding, annular rupture or device malpositioning.

With a multidisciplinary team of highly specialized interventional cardiologists, heart surgeons, cardiac anesthesiologists, valve nurses and technicians, TAVI procedures in Mainz are performed in a hybrid OR. Besides the interventional expertise, a detailed planning of the procedure is key for success. Every patient receives a multislice CT before the procedure in order to determine access route, prosthesis type and size (Fig. 5)

In contrast to open heart surgery, direct visualization of cardiac structures is not possible with catheter-based treatment options and therefore high-quality imaging is important and in complex procedures mandatory. Thanks to a longstanding expertise in echocardiography and other imaging modalities, the team has co-operations with the developing units of the echo industry and early access to innovate imaging techniques such as 3D virtual reality echocardiography or fusion imaging (CT/fluoroscopy; echo/fluoroscopy) (Fig. 6).

### Minimally invasive right heart valve procedures involving the tricuspid valve

The Department of Cardiology of Mainz University Medical Center is also very successful in the treatment of right-sided heart valve disease. Only a few hospitals are able to offer catheter-based treatments of the tricuspid valve. In fact, only just over

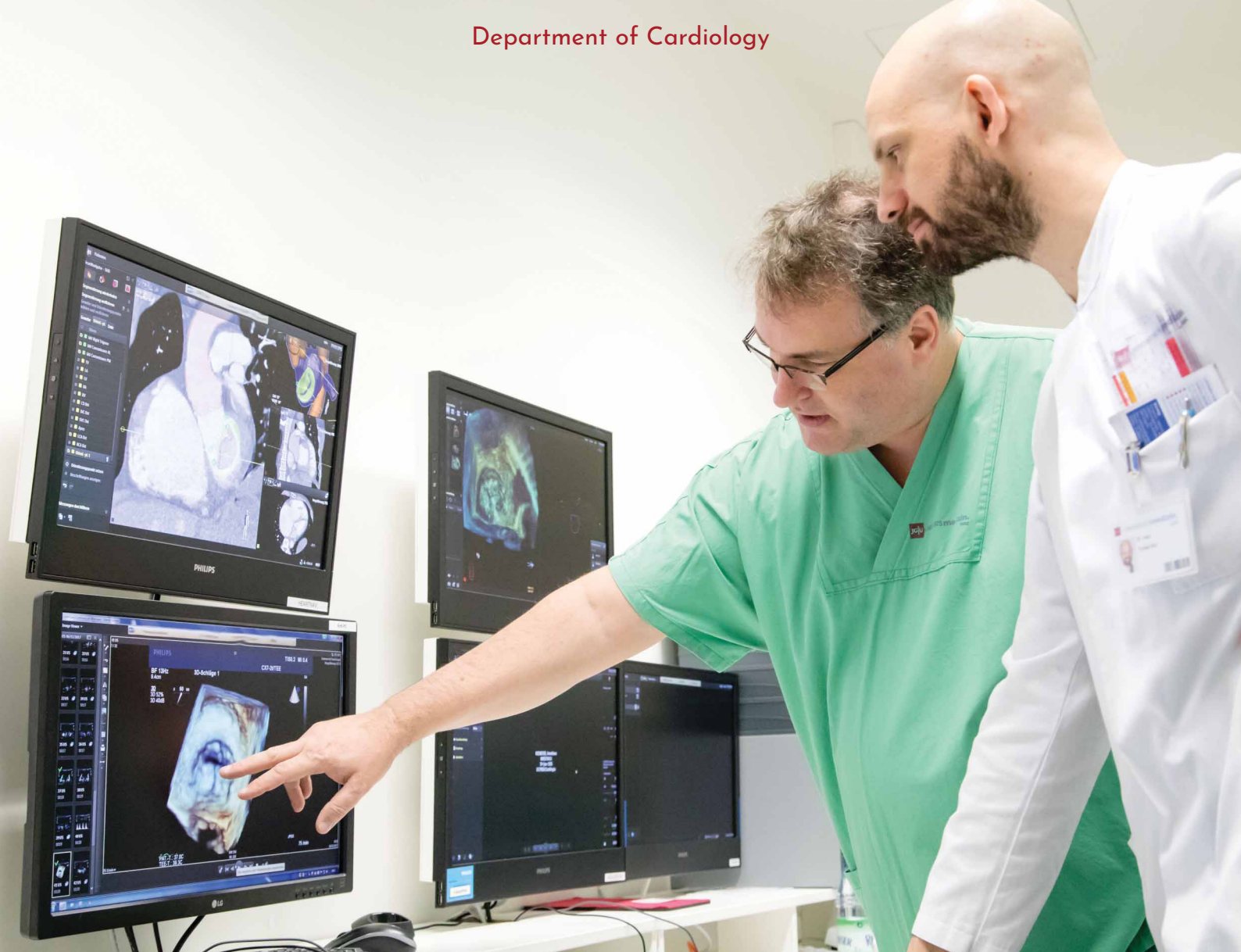


Fig. 7 The Valve Team during a case conference and in the hybrid operating theater

300 such procedures have been performed for therapeutic reasons or as part of clinical trials in recent years. Thus, our department is one of the few centers able to offer this kind of treatment.

In a patient with tricuspid valve regurgitation, one of the undesirable side effects is accumulation of fluids in the legs and abdomen and in particular the quality of life of those affected deteriorates significantly. 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.

The team under Dr. Ralph Stephan von Bardeleben and Prof. Eberhard Schulz now employs two new techniques for the treatment of tricuspid valve

regurgitation, the cardioband® or a tricucip® (Fig. 7 and 8). These techniques have already been used in more than 60 patients to date, putting 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 heart valve disease, offer basic insights into the situation and 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.



Fig. 8 A tricuspid valve procedure



## The first European Heart Valve Unit (HVU)

Due to increasing life expectancy, more and more people worldwide are suffering from valvular heart diseases. These include 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 numerically outperformed open-heart valve surgery during the last few years 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/2017 Report by the decision research group (<https://decisionresourcesgroup.com/report/14453-medtech-heart-valve-devicesmedtech-360-market/>). 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 Germany and worldwide<sup>1-4</sup> for mitral and tricuspid valve interventions (including MitraClip NT/NTr/XTr, TricuClip and Cardioband Mitral / Tricuspid). It is expecting to treat approximately 700 heart valves in 2018.

