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FUTURE PERSPECTIVES IN CARDIOVASCULAR MEDICINE

ABSTRACT BOOK

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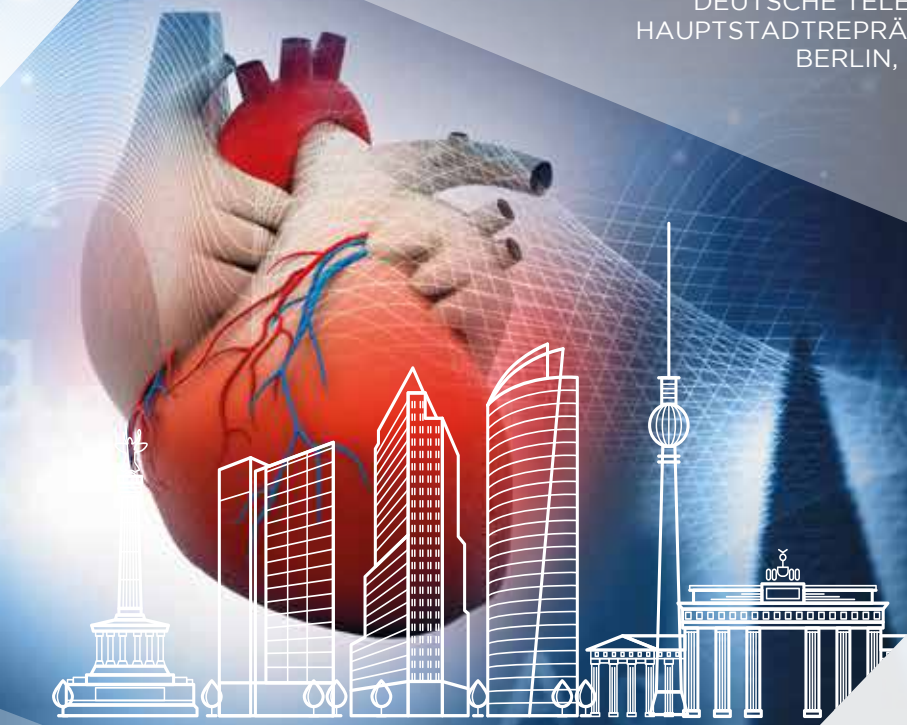

Organized by:
Professor Ulf Landmesser
Cardiovascular Center - Charité
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Dear colleagues,

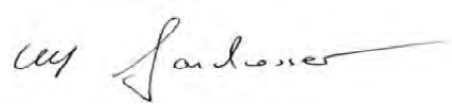
It is with great pleasure to give you a warm welcome to the symposium "Future Perspectives in Cardiovascular Medicine" that has been organized with the Charité Universitätsmedizin Berlin.

We will discuss state of the art and future perspectives of cardiovascular medicine, including prevention and management of coronary disease, novel developments in treatment of valvular and structural heart disease, arrhythmia and heart failure. The important implications of multi-modality cardiovascular imaging approaches towards optimized clinical management will be highlighted.

Charité Berlin has an important history in cardiovascular medicine, including the nobel laureate Werner Forssmann, who first delivered a catheter to the heart that has opened a new door in management of cardiovascular disease. We will also discuss the important role of big data and digital health in the future approach towards cardiovascular disease.

We have an outstanding national and international faculty of experts and we are looking forward to welcoming you to the rapidly developing Berlin and the Charité.

Prof. Ulf Landmesser
President of the Meeting



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Abstract Book

Session I – The Developing Science of Maintaining Cardiovascular Health: Role and Value of Cardiac CT Imaging

David E. Newby
University of Edinburgh, Edinburgh, UK

Cardiac computed tomography now allows for the direct assessment of coronary heart disease. Calcium scoring and coronary computed tomography coronary angiography are powerful techniques that can determine the presence of coronary heart disease in asymptomatic and symptomatic individuals. This can impact on the diagnosis and risk stratification of patients that informs downstream investigations and treatments. This diagnostic and prognostic information leads to better application of evidence-based treatments and can ultimately reduce future coronary events. Cardiac computed tomography is arguably the first non-invasive imaging approach that has delivered such benefits for our patients.

