On November 26th the ESC WG Coronary Pathophysiology & Microcirculation together with the German National Centre for Cardiovascular Research (DZHK, partner site Berlin) organized a joint symposium to exchange knowledge and stimulate interaction between basic and clinical scientists in the field of Coronary Pathophysiology and Microcirculation. The one-day joint meeting was held in the historic Harnack-Haus in Berlin. The meeting was nicely built around four interactive scientific sessions, covering a wide array of topics, but with a special emphasis on experimental and clinical research of both large and small vessels and their biology in health and in disease states, in particular acute coronary syndromes and heart failure.

Below is a summary of each of the sessions, during which each lecture was followed by a lively discussion. The meeting was a great success and sets an excellent example of how synergistic interaction can be created by ESC bodies and national cardiovascular research institutions when joining forces!
Session 1:
Title: Acute Coronary Syndrome: The Importance of Both Large and Small Vessels
Chairs: Holger Gerhardt & Dirk Duncker
This session included six lectures that assessed experimental and clinical aspects of acute coronary syndromes covering not only large epicardial coronary artery pathology, such as plaque rupture, but also the involvement of the coronary microvascular compartment, including microvascular no-reflow. Overall this session revealed several important novel insights into the pathophysiology, diagnosis and treatment of acute coronary syndrome.

Lina Badimon: Tissue Factor: Yin/Yang in the Circulation Spanning from Thrombosis to Angiogenesis.
Beyond its role as cofactor of Factor VIIa to trigger the coagulation cascade and induce thrombosis on atherosclerotic plaques, TF has non-haemostatic functions as a multi-faceted signalling receptor involved in the regulation of angiogenesis. TF naturally occurs in two different variants: full length TF (flTF) and alternatively spliced TF (asTF). flTF is a ~45-47 kDa integral membrane protein that can be released from the cell membrane in the form of microvesicles, whereas asTF is a protein that lacks a transmembrane domain and can thus be secreted in a soluble form. Recently, we have demonstrated that microvascular endothelial cells (mECs) release TF in a highly regulated fashion to promote microvascular networks. Further, Wnt5a-released by monocytes interact with FZD5 in the membrane of mECs to trigger intracellular signalling through the noncanonical pathway with increased intracellular Ca²⁺ release and NF-κB activation, which in turn upregulated TF expression and induces angiogenesis. TF can also exert angiogenic effects by promoting mobilization and transdifferentiation of Mo into ECL cells. Indeed, we observed that TF secreted from mECs might promote monocyte/ECL transdifferentiation and tube-like formation with specific upregulation of surface VEC markers such as: VE-Cadherin, vWF and eNOS expression and downregulation of monocyte cell-specific marker CD14. This transdifferentiation process is likely mediated by TF/β1-integrin TF interaction. In summary, we have discovered novel mechanisms triggered by TF (flTF as well as asTF) that promote angiogenesis and microvessel formation, beyond the well-known effects of TF on coagulation and thrombus formation.

Dimitris Tousoulis: New Insights in Plaque Vulnerability: from Diagnosis to Treatment
Plaque rupture is the main cause of acute coronary syndromes. In the clinical practice a challenge is to treat the vulnerable patient rather than vulnerable plaque because thin cap fibroatheromas are often multiple and affect several arterial beds and often persist for years without causing significant events. Moreover, statin treatment and other preventive measures have begun to modify the disease process, and plaque rupture declines as a cause of acute coronary syndromes (ACS), while erosion is on the rise. According to the recent guidelines of the ESC, an ACS it is possible to occur without underlying significant stenosis (MINOCA). The prevalence of MINOCA is about 5-10% in contemporary clinical practice. There are epicardial causes of MINOCA such as positive remodelling and plaque erosion, as well as microvascular causes such as unstable microvascular angina, Takotsubo cardiomyopathy, myocarditis and cardio-embolism. The current treatment of ACS in NSTEMI patients includes statins, beta blockers and dual antiplatelet therapy (DAPT). DAPT duration is dependent on several factors and important scores have been introduced such as PRECISE-DAPT and DAPT to identify the patients who need longer antiplatelet treatment. In conclusion, the vulnerable patient rather the vulnerable plaque is important to be treated. MINOCA is common in ACS patients and the optimal duration of antiplatelet treatment is controversial.
Ulf Landmesser: Clinical translational studies: Novel Pathophysiologlical Mechanisms in Coronary Disease