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 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 are 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;
- transfer within the HVU from IMC to monitor beds for heart rhythm documentation and initiation of optimal and in particular consistent medical therapy; and
- complete 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 patients to different wards. The heart valve unit in Mainz consists of 25 beds, including 8 IMC beds and 17 normal beds equipped with monitors. 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.<sup>5</sup>

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



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

# Coronary diagnostics, interventions and research



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

**M**ore than 4,200 patients undergo coronary angiography every year in our catheterization laboratory and 2,200 receive a stent. Among those more than 700 patients with an acute coronary syndrome are treated. This numbers make us one of the largest centers in Germany. The rapidity and efficacy of these coronary interventions really change people's life: 50% of the patients who die of heart attack do so before they reach the hospital. Our staff is trained to react 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 tell how much time it takes between patient arrival in the hospital and opening of the blood vessel), is below 30 minutes and therefore clearly better than the average in Germany. With the next paragraphs we will introduce some examples of diagnostic

procedures and interventional techniques for our patients with coronary artery disease and pulmonary embolism.

## Coronary Intervention

Special types of coronary interventions represent particular challenges: for instance the treatment of bifurcation lesions, i.e. lesions that are placed in segments where two blood vessels part from each other. These lesions may be complex to treat because both branches of the blood vessels need to be treated and kept open. To overcome this specific challenge, our team developed a new method to treat this type of disease, which we are now testing in a study. The method is called reverse TAP (T and protrusion), and is surely faster and technically less challenging than traditional methods (Fig.11).

## Intravascular Ultrasound (IVUS)

Similar concepts apply to the use of imaging techniques such as optical coherence tomography and intravascular ultrasound. Intravascular ultrasound (IVUS) uses ultrasound produced by a small probe that is inserted over a guidewire into the coronaries. The frequency of the ultrasounds emitted by this probe reaches 60MHz, which allows visualizing the vessels' walls with a ~30 micrometer resolution. Post-hoc processing of the frequency shift also allows characterization of the composition of the wall, identifying calcific, fatty and fibrotic lesions (Fig.12).