Session I – Future Education and Publication in Cardiovascular Medicine

Thomas F. Lüscher
Research, Education & Development, Royal Brompton and Harefield Hospital Trust, London, UK

Cardiology has experienced an impressive development over the last 50 years and progress continues at an increasing speed. This is exciting and challenging at the same time for both trainees and established cardiologists as well as for those involved in education and publication. Indeed, the time from discovery to clinical application has norrowed substantially; For instance, from the discovery of mutations in the Proproteinkonvertase Subtilisin/Kexin Typ 9 (PCSK9) gene to the introduction of monoclonal and humanized antibodies into clinical practice occured within a decade. Similarly, the transarterial valve implantation (TAVI) matured into a routine procedure within 10 years. Thus, educational products must adapt quickly to the new developments and journals must publish at an increasing pace. Fruthermore, the reading behavious has changed, particularly among the youngest generation of physicians from reading to surfing and scanning and from paper to electronic. Of note, among the young cardiologists two thirds read only online, while among the elderly collegues two thirds prefer paper.

Textbooks in the traditional sense are no longer serving the needs of todays readers. Indeed, once they are published in print, they are already outdated. Thus, the European Society of Cardiology decided that the third edition edition of the *ESC Textbook of Cardiovascular Medicine* should be primarily a huge electronic database with continous updating. As such, the editors, i.e. John A. Camm, Thomas F. Lüscher, Gerald Maurer and Patrick W. Serruys,

have presented the *ESC CardioMed* at the Annual Congress of the *European Society of Cardiology* this August in Munich, an electronic database with 64 sections and 792 chapters written by hundreds of authors. There will also be a shorter printed version, but the main product is electronic and will be updated three times a year to cope with the developments of cardiology.

Also journals are faced with this challenge: *The European Heart Journal* therefore has a FAST TRACK for manuscripts reporting truly important and novel findings. This track allows for a first decision within 7-10 days and papers can be online within a months. At the Annual Congress of the *European Society of Cardiology* this August in Munich the *European Heart Journal* has again published a series of FAST TRACK papers from the Hotline sessions. Another challenge is the wealth of information with around 100'000 scientific journals of different kind currently appearing.

Thus, the selection of the important and novel is crucial.
As a consequence, the *European Heart Journal* accepts less than 10% of the submissions and concentrates on the very best. This allowed for a marked improvement in quality and impact. Indeed, thanks to this strategy, for the second year now, the *European Heart Journal* is the best rated cardiovascular journal worldwide with an impact factor of 23.425.is arguably the first non-invasive imaging approach that has delivered such benefits for our patients.

Session I – How to Effectively Start and Deliver Coronary and Cardiovascular Disease Prevention?

John E. Deanfield
UCL Institute of Cardiovascular Sciences, London, UK

Despite major advances in clinical care, cardiovascular disease remains the biggest cause of morbidity and mortality in the population. This also is placing an increasing financial burden on healthcare systems. These need therefore to focus on strategies for prevention of disease and "wellness" maintenance.

It has become clear that exposure to several potentially modifiable risk factors begins at an early stage (often from childhood) and that this drives initiation and progression of cardiovascular disease (CVD). Mendelian randomisation studies suggest that lower lifetime exposures should result in fewer clinical events in later life. Furthermore, evidence is accumulating that common biological pathways and behaviours underlie multiple non-communicable diseases, including dementia, cancer, diabetes and CVD. Early intervention may thus give leverage gains for multiple conditions.

A strategy for "Investing in your Arteries" should promote partnership with the population who need to take ownership of their cardiovascular health. This will require novel, understandable communication not only on risk but also on opportunity. This approach has been taken by the UK JBS3 guidelines.

The recent UK "Heart Age" initiative reveal that the public is highly motivated to understand their lifetime cardiovascular risk. Follow through to deliver change needs to be developed.

A targeted approach to identify individuals on accelerated trajectories to cardiovascular event is also required. This will include genetic evaluation, as well as use of bio-markers and imagining. To do this, healthcare systems need to embrace the “digital revolution” for measurement of behaviour, assessment of risk factors, monitoring of interventions and risk prediction.

The role of the doctor in this new healthcare environment is changing, with the aim of “wellness maintenance” and “healthy aging” and not merely disease management. This will require a change in mind-set of clinicians, training as well as redistribution of resources.

Session I – New Digital Technologies and Maintenance of Cardiovascular Health – "One Brave Idea?"

