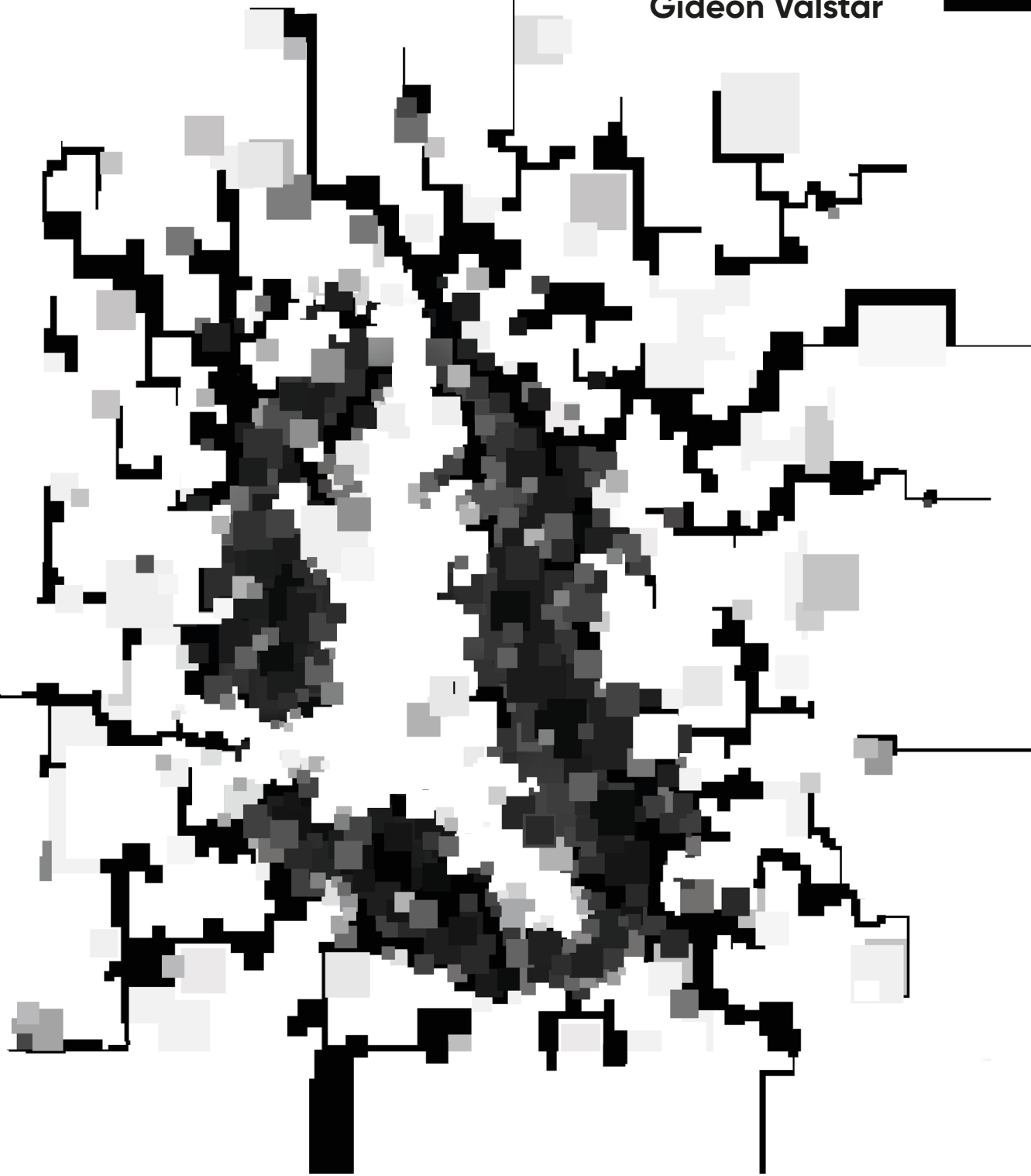
Left Ventricular Diastolic Dysfunction towards a HELPFul role of biomarkers

Gideon Valstar



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Left Ventricular Diastolic Dysfunction towards a HELPFul role of biomarkers

Linker Ventrikel Diastolische Dysfunctie
richting toegevoegde waarde van biomarkers
(met een samenvatting in het Nederlands)

Proefschrift

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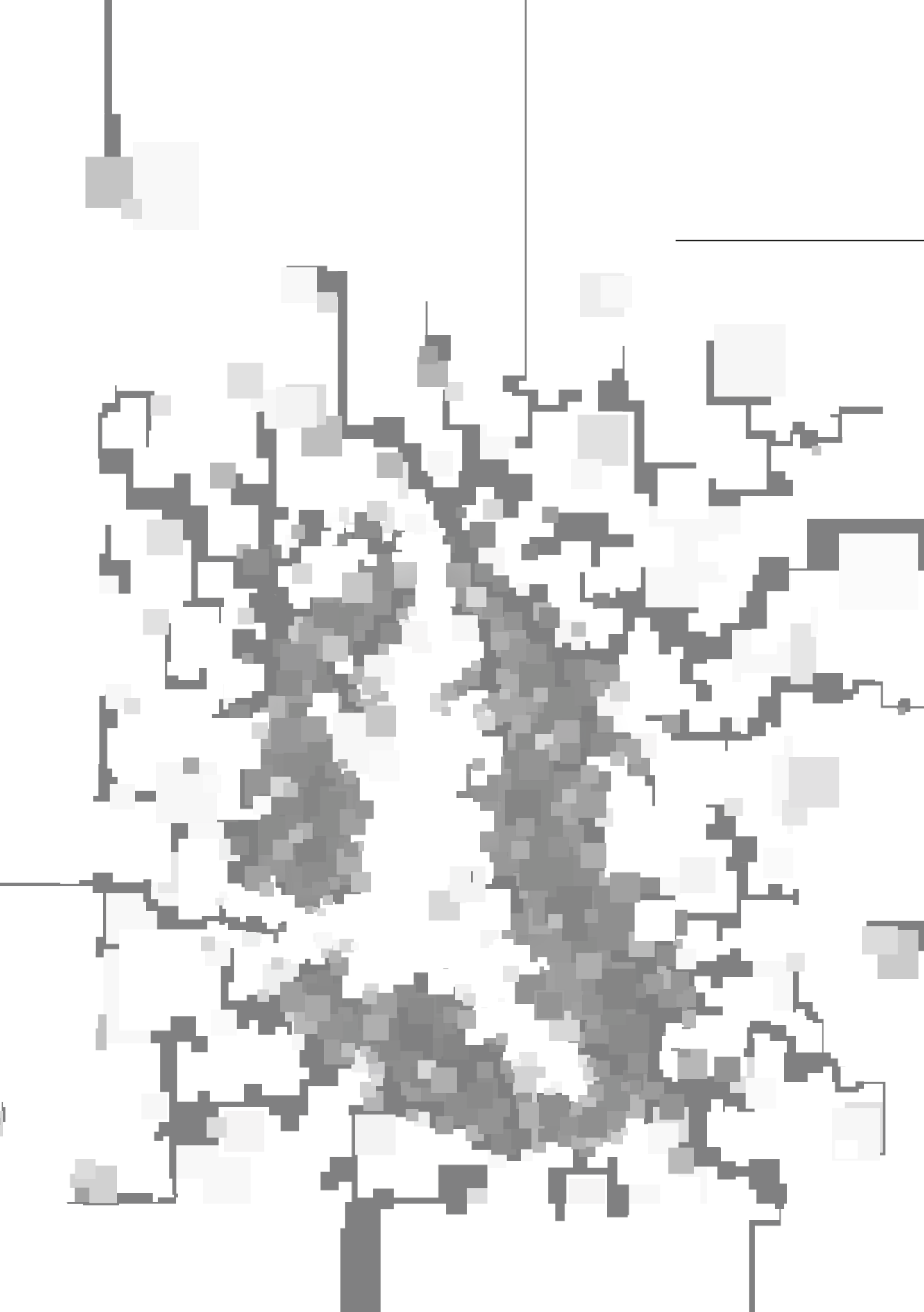
Copromotoren:	Dr. M.J. Cramer