## Optical coherence tomography (OCT)

Optical coherence tomography is a technology that is based on infrared light to achieve a resolution that is in the range



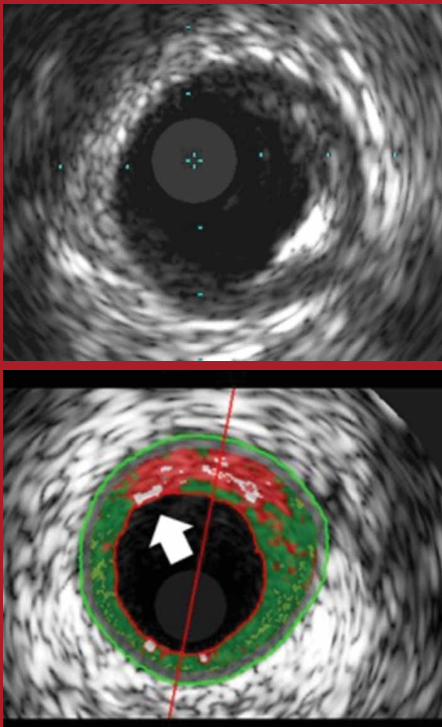


Fig. 12 Intravascular ultrasound (IVUS) and (bottom) virtual histology, green: fibrous tissue, red: necrotic core, white: calcium

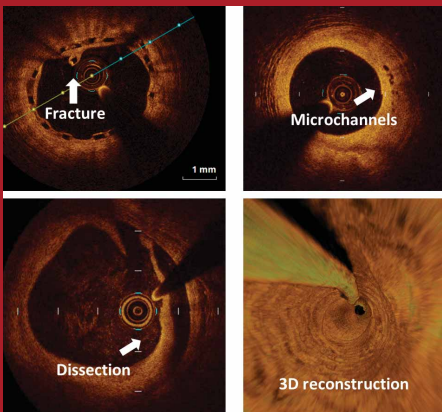
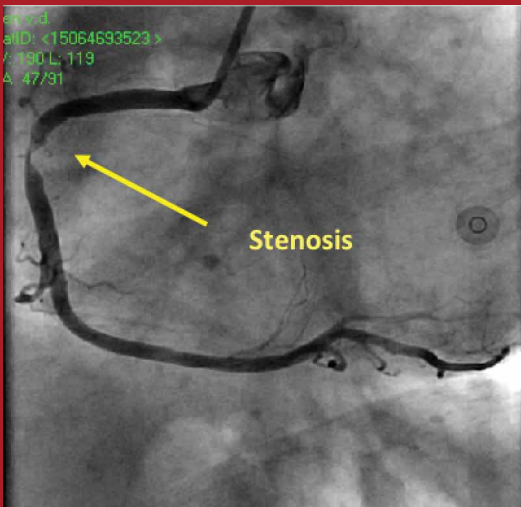


Fig. 13 Examples of OCT imaging in the catheterization laboratory



of 10micrometers (Fig. 13). Post-hoc computer three- dimensional reconstructions allow imaging the vessel 'from within', using so-called fly-through views. These modern technologies allow detection of coronary artery abnormalities with an unprecedented level of accuracy. For instance, stent fractures, a condition in which the metal of the stent is broken, potentially causing inflammation of the vessel wall, can only be diagnosed using these methods. Other examples include the presence of micro vessels in the blood vessel wall, which predispose the blood vessel to rupture or occlude, causing a myocardial infarction. Or the diagnosis of coronary wall dissections, i.e. a rupture of the vessel wall which causes the lumen (inner cavity of the blood vessel to occlude). These types of diagnoses are extremely important in cases in which traditional angiography is not sufficient to allow accurate diagnosis. In our experience, this accounts to up to 50% of the patients. These data show how the use of modern technologies, in a center that has adequate experience, is important for the prognosis of the patients.

### Coronary Flow Reserve

The assessment of the hemodynamic relevance of a stenosis and of the function of the coronary microcirculation has prognostic implications for the patient and can be performed using techniques called coronary flow reserve and fractional flow reserve (Fig. 14).