Calum MacRae
Brigham and Women's Hospital, Boston, US
Harvard Medical School, Boston, US

There are numerous efforts underway in modern healthcare to improve the use of medical data or to augment existing data with continuous digital measurements or other phenotypes. To date these have failed to have a substantive impact on biomedical science or medical care. The underlying issues with biomedical data and potential solutions to these problems will be outlined in the context of coronary heart disease. The fundamental challenges with current biomedical data are limited dynamic range, low information content, limited scale and the virtual absence of organizing metadata. Some potential approaches to these challenges and progress in testing these will be outlined.

Session II – Current and Future Role of Imaging in CV Prevention and Management

Lale Tokgözoğlu
Hacettepe University, Ankara,TR

Identification of patients at risk of having a cardiovascular event while still in the asymptomatic phase is important. Instead of trying to determine the vascular age of the patient from the risk factor profile, imaging the artery itself gives more information about the vascular age and the presence of subclinical atherosclerosis.There are several different imaging methods to detect subclinical atherosclerosis: Ultrasound of the carotid arteries, abdominal aorta and femoral arteries, computerised tomography, MRI, PET, Ankle-brachial index, and invasive methods such as intravascular ultrasound, OCT, NIR Spectroscopy or a combination of these tecniques can be used.

Because it is noninvasive, involves no radiation and it is relatively cheap ultrasound imaging of the arteries has been used in several studies. Detecting plaque by ultrasound in the superficial arteries can provide better risk prediction than IMT alone. In the ARIC study, 13,145 patients were imaged with carotid US. Presence of plaque in the risk prediction model reclassified over 10% of individuals into the higher risk category beyond the levels of carotid intima-media thickness (CIMT) and traditional risk factors. There was a stepwise increase in coronary events in those with carotid plaque and higher cIMT values. Another landmark study was the HRP-BioImage study evaluating imaging-based biomarkers that directly quantify atherosclerosis in different vascular beds performed in a single cohort and seeking to identify imaging biomarkers that predict 3 year atherothrombotic events. The BioImage Study enrolled 5,808 asymptomatic U.S. adults (mean

age: 69 years, 56.5% female) in a prospective cohort evaluating the role of vascular imaging on cardiovascular risk prediction. Major cardiac events increased with increasing calcium scores and carotid plaque burden. Net reclassification significantly improved with either cPB or CAC. Subclinical atherosclerosis was highly prevalant in 60 % of participants and seen even in those with low risk categories.The more recent PESA study evaluated 3860 participants awith a mean age of 45.8 years and explored bilateral carotid and femoral territories with 3D ultrasound to quantify the plaque burden. Plaque burden correlated strongly with risk factors. 60 % of the participants had subclinical atherosclerosis.

Calcium scoring is another noninvasive method to detect subclinical atherosclerosis by CT. Agatston score analyses calcium score and plaque burden objectively ,quickly and with minimal interinstitutional variation. The early MESA Study showed that calcium score predicts the cumulative incidence of coronary events . Patients with a score over 300 were the ones most at risk. Recently the 10 year follow up of MESA was published showing independent and strong association with events regardless of age, gender or race . Ca scoring has been shown to reclassify risk over traditional models.

CT angiography involves radiation and contrast injection, but gives us high resolution images of the coronary tree. CT can accurately detect plaques and has been shown to have a high negative predictive value. The CONFIRM Trial in 24775 patients without known coronary disease showed that the survival rates were high in those with normal CT, lower in those with nonobstructive disease and lowest in those with obstructive disease in 3 years. More sensitive detector technologies are decreasing radiation and image resolution.

MRI of the carotid, coronary arteries and aorta can detect subclinical atherosclerosis. It is noninvasive, with no radiation exposure to the patient.

MRI identifies plaque content and can show vulnerability parameters such as lipid content, calcium, and presence of thrombus. It performs best for large or static arteries, the mobile coronaries are more difficult to image. MRI can be performed only in specialised centers is expensive and can not be used for screening.

However, seeing the plaque by morphological imaging does not show us the plaque characteristics while biologic imaging can. MRI,PET and hybrid methods can help us image vulnerability noninvasively. Tracers to detect inflammation, microcalcification and angiogenesis are present. However, they can be performed only in specialised centers, need experienced staff and are expensive. Lack of outcome data on imaging the vulnerable plaque limits its use to research and is not recommended for clinical purposes.Invasive techniques also show plaque. IVUS is the gold standart for subclinical AS and anatomy of the vessel wall. OCT and Near infrared Spectroscopy show both plaque structure and composition.