Coronary disease and its clinical manifestations as acute coronary syndromes and/or ischemic cardiomyopathy remain a major cause of morbidity and mortality. Given that coronary disease develops sub-clinically over several decades, more effective and earlier prevention strategies can in the future substantially reduce the burden of coronary disease, i.e. support the strategy of maintaining cardiovascular health. Genetic studies have strongly supported the causal role of lipoproteins, in particular LDL cholesterol for development and progression of coronary disease, and have highlighted the concept of “LDL burden” over time as the critical determinant for the clinical manifestation of coronary disease. Therefore, earlier and more intense LDL cholesterol lowering in patients with clinical manifest ACVD can markedly reduce cardiovascular risk. Recently the largest human siRNA-based treatment study, ORION-1, has been completed and demonstrated that a single subcutaneous PCSK9-siRNA could reduce LDL cholesterol levels by 50% over a period of >6 month. These approaches are further developed and will provide a highly effective and attractive treatment approach for prevention of coronary disease. Moreover, we and others have obtained data suggesting an important role of microbiome-dependent metabolites, such as TMAO, for progression of atherosclerotic cardiovascular disease – and targeting the gut microbiome is being developed as a novel preventive treatment. Finally, high resolution intracoronary imaging by optical coherence tomography can identify different mechanisms leading to acute coronary syndromes, e.g. plaque rupture or plaque erosion, and translational studies have provided novel insights about the role of the immune system in these diverse acute events, and targeted immunomodulation may provide another novel treatment strategy in prevention of coronary disease.

Edina Cenko: Sex Differences in Outcomes after STEMI in Younger Patients: ISASC TC Studies

Although ST-segment elevation myocardial infarction (STEMI) mainly occurs in individuals >60 years, younger adults can be affected as well. Previous studies have shown that there are trends towards decreases in both the proportion and absolute number of acute MIs in both sexes. However, women continue to be at higher risk of early mortality after STEMI, even in the current era of improved evidence-based treatments and percutaneous coronary intervention (PCI). These data imply that women and physicians all need greater awareness that MI do occur in young middle-aged women. Acute MIs is often perceived as something that affects older women, yet more young women than ever before are at risk. Previous work has suggested that the reason for the differences in outcome is likely multifactorial and may partially be explained by some of the following factors: a disproportionate burden of coronary risk factors and comorbidities, the absence of chest pain at presentation, delayed presentation and/or reperfusion in STEMI, under-diagnosis of MI at first medical contact, and underuse of acute medications. While these hypotheses may be true, recent studies pointed out that the proportion of women presenting within 2 hours after symptom onset was greater in the younger than in older cohorts. In addition, sex differences in administration of adjunctive medical therapies were greater in the older than in the younger cohort. Thus, there is not any one of the abovementioned factors able to explain the increase in mortality in the young women. Disparities alone could not account for the gap in mortality across sexes. There are profound differences in genetics and hormones between sexes. Unless the effects of sex are studied, we will continue to have gaps in the knowledge of potential different mechanisms leading young women and men to die after acute coronary syndromes, which may result in missed opportunities for implementing a better health in our community. Women should be encouraged to participate in trials. Balancing the sexes as well as powering studies to detect sex differences is warranted in future research.
Olivia Manfrini: Pathophysiology of Coronary No-Reflow: Experimental and Clinical Aspects

In the last few years, several experimental and clinical studies (randomized clinical trial, observational studies and meta-analysis) explored strategies on the prevention and treatment of no-reflow phenomenon. On the basis of its pathogenic mechanisms (ischemic injury, reperfusion injury, distal micro-embolization and individual predisposition), We elucidated the results coming from antiplatelet and anti-coagulant agents, vasodilators and statins, as well as thrombectomy and distal protection devises, which are the treatment and preventive options most investigated, but with different criteria and technique for its assessment. Conventional criteria to define a clinically relevant no-reflow phenomenon are needed to standardize the results of clinical studies. Anyhow, antiplatelet agents and statins had proved, without any controversy, beneficial effects both on no-reflow and patient outcome evaluated by 30-day major adverse cardiovascular events. Vagal nerve stimulation gives promising results in animal models, but this awaits confirmation in clinical trials.