Our laboratory has a large clinical and research experience in this field. While these procedures are well established, our ambition is to continue to improve their quality, safety and efficacy. We believe that education has a central importance for this purpose. Our cardiac catheterization team regularly holds conferences during which complex cases are discussed and participates in a number of national and international congresses each year.

As well, we have now achieved a national and international lead in the use of modern technologies that allow the assessment and treatment of blood vessel function: for instance, in 2017, we published an atlas on the techniques used for the hemodynamic assessment of coronary artery stenoses, i.e. they allow detecting which blood vessel tightening causes a decrease in the blood supply to the heart. Such information can only be derived with a significantly larger margin of error from a traditional cardiac catheterization. These methods have a resolution that is as low as one millimeter, and therefore are of critical importance for decisions on which patients and blood vessels need to be treated.

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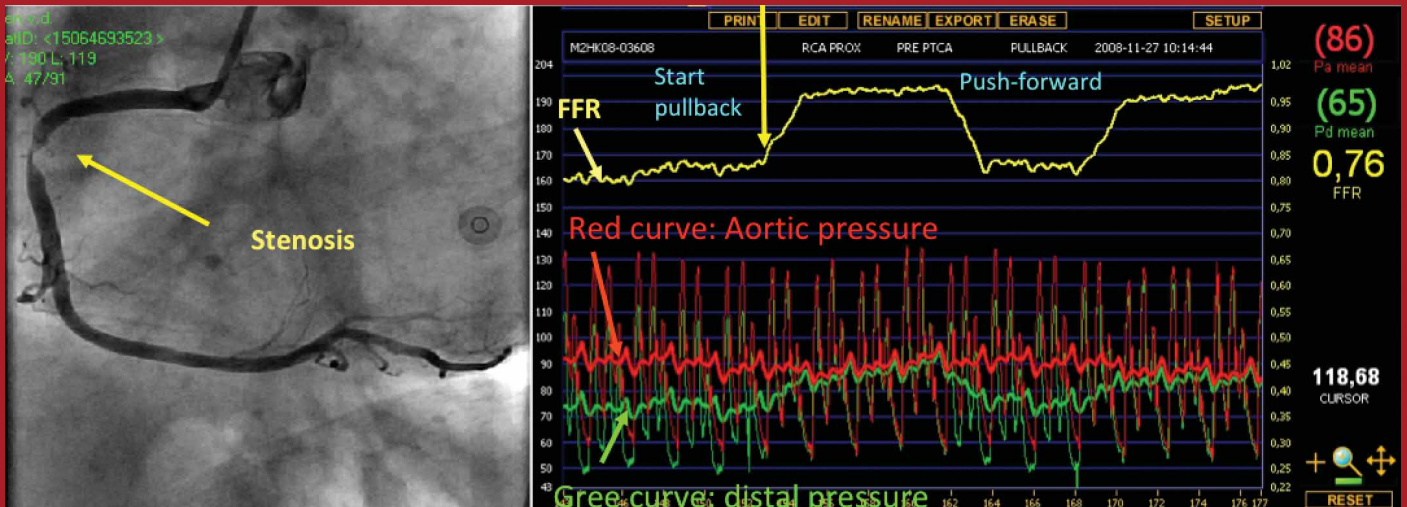


Fig. 14 The left panel shows a typical stenosis of the right coronary artery. In the right panel, the hemodynamic relevance of the stenosis was assessed using FFR. The two pressure curves (red for the aortic pressure and green for the pressure distal to the stenosis) diverge when the FFR pressure sensor is pushed into the vessel



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**The Pulmonary Embolism Rapid Response Team (PERT)**

Beyond treatment of heart blood vessels, our catheterization laboratory performs a number of other procedures. As one of the few centers in Germany, we have a so-called PERT, a group of physicians specialized in the treatment of acute lung embolism, one of the most frequent causes of death. Pulmonary embolism is an extremely dangerous disorder that in many cases proves fatal. Employing an innovative technique, we can now extract the blood clots using catheters, thus helping those patients at extreme risk. The picture below shows one of these cases (Fig. 15).