Table of Content



Chapter 1

Introduction

Based on predictions by the Dutch Central Bureau of Statistics (CBS), the Dutch population above the age of 75 years is expected to double in the next 20 years from 1.2 million in 2011 to 2.6 million in 2040 (1). This speculated increase would go accompanied by a concomitant doubling of the prevalence of heart failure from 130,000 patients in 2011 to 275,000 patients in 2040 (1). The increased burden of heart failure would, however, not only be driven by aging, but also by improved survival after an acute coronary syndrome, and increased prevalence of important comorbidities underlying the development of heart failure, e.g. hypertension, obesity, type 2 diabetes and atrial fibrillation (2). Continuous availability of up to date information on (national) trends of heart failure and the determinants that drive it in order to provide information on the impact of heart failure on society is therefore of importance.
Historically, most attention went to heart failure with reduced ejection fraction (HFrEF), and new drug developments were based on landmark trials that included mainly relatively young men with no or only few comorbidities. Only since the beginning of the 21th century, heart failure with preserved ejection fraction (HFpEF) has started receiving more attention. Before that period, HFpEF was often either considered 'non-existent' or not important. However observational studies from the last two decades have clearly showed that HFpEF is relatively more on the increase than HFrEF in recent years and that especially older women seem to be affected by HFpEF (3,4). Typically, HFrEF develops years after a myocardial infarction or after longer duration in case of dilated cardiomyopathy. Nevertheless, left ventricular diastolic dysfunction (LVDD) may also be an early stage of HFrEF, certainly if also patients with a left ventricular ejection fraction between 40-50% are considered as reduced ejection fraction. But LVDD is better known as an 'early or preclinical stage' of HFpEF. Evidence of LVDD (i.e. structural or functional cardiac abnormalities with echocardiography in rest) is considered an integral part of the definition of HFpEF these days, next to symptoms suggestive of HF and a LVEF >50% (2).

Although, prevalence estimates of LVDD and HFpEF differ substantially between studies, it is well known that very high prevalence rates may be expected notably in the adults at high-risk in the community, e.g. those with chronic obstructive pulmonary disease (COPD) and type 2 diabetes (5-7). Prevalence may be as high as 50% for LVDD and 25% for HFpEF in community patients with type 2 diabetes aged 60 years and over, with a possibly equal distribution of LVDD among the sexes, but clearly higher prevalence of HFpEF in women (6). Since type 2 diabetes is increasing in Western societies, HFpEF prevalence estimates from systematic approaches are needed.

Progression on the knowledge of HFpEF was not only hampered by an unclear view of the situation regarding HFpEF for a long period of time, but also by the lack of clearly defined criteria and cut-points for echocardiographic structural and functional abnormalities to classify LVDD. Because of the lack of a reference standard ('gold standard') for LVDD and thus also HFpEF, observational studies have applied different criteria to classify patients for LVDD or in the presence of symptoms of HF, for HFpEF (3). A panel of experts who base their diagnosis on available guidelines on echocardiographic criteria, but also on all available diagnostic information from history taking, physical examination, electrocardiography, laboratory results (notably B-type natriuretic peptides) and transthoracic echocardiography seems for the being the best option, however, this option is very labor-intensive and not feasible for diagnosis in everyday practice (9). Quantification of the effects of various definitions on the classification of groups of patients is due and needed for context when comparing results from studies.

Opportunistic screening of high-risk older adults from the community also clearly showed underdiagnosis of heart failure, notably HFpEF (5,6). With cross-sectional studies, up to 80% of patients with HF may remain undetected in older patients with COPD or type 2 diabetes. A major reason for unrecognized HF, notably HFpEF is that symptoms of the syndrome are not specific in the early phase. Shortness of breath, fatigue and also ankle oedema may be caused by other disorders such as chronic obstructive pulmonary disease (COPD) or chronic venous insufficiency (2). Misclassification of patients to COPD or deconditioning is very common (10). In health care organizations with a strong primary care, general practitioners (GP) are often the gatekeeper to hospital care, and the large majority of patients first receive a 'working diagnosis' in general practice. However, the GP has only history taking, physical examination and some blood tests (e.g. natriuretic peptides) at his or her disposal, but will need to refer to the cardiologist for echocardiography. Notably, in patients with HFpEF, the natriuretic peptide levels (BNP or NTproBNP) may be normal, especially if blood is drawn at a point in time the patient has no substantial pulmonary congestion (2). In general, natriuretic peptide levels are lower in HFpEF than in HFrEF , because natriuretic peptides are released in case of increased cardiac wall stress, which follows the law of Laplace's(wall stress = pressure x radius/ 2x wall thickness). Wall tension is however much lower in HFpEF than in HFrEF at the same level of increased left ventricular pressures. This difference stems from the eccentric remodeling, with as a result a dilated left ventricle with a thin cardiac wall, that is generally observed in patients with HFrEF, whereas in patients with HFpEF there is concentric remodeling with a normal or even small left ventricle and a thickened cardiac wall (8).

Nowadays, much attention is paid to prevention of diseases, including cardiovascular disease. Lifestyle recommendations, and early treatment of hypertension, dyslipidemia, and type 2 diabetes combined with structured monitoring is a mainstay in primary care disease management programs. Moreover, community adults increasingly undergo one-stop assessments at cardiology outpatient clinics. These developments provide an opportunity to improve the process of early diagnosis of LVDD and HFpEF in the community. Validated diagnostic prediction algorithms may be of help for referral of patients at risk of having LVDD and HFpEF for further diagnostic assessment to these clinics. Furthermore, biomarkers may help to improve prediction algorithms. Several of the discussed aspects around heart failure will be addressed in the present thesis.

Objectives of this thesis:

1. To address the impact of hospitalisation of heart failure over time in the Netherlands;
2. To assess the role of several potential determinants of left ventricular dysfunction and heart failure with preserved ejection fraction;
3. To quantify the effect of different published diagnostic guidelines on the classification of individuals suspected of LVDD;
4. To develop, validate and potentially update a diagnostic prediction algorithm for LVDD and HFpEF that can be used in general practice.

In chapter 2 we describe difference in prognosis of men and women after a first hospital admission for heart failure in the Dutch population.

In chapter 3 we present the rationale and design of the HELPFul case-cohort study in patients visiting a Dutch cardiology outpatient clinic.

In chapter 4 we evaluate the relation between renal function and LVDD with univariable and multivariable analyses.
In chapter 5 we perform a systematic review and meta-analysis of studies on the prevalence of LVDD and HFpEF in patients with type 2 diabetes, and summarize the results for men and women separately.

In chapter 6 we quantify the effect of different currently available international recommendations for the diagnosis of LVDD on the prevalence estimates of LVDD and reclassification in the study population in HELPFul.

In chapter 7 we developed a diagnostic, sex-specific prediction rule for LVDD/HFpEF in a diagnostic individual patient data meta-analysis consisting of four community cohorts at high-risk for cardiovascular disease.

In chapter 8 we validate the prediction rule developed in chapter 4.2 in the HELPFul study population and evaluated with classic logistic regression and penalized maximum likelihood estimation modelling techniques whether kidney (creatinine, cystatin-c) and other blood biomarkers (hs-TnI, BNP, CKMB, Vitamin D, Lipoprotein (a), hs-CRP, lipids, albumin, ASAT) improved discrimination and calibration of the sex-specific models.

Finally, in chapter 9, the general discussion, the main findings and conclusions of this thesis are summarized. In addition, we will discuss the problems caused by the lack of consensus on the diagnostic criteria for LVDD and HFpEF.

