The transition from hypertension to hypertensive heart disease and heart failure: the PREFERs Hypertension study

Mattias Ekström1*, Anna Hellman1, Jan Hasselström2, Camilla Hage3, Thomas Kahan1, Martin Ugander4, Håkan Wallén1, Hans Persson1 and Cecilia Linde3

1Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, Karolinska Institutet, Solna, Sweden; 2Department of Neurobiology, Care Sciences and Society, Centre for Family Medicine, Karolinska Institutet, Solna, Sweden; 3Department of Medicine, Division of Cardiology, Karolinska Institutet, Solna, Sweden; 4Department of Molecular Medicine and Surgery, Department of Clinical Physiology, Karolinska Institutet, Solna, Sweden

Abstract

Aims Despite evidence-based therapeutic approaches, target blood pressure is obtained by less than half of patients with hypertension. Hypertension is associated with a significant risk for heart failure, in particular heart failure with preserved left ventricular (LV) ejection fraction (HFpEF). Although treatment is suggested to be given early after hypertension diagnosis, there is still no evidence-based medical treatment for HFpEF. We aim to study the underlying mechanisms behind the transition from uncomplicated hypertension to hypertensive heart disease (HHD) and HFpEF. To this end, we will combine cardiac imaging techniques and measurements of circulating fibrosis markers to longitudinally monitor fibrosis development in patients with hypertension.

Methods and results In a prospective cohort study, 250 patients with primary hypertension and 60 healthy controls will be characterized at inclusion and after 1 and 6 years. Doppler echocardiography, cardiac magnetic resonance imaging, and electrocardiogram will be used for measures of cardiac structure and function over time. Blood biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction will be analysed. As a proxy for HFpEF development, the primary endpoint is to measure echocardiographic changes in LV function and structure (E/e’ and LAVI) and to relate these measures of LV filling to blood pressure, biomarkers, electrocardiogram, and cardiac magnetic resonance.

Conclusions We aim to study the timeline and transition from uncomplicated hypertension to HHD and HFpEF. In order to identify subjects prone to develop HHD and HFpEF, we want to find biomarkers and cardiac imaging variables to explain disease progression. Ultimately, we aim at finding new pathways to prevent HFpEF.

Keywords Hypertension; Hypertensive heart disease; Heart failure; Biomarkers; Diastolic function

Received: 23 October 2019; Revised: 28 November 2019; Accepted: 22 December 2019

Clinical Trial Registration: https://www.clinicaltrials.gov (ID: NCT04190420).

Introduction

Hypertension is common with a prevalence of approximately one third of the adult Swedish population1, and similar figures are reported worldwide.2 It is associated to cardiac structural (e.g. myocardial fibrosis, atrial and ventricular remodelling, and hypertrophy) and functional changes (e.g. impaired systolic and diastolic functions and arrhythmias) as well as vascular dysfunction, which all can be delayed or reversed by appropriate antihypertensive treatment.3 Although blood pressure (BP) control is improving, target BP is still reached by less than half of the treated patients.4 Hypertension is the single risk factor with the greatest attributable risk for incident heart failure (HF)5 and is considerably more common in HF with preserved left ventricular (LV) ejection fraction (HFpEF) than in HF with reduced ejection fraction (HFrEF).6 In patients with established HFpEF, hypertension ranges between 50% and 70%.7 However, the exact
mechanisms for the transition from hypertension to hypertensive heart disease (HHD) and HFrEF are less well understood. In contrast, pathophysiology and progression of HFrEF are better elucidated and may successfully be reversed by seven to eight evidence-based treatments.8

The evolution of myocardial fibrosis may be one early important mechanism in the transition from hypertension to HHD and subsequent HF. This can be studied through the recent development of cardiac imaging with advanced Doppler echocardiography,9 cardiac magnetic resonance (CMR) imaging,10 and assessment of circulating biomarkers reflecting myocardial fibrosis turnover, inflammation, and endothelial dysfunction.11,12 Indeed, echocardiographic left chamber longitudinal strain and extracellular volume measured by CMR have recently been demonstrated to be useful to discriminate between healthy controls, patients with hypertension, and patients with HFrEF.13 Also, circulating plasma biomarkers reflecting altered myocardial tissue turnover can differentiate patients with left ventricular hypertrophy (LVH) from patients with LVH and HFrEF.14 In addition, biomarkers may identify phenotypes of high collagen cross-linking, which has been suggested to have impact on the response to medical treatment in HFrEF.15