As for the current clinical appicability of imaging for risk determination, the 2016 ESC/EAS Prevention Guidelines recommend only calcium scoring and carotid ultrasound for imaging as a Class IIb recommendation. Lack of RCT and cost effectiveness are the major limitations for not having a greater class of recommendation.

Session II – Genetics and Pharmacogenomics in Prevention and Management of Coronary Disease

Heribert Schunkert
Catholic University of the Sacred Heart, Munich, DE

The primary manifestation of coronary disease occurs often suddenly and unexpectedly in form of myocardial infarction. Thus, the prediction of silent atherosclerotic alterations in coronary arteries is a highly relevant medical need. Recent genomic research identified numerous genetic variants that associate with a higher prevalence of coronary disease. At present, association with coronary artery disease has been demonstrated at more than 160 chromosomal locations with risk alleles increasing relative risk by 5-25% per allele. Moreover, genetic variants primarily affecting cardiovascular risk factors such as hypertension or LDL cholesterol were shown to affect the risk of coronary disease as well.

This enormous progress has been facilitated by genome-wide association studies. By nature, these studies focus on frequent alleles. Thus, the alleles that have been identified to increase the risk of coronary disease are also relatively frequent in our population. As a consequence, virtually all individuals of our population carry a variable degree of genetic predisposition for coronary artery disease. More recently, the focus turned to rare variants with more profound effects. In this regard, the domain of human genetics, i.e. family based research and counseling, received more attention – once again. The presentation will address how this information can be utilized for a better understanding of disease mechanisms as well as for genomic prediction of coronary artery disease.

Session II – Novel Insights on Mechanisms of Acute Coronary Syndromes

Filippo Crea
Catholic University of the Sacred Heart, Rome, IT

Well into the 21st century, we still triage acute myocardial infarction on the basis of the presence or absence of ST-segment elevation, a century-old technology. Meanwhile, we have learned a great deal about the pathophysiology and mechanisms of acute coronary syndromes (ACS) at the clinical, pathological, cellular, and molecular levels. In particular, contemporary imaging studies have shed new light on the mechanisms of ACS. Plaque rupture has dominated our thinking about ACS pathophysiology for decades. However, current evidence suggests that a sole focus on plaque rupture vastly oversimplifies this complex collection of diseases and obscures other mechanisms that may mandate different management strategies. Coronary artery thrombosis caused by plaque rupture can be segmented into cases with or without signs of concomitant inflammation.

This distinction may have substantial therapeutic implications as direct anti-inflammatory interventions for atherosclerosis emerge. Coronary artery thrombosis caused by plaque erosion may be on the rise in an era of intense lipid lowering. Identification of patients with of ACS resulting from erosion may permit a less invasive approach to management than the current standard of care. We also now recognize ACS that occur without apparent epicardial coronary artery thrombus or stenosis. Such events may arise from spasm, microvascular disease, or other pathways.

Emerging management strategies may likewise apply selectively to this category of ACS. Thus, to move forward in the management of ACS, we

should strive for a more personalized approach to therapy based on criteria more tightly linked to the diverse pathophysiological mechanisms than ECG repolarization abnormalities. We need to develop and validate soluble and imaging biomarkers that reflect the underlying mechanism that yields acute ischemia. Point-of-care assessment of such biomarkers would help render their use clinically practical in the triage of patients who present with ACS, with the goal of sparing some the need for urgent invasive diagnostic or therapeutic measures. We then need rigorous clinical evaluation of targeted therapies guided by a more precise pathophysiological classification of ACS that reaches beyond our current dichotomous approach based on the ECG.

Session II – Novel Approaches Towards Optimal Management of Arterial Hypertension?

Massimo Volpe
University of Rome Sapienza, Rome, IT

Hypertension represents the first and most diffuse condition causing cardiovascular disease and death. In spite of the impressive progress in the pathophysiology, diagnosis and treatment of hypertension in the last 30 years, the management today is still unsatisfactory and the proportion of the patients whose blood pressure is well controlled remains around 50 to 60% even in the Western Countries.