Raffaele Bugiardini: Late PCI in STEMI Patients and Outcomes: Heterogeneity of Treatment Effects

Primary percutaneous intervention (PCI) within 12 hours after symptom onset has been shown to improve survival, and reduce the risk of recurrent myocardial infarction, and stroke in patients with ST segment elevation myocardial infarction (STEMI). However, approximately 30% of people with STEMI do not undergo cardiac catheterization within 12 hours from symptom onset. Many patients are referred to hospital without catheterization facilities and are managed acutely in a non-invasive manner. The impact of a mechanical reperfusion strategy beyond a 12-hour cut-off is still unsettled. There is general agreement that PCI could be done later than 12 hours after symptom onset if there is clinical and/or electrocardiographic evidence of ongoing ischemia, or cardiogenic shock. There is, instead, no consensus as to whether late PCI beyond the 12 hours limit is also beneficial in relatively stable patients especially if these patients were not previously given fibrinolysis. Uncertainty stems from a paucity of evidence supporting benefits of revascularization compared with routine medical treatment (RMT). The principal findings of the ISACS-TC registry were that clinically stable patients with STEMI may benefit of PCI beyond the 12-hour cut-off. This association is substantially modified by patient delay to PCI with improvement in survival concentrated among patients undergoing PCI between 25 and 48 hours after symptom onset. The findings of the ISACS-TC registry may prospectively represent a potential new treatment paradigm for patients who fail a timely, within 12 hours, reperfusion therapy, and are in stable conditions. In these patients, an initial watch and wait approach seems to be a valid strategy to achieve better outcomes. In addition, there are some ethical issue on acquiring a valid informed consent that can be improved waiting 12 to 24 hours more. In the acute phase of STEMI, patients typically are distressed and prefer to leave all treatment decisions to the physician. Although distress may be present regardless of whether PCI is performed within 24 hours or 48 hours form symptom onset, introducing a “time break” could help patients to better understand the clinical risks and benefits of PCI by giving them the opportunity for discussion with (other) physicians or their family.
Session 2
Title: Vascular Biology in Health and Disease
Chairs: Ulf Landmesser & Olivia Manfrini
This session included four highly diverse lectures that addressed experimental as well as clinical aspects of the physiology and biology of both large and small blood vessels in health and in disease conditions such as hypertension and atherosclerosis.

Cor De Wit: The Physiologic Function of the Endothelial Muscarinic Receptor
Muscarinic acetylcholine receptors (AChMR) mediate cellular responses upon release of acetylcholine (ACh) from parasympathetic nerves. In addition, ACh is the prototypical agonist stimulating endothelium-dependent dilation, but most blood vessels lack parasympathetic innervation, raising the question as to the physiologic function of endothelial AChMR. In his presentation, Cor de Wit presented results of studies performed in mice lacking the endothelial muscarinic receptor (AChMR3). The microvascular dilation upon ACh was selectively attenuated in these mice. Nevertheless, arterial pressure remained unaltered and cardiac hypertrophy was not found despite life-long deletion of this receptor in endothelial cells. These results leave the physiologic function of these endothelial receptors still obscure despite their role in the mediation of the well-known powerful dilatory effect of ACh in the microcirculation.

Akos Koller: Regulation of Coronary Microvascular Tone by Pericardial Fluid
Pericardial fluid (PF) is a ~ 15-50 ml viscous, pale yellow fluid layer between the layers of the pericardium. The primary function of PF is to ensure a proper friction between the pericardium and the heart, but in pathological conditions it can elicit pericardial tamponade leading to increases in systemic and pulmonary venous pressures, tachycardia, reduced ejection fraction and reduced coronary blood flow. PF contains biologically active substances, which could originate from the blood, cardiac interstitial space and/or pericardial membranes. These molecules may reflect the function of the cardiac muscle and exert vasomotor activity. Recently we have found a positive correlation between the elevated levels of asymmetric dimethyl arginine (ADMA) in the PF and the indices of cardiac hypertrophy. ADMA can reduce the role of nitric oxide (NO), lead to activation of RAS and oxidative stress, which may promote the synthesis of endothelin (ET1) in the PF. ET1, can cause arrhythmia, sub-epicardial ischaemia and ST-elevation. Correspondingly, we have found that PF of [Coronary Artery Bypass Graft (CABG) and Valve Replacement (VR) patients] elicited substantial constrictor responses in isolated arteries (constriction), which were significantly reduced by an endothelin receptor antagonist. Since pericardial fluid can freely circulate in the pericardial sac, vasomotor molecules, various cytokine, and cells can circulate in it and modulate the tone of coronary arteries, thus coronary blood flow, but also cardiac contractility and remodelling.