An increased understanding of these mechanisms allows the development of specific treatments, guided by cardiac imaging and/or biomarker assessments, to delay or prevent the transition from hypertension to HF.6 This may have considerable clinical implications in reducing cardiovascular complications to hypertension. Thus, the aim of the present study is to characterize and study the timeline and the transition from uncomplicated hypertension to HHD and HFrEF in subjects with primary hypertension using advanced cardiac imaging techniques and bioinformatics (Table 1). Furthermore, we aim to compare changes of HFrEF variables and biomarkers in this study with patients with new onset symptomatic HFrEF in the Stockholm PREFERS Heart failure study.16

### Study design

The study PRE-FERS Hypertension is the last part of the PRE-FERS (Preserved and Reduced Ejection Fraction Epidemiological Regional Study in Stockholm, Clinical trial NCT03671122), a clinical trial first aiming at describing underlying pathophysiological mechanisms in new onset HF, either HFrEF or HFrEF with approximately 600 patients.16 PREFERS Hypertension study is a single-centre, prospective clinical cohort study performed in collaboration between the Department of Cardiology at Danderyd Hospital and the Primary Health Care Services in Stockholm, Sweden. The study will recruit patients with a diagnosis of primary hypertension with an ongoing antihypertensive drug treatment as well as healthy control subjects, for comparison as previously described.17 For inclusion and exclusion criteria, see Table 2. All subjects will be assessed at the Cardiovascular Research Laboratory, which is part of the Clinical Research Centre at Danderyd University Hospital (Figure IA and IB).

Primary hypertension is defined as a diagnosis documented in primary care at some time point within the last 24 months and ongoing antihypertensive drug treatment (maximum up to two to three drugs). The currently recommended definition of hypertension as a systolic office BP >140 mmHg and/or diastolic BP >90 mmHg18 is widely adapted in primary health care. Exclusion of secondary hypertension is at the discretion of the primary health care physician or may be excluded at the inclusion visit. Controlled hypertension is defined as <140/90 mmHg.

### Table 1 Hypotheses and aims

| Hypotheses of the present study: |
|----------------------------------|
| 1. Hypertension with normal left atrial/ventricular function deteriorates over time, starting with increasing filling pressure, left atrial enlargement followed by reduced global longitudinal strain with LVEF >50% and heart failure symptoms (HFrEF) |
| 2. Circulating biomarkers reflecting myocardial fibrosis, inflammation and endothelial dysfunction reflects the transition from hypertension to hypertensive heart disease and HFrEF |

As a proxy for HFrEF development, our overall aim is to investigate:

- if change in diastolic cardiac function E/e′ or LAVI after 1 year is associated to blood pressure at baseline.

Specific aims:

- a. to study if change in diastolic cardiac function measured with E/e′ or LAVI after 1 year is associated to change in blood pressure from baseline to 1 year
- b. to assess if blood pressure control at baseline (according to guidelines and age adjusted) is associated to diastolic cardiac function measured with E/e′ or LAVI after 1 year
- c. to investigate if blood pressure control after 1 year (according to the guidelines and age adjusted) is associated to diastolic cardiac function measured with E/e′ or LAVI after 1 year
- d. to study the temporal evolution (baseline, 1 year, six years) of the diastolic function measured with E/e′ or LAVI
- e. to investigate gender aspects on the temporal evolution (baseline, 1 year, and 6 years) of the diastolic function measured with E/e′ or LAVI
- f. to study the temporal evolution (baseline, 1 year, and 6 years) of the diastolic function measured with echocardiography and CMR
- g. to assess if temporal changes (baseline, 1 year, and 6 years) in circulating levels of biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction are associated with changes in blood pressure
- h. to assess if temporal changes (baseline, 1 year, and 6 years) in circulating levels of biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction are associated with changes in diastolic function

CMR, cardiac magnetic resonance imaging; HFrEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index.
**Table 2 Inclusion and exclusion criteria in the PREFERS Hypertension study**

**Inclusion criteria**
- Primary hypertension
- Age ≥ 18 years
- Preserved cognitive function and expected longevity 1 year
- Written informed consent

**Exclusion criteria**
- Heart failure and/or reduced LVEF
- Valvular heart disease of haemodynamic importance
- Resistant hypertension
- Pregnancy
- Renal failure, GFR <30 mL/min/1.73 m²

GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.