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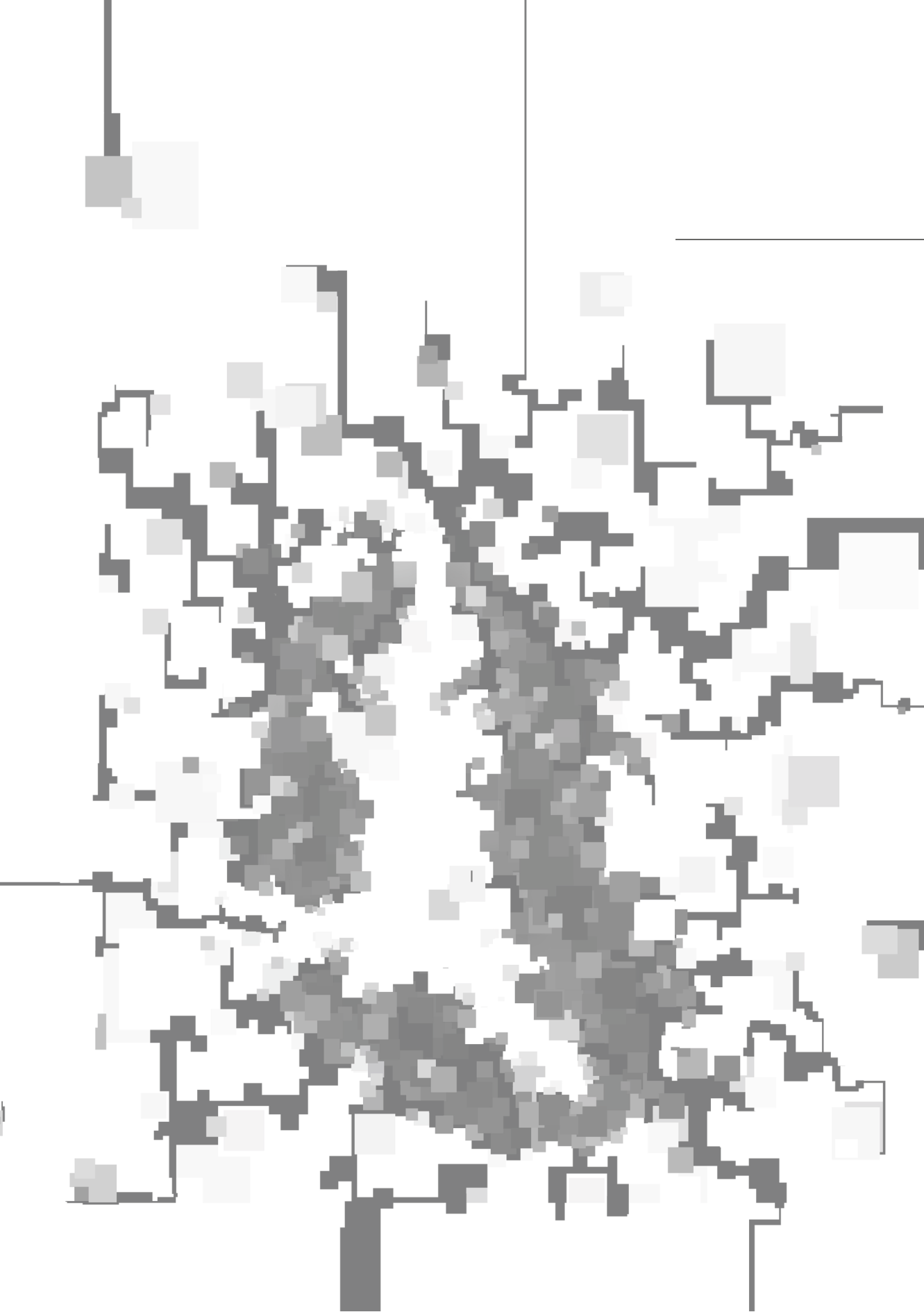
PART ONE

Heart Failure prognosis



Chapter 2

Mortality after hospital admission for heart failure: Improvement over time, equally strong in women as in men.

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1

ABSTRACT

Background
To assess the trend in age- and sex-stratified mortality after hospitalization for heart failure (HF) in the Netherlands.

Methods
Two nationwide cohorts of patients, hospitalized for new onset heart failure between 01.01.2000 - 31.12.2002 and between 01.01.2008 - 31.12.2010, were constructed by linkage of the Dutch Hospital Discharge Registry and the National Cause of Death registry. 30-day, 1-year and 5 year overall and cause-specific mortality rates stratified by age and sex were assessed and compared over time.

Results
We identified 40,230 men and 41,582 women. In both cohorts, men were on average younger than women (74-75 and 78-79 years, respectively) and more often had comorbid conditions (37% and 30%, respectively). In the 2008-10 cohort, mortality rates for men were 13%, 32% and 64% for respectively 30-day, 1-year and 5-year mortality and 14%, 33% and 66% for women. Mortality rates increased considerably with age similarly in men and women (e.g. from 10.5% in women aged 25-54 to 46.1% in those aged 85 and older after one year). Between the two time periods, mortality rates dropped across all ages, equally strong in women as in men. The 1-year absolute risk of death declined by 4.0% (from 36.1 to 32.1%) in men and 3.2% (from 36.2 to 33.0 %) in women.

Conclusions
Mortality after hospitalization for new onset HF remains high, however, both short-term and long-term survival is improving over time. This improvement was similar across all ages and equally strong in women as in men.

2

Background

The burden of heart failure on Western societies is increasing and is projected to continue to do so in the future (1,2). Ageing, with its associated increase in comorbid conditions, is a driving force behind the emerging epidemic (3,4), as is the considerably improved survival after an acute myocardial infarction (5). Hospitalization for heart failure comes with a high risk of both short-term and long-term mortality (4). The mortality risk increases with age, as has been shown in a variety of studies (6,7). Several studies indicated that the prognosis after hospitalization is worse for men than for women (4,6,7). Others suggested that the sex difference seems to attenuate towards comparable mortality risks (7,8). Data on time trends in short-term and long-term survival, stratified for both age and sex, is sparse (1,6), but needed to establish if sex differences matter in prognosis after heart failure hospitalization (9). Therefore, we assessed contemporary age- and sex-stratified overall and cause-specific short-term and long-term mortality after hospitalization using nationwide cohorts of patients hospitalized for new onset for heart failure in the Netherlands.

Methods

Registries and linkage procedure

Details of the registries and linkage procedures used to construct nationwide cohorts of patients hospitalized for the first time for heart failure have been previously described (10,11). Briefly, the data of the Dutch Hospital Discharge Register (HDR), the Dutch Population Register (PR), and the National Cause of Death Register were linked using a unique record identification number based on a combination of birth, sex and postal code (unique for 84% of the population). The PR was used to obtain data on demographic characteristics, HDR was used to identify patients with a hospital admission for heart failure, and cause of death statistics were used to obtain data on causes of death following admission for heart failure (11). The PR became electronically available from 1995. Linkage of the registries is therefore possible from 1995 and onwards. For this study data was available from 1995 to 2015. All linkages and analyses were performed in agreement with the privacy legislation in the Netherlands and conforms with the principles outlined in the Declaration of Helsinki (12).

Study population

A prospective cohort of patients with heart failure was built by selecting patients from the HDR with a primary admission for the following International Classification of Diseases (ICD) 9th revision codes for heart failure: 428.0, 428.1, 428.9, 402.01, 402.11 and 402.91. Those with a hospital admission for heart failure in the previous five years were excluded to ensure that the admissions for heart failure were, with a high probability, first new onset admissions. To investigate differences in mortality risk over time, two cohorts were created: one cohort containing information about patients admitted for heart failure between 1 Jan 2000 and 31 Dec 2002 (short: the 2000-02 cohort) and one cohort containing information from patients admitted between 1 Jan 2008 and 31 Dec 2010 (short: the 2008-10 cohort). For both cohorts, patients were additionally divided in isolated left-sided heart failure (ICD-9: 428.1) and other heart failure (ICD-9: 428.0, 428.9, 402.01, 402.11 and 402.91) to allow evaluation of the value of this ICD subdivision.

Outcomes
The main outcomes were 30-day, 1-year and 5-year overall mortality. Follow-up was defined as time from hospital admission for heart failure to the day the patients died or the end of study period. Cause specific mortality is reported for cardiovascular mortality (separately for heart failure, ischemic heart disease, cerebrovascular disease, and other cardiovascular disease), cancer mortality (separately lung cancer) and respiratory mortality (separately chronic obstructive pulmonary disease (COPD)), and chronic kidney disease/renal failure mortality. All ICD codes used are mentioned in Appendix 1.

Other characteristics
Demographic information comprises age, sex, and marital status. We determined the presence of comorbidity by the Charlson comorbidity index based on previous hospital admissions (13), which is considered a valid measure to estimate comorbidity in clinical research (14). The mean Charlson comorbidity index was calculated as well as the proportion of patients that had an index score of 1 or more. Data on the duration of the hospital admission was available. No information was available on severity of heart failure at the time of admission, nor was data available to allow for differentiation between heart failure with preserved ejection fraction and reduced ejection fraction.

Validation of heart failure discharge codes
The accuracy of the heart failure discharge codes were assessed in a dedicated validation study. For each precision digit of code ICD-9 code 428, 50 patients of the University Medical Center Utrecht were randomly selected and the medical records of these patients were manually checked for correct discharge ICD-9 code and discharge date. These codes were 428.0 (congestive heart failure, unspecified), 428.1 (left heart failure), and 428.2 (heart failure, unspecified).