Maria Dorobantu: The Long and Winding Road of Hypertension to Heart Failure Revealed by Biomarkers
Even though heart failure (HF) is a global public health problem, its diagnosis is often quite challenging, especially in the initial stages. Biomarkers are useful instruments which could facilitate the early diagnosis and prompt therapy initiation in a patient-tailored manner. Substantial advancements have been made in recent years, so reasonably priced omics-based technologies have permitted on the dot identification of a wide array of biomarkers. But not all biomarkers can be used into clinics as these must be precise, sensitive and specific for the pathology investigated. HF is characterized by a systemic inflammatory response, myocardial fibrosis and increased myocyte stress leading to organ damage. In view of that, these biomarkers are categorized into markers related to fibrosis, inflammation, myocyte stress and microRNAs. The assessment by multiple biomarker strategy is recommended in case of early-stage HF patients. In addition to validated biomarkers, such as natriuretic peptides (for cardiac decompensation), high-sensitivity cardiac troponins, suppressor of tumorigenicity 2, galectin-3 (related to myocardial injury/fibrosis), there are
some new markers waiting to prove their prognosis value (procollagen type III N-terminal peptide, matrix metalloproteinases). The validation of biomarkers is hindered by low statistical power and poor reproducibility of results. Hence, further research should address key issues related to validation of emerging biomarkers by using precise and robust outcomes and use of multi biomarker strategies to streamline the risk stratification, diagnosis and prognosis.

**Teresa Padro: Extracellular Matrix Remodelling and Plaque Vulnerability**

Lipid rich atherosclerotic plaques with low content in smooth muscle cells (VSMC) are vulnerable and associated with acute coronary syndromes. The matrisome-fraction (functional non-structural proteins) of the vascular extracellular matrix (ECM) is thought to regulate progression of the atherosclerotic lesions. Under the title "Extracellular matrix remodelling and plaque vulnerability", Teresa Padro presented results on proteomic studies providing evidence of a distinct matrisome-signature in the ECM of advanced plaques in human arteries. Results of in vitro cell culture and mechanistic studies highlight the relevance of the ECM (matrisome)-VSMC interactome as key mediator of LDL-induced detrimental effects on the VSMC phenotype and function, such as cytoskeleton dynamics and cell migration capacity, directly involved in vascular remodelling related to atherosclerotic plaque growing and destabilization.

**Dmitry Tsvetkov: Perivascular Fat Tissue and Implications for Resistant Hypertension**

Hypertension is the most important single contributor to the global burden of cardiovascular disease and mortality. In his presentation titled 'Perivascular adipose tissue (PVAT): Implications for resistant hypertension', Dmitry Tsvetkov discussed the recent results of experimental studies on vascular tone regulation by PVAT. The anti-contractile effect of PVAT is an important mechanism in the modulation of vascular tone in peripheral arteries. Recent evidence has implicated a possible role of XE991-sensitive voltage-gated KV (KCNQ) channels in this process, with KV7.3-7.5 channels representing most likely candidates. Thus, activating these channels in vascular smooth muscle cells might represent a potential novel drug target for treatment of resistant hypertension.
Session 3
Title: Novel Imaging Modalities: Applications in Cardiovascular Medicine
Chairs: Axel R. Pries & Akos Koller
In this session the potential use of novel imaging modalities in discovering novel mechanisms - which could not have been done with other methods - have been presented by four speakers. Overall, this session demonstrated that novel imaging modalities are available and already used in basic and applied sciences and they are waiting to be introduced in the clinical arena for a better diagnosis and treatments of patients with cardiovascular diseases.

Benjamin Judkewitz: Transparent Danionella translucida as a genetically tractable vertebrate brain model
Neuronal networks of a translucent organism allow the visualization of the interconnections among various senses and neural centres. Understanding how distributed neuronal circuits integrate sensory information and generate behaviour is a central goal of neuroscience. However, it has been difficult to study neuronal networks at single-cell resolution across the entire adult brain in vertebrates because of their size and opacity. We addressed this challenge by introducing the fish Danionella translucida to neuroscience as a potential model organism. This teleost remains small and transparent even in adulthood, when neural circuits and behaviour have matured. Despite having the smallest known adult vertebrate brain, D. translucida displays a rich set of complex behaviours, including courtship, shoaling, schooling, and acoustic communication. In order to carry out optical measurements and perturbations of neural activity with genetically encoded tools, we established CRISPR-Cas9 genome editing and Tol2 transgenesis techniques. We showed that these features make D. translucida a promising model organism for the study of adult vertebrate brain function at single-cell resolution.