**Recruitment of study participants and timeline**

Hypertension in Sweden is usually managed at primary health care centres. Through a collaboration between hospital and primary care, the patients will be recruited from health care centres in various socio-economic areas in Stockholm (approximately 10 care centres, total catchment area of 100 000 inhabitants). To include 250 patients and with an expected response rate of 25–30%, each health care centre will identify and randomly select and invite 100 patients, gender 1:1 using the software MedRave4 (Medrave Software AB, Stockholm, Sweden; Figure 1A). Patients will be characterized at baseline and after 1 and 6 years per standardized protocol (Figure 1B), and they will have their medication optimized at baseline and follow-ups, according to the guidelines. Parallel with patient recruitment, healthy control subjects, matched in age and gender, will be recruited by advertisement in local newspapers. Inclusion will be performed following a telephone interview, confirming they are apparently healthy and have no daily medication. Control subjects will follow the same study protocol as the patients but planned to be examined at inclusion only. The study protocol has been approved by the regional Ethics Committee and the Stockholm Health Care services, and all study participants will give their written informed consent.

**Measurements**

All study data will be collected into electronic case report forms using the Research Electronic Data Capture.

**Blood pressure measurements and pulse wave velocity**

Seated BP measurements will be made in accordance to the current guidelines. Three consecutive BP measurements are recorded, 1–2 min apart, using an oscillometry device (Omron M3 Comfort, OMRON Healthcare Co., Ltd. Kyoto, Japan). BP will also be measured 1 and 3 min after standing from a seated position to assess orthostatic hypotension. To screen for lower extremity artery disease, an ankle-brachial index will be recorded, using continuous wave Doppler.

Ambulatory blood pressure monitoring during 24 h will be assessed by a Spacelabs ABP monitoring 90217A device (Spacelabs Healthcare, Snoqualmie, WA, USA), programmed to record BP at 20 min intervals to provide an average BP value for daytime, night-time, and 24 h. A diary of the patients’ activities and sleep-time will be recorded. A minimum of 70% useable BP recordings are required for a valid ambulatory blood pressure monitoring session. The diagnostic threshold for hypertension is according to the ESC guidelines. The carotid-femoral pulse wave velocity (PWV) is assessed by the SphygmoCor XCEL device (AtCor Medical, Sydney, Australia), which allows for non-invasive assessment of the central arterial pressure waveform and measures of aortic stiffness.

**Electrocardiogram**

Twelve lead ECG data will be stored digitally (EC store version 4.1; Cardiolex Medical AB, Stockholm, Sweden). In harmony with the PREFERS HF study, LVH will be assessed according to the Sokolov Lyon index. In addition, beside a conventional 12-lead ECG, we will analyse a resting 12-lead ECG that combines advanced and conventional ECG parameters within computerized ECG scores that have been demonstrated to increase the detection accuracy of concentric LVH and in screening for LV systolic dysfunction.

**Echocardiographic and cardiac magnetic resonance measurements**

We will follow current recommendations for echocardiography to record two-dimensional echocardiographic and Doppler variables and perform Doppler tissue imaging similar to those measured in the PREFERS HF study (Table 3). All measurements will be presented as mean values of three cardiac cycles. A Vivid E9® (GE, Waukesha, Wisconsin, USA) Ultrasound System will be used. To reduce interobserver variability, only two sonographers will perform the investigations, which will be stored on a digital server and will be analysed offline.

For CMR, a Siemens Aera system (Siemens Healthcare, Erlangen, Germany) will be used to deliver standard measurements of chamber dimensions and function and signs of tissue scars of ischaemic and non-ischaemic origin. Myocardial extracellular matrix and signs of fibrosis will be examined by T1 mapping. Fully automated quantitative perfusion mapping during rest and adenosine stress will give a quantitative measurement for perfusion in mL/min/g, which will be used to search for perfusion defects; both focal defects

ESC Heart Failure 2020;7: 737–746  
DOI: 10.1002/ehf2.12612
**Figure 1** (A) Flow chart demonstrating recruitment, inclusion, and study protocol. (B) Flow chart demonstrating study protocol and follow-up plan.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CMR cardiac magnetic resonance imaging; GP, general practitioner.
due to obstructive coronary artery disease and defects in the global myocardial perfusion reserve due to coronary microvascular disease.