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. Finally, and

most importantly, we take the safety of our patients at heart. In comparison with other types of exams, cardiac catheterization is surely more invasive, which means it that it also involves risks. It is therefore important that patients understand what the indication and the possible consequences of a heart catheterization are, since the safety of patients is the priority when performing this type of procedures. Information is therefore one of the major focuses of our group: we organize trainings for physicians, and provide patients with information material that prepares them for this type of procedure.

**Research in interventional cardiology**

Beyond patient care, our mission is also the investigation of 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 three fields: the first is the use of the intravascular imaging techniques such as OCT in the diagnosis of complex diseases of the coronary arteries. Our group contributed to the classification and standardization of the diagnosis of particular images called 'peri-strut low intensity areas' (PSLIA - Fig. 16) evaginations.

We are also conducting a study to classify stent fractures and investigate their impact on the outcome after implantation of stents. Our Core Labs also provides support for external cooperation partners who ask us to analyze their data in a standardized, certified way. Based on this experience, we recently founded the German Center for Cardiovascular Research (DZHK), a network of centers in Germany participating in common projects in this field of research.

The second area of research includes outcome and mechanistic research in the field of coronary bioresorbable scaffolds, a novel technology which one day might substitute traditional metallic stents. In this area we recently identified the mechanisms that lead to scaffold thrombosis, a potentially very

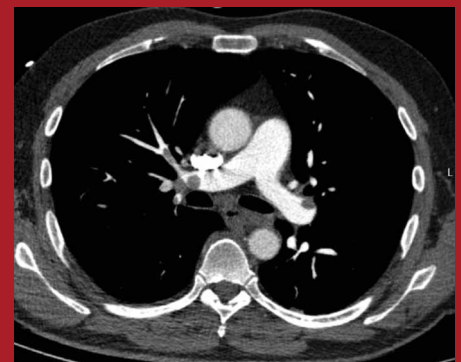
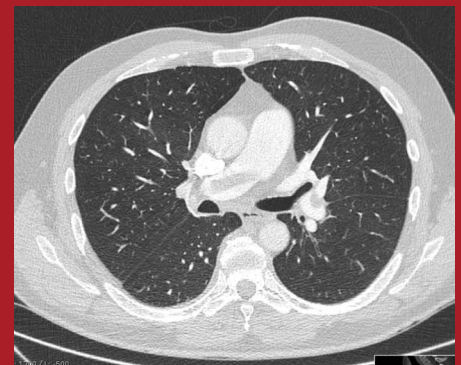
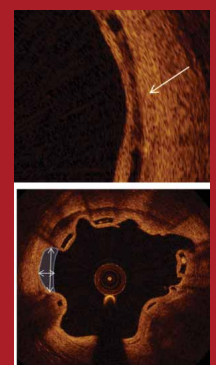


Fig. 15 Top is a CT angiogram before thrombus aspiration, in the middle the thrombus, and bottom the same CT after aspiration

Fig. 16 Example of coronary evaginations in a patient treated with a bioresorbable scaffold, particular images called "peri-strut low intensity areas" evaginations







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dangerous complication (with a mortality of up to 45%) that was observed with this type of devices.

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

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



## CHEST PAIN UNIT

Fig. 17 CPU of Mainz certified by the German Society of Cardiology



**N**ow that our Chest Pain Unit (CPU) is 13 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 **Prof. Thomas Münzel** and **Prof. Gerd Heusch** was recently published in the *Journal of the American College of Cardiology* 2017.<sup>1</sup>

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 catheterization lab. It is essential that a chest pain unit has immediate access to a cardiac catheterization 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 Prof. 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 realization of this concept throughout Europe.

**Every minute counts. Time is heart muscle**

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Fig. 18 Medical round on the CPU



## University Center for Preventive Medicine Mainz

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
- Gynecology
- Gastroenterology
- Endocrinology
- Dermatology