Data analysis
Baseline characteristics are presented as absolute numbers and percentages for both the 2000-02 and the 2008-10 cohorts. Secondly, we provided absolute numbers and percentages of all-cause mortality, cardiovascular mortality, cancer mortality, respiratory mortality and renal mortality of patients who died within 30-days, 1-year and 5-years after admission for heart failure in the recent cohort, and presented that by sex. Next, we estimated the 30-days, 1-year and 5-year mortality risk after first admission for heart failure in the 2000-02 and the 2008-10 cohorts and stratified these results by age and sex. Potential differences in mortality in sex and age groups were tested with logistic regression analyses. All analyses were adjusted for the Charlson Comorbidity Index (Table 3). To explore whether change in mortality over time was statistically different between men and women, we added an interaction term between sex and time and compared this model with the model without the interaction term using the likelihood ratio test. Then, we investigated whether a previous hospital admission for overall cardiovascular disease, acute myocardial infarction, or chronic pulmonary disease was associated with increased 30-day, 1-year and 5-year mortality in men and women using Cox proportional hazard models adjusted for age. Finally, we estimated the mortality risks of isolated left-sided heart failure (ICD-9: 428.1) and other heart failure (ICD-9: 428.0, 428.9, 402.01, 402.11 and 402.91), by age and sex. All analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and a p-value < 0.05 was considered statistically significant.

Results

Cohort study

We identified 38,848 patients (19,309 men and 19,539 women) with a first admission for heart failure in the earlier cohort 2000-02 and 42,964 patients (20,921 men and 22,043 women) in the recent cohort 2008-10 (Table 1). In both cohorts, women were on average 4 years older than men at the time of hospital admission for heart failure. Charlson comorbidity index was ≥1 in 37% of men and 30% in women. Length of admission reduced with 2 days over time, from 8 to 6 days in men and from 9 to 7 days in women (Table 1). Of the patients in the 2008-2010 cohort who died within 30-days, 1-year and 5-years, the majority died from a cardiovascular cause (53%-65%), with no clear differences between men and women. The proportion of cardiovascular mortality as cause of death decreased with increasing survival time, while the proportion of cancer to the overall mortality increased with survival time (Table 2).

Thirty-day mortality

Short term mortality increased with age for both sexes (Figure 1, Table 3A and B). Between 2000-02 and 2008-10, mortality after hospitalization for heart failure decreased in all age groups in both men and women. These decreases were statistically significant in men of most ages, except men aged 25-54, and in women aged 64 years or younger (Table 3A and B). Table 3C shows that the decline in mortality between the two time periods did not significantly differ between men and women.

One-year mortality

One-year mortality also increased with age for both sexes (Figure 1, Table 3A and B). Between 2000-02 and 2008-10, one-year mortality after hospitalization for heart failure decreased in all age groups in both men and women. These decreases were statistically significant in all men and women (Table 3A and B). Table 3C shows that the decline in mortality between the two time periods did not significantly differ between men and women.

Five-year mortality

Lastly five-year mortality increased with age for both sexes (Figure 1, Table 3A and B). Between 2000-02 and 2008-10, five-year mortality after hospitalization for heart failure decreased in all age groups in both men and women. These decreases were statistically significant in men and women at all ages (Table 3A and B). Table 3C shows that the decline in mortality between the two time periods was more pronounced in men compared to women when age groups were combined (decline men: 4.2% and women: 2.6%, p-value=0.01) as well as in those aged between 55 to 64.

Previous admission for cardiovascular disease

A previous hospital admission for cardiovascular disease yielded significantly lowered Hazard Ratio's (HR) for 30-day mortality in both men and women and for 1-year mortality in women (Table 4). For example, an hospital admission any time in the five years preceding the hospital admission for heart failure was associated with 24% less risk of dying within 30 days (HR: 0.76, 95% confidence interval (CI): 0.67-0.86)). In men, a hospital admission for chronic pulmonary disease 1 or 5 years before hospital admission for heart failure was associated with 28% and 29% lower risk of dying within 30 days after hospitalization for heart failure. In women, a similar relation for a previous hospital admission for chronic pulmonary disease was observed only for dying within one year after hospital admission for heart failure (Table 4).

Validation study

ICD codes were validated for 152 patients using the medical information registered in the electronic patient data system of the University Medical Center Utrecht (Table 5). 80% of these patients were correctly diagnosed with heart failure. However, this value varied across subcodes, from 76% for ICD-9 428.9 to 87% for ICD-9 428.0. In addition, 12% (428.0) to 22% (428.9) of the patients had heart failure as a complication during hospital stay. The remaining 2-6% did not have heart failure during hospital admission nor in their history, and may be considered misclassified. In figure Appendix 2 we explored the value of the ICD heart failure subcoding in terms of mortality risk. There were no differences in one-year mortality between those classified as isolated left-sided heart failure compared to the other codes in men, nor in women stratified for age. These results hold for 30-day and five-year mortality rates (results not shown).

Discussion

In this study we showed improvement in short-term and long-term survival after hospital admission for new onset heart failure hospitalizations between 2000 and 2010, although mortality rates are still high. This improvement was similar across all ages and equally strong in women as in men.

Trends in survival

Our finding of a decline in mortality over this time period are in line with several other population based studies (1–9). A similar decline in women as in men is in line with contemporary data suggesting that hospital care is similar for men and women with heart failure (15), and acute myocardial infarction (16). These studies suggested that the decline is a result of better adherence, with no differences regarding sex, to optimized treatment as recommended in guidelines for heart failure. We confirm the steep increase in mortality after hospitalization for heart failure with increasing age, which also has been observed in a large number of previous studies (6,7). Interestingly, previous hospital admission for some conditions that may underlie the development of heart failure, e.g. cardiovascular disease, myocardial infarction and chronic pulmonary disease was associated with a reduced mortality risk of those admitted for new onset heart failure. Although surprising, this observation may be explained by the notion that patients with a known history of cardiovascular disease or respiratory disease may be referred to the hospital earlier compared to patients without known cardiovascular or respiratory disease. As a result, their stage of heart failure may be less advanced. Furthermore, due to the initiation of preventive cardiovascular medication, their cardiovascular condition may be better and thus their cardiovascular risk may be lower at the time of hospital admission when compared to a patient presenting with heart failure without a previous cardiovascular condition. This is however speculative and could not be investigated with the current data.

An in-depth explanation of observed trends in mortality with the current data is hampered by the fact that the database does not contain information on cardiovascular risk factors and medication use linked to the individuals. We know from previous work into coronary heart disease mortality trends that in the time window 1997-2007, on a population level systolic blood pressure fell, cholesterol level declined, and favorable changes occurred in smoking and physical activity (17). These risk factor changes may have potentially led to an improved cardiovascular status at the time of heart failure hospitalisation leading to leading to a reduction of risk afterwards. Furthermore, the uptake of beta-blockers in heart failure patients in the acute phase and for secondary prevention more than doubled between 1997 and 2007 (18). Also the uptake of lipid lowering, blood pressure lowering drugs and beta blockers in the acute phase and secondary

prevention phase of conditions predisposing to heart failure, such as acute coronary syndrome, may have favorably affected prognosis in the event that heart failure developed (18).

Trends in survival stratified by sex

We confirm previous findings that showed significant decreases in mortality over time in both men and women and in all age groups (3,19). Heart failure with reduced ejection fraction (HFrEF) has been better recognized in the last decade and contemporary heart failure treatment largely improved mortality of patients with HFrEF, but not for those with preserved ejection fraction (HFpEF) (20). Because men more often have HFrEF than women (2,20), we expected to observe a more pronounced mortality decline in men similar to some previous studies (3,19). However, our data only show a somewhat more pronounced decline in five-year mortality for men, whereas no significant differences in decline for 30-day and one-year mortality were observed between men and women.

Validity of ICD code

Validation of the ICD-9 heart failure codes yielded a high percentage of accuracy for the diagnosis of heart failure. Previous studies reported positive predictive values for the use of ICD-9 code 428 to identify patients with heart failure between 80% (21) and 94% (22). This is in line with our estimate for 428 (80%) and supports the potential of using such data.