Recent efforts aimed at achieving a better control of BP have been incorporated in the new guidelines both in European and U.S.
In particular, the new 2018 ESC/ESH guidelines, just published, offer a wide range of novel recommendations for the management of hypertension that will most likely lead to a better control and to a reduced burden of cardiovascular disease associated to hypertension.

This presentation will focus on the new aspects of the guidelines with regard to blood pressure measurement, risk assessment, blood pressure targets, initiation of treatment, new algorythms of treatment and the issue of adherence.

Session II – Diabetes and Cardiovascular Disease: Novel Therapeutic Strategies

Francesco Cosentino
Karolinska Institute and Karolinska University Hospital, Stockholm, SW

Type 2 diabetes (T2D) mellitus portends a high risk of adverse cardiovascular outcomes, including death, translating into an estimated reduction in life expectancy of 12 years. Despite this alarming risk, 30 to 50% of patients with diabetes do not meet guideline-recommended treatment goals for glycated haemoglobin ($HbA1_c$) and other cardiovascular risk factors such as blood pressure or cholesterol. Providing patients with optimal cardioprotection treatment strategies thus remains a major unmet need in this population.

The sodium-glucose cotransporter 2 (SGLT2) inhibitors empagliflozin and canagliflozin and the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide and semaglutide have now been shown in major randomized trials to improve cardiovascular outcomes in patients with T2D at high risk for or with a previous cardiovascular event. Using evidence based SGLT2 inhibitors or GLP-1 receptor agonists, physicians have an opportunity to both achieve goals for glycaemic control and improve cardiovascular outcomes for their patients with T2D who are at high risk or have established cardiovascular disease. Although some gaps in knowledge remain in their application, SGLT2 inhibitors and GLP-1 receptor agonists provide a new opportunity, not previously shown with other antihyperglycaemic drugs, to modify cardiovascular risk in patients with T2D.

Session III – Inflammation as a Therapeutic Target in Coronary Disease – the Road Ahead

Peter Libby
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Harvard Medical School, Boston, US

All phases of atherosclerosis involve inflammation – from the initiation, through the long phase of progression, and ultimately the thrombotic complications that cause myocardial infarctions and many ischemic strokes. Reports of experimental results in this field often end with a promissory note regarding translation. Yet, a gap yawns between the elegant scientific findings in genetically modified mice, and the reduction to practice. Statin therapy, an intervention that has anti-inflammatory actions independent of lipid lowering, limits cardiovascular complications. Even on maximum current therapy, however, including high dose statin, many with established atherosclerosis remain at risk for recurrent events. Thus we need new approaches to addressing this residual burden of risk.

Inflammation furnishes a possible therapeutic target in this regard. Targeting the prominent inflammatory mediator interleukin-1 (IL-1) beta is the first direct anti-inflammatory therapy that showed improved cardiovascular outcomes. Cholesterol crystals found in plaques selectively activate the inflammasome, the molecular machinery that converts the inactive precursor of IL-1 beta to its functional pro-inflammatory form. CANTOS, a >10,000 clinical trial showed that treatment with a monoclonal antibody that neutralizes IL-1 beta can reduce cardiovascular events in patients, stable post acute coronary syndrome, on a full standard of care secondary prevention regimen including statin therapy, with persistent inflammation indicted by above median C-reactive protein. CANTOS is yielding new

information about anti-inflammatory therapy in participants with diabetes, impaired renal function, and heart failure. Beyond IL-1 beta, other anti-inflammatory therapies under evaluation include other pro-inflammatory cytokines, methotrexate, inflammasome inhibitors, and colchicine.

The application of biological insights about inflammation in atherogenesis has already sharpened risk prediction, aided allocation of treatments, and has provided new targets for therapy now proven efficacious in large scale clinical trials.

Session III – Coronary Microcirculation as a Therapeutic Target

Paolo G. Camici
Vita Salute University, Milan, IT

In recent years, it has become apparent that coronary microvascular dysfunction plays a pivotal pathogenic role in angina pectoris. Functional and structural mechanisms can affect the physiological function of the coronary microvasculature and lead to myocardial ischemia in people without coronary atheromatous disease and also in individuals with obstructive coronary artery disease.

Abnormal dilatory responses of the coronary microvessels, coronary microvascular spasm and extravascular compressive forces have been identified as pathogenic mechanisms in both chronic and acute forms of ischemic heart disease. The condition characterized by anginal symptoms and evidence of myocardial ischemia triggered by coronary microvascular dysfunction, in the absence of obstructive coronary disease, is known as "microvascular angina". The concept of microvascular angina however, may extend further to include patients with obstructive coronary artery disease and individuals with angina post coronary revascularization or heart transplantation, since coronary microvascular dysfunction contributes to myocardial ischemia in many such patients.