Fig. 19 Our expertise for your health

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

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

## 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;

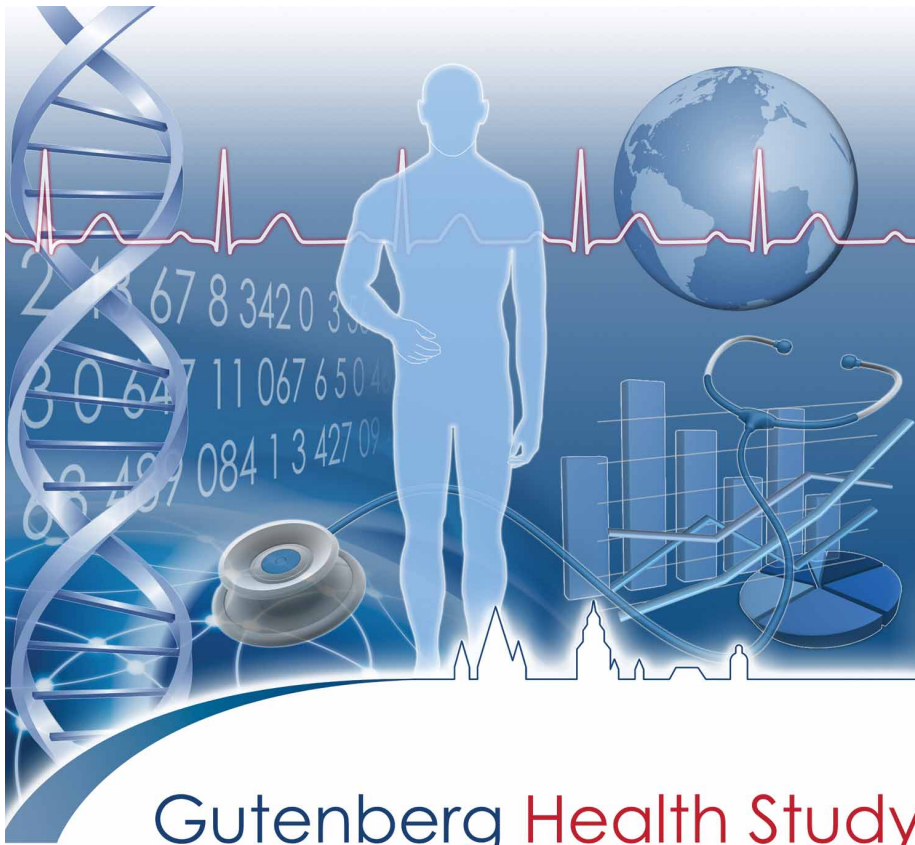
- understand the variability of disease in humans; and
- improve patient care.

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 centralized repository of biomaterials with approx. seven million biospecimens of various sources and qualities.



Fig. 20 Medical data are recorded in a centralized electronic file, which allows for monitoring health development over sequential visits over years. The findings are explained by specialists and summarized in a comprehensive concluding review with a prevention specialist. A comprehensive checkup 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: Population-based science with a large-scale, state-of-the-art cohort study with a multidimensional biodataBASE



## Gutenberg Health Study

**BY** the time the fourth round of follow-up examinations was started in 2017, it had been ten years since the First Patient First Visit (FPFV) for the Gutenberg Health Study (GHS). The GHS 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 standardized 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 organizations. The 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 institutionalized samples from the University Medical Center Mainz (UMCM) 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



Fig. 21 Cohorts with comprehensive biobanking are available for research in various indications in the field of cardiovascular medicine

(arterial hypertension, diabetes mellitus, dyslipidemia).

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

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 (Fig. 22). Various cooperative projects were launched within the framework of the 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 for many years that noise can cause cardiovascular disease but the mechanisms underlying noise induced vascular dysfunction remained obscure. In 2013 we demonstrated for the first time that nighttime aircraft noise causes endothelial dysfunction in healthy volunteers.<sup>1</sup> 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, nighttime 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 a Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (phagocytic Nox2) and an uncoupled nitric oxide synthase were identified.<sup>2</sup> 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.<sup>3</sup>

In addition, we have demonstrated that the disturbance of sleep and of the circadian rhythm causes vascular and brain damage,<sup>3</sup> 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 the findings in our recent translational patient and animal studies we developed a scheme with a pathophysiological concept how noise causes vascular damage (Fig. 23).