Measurements questionnaires

Quality of life measurements are to be assessed with validated instruments: the EuroQol-5 dimensions, the Kansas City cardiomyopathy questionnaire, and the Minnesota living with heart failure questionnaire. To screen for excessive daytime sleepiness, we will use the Epworth Sleepiness Scale version 1.0.

Screening for obstructive sleep apnoea

Screening for sleep disorders and obstructive sleep apnoea is performed at inclusion by the SOMNOcheck micro CARDIO (Weinman, Hamburg, Germany), self-applied by the study participants at home before bedtime. The ambulatory overnight cardio-respiratory polygraphy recording will measure apnoea/hypopnea, desaturation, and arousal indices.

Peripheral venous blood and urine sampling

Peripheral blood and urine will be collected after overnight fasting with no ingestion of caffeine or nicotine within at least 12 h. Clinical routine analyses of plasma and urine will be performed directly, but for future analysis of biomarkers and DNA extraction, aliquots of whole blood, plasma, and serum will be stored at −80°C in the Stockholm Medical Biobank until further analysis. This ensures a standardized handling of biomaterial with high security and traceability also for long-term storage. In the PREFERS Hypertension study, we plan to analyse the same panel of biomarkers as for the PREFERS HF study, which will enable a comparison between the two cohorts. Here, we focus on biomarkers indicative of various pathophysiological mechanisms relevant to HFrEF, including those reflecting myocardial fibrosis, inflammation, and endothelial dysfunction, as listed in Table 4.

Outcome measures

Mortality data outside hospital and incident admission to hospital due to HF will be obtained by merging the Swedish
cause of death register and the Swedish national inpatient register. The unique personal identification number of all Swedish citizens will ascertain complete follow-up.

**Primary endpoint and statistical power**

As a proxy for HfPEF development, our overall aim is to investigate if change in diastolic cardiac function $E/e$' or left atrial (LA) volume index after 1 year is associated to BP at baseline. Therefore, the primary endpoint in this study is either mean change of $E/e$' of 2 or more or mean change of LA volume index of 4 mL/m² or more after 1 year. These assumptions are based on a cross-sectional analysis of a big cohort from Olmsted County, Minnesota, where clear-cut differences were shown for these echocardiographic variables in patients with hypertension, HfPEF, and healthy controls. To reach 80% power at a two-sided level of significance of 0.05, the present study planned to recruit 250 patients and 60 healthy controls, including 20% drop outs.

**Discussion**

In the present study, we hypothesize that hypertension might be a pivotal upstream pathophysiological phase that initiates the deterioration over time (Table 1). Uncomplicated hypertension may start the evolution of extracellular changes and myocardial fibrosis that might be an early mechanism in the transition from hypertension to HHD and subsequent HF. Early signs of myocardial fibrosis might be the initial step that leads to decreased LA and LV compliance, which may start with deteriorated LA strain, followed by increased filling pressure, LA enlargement, and subsequent reduced global longitudinal strain with LVEF >50% and HF symptoms (HfPEF). However, the timeline as well as the upstream pathophysiological mechanisms for transition from hypertension to HHD need to be elucidated. Most likely, signs of myocardial fibrosis could be found early in patients with hypertension. Our rationale is that there may be subjects more prone to disease than others, and it is important not only to identify them early but also to find new strategies to prevent or delay disease progress. Therefore, we aim to perform a longitudinal study on the transition from uncomplicated hypertension to symptomatic HfPEF using clinical, extensive imaging, and biomarker parameters. Cardiac imaging modalities as echocardiography and CMR are keys to describe both functional and structural changes during this transition. In addition, biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction could be used as early non-invasive measures and could lead to new treatment strategies.

**Timeline**

To monitor the transition from hypertension to HHD and impaired diastolic function, we plan to examine our study cohort at inclusion and after 1 and 6 years. Even though our patients might not develop HfPEF within 6 years, our power calculation is made to detect clinically relevant changes and signs of increased LV filling pressure, as a proxy for HfPEF. Beyond analyses of underlying pathophysiological mechanisms in both cardiac imaging data and blood biomarkers during the study period, we have the opportunity to later analyse outcome measures, by merging our database with the national registries for incident HF and admission to hospital.