Strengths and limitations

Strength of our study is the nationwide design with accordingly a large sample size which enabled us to stratify our results for age and sex. Furthermore, the validity of the linkage of registries in The Netherlands has been proven to be high (21,23–25). Limitations of our study arise from the nature of hospital administrative data. Patients were identified on the basis of ICD-9 codes for heart failure. The ICD coding does not distinguish HFrEF and HFpEF. In addition, information on severity and prescribed medical treatment is not routinely collected in these registries, and thus more in depth analyses in causes underlying the observed trends is limited. Next, the Dutch hospital discharge register was electronically available from 1995. As we used data from 2000, the maximum wash-out-period to limit subsequent hospital admissions for heart failure was 5 years. As a result we may have included some patients with a recurrent admission for heart failure. The prognosis of these patients may be different from patients with a first admission for heart failure. The reported mortality rates may therefore in reality be somewhat lower or higher. However, we used a 5 years wash-out-period for both the 2000-02 cohort and the 2008-10 cohort and therefore it is not likely this has affected our trend estimates.

Conclusion

In conclusion, mortality after hospitalization remains high, however, both short and long term survival is improving over time. This improvement was similar across all ages and equally strong in women and in men. These observational findings do not allow detailed evaluation of the underlying mechanisms.

1

LIST OF ABBREVIATIONS

AMI Acute myocardial infarction
CI Confidence Interval
COPD Chronic Obstructive Pulmonary Disease
CPD Chronic pulmonary disease
CVD Cardiovascular Disease
HDR Hospital Discharge Register
HF Heart Failure
HFpEF Heart Failure with preserved Ejection Fraction
HFrEF Heart Failure with reduced Ejection Fraction
HR Hazard Ratio
ICD International Classification of Disease
IQR Interquartile Range
PR Population Register
SD Standard Deviation

DECLARATIONS

Ethics approval and consent to participate: Not applicable.
Consent for publication: Not applicable. Availability of data and material: The data that support the findings of this study are available from the Central Bureau of Statistics Netherlands but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Central Bureau of Statistics Netherlands
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Authors' contributions: JB undertook the analysis of the data and drafted the manuscript. GV validated the ICD-9 discharge codes and drafted the manuscript. ID was involved in data acquisition and analysis. FV supervised the design of the study and participated in interpreting the data. FR and HdR reviewed and edited the manuscript. IV and MB supervised the design of the study, participated in interpreting the data and revised the manuscript. All authors provided critical revisions. All authors have read and approved the final manuscript and have agreed to be personally accountable for the author's own contributions.
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Table 1.
Characteristics of men and women with a hospiral admission for heart failure in the periods between 2000-2002 and 2008-2010

Table 2.
Characteristics and causes of death of patients who died after hospital admission for heart failure in the period between 2008-2010

	2000-02 Men		2008-10 Men		2000-02 Women		2008-10 Women	
	n	%	n	%	n	%	n	%
Total No. patients	19,309		20,921		19,539		22,043	
Mean age in years at admission (SD)	74 (11)		75 (11)		78 (11)		79 (11)	
Mean Charlson comorbidity index (SD)	0.7 (1.1)		0.7 (1.2)		0.5 (1.0)		0.5 (1.0)	
Charlson comorbidity index score ≥1	7,119	37%	7,711	37%	5,875	30%	6,497	30%
Myocardial infarction	2,866	15%	2,485	12%	1,690	9%	1,514	7%
Stroke	1,053	5%	1,294	6%	941	5%	1,319	6%
Peripheral artery disease	1,122	6%	1,085	5%	541	3%	496	2%
Renal disease	496	3%	800	4%	346	2%	534	2%
Cancer	1,219	6%	1,839	9%	996	5%	1,400	6%
Marital state Single	7,572	39%	7,988	38%	15,249	78%	16,338	74%
Married[1]	11,737	61%	12,933	62%	4,290	22%	5,705	26%
Median length of admission in days (IQR)	8 (9)		6 (8)		9 (10)		7 (10)	

Abbreviations: SD Standard Deviation; IQR Interquartile Range

[1]Married or registered partnership

	30-day mortality				1-year mortality				5-year mortality			
	Men		Women		Men		Women		Men		Women	
	n	%	n	%	n	%	n	%	n	%	n	%
Total deaths	2,738	100%	3,056	100%	6,713	100%	7,265	100%	13,351	100%	14,521	100%
Mean age at admission in years (SD)	81 (9)		84 (9)		80 (9)		83, 9		78, 9		82, 9	
Median survival time in days (IQR)	8 (13)		7 (12)		52 (157)		49 (148)		360 (884)		365 (905)	
Cause of death												
Cardiovacular disease	1,748	64%	1,996	65%	3,845	57%	4,350	60%	7,126	53%	8,021	55%
Heart failure	563	21%	725	24%	1,153	17%	1,499	21%	2,151	16%	2,804	19%
Ischaemic heart disease	628	23%	516	17%	1,302	19%	962	13%	2,293	17%	1,659	11%
Myocardial infarction	298	11%	275	9%	553	8%	481	7%	929	7%	811	6%
Cerebrovascular disease	52	2%	57	2%	144	2%	216	3%	361	3%	525	4%
Other cardiovascular disease	505	18%	695	23%	1,246	19%	1,673	23%	2,321	17%	3,033	21%
Cancer	240	9%	170	6%	867	13%	653	9%	1,878	14%	1,362	9%
Lung cancer	64	2%	30	1%	253	4%	116	2%	538	4%	245	2%
Respiratory disease	382	14%	427	14%	910	14%	834	12%	1,758	13%	1,669	12%
COPD	158	6%	182	6%	437	7%	380	5%	932	7%	799	6%
Chronic kidney disease/ Renal failure	31	1%	35	1%	114	2%	141	2%	259	2%	326	2%
Other cause	337	12%	428	14%	977	15%	1,287	18%	2,330	18%	3,143	22%

Abbreviations: COPD Chronic Obstructive Pulmonary Disease

Table 3. Difference in 30-day, 1-year, and 5-year mortality risk between the 2000-02 cohort and the 2008-10 cohort in men (A) and in women (B) and the difference in mortality risk between 2000-02 and 2008-10 between men and women (C).