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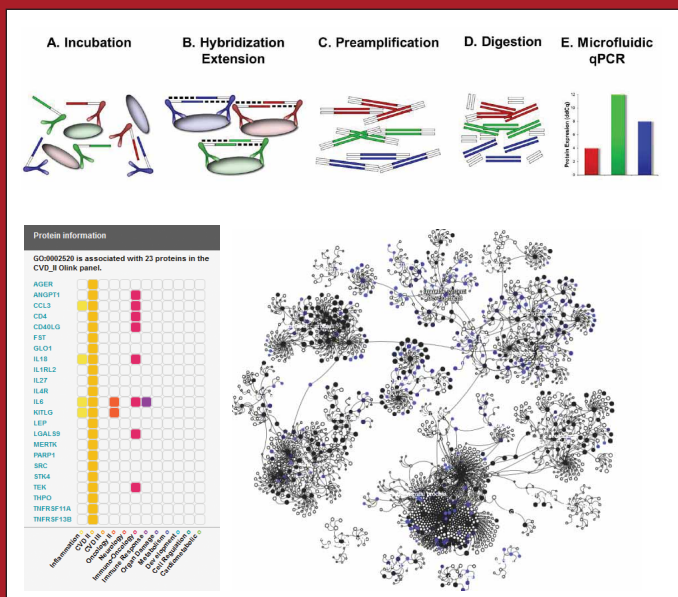


Fig. 22 A protein profiling platform based on the PEA-technology (OLINK, Uppsala, Sweden) is available for high-throughput investigations

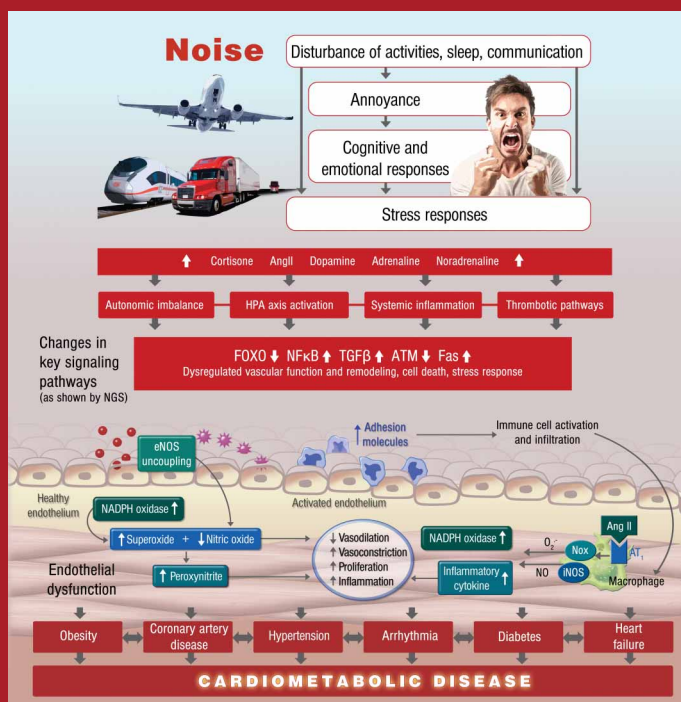


Fig. 23 Complex cartoon about the mechanisms of how noise can cause vascular damage because of a review published in the *Journal of the American College of Cardiology*, *TIME* was making a brilliant movie summarizing our review (<https://www.youtube.com/watch?v=fkraKdJXsY>).

# Foundation Heart of Mainz



STIFTUNG  
MAINZER HERZ

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. A total of 4,000 school children from the Rhineland Palatinum, Hessen and Saarland regions have since participated in the program. The main topics of this education program are to teach the children how our heart and our circulation works, why not to smoke cigarettes, why not to smoke E-cigarettes and Shisha, to inform about healthy food habits and why to do exercise (Fig. 24).

The children also learn how to resuscitate patients with a sudden cardiac arrest (Fig. 25).

It is exciting that the Prime Minister of the Rhineland Palatinum, Mrs Malu Dreyer, has always loved being the chair of our academy.

The foundation raises around €500,000 in support of research with a focus on health and the environment. The most important event is the Heart Gala held every year since 2007 in Mainz Castle (Fig. 26).



Fig. 24 Children in our walk-in heart leaning how the heart functions and how to listen to heart sounds



Fig. 25 Children during resuscitation training



Fig. 26 10th Anniversary of the Mainz Castle Heart Gala, November 2017





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