**Blood pressure measurements and pulse wave velocity**

Large artery stiffening is associated to systolic hypertension and age-dependent increase in pulse pressure, and PWV is the gold standard to measure large artery stiffness. In addition, elevated arterial stiffness is also associated to cardiovascular disease and mortality. In a cross-sectional study, subjects with hypertension and HfPEF had elevated arterial stiffness compared with people with normal BP.
Furthermore, Framingham data have shown that greater aortic stiffness is associated with increased risk of HF. Most likely, elevated PWV reflects both the duration of hypertension and the effects of antihypertensive treatment, but still, the association of central aortic stiffness with incident HHD and HFrEF physiology over time is not well described. PWV might be one relevant and easily available marker of disease progression.

Electrocardiogram

A conventional 12-lead ECG will be assessed at each follow-up, but to extend the protocol, we will also analyse advanced ECG parameters. ECG information occurring with signs of LVH and increased LV mass predicts adverse clinical outcome. Using advanced ECG parameters may increase both sensitivity and specificity when analysing signs of LVH as well as other signs of HHD. These ECG findings, common in hypertension patients, may be reversible with effective pharmacological antihypertensive treatment. However, a conventional 12-lead ECG has limited sensitivity for detecting increased LV mass because myocardial mass and diffuse fibrosis have opposing effects upon ECG voltage measures of LVH. Consequently, myocardial fibrosis may disguise the ECG signs of increased LV mass.

Echocardiography and cardiac magnetic resonance

Hypertension affects cardiac function through the interplay between the LV performance and the arterial system, the ventricular–arterial coupling. The left ventricle wall thickens in response to neurohormonal activation, increased afterload, and cytokines, which all are associated with arterial hypertension. HFrEF patients have also been suggested to have a subtle systolic dysfunction not reflected in ejection fraction but LV contractility. Interestingly, LV longitudinal strain is impaired in both HHD and HFrEF and is also associated to prognosis in HFrEF. To further investigate the ventricular–arterial coupling, we plan to assess measures of elevated filling pressure and PWV over time in the present study. LA enlargement reflects cardiac structural remodelling and is an early sign of HHD. Usually, LA enlargement is found before the development of LVH and LA enlargement is up to three-fold more common in patients with hypertension compared with healthy controls. LA mechanical deterioration or LA dysfunction is also often found before structural changes occur. Recently, LA global strain has been demonstrated as a feasible method to evaluate LA function and an inverse relationship between LA–global strain and diastolic LV filling pressures has been shown.

We will use an advanced protocol for CMR that give us opportunity to investigate cardiac diastolic function and to gain our knowledge regarding pathophysiological mechanisms. We will perform a complete evaluation of the LV diastolic function, according to the updated international echocardiographic guidelines. In addition, we will use a quantitative perfusion mapping during rest and adenosine stress to confirm or exclude ischaemic coronary artery disease and to obtain quantitative measurements of microvascular function or the myocardial perfusion reserve, corresponding to the coronary flow reserve. Late gadolinium enhancement is the reference standard for non-invasive imaging of myocardial scar and focal fibrosis. With this non-invasive method, changes in the myocardium over time may be assessed. Previously, both LV global longitudinal strain, measured with echocardiography, and extra-cellular volume, measured with CMR, have been demonstrated able to discriminate between HHD and HFrEF. CMR is therefore one way to find early signs of myocardial fibrosis.

Biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction

Myocardial fibrosis is characterized by excessive deposition of collagen type I and collagen cross-linking (CCL) and is involved in LV stiffening and diastolic dysfunction. Still, clinical evaluation of myocardial extracellular matrix and fibrosis is difficult; until now, the gold standard has been myocardial tissue biopsies—an invasive procedure not without risks. The measurement of fibrosis markers in the circulation has evolved as an alternative strategy, which we will analyse and relate to the findings obtained by the different cardiac imaging methods.