Jens Dreier: Monitoring microvascular perfusion variations with laser speckle contrast
The research group Translation in Stroke Research (TSR) at the CSB investigates human ischemic stroke with subdural electrocorticography (ECoG), brain tissue partial pressure of oxygen (pO2), regional cerebral blood flow and serial magnetic resonance imaging (Dreier, J.P., et al. Neuron 86, 902-922 (2015)). Using this approach, we found that terminal spreading depolarization (SD) is the key process leading to irreversible injury in human stroke (Luckl, J., et al. Brain 141, 1734-1752 (2018)). In a process of reverse translation from ‘bedside’ to ‘bench’, we are studying whether disturbed capillary flow patterns could contribute to terminal SD because they favour inverse hemodynamic responses to SD (Dreier, J.P. Nat. Med 17, 439-447 (2011)). This potential therapeutic target is tackled in the rodent brain using microelectrode technologies combined with either laser speckle contrast analysis imaging or a novel system integrating diffuse reflectance spectroscopy and laser-Doppler flowmetry to determine time courses of the absolute perfusion level, speed resolved perfusion, red blood cell oxygen saturation, pO2, extracellular ion concentrations and ECoG.

Ingolf Sack: In vivo multimodal mechanical imaging of the heart and aorta
The heart being the motor of blood circulation propels blood through the systemic and pulmonary circulation by periodic contraction and dilatation of the four cardiac chambers. This mechanical action can be described by a series of time-dependent physical parameters such as volume, strain, shear modulus and pressure. Unfortunately, those parameters cannot be measured in-vivo by morphological imaging alone but require the application of external stress. Elastography uses stress waves induced by externally placed actuators to palpate remotely the heart, the aorta or surrounding tissues. Induced tissue deformations can be measured by motion-sensitive magnetic resonance imaging or ultrasound techniques. In this talk, approaches in cardiac and aortic elastography were presented, highlighting promising applications and discussing current limitations. Notwithstanding their current limitations, cardiac MRI and ultrasound elastography have already revealed the basic mechano-functional properties of the living heart and have demonstrated important clinical applications. Therewith they pave the way for further developments of cardiac elastography.
towards quantitative biomarkers of the mechanical function of cardiac and aortic tissue.

Axel Pries: Imaging modalities in studies of microvascular networks
There is tremendous future potential for imaging modalities in studies of microvascular networks, which are responsible for about 80% of peripheral vascular resistance, and which are usually treated as a “black box” by clinicians. Coronary microvascular networks play the key role in determining blood flow distribution in the heart. The importance of pathophysiological events in the coronary microcirculation for relevant clinical conditions including angina in patients with normal or near normal coronary angiograms (microvascular angina) is increasingly recognized. Such conditions are typically defined and analysed by non-invasive imaging approaches. While the development of clinical imaging modalities was very dynamic and successful over the last decades, they lack the spatial resolution to define pathophysiological mechanisms on the microvascular level. Thus, a calibration with high resolution (optical) imaging approaches in experimental settings is needed. This will require the targeted interaction of researchers from the clinical, the medical imaging and the experimental imaging fields.
Session 4
Title: The Role of Microvascular Dysfunction in Heart Failure
Chairs: Burkert Pieske & Maria Dorobantu
This session consisted of four lectures on the role of coronary microvascular dysfunction in heart failure. The speakers presented solid data coming from both preclinical and clinical studies, demonstrating that coronary microvascular dysfunction is an important pathophysiological factor in both heart failure with preserved ejection fraction (HFpEF) and in heart failure with reduced ejection fraction (HFrEF). In HFpEF, the coronary microvascular dysfunction is promoted by the pro-inflammatory milieu resulting from the clustering of several risk factors, such as hypertension, dyslipidaemia and hyperglycaemia. This recent paradigm on the pathophysiology of HFpEF is constantly getting confirmation from the most recent research. In this context, coronary microcirculation is an attractive therapeutic target for the treatment of cardiovascular disease and future prospective studies are needed to establish the role of microcirculation-targeted therapies on the patients’ outcomes.