		30-day mortality				1-year mortality				5-year mortality			
A	**Age group**	2000-02	2008-10	OR[a] (95% CI)	*p*	2000-02	2008-10	OR[a] (95%CI)	*p*	2000-02	2008-10	OR[a] (95%CI)	*p*
Men	25-54 (%,n)	5.4% (60)	3.9% (45)	0.73 (0.49-1.08)	0.12	14.4% (160)	9.8% (114)	0.68 (0.52-0.88)	<0.01	32.1% (357)	22.1% (256)	0.62 (0.51-0.75)	<0.01
	55-64 (%,n)	7.2% (172)	4.8% (125)	0.65 (0.51-0.82)	<0.01	18.7% (446)	14.3% (374)	0.73 (0.62-0.85)	<0.01	45.0% (1075)	34.5% (901)	0.64 (0.57-0.72)	<0.01
	65-74 (%,n)	11.3% (645)	8.0% (412)	0.68 (0.60-0.78)	<0.01	28.6% (1629)	22.6% (1155)	0.75 (0.66-0.78)	<0.01	59.5% (3384)	52.9% (2707)	0.76 (0.70-0.82)	<0.01
	75-84 (%,n)	17.8% (1330)	14.2% (1125)	0.76 (0.70-0.83)	<0.01	42.8% (3201)	36.3% (2888)	0.75 (0.71-0.80)	<0.01	78.8% (5895)	73.4% (5833)	0.73 (0.67-0.78)	<0.01
	85+ (%,n)	30.3% (800)	25.2% (1031)	0.79 (0.71-0.88)	<0.01	58.3% (1539)	53.4% (2182)	0.82 (0.74-0.90)	<0.01	91.7% (2421)	89.5% (3654)	0.75 (0.63-0.89)	<0.01
	Total (%,n)	15.6% (3007)	13.1% (2743)	0.74 (0.70-0.79)	<0.01[1]	36.1% (6975)	32.1% (6713)	0.75 (0.72-0.78)	<0.01[1]	68.0% (13132)	63.8% (13351)	0.72 (0.69-0.76)	<0.01[1]
B	25-54 (%,n)	4.7% (36)	3.8% (31)	0.81 (0.50-1.33)	0.38	13.7% (104)	10.5% (85)	0.77 (0.56-0.15)	0.10	26.7% (203)	20.4% (166)	0.72 (0.56-0.92)	<0.01
	55-64 (%,n)	6.4% (76)	5.8% (84)	0.91 (0.66-1.25)	0.57	19.3% (231)	16.0% (231)	0.79 (0.65-0.98)	0.03	39.4% (470)	35.4% (512)	0.85 (0.72-0.99)	0.055
	65-74 (%,n)	10.4% (389)	8.1% (270)	0.76 (0.64-0.90)	<0.01	25.6% (957)	21.1% (705)	0.78 (0.70-0.87)	<0.01	53.0% (1981)	45.8% (1532)	0.75 (0.69-0.83)	<0.01
	75-84 (%,n)	15.5% (1276)	12.6% (1055)	0.79 (0.72-0.86)	<0.01	35.6% (2940)	30.2% (2534)	0.78 (0.73-0.83)	<0.01	70.8% (5837)	64.9% (5447)	0.76 (0.71-0.81)	<0.01
Women	85+ (%,n)	23.6% (1323)	20.1% (1616)	0.82 (0.75-0.89)	<0.01	50.8% (2843)	46.1% (3710)	0.83 (0.77-0.89)	<0.01	87.3% (4887)	85.3% (6864)	0.84 (0.76-0.93)	<0.01
	Total (%,n)	15.9% (3100)	13.9% (3056)	0.79 (0.75-0.83)	<0.01[1]	36.2% (7075)	33.0% (7465)	0.79 (0.76-0.83)	<0.01[1]	68.5% (13378)	65.9% (14521)	0.78 (0.75-0.82)	<0.01[1]
C		**Differences men and women**											
		Men Δ2000-02 2008-10	Women Δ2000-02 2008-10	OR[b] (95%CI)	*p*	Men Δ2000-02 2008-10	Women Δ2000-02 2008-10	OR[b] (95%CI)	*p*	Men Δ2000-02 2008-10	Women Δ2000-02 2008-10	OR[b] (95%CI)	*p*
	25-54	-1.5%	-0.9%	1.13 (0.60-2.11)	0.71	-4.6%	-3.2%	1.12 (0.75-1.68)	0.58	-10.0%	-6.3%	1.15 (0.84-1.57)	0.29
	55-64	-2.4%	-0.6%	1.40 (0.94-2.09)	0.10	-4.5%	-3.4%	1.10 (0.85-1.41)	0.48	-10.5%	-4.0%	1.32 (1.09-1.63)	<0.01
	65-74	-3.3%	-2.3%	1.11 (0.90-1.36)	0.34	-5.1%	-4.5%	1.09 (0.94-1.25)	0.35	-6.6%	-7.2%	1.00 (0.89-1.13)	0.99
	75-84	-3.6%	-2.9%	1.03 (0.91-1.16)	0.67	-6.5%	-5.5%	1.03 (0.94-1.13)	0.48	-5.4%	-5.1%	1.05 (0.95-1.16)	0.38
	85+	-5.1%	-3.6%	1.04 (0.90-1.19)	0.62	-4.9%	-4.7%	1.01 (0.90-1.14)	0.86	-2.2%	-2.0%	1.11 (0.91-1.34)	0.29
	Total	-2.5%	-2.0%	1.04 (0.97-1.13)	0.29[1]	-4.0%	-3.2%	1.05 (0.98-1.11)	0.16[1]	-4.2%	-2.6%	1.09 (1.02-1.15)	0.01[1]

[1]Adjusted for age

Abbreviations: CI confidence interval, OR Odds Ratio

[a] Odds Ratio (OR) represents the odds of mortality after hospital admission for heart failure between 2008-2010 compared to 2000-2002 stratified by age and adjusted for Charlson comorbidity index.
[b] OR represents the odds of change in mortality (after hospital admission for heart failure between 2008-2010 compared to 2000-2002) in men compared to the same change in mortality in women stratified by age and adjusted for Charlson comorbidity index.

Table 4. Previous admission for cardiovascular disease and the risk of death within 30 days, 1 year and 5 years after hospital admission for heart failure in the period between 2008-2010.

	30-day mortality		1-year mortality		5-year mortality	
	Men	Women	Men	Women	Men	Women
Previous hospital admission for						
AMI: 30 days prior to HF admission	1.00 [0.69-1.43]	0.82 [0.51-1.30]	0.95 [0.82-1.10]	0.83 [0.66-1.05]	0.95 [0.82-1.10]	1.02 [0.88-1.21]
AMI: 1-year prior to HF admission	0.88 [0.70-1.11]	0.90 [0.67-1.21]	0.94 [0.86-1.02]	0.86 [0.74-1.01]	0.94 [0.86-1.02]	0.95 [0.86-1.06]
AMI: 5-year prior to HF admission	**0.78 [0.65-0.94]**	0.87 [0.69-1.09]	**0.93 [0.87-1.00]**	**0.77 [0.67-0.87]**	**0.93 [0.87-1.00]**	1.00 [0.91-1.10]
CVD: 30 days prior to HF admission	0.85 [0.62-1.15]	**0.70 [0.49-0.99]**	0.95 [0.83-1.08]	0.92 [0.75-1.12]	0.95 [0.83-1.08]	0.96 [0.84-1.10]
CVD: 1-year prior to HF admission	**0.75 [0.64-0.88]**	**0.79 [0.65-0.96]**	0.98 [0.92-1.05]	**0.88 [0.78-0.98]**	0.98 [0.92-1.05]	1.00 [0.92-1.07]
CVD: 5-year prior to HF admission	**0.76 [0.67-0.86]**	**0.79 [0.68-0.91]**	0.96 [0.92-1.01]	**0.81 [0.75-0.88]**	0.96 [0.92-1.01]	1.02 [0.96-1.08]
CPD: 30 days prior to HF admission	0.94 [0.63-1.39]	0.65 [0.42-1.00]	1.03 [0.88-1.20]	1.09 [0.83-1.43]	1.03 [0.88-1.20]	1.05 [0.87-1.27]
CPD: 1-year prior to HF admission	**0.72 [0.59-0.90]**	0.80 [0.63-1.01]	1.03 [0.94-1.12]	0.87 [0.76-1.01]	1.03 [0.94-1.12]	1.06 [0.96-1.17]
CPD: 5-year prior to HF admission	**0.71 [0.60-0.88]**	0.88 [0.69-1.14]	1.01 [0.92-1.10]	**0.85 [0.73-0.98]**	1.01 [0.92-1.10]	1.01 [0.91-1.11]

Multivariate Cox Regression model adjusted for age. Results are expressed as hazard ratios with 95% confidence intervals.

Abbreviations: AMI Acute myocardial infarction; CVD Cardiovascular Disease (including AMI, Cerebrovascular Accident, Rheumatic Heart Disease and Peripheral Vascular Disease); CPD Chronic pulmonary disease

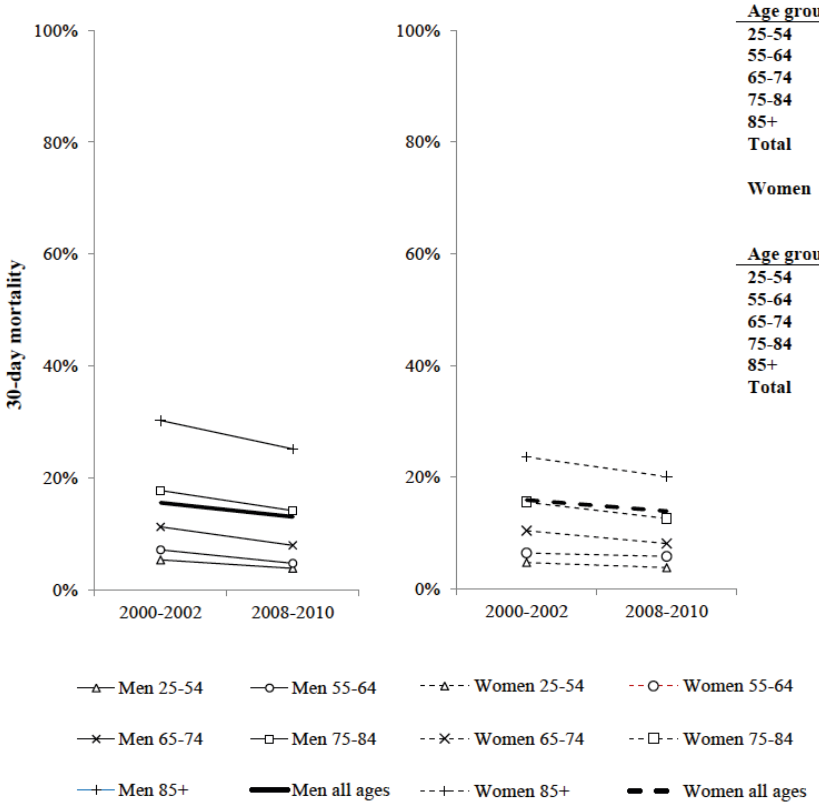
Table 5. Results of validation of International classification of disease codes 428.0, 428.1 and 428.9.