Cardiac fibroblasts are central for the synthesis of collagen and matrix metalloproteinase (MMP), fibrinolytic enzymes that degrades collagens. Interestingly, collagen type I synthesis and degradation can be assessed indirectly in the circulation, by measuring the degradation products procollagen type I c-terminal propeptide and collagen type I C-terminal telopeptide, respectively. We have earlier demonstrated that the collagen split product procollagen type I c-terminal propeptide is related to other markers of HF, such as brain natriuretic peptide, LV size, and diastolic function in HFrEF. Furthermore, the degree of myocardial CCL determines collagen’s resistance to degradation by MMP-1, and excessive CCL is associated with hospitalization for HF in hypertensive patients. In addition, the serum collagen type I C-terminal telopeptide: MMP-1 ratio has been demonstrated to identify patients with increased CCL. Other interesting biomarkers of HF and remodelling are suppression of tumourigenicity-2 and galectin-3 (Gal-3). Plasma levels of suppression of tumourigenicity-2 are higher in patients with HFrEF than in patients with HFrEF but have similar effect on predicting prognosis in both patient groups.

Gal-3 is expressed by...
activated macrophages and plays a regulatory role in inflammation and cardiac fibrosis in animal studies.\textsuperscript{42} Interestingly, human data from the Framingham study have shown that increased circulating levels of Gal-3 are associated to incident HF.\textsuperscript{43}

The transition from hypertension to HHD and HF is characterized by increased levels of natriuretic peptides, where N terminal pro brain natriuretic peptide is associated to increased LV wall stress. However, myocardial fibrosis, inflammation, and coronary artery disease may have a central pathophysiological role in disease progression.\textsuperscript{12} Other HFpEF co-morbidities, mainly obesity and diabetes mellitus, induce a pro-inflammatory state, which starts and maintains a chronic activation of reactive oxygen species, which limits the bioavailability of nitric oxide in cardiomyocytes. Interestingly, nitric oxide is important for endothelial function, which probably has a central role in the pathophysiology of HFpEF. The endothelium regulates vasomotor tonus and communicates closely with nearby smooth muscle cells that regulate BP. Furthermore, hypertension has been suggested to promote inflammation, and endothelial dysfunction in hypertensive patients correlates with biomarkers of inflammation including tumour necrosis factor $\alpha$, interleukin 6, C-reactive protein, E-selectin, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.\textsuperscript{12} The pro-inflammatory state may result in an impaired microvascular and macrovascular functions and might cause downstream reactions that stiffen cardiomyocytes through hypo-phosphorylation of titin and increased collagen deposition, causing LV dysfunction and HFpEF.\textsuperscript{12}

Conclusions

Because hypertension is usually managed at primary health care centres, the present study is built upon a scientific collaboration between hospital and primary care. We aim to characterize and study the timeline and the transition from uncomplicated hypertension to HHD and HFpEF in subjects with primary hypertension using advanced cardiac imaging techniques and bioinformatics. Further, we want to find cardiac imaging variables and biomarkers to explain and monitor disease progression and identify phenotypes prone to develop HHD and HFpEF. Ultimately, the present study may contribute to finding new treatment strategies of hypertension in order to prevent HFpEF. The results will guide and support health care providers in both hospital and primary care to provide an optimal and individualized treatment, which may change and ultimately improve living conditions for a large patient group.

Conflicts of interest

None declared.

Funding

This work is supported by grants from the Stockholm County Council and the Swedish Society of Medicine and the Novartis Foundation for bio-medical research.

References

1. Lindholm L, Agenäs I, Carlberg B, Dahlgren H, de Faire U, Hedblad B, et al. Moderately elevated blood pressure. A systematic literature review. The Swedish Council on Technology Assessment in Health Care SBU-rapport. 2004;170:1-2.
2. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet 2017 389: 37-55.
3. Jekell A, Nilsson PM, Kahan T. Treatment of hypertensive left ventricular hypertrophy. Curr Pharm Des 2018; 24: 4391-4396.
4. Holmquist C, Hasselstrom P, Bengtsson Bostrom K, Manhem K, Wettermark B, Hjerre P, Kahan T. Improved treatment and control of hypertension in Swedish primary care: results from the Swedish primary care cardiovascular database. J Hypertens 2017 35: 2102-2108.
5. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA; 275: 1557–1562.
6. Donal E, Lund LH, Oger E, Hage C, Persson H, Reynaud A, Ennezet PV, Bauer F, Sportouch-Dukhan C, Drouet E, Daubert JC, Linde C, KaRen I. Baseline characteristics of patients with heart failure and preserved ejection fraction included in the Karolinska Rennes (KaRen) study. Arch Cardiovasc Dis 2014; 107: 112–121.
7. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011; 13: 18–28.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parisi J, Pieke B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent LB, Cleveland O, Novara I, Rochester M, Bucharest R, St. Louis M. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the
American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016; 17: 1321–1360.