Patients with microvascular angina constitute a sizeable proportion of all cases of stable angina undergoing diagnostic coronary angiography and of those with persisting angina after successful coronary revascularization. Coronary microvascular dysfunction is also often responsible for angina in individuals with cardiomyopathy and heart valve disease as well as

acute coronary syndrome cases such as Takotsubo syndrome and MINOCA (myocardial infarction with no obstructive coronary artery disease). Patients with stable microvascular angina present typically with effort and/or rest chest pain and a reduced coronary flow reserve or microvascular spasm. This condition, which affects women and men, can markedly impair quality of life and prognosis, and represents a substantial cost burden to healthcare systems and individuals alike. In recent years, progress in the diagnosis of myocardial ischemia and the use of tests to investigate functional and structural causes for a reduced coronary flow reserve and microvascular spasm have allowed the identification of an increased number of cases of microvascular angina in everyday clinical practice. Although some of the available anti-anginal drugs may be helpful, treatment of coronary microvascular dysfunction remains a major challenge.

Session IV – TAVR – State of the art and what more can we expect in the next years?

Alain Cribier
University of Rouen, Rouen, FR

In 1999, with a start-up company (Percutaneous Valve Technologies, NJ, USA) with on my side 2 engineers Stan Rowe and Stan Rabinovich and one cardiologist, Martin Leon, we could evaluate in the animal model the first prototypes of balloon expandable transcatheter heart valve. The First-in Man implantation was performed by us in Rouen in April 2002, and thereafter, this technique (called TAVI) has been incredibly expanding worldwide. In the hand of Edwards Lifesciences since 2004, the initial valve and delivery systems were improved (SAPIEN valve, and specific delivery systems for transfemoral and transapical approaches). After several feasibility studies, FDA approval was obtained for the SAPIEN valve based on the results of the pivotal "Placement of Aortic Transcatheter Valve (PARTNER) Trial", a randomized US trial published in 2011 and 2012 (for non-surgical patients and high-risk patients, respectively). TAVI was shown to save 25% of lives in non operable patients and to compare favourably to surgery in high risk patients. These results were unchanged at 5 years. Similar comparable results versus surgery were obtained in 2014 with a concurrent valve, the self-expanding CoreValve which was launched in 2004.

Expansion of clinical indications and further growth of the procedure could be anticipated. New models of valve, that need smaller size delivery systems have favourably impacted the incidence of the three leading complications, stroke, paravalvular leak (PVL) and vascular complications, more particularly in lower risk patients. Two generations of Edwards valve were launched, the SAPIEN XT in 2009, and the SAPIEN 3 in 2012 requiring smaller introducers and having solved the problem of paravalvular leaks.

These devices made simpler and safer the transfemoral approach available now in 90% of cases. They can be implanted using a minimalist strategy under local anaesthesia, with early discharge. The positive 2-year results (March 2016) of the randomized PARTNER 2 trial (USA) with the SAPIEN XT, an evidence-based comparison of TAVI vs SAVR in intermediate risk patients, further opened the road to an expansion of the procedure to lower risk patients. On propensity score analysis, the SAPIEN 3 valve, compared to the SAVR group of PARTNER 2, has eventually proven to be superior to SAVR in matter of mortality and stroke at one year. Comparable results were obtained with the Medtronic CoreValve in this subgroup of patients, leading to the recent FDA approval of TAVI in intermediate risk patients. Next, the ongoing PARTNER 3 trial with the SAPIEN 3 valve vs SAVR, and three other studies with other devices are addressing low risk patients > 65 years. The results of these studies, expected in the fall, should have enormous consequences on the future of TAVI. However, some questions remained unsolved yet, such as the long-term durability of transcatheter valves in comparison to surgical bioprosthesis even though no alarm on durability beyond 5 years has been shown in several reports. This is an important issue when TAVI might soon be offered to younger and low-risk patients.