	428.0	428.1	428.9
Correct use of ICD code n, % (95% CI)	45, 87% (77-96%)	40, 80% (69-91%)	38, 76% (64-88%)
Incorrect use of ICD code n, % (95% CI)	1, 2% (0-6%)	3, 6% (0 -13%)	1, 2% (0-6%)
Heart failure is complication during hospital stay n, % (95% CI)	6, 12% (3-21%)	7, 14% (4-24%)	11, 22% (11-33%)
Total (n)	52	50	50

Abbreviations: CI confidence interval, ICD International Classification for Disease

Figure 1. Trends in the 30-day (A), 1-year (B) and 5-year (C) mortality by sex and age

A.



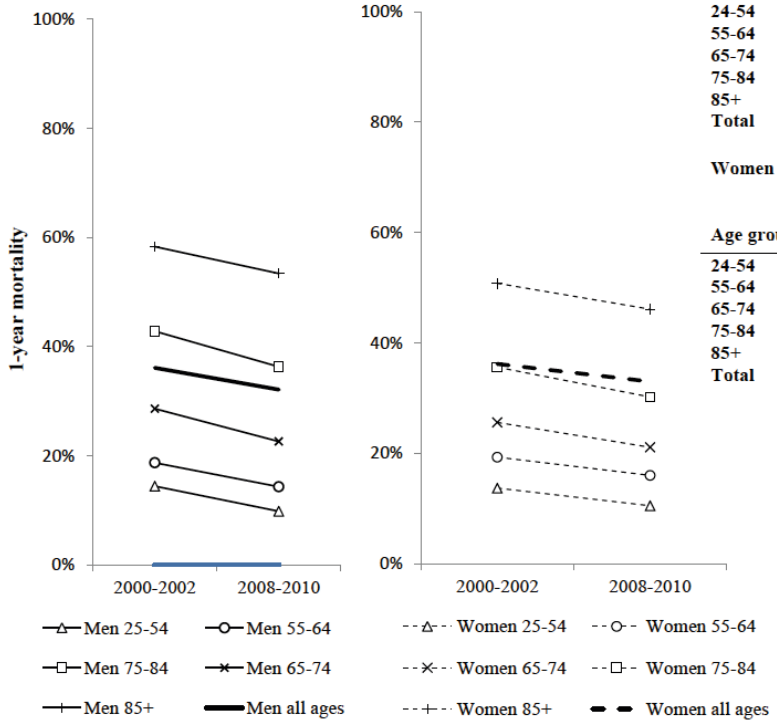
Men

Age group	Cohorts 2000-02	2008-10
25-54	5.4%	3.9%
55-64	7.2%	4.8%
65-74	11.3%	8.0%
75-84	17.8%	14.2%
85+	30.3%	25.2%
Total	15.6%	13.1%

Women

Age group	Cohorts 2000-02	2008-10
25-54	4.7%	3.8%
55-64	6.4%	5.8%
65-74	10.4%	8.1%
75-84	15.5%	12.6%
85+	23.6%	20.1%
Total	15.9%	13.9%

B.



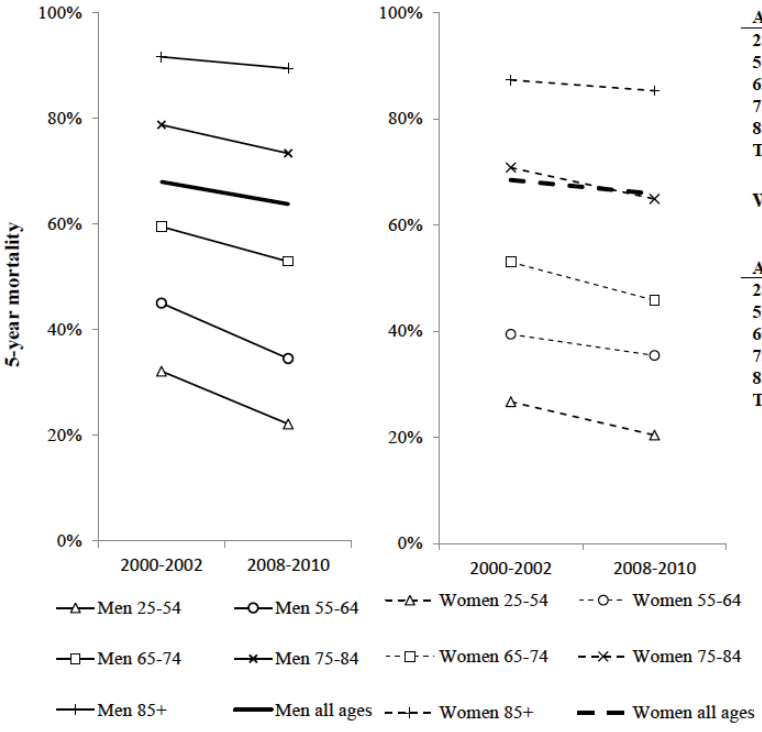
Men

Age group	Cohorts 2000-02	Cohorts 2008-10
24-54	14.4%	9.8%
55-64	18.7%	14.3%
65-74	28.6%	22.6%
75-84	42.8%	36.3%
85+	58.3%	53.4%
Total	36.1%	32.1%

Women

Age group	Cohorts 2000-02	Cohorts 2008-10
24-54	13.7%	10.5%
55-64	19.3%	16.0%
65-74	25.6%	21.1%
75-84	35.6%	30.2%
85+	50.8%	46.1%
Total	36.2%	33.0%

C.



Men

Age group	Cohorts 2000-02	2008-10
25-54	32.1%	22.1%
55-64	45.0%	34.5%
65-74	59.5%	52.9%
75-84	78.8%	73.4%
85+	91.7%	89.5%
Total	68.0%	63.8%

Women

Age group	Cohorts 2000-02	2008-10
25-54	26.7%	20.4%
55-64	39.4%	35.4%
65-74	53.0%	45.8%
75-84	70.8%	64.9%
85+	87.3%	85.3%
Total	68.5%	65.9%

Appendix 1. ICD-codes used in this study.

Hospital admissions were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9).

Heart failure:
428.0, 428.1, 428.9, 402.01, 402.11 and 402.91

Left isolated heart failure:
428.1

Other heart failure:
428.0, 428.9, 402.01, 402.11 and 402.91

Acute myocardial infarction:
410

Chronic pulmonary disease:
490-505, 506.4

Cerebrovascular disease:
430-438

Causes of death were coded according to ICD-10.