10. Webb J, Fovargue I, Tondel K, Porter B, Sieniewicz B, Gould J, Rinaldi CA, Ismail T, Chiribiri A, Carr-White G. The emerging role of cardiac magnetic resonance imaging in the evaluation of patients with HFPeF. *Curr Heart Fail Rep* 2018; 15: 1–9.

11. Gyngmosi M, Winkler J, Ramos I, Do QT, Fritz H, McDonald K, Gonzalez A, Thum T, Diez J, Jaisser F, Pizard A, Zannad F. Myocardial fibrosis: biomedial research from bench to bedside. *Eur J Heart Fail* 2017; 19: 177–191.

12. Paulus WJ, Tchope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* [Review] 2013; 62: 263–271.

13. Mordi IR, Singh S, Rudd A, Srinivasan J, Mace L, Tondel K, Porter B, Bursi F, Webb J, Fovargue L, Tondel K, Porter B, Zannad F, Garcia D, Garcia A. Rationale and design of the PREFERS Hypertension study. *J Hypertens* 2018; 36: 2081–2089.

14. Zile MR, Desai NS, Baicu CF, Stroud RE, Thompson SB, McClure CD, Mehurg RE, Thompson SB, McClure CD, Mehurg RE, Thompson SB, McClure CD, Mehurg RE. Plasma biomarkers that differentiate among heart failure with preserved ejection fraction patients, hypertensive patients, and healthy control subjects. *JACC Cardiovasc Imaging* 2018; 11: 577–585.

15. Zile MR, Boudis SA, Baicu CF, Stroud RE, Thompson SB, McClure CD, Mehurg SM, Spinales FG. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. *Circ Heart Fail* 2011; 4: 246–256.

16. Linde C, Eriksson MJ, Hage C, Wallen H, Persson B, Corbasco M, Lundeberg J, Maret E, Ugander M, Persson H, Stockholm County/Karolinska Institutet Dhi. Rationale and design of the PREFERS (Preserved and Reduced Ejection Fraction Epidemiological Regional Study) Stockholm heart failure study: an epidemiological regional study in Stockholm county of 2.1 million inhabitants. *Eur J Heart Fail* 2016; 18: 1289–1299.

17. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Omren SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction. 2016; 16: 193–202.

18. Williams B, Mancia G, Spering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruloipe L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruszhitska F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyons V, Desormais I, Group ESCCVD. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021–3104.

19. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Crichtshank JK, De Backer T, Filippovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T, Artery S. European Society of Hypertension Working Group on Vascular S, Function, European Network for Noninvasive Investigation of Large A. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30: 445–448.

20. Schlegel TT, Kulecz WB, Feiveson AH, Greco EC, DePalma JL, Stark V, Vrtovec B, Rahman MA, Bungo MW, Hayat MJ, Bauch V, Warden SG, Nunez-Medina T, Medina R, Jugo D, Arheden H, Pahlom O. Accuracy of advanced versus strictly conventional 12-lead ECG for detection and screening of coronary artery disease, left ventricular hypertrophy and left ventricular systolic dysfunction. *JMC Cardiovasc Disord* 2010; 10: 28.

21. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Maruura D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the American Association for Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–9, e14.

22. Haef C, Louis J, Touati H, Messroghli DR, Broadbent DA, Greenwood JP, Ples S, Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. *J Cardiovasc Magn Reson* 2016; 18: 89.

23. Engblom H, Xue H, Alil S, Carlson M, Hindorf C, Oddsgt J, Hedeer F, Hansson MS, Aletas AH, Kellman P, Arheden H. Fully quantitative cardiovascular magnetic resonance myocardial perfusion ready for clinical use: a comparison between cardiovascular magnetic resonance imaging and positron emission tomography. *J Cardiovasc Magn Reson* 2017; 19: 78.

24. Laurent S, Crockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson J, Struik-Boudier H. European Network for Non-invasive Investigation of Large A. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27: 2588–2605.

25. Willlum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijis L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; 113: 664–670.