In 2018, TAVI can be recognized a breakthrough technology with significant and positive socio-medical cultural consequences. This disruptive technology is today recognized by the whole medical community. More than 300 000 patients have been treated worldwide in 65 countries. The biomedical industrial partnership is fascinating. TAVI is now entering a new era with remarkable technology enhancements leading to dramatic improvement of outcomes. Within 5 years the impact of TAVI on AS therapy will continue to grow. TAVI might become the default strategy for the vast majority of AS patients, SAVR remaining an alternative option in suboptimal TAVI indications.

Session V – Atrial Fibrillation
Novel Concepts on Pathophysiology

Sabine Ernst
Imperial College London, London, UK

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice with a substantial burden for both patients and the health care system. Curative intended management strategies have so far focused on either eliminating the initiating electrical trigger (mostly by pulmonary vein isolation) or modification of the atrial substrate to sustain the arrhythmia (by linear lesions or surgical incisions). These commonly applied strategies will be reviewed and in addition evidence from novel functional imaging will be discussed that facilitate the understanding of the individual components of the autonomic nervous system for the initiation and maintenance of atrial fibrillation. Finally, results from the first pilot trial on modulation of the sympathetic input (so called ganglionated plexus) in patients undergoing AF ablation will be presented, as well as the implications for future research in AF pathogenesis.

Session V – LAA Closure – an interesting case

Carsten Skurk
Charite Universitätsmedizin Berlin, Berlin, DE

Percutaneous left atrial appendage closure is an alternative therapy for stroke prevention in atrial fibrillation patients with high stroke and bleeding risk. Since introduction of the procedure, its safety profile has been significantly improved.

A 63 year old male with high stroke (CHA2DS2-Vasc Score 4) and high bleeding (HASBLED Score 3) risk status post recurrent gastrointestinal bleedings underwent LAA occlusion with an Occlutech device. Post-interventional angiography as well as Doppler-TEE showed complete closure of the left atrial appendage. At three-month follow up, a translocation of the device into a superior and anterior located lobe was determined exposing a significant leak detected by Doppler-TEE. Oral anticoagulation with a NOAC was reintroduced and the patient was scheduled for a repeated procedure.

During this procedure, the leak could be confirmed by TEE and an additional lobe was detected by angiography exposed by the rotation and dislocation of the occlutech device. Under careful exploration of the additional lobe by a pigtail catheter, a wire and a Lambre sheet could be introduced into the newly uncovered lobe without dislodging the occlutech device. Afterwards, a Lambre device was successfully implanted securing the Occlutech occluder in place and sealing the left atrial appendage ostium. Complete closure of the LAA was confirmed by angiography and TEE-Doppler. The 3 D-TEE showed adequate sizing and sealing of the LAA ostium. The Lambre

device was successfully released. No further complications were detected. The 3-month follow-up determined both devices were still in place with complete sealing of the left atrial appendage closure.

This case outlines the importance of careful examination of LAA morphology as well as adequate device selection. Future pre-procedural imaging by CT might improve the efficacy and safety of the procedure.

Session VI – Cardiomyopathy Classification: Role of Pathology - Imaging and Genetics?

Gaetano Thiene
University of Padua, Padua, IT

The concept of non-ischemic and non-overload myocardial dysfunction is an acquisition of the last 40 years. These diseases are particularly challenging since they are frequently hereditary. The first WHO classification identified 3 types: dilated, hypertrophic and restrictive-obliterative. Subsequently new conditions have been discovered: arrhythmogenic, restrictive (myocardial) and non-compaction which required an update of WHO classification in 1995-6. In that occasion myocarditis, which had been the first non-ischemic myocardial disease to be reported in the history, was also included with the term of inflammatory cardiomyopathy.,The definition of cardiomyopathy was changed as myocardial disease with cardiac dysfunction.

The discovery of PCR led to an exponential development of investigations with the aim of establishing the etiology of transmissible myocardial diseases, whether genetic or infective. It was thus possible to discover gene mutations in hypertrophic and restrictive cardiomyopathies (sarcomeric disease), in arrhythmogenic cardiomyopathy (desmosomal disease), in dilated cardiomyopathy (cytoskeleton disease). Ion channel gene mutations were found to account for hereditary disease with arrhythmic disorders and structurally normal heart, like Long QT (Na+, K+), catecholaminergic polymorphic ventricular tachycardia (Ca++ ryanodine receptor), Brugada syndrome (Na+). Also familiar av block was found to be a cardiomyopathy of the specialized myocardium of the conduction system due to Na+ channel mutations. Overall these diseases are known as channelopathies. The more recent classifications of the AHA and ESC granted the progress in the

genetic background of cardiomyopathies. In particular, AHA classification recognized channelopathies as cardiomyopathies because arrhythmic cardiac dysfunction, despite the heart being structurally normal.