Cardiovascular disease:
D18, G45, I00-I99, K55, M30-M31, P29.3, Q20-Q28, R00-R01, R07.1-R07.4, R09.8, R23.0 and R59

Heart failure:
I50

Ischaemic heart diseases:
I20-I25

Acute myocardial infarction:
I21

Cerebrovascular disease:
I60-I69

Cancer:
C00-C97, D00-D48

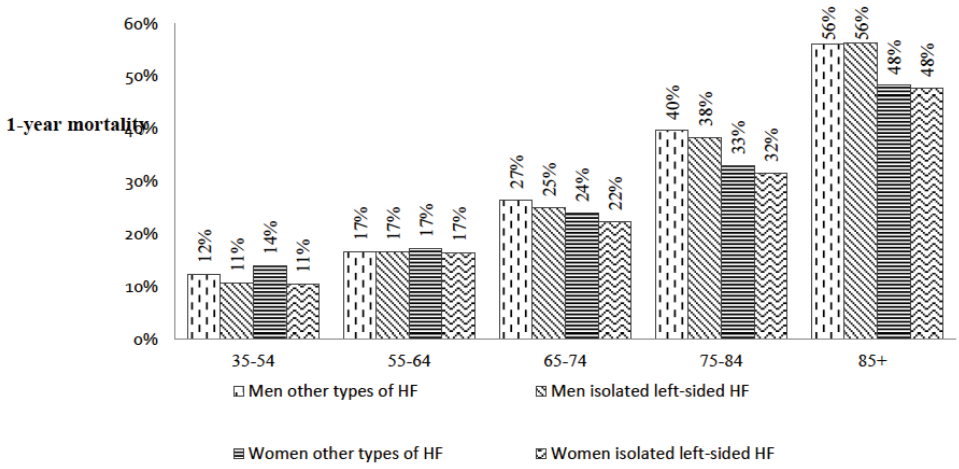
Lung cancer:
C34

Respiratory disease:
J00-J99

Chronic Obstructive Pulmonary Disease (COPD):
J44

Chronic kidney disease / Renal failure:
N17-N19

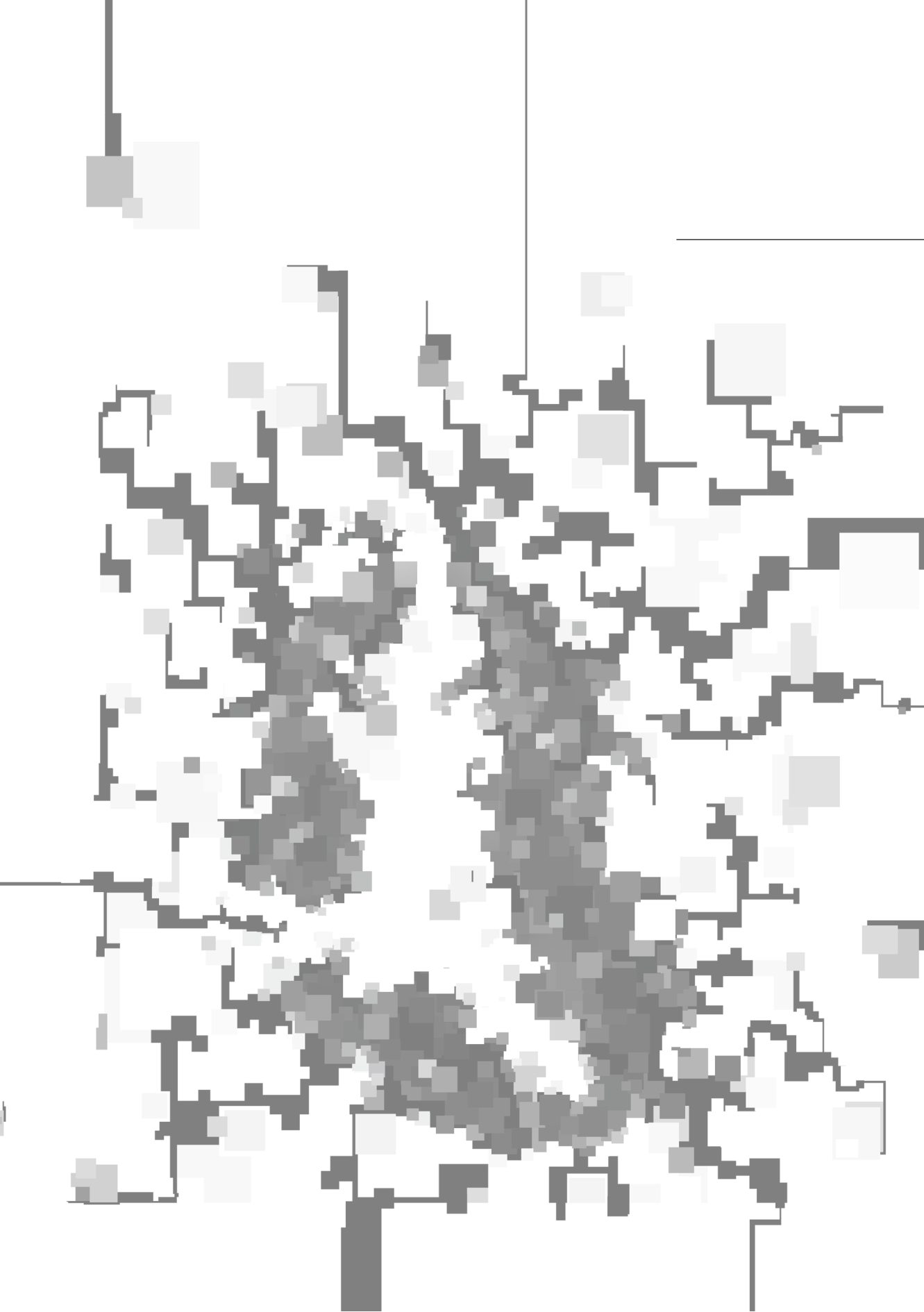
Appendix 2. 1-year mortality by heart failure type, sex and age group



2

PART TWO

Determinants of LVDD



Chapter 3

Discovery of biomarkers for the presence and progression of left ventricular diastolic dysfunction and **HE**art fai**L**ure with **P**reserved ejection **F**raction in patients at risk for cardiovascular disease.
Rationale and design of the HELPFul case-cohort study in a Dutch cardiology outpatient clinic.

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2

ABSTRACT

Introduction
Left ventricular diastolic dysfunction (LVDD) is a common condition in both sexes that may deteriorate into heart failure (HF) with preserved ejection fraction (pEF), although this seems to happen more often in women than in men. Both LVDD and HFpEF often go unrecognized, necessitating the discovery of biomarkers that aid both the identification of individuals with LVDD at risk of developing HF and identification of individuals most likely to benefit from treatment.

Methods and analysis
HELPFul is an ongoing case-cohort study at a Dutch cardiology outpatient clinic enrolling patients aged 45 years and older without history of cardiovascular disease, that were referred by the general practitioner for cardiac evaluation. We included a random sample of patients and enriched the cohort with cases (defined as an E/e'≥ 8 measured with echocardiography). Information about medical history, cardiovascular risk factors, electrocardiography, echocardiography, exercise test performance, common carotid intima-media thickness measurement and standard cardiovascular biomarkers was obtained from the routine care data collected by the cardiology outpatient clinic. Study procedure consists of extensive venous blood collection for biobanking and additional standardized questionnaires. Follow-up will consist of standardized questionnaires by mail and linkage to regional and national registries. We will perform cardiac magnetic resonance (CMR) imaging and coronary computed tomography angiography (CCTA) in a subgroup of patients to investigate the extent of macro- and microvascular coronary disease.

Ethics and dissemination
The study protocol was approved by the Institutional Review Board of the University Medical Center Utrecht. Results will be disseminated through national and international conferences and in peer-reviewed journals in cardiovascular disease.

Strengths and Limitations
- Case-cohort study in novel setting: patients at risk of cardiovascular disease at a Dutch cardiology outpatient clinic positioned between the general practitioner and hospitals.
- Venous blood sampling of multiple types of plasma as well as serum, cells and DNA for biobanking.
- Designed to accommodate the changing definitions of left ventricular diastolic dysfunction (LVDD) and (subtypes of) heart failure (HF).
- Initial results show a high prevalence of hypertension, but low prevalence of chronic inflammatory comorbidities, such as diabetes mellitus and overweight, for a study investigating LVDD and HF.
- No information on reason for referral by the general practitioner.

3

Introduction

Cardiac disease is a leading cause of morbidity and mortality in industrialized societies [1]. There is an urgent need for early detection of structural and functional cardiac abnormalities before coronary events occur or before (heart failure) HF develops. HF has a poor prognosis in both sexes, with data from the Netherlands showing high mortality rates 30 days, one year and five years after first hospital admission for HF (13%, 32% and 64% for men and 14%, 33% and 66% for women, respectively). Mortality rates increased considerably with age, in both men and women, for example one year mortality was 10.5% in women aged 25-54 years and increased to 46.1% in those aged 85 years and older [2]. This is alarming because HF is common among elderly in the general population with a median prevalence rate of 11.8% [2,3]. HF can be divided into two types: HF with preserved ejection fraction (HFpEF) with a left ventricular ejection fraction (LVEF) >50% and HF with reduced ejection fraction (HFrEF) with a LVEF <40% [4]. HF is characterized by insufficient pumping of the heart or close to sufficient at the price of increased left ventricular (LV) filling pressures