26. Tso J, Lyass A, Larson MG, Levy D, Hamburg NM, Vita JA, Benjamin EJ, Mitchell GF, Vasan RS. Relation of central arterial stiffness to incident heart failure in the community. *J Am Heart Assoc* 2015; 23: 4.

27. Levy D, Salomon M, D’Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; 90: 1786–1793.

28. Peter SI, Holmquist F, Platonov PG, Steding K, Arheden H, Pahlom O, Stark V, McKenna WJ, Schlegel TT. Detection of hypertrophic cardiomyopathy is improved when using advanced rather than strictly conventional 12-lead electrocardiogram. *J Electrocardiol* 2010; 43: 713–718.

29. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julious S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Dahlof B. Losartan Intervention for Endpoint reduction in hypertension Study I. Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. *Circulation* 2003; 108: 684–690.

30. Manja M, Wieslander B, Schlegel TT, Bacharova L, Abu Daya H, Fridman Y, Wong TC, Schelbert EB, Ugander M. Diffuse myocardial fibrosis reduces electrocardiographic voltage measures of left ventricular hypertrophy independent of left ventricular mass. *J Am Heart Assoc* 2017; 22: 6, pii: e003795.

31. Heinzel FR, Hohendanner F, Jin G, Sedej S, Ketteler M, Lijnen F, Hombach F. Myocardial hypertrophy and its role in heart failure with preserved ejection fraction. *J Appl Physiol* (1985) 2015; 119: 1233–1242.

32. Shah AM, Claggett B, Switzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation* 2015; 132: 402–414.

33. Milan A, Puglisi E, Magnino C, Naso D, Abram S, Avenanti E, Rabbia F, Mulato P, Veglio F. Left atrial enlargement in essential hypertension: role in the assessment of subclinical hypertensive heart disease. *Blood Press* 2012; 21: 88–96.

34. Teo YI, Chan LL, Lam CS. Heart failure with preserved ejection fraction in hypertension. *Curr Opin Cardiol* 2016; 31: 303–308.

35. Nakami K, Ohte N, Asada K, Fukuta H, Goto T, Mukai S, Nariha T, Kimura G. Correlation between left ventricular end-diastolic pressure and peak left
atrial wall strain during left ventricular systole. J Am Soc Echocardiogr 2009; 22: 847–851.
36. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P, Min JK. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J 2017; 38: 991–998.
37. Ugander M, Oki AJ, Hsu LY, Kellman P, Greiser A, Aletras AH, Sibley CT, Chen MY, Bandettini WP, Arai AE. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. Eur Heart J 2012; 33: 1268–1278.
38. Mordi IR, Singh S, Rudd A, Srinivasan J, Frenneaux M, Tzemis N, Dawson DK. Comprehensive echocardiographic and cardiac magnetic resonance evaluation differentiates among heart failure with preserved ejection fraction patients, hypertensive patients, and healthy control subjects. JACC Cardiovasc Imaging 2017; 11: 577–585.
39. Lofsjögaard J, Kahan T, Diez J, Lopez B, Gonzalez A, Edner M, Henriksson P, Mejhurst M, Persson H. Biomarkers of collagen type I metabolism are related to B-type natriuretic peptide, left ventricular size, and diastolic function in heart failure. J Cardiovasc Med (Hagerstown) 2014; 15: 463–469.
40. Lopez B, Ravassa S, Gonzalez A, Zubillaga E, Bonavila C, Berges M, Echegaray K, Beaumont J, Moreno MU, San Jose G, Larman M, Querejeta R, Diez J. Myocardial collagen cross-linking is associated with heart failure hospitalization in patients with hypertensive heart failure. J Am Coll Cardiol 2016; 67: 251–260.
41. Sanders-van Wijk S, van Empel V, Davarzani N, Maeder MT, Handschin R, Pfisterer ME, Brunner-La Rocca HP. Investigators T-C. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. Eur J Heart Fail 2015; 17: 1006–1014.
42. de Boer RA, Yu L, van Veldhuisen DJ. Galectin-3 in cardiac remodeling and heart failure. Curr Heart Fail Rep 2010; 7: 1–8.
43. Ghorbani A, Bhambhani V, Christenson RH, Meijers WC, deBoer RA, Levy D, Larson MG, Ho JE. Longitudinal change in galectin-3 and incident cardiovascular outcomes. J Am Coll Cardiol 2018; 72: 3246–3254.