The Copernican revolution in genetics open new diagnostic avenues for identifying asymptomatic carriers for sudden deasth prevention. We wonder whether a new classification based on genetic etiology be warranted.
Finally inflammatory cardiomyopathies find frequently an explanation in myocardial infections by RNA and DNA cardiotropic viruses, with the exception of giant cells and sarcoid myocarditides, immune-mediated still in search of an author.

Session VI – Inflammatory Cardiomyopathies Diagnosis and Future Therapeutic Perspectives

Heinz-Peter Schultheiß
Institute of Cardiac and Diagnostic Therapy (IKDT), Berlin, DE

Myocarditis and inflammatory cardiomyopathy (CMi) are a challenging diagnosis due to the heterogeneity of clinical presentation which is highly variable and ranges broadly from subclinical symptoms to fulminant heart failure. Because the clinical course of myocarditis and CMi is unpredictable and the non-invasive diagnostic tests – including ECG, echocardiography, MRI, and serological tests - are limited in their ability to make a clear cut diagnosis. Therefore, all patients with clinically suspected myocarditis and CMi have to undergo endomyocardial biopsy (EMB), before irreversible and thus untreatable damage to the myocardium has developed.

EMB-based histological, immunohistological and molecular biological informations are prerequisites to establish an accurate diagnosis and successful management of patients. The exact analysis and quantification of intramyocardial inflammation (including lymphocytes, macrophages, cytotoxic cells and cell-adhesion molecules) has been shown to be predictors of the clinical outcome. Moreover, because of a very high sampling error especially in patients with giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis, novel biomarkers like microRNAs and gene expression profiling are introduced in the molecular examination of EMBs and are new tools for a significant improvement of diagnosis. Thus, EMB-based analysis has led to the identification of novel diagnostic, prognostic markers and therapeutics targets in the future.

Viruses are considered the most common cause of acquired myocarditis

and CMi. Persistence of entero/and adenovirus in the myocardium has been associated with ventricular dysfunction and viral genome clearance with improvement of ventricular function and a better 10-year prognosis. Furthermore, distinct genotypes of erythroviruses including parvovirus B19 and human herpesvirus type 6 (HHV6A/B), among many others, have been identified with varying degrees of frequency in cardiac tissues. For example, erythrovirus genomes with proof of active replication - accompanied with intramyocardial inflammation - is associated with worse prognosis.

The effectiveness of anti-viral-therapy has been proven in recent studies, showing that enterovirus/ adenovirus – positive patients benefit from anti-viral therapy with interferon beta-1b, whereas in patients suffering from parvovirus B19 infection no established therapy exists. However, the nucleoside analogues Telbivudine seems to be a promising drug in patients with proof of active viral replication. Myocardial inflammatory processes due to autoimmunity warrant pharmacological approaches including immunosuppressive therapy, high-dose i.v. immunoglobulin treatment and immunoadsorption in order to prevent immune-mediated myocardial injury. Immunosuppression (treatment with prednisone and azathioprine for 6 months) demands biopsy-based exclusion of virus since virus-positive patients do not improve or even deteriorate under anti-inflammatory treatment, while virus-negative patients with post-infectious, auto-immune inflammatory process respond well in clinical trials, and - after termination - long lasting LVEF improvement has been documented.

Moreover, because of a very high sampling error especially in patients with giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis, novel biomarkers like microRNAs and gene expression profiling are introduced in the molecular examination of EMBs and are new tools for a significant improvement of diagnosis.

In conclusion, myocarditis and inflammatory cardiomyopathy remain a major challenge in modern cardiology. The autoimmune process is responsible for the self-sustained inflammation and progression to tissue damage leading to dilated cardiomyopathy. This underscores the need to explore innovative new therapeutic options, which allow a sufficient antiviral defence and – on the other side - a balanced immune response preventing inflammatory toxicity. The detailed examination of histology, immunohistology, virology and molecular biology, and recently identified immune factors that can be explored as targets for new treatments are the basis for a rational, causal, personalized and specific therapy.

NOTES

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