Carsten Tschöpe: Myocardial Microvascular Inflammatory Endothelial Activation in HFpEF
Following the paradigm of Paulus and Tschöpe (JACC 2014), which postulates that endothelial activation triggered by a comorbidity-driven systemic inflammatory state underlies subsequent cardiac remodelling in HFpEF, this presentation outlined how endothelial inflammation and dysfunction go along with endothelial oxidative stress and coronary microvascular dysfunction, which in turn induces cardiomyocyte hypertrophy and stiffening as well as cardiac fibrosis. Transdifferentiation of endothelial cells into fibroblasts, a phenomenon called endothelial-to-mesenchymal transition, hereby contributes to cardiac fibrogenesis and vascular (capillary) rarefaction. Thus, global myocardial ischaemia due to coronary microvascular dysfunction contributes to the cardiac pathology in HFpEF.

Dirk Duncker: Microvascular Dysfunction and Heart Failure: Lessons from Large Animal Models
The contribution of coronary microvascular dysfunction to a variety of cardiovascular diseases, including ischemic heart disease, cardiac hypertrophy and heart failure is being increasingly recognized. In this presentation the results of translational studies pertaining to coronary microvascular dysfunction in swine models of systolic dysfunction (post-infarct remodelling) and diastolic dysfunction (co-morbidities, including diabetes mellitus, dyslipidaemia) and chronic kidney disease were discussed. The results from these studies indicate that microvascular dysfunction is a key feature of these pathophysiological states, resulting in perturbations in myocardial oxygen balance during exercise. These findings lend further support to the notion that the coronary microcirculation represents an increasingly important therapeutic target for the treatment of cardiovascular disease.

Vera Regitz-Zagrosek: Sex Differences in Microvascular Disease with a Focus on the Cellular Level and Effects of Oestrogen.
To understand sex differences in microvascular dysfunction and plaque erosion, we analysed oestrogen effects in the cells involved. Oestradiol (E2) activated signalling and gene expression in endothelial cells (HUVEC) in a sex-specific manner. To study the effect of E2 on the development of cardiac fibrosis we used isolated rat cardiac fibroblasts. E2 decreased collagen I and III mRNA and protein in female cells via oestrogen receptor (ER) alpha and increased it in males via ER beta. Moreover, E2 regulated collagen I and III in a sex-specific manner in 3D Engineered Connective Tissues (CVR 2018). Cardiomyocyte-specific ER-alpha overexpression in mice induced cardiac hypertrophy in both sexes, but lymph-angiogenesis and capillary angiogenesis in females only. Female ER-alpha overexpressors with MI develop less fibrosis than WT females or males with MI. Finally, they studied sex differences in bone marrow-derived macrophages. After polarization into a pro-inflammatory phenotype with LPS and INF-gamma, the mRNA expression of NF-kB, IL-1-beta and TNF-alpha increased in male, but not in female macrophages, indicating that LPS and INF-gamma promote a
pro-inflammatory phenotype only in the male cells. In summary, sex-specific E2/ER mediated gene regulation induces sex differences in cardiac fibrosis, endothelial cell and immune cell function and angiogenesis.

**Danijela Trifunovic: Microvascular Dysfunction and HFpEF – From a Clinician’s Perspective**

Recently, coronary microvascular dysfunction (CMD) has been regarded as one of the main causal mechanisms in HFpEF. The novel paradigm suggests that a progressive clustering of risk factors (hypertension, dyslipidaemia, dysglycaemia, and oestrogen loss) promote a pro-inflammatory and pro-oxidative state, rendering the coronary microvasculature vulnerable to repeated episodes of myocardial ischaemia, which may lead to left ventricular diastolic dysfunction, and ultimately the development of heart failure. Coronary flow reserve (CFR) is reduced in patients with aortic stenosis, hypertrophic cardiomyopathy and in hypertensive patients with LV hypertrophy, and correlates with NT-proBNP, troponin and E/e'. Moreover, impaired CFR is an independent and strong predictor of future risk of HFpEF hospitalization in patients without significant epicardial coronary artery disease (CAD). Nevertheless, further research is needed to establish whether CMD is causal for ventricular remodelling and diastolic dysfunction or whether ventricular remodelling and diastolic dysfunction are causal for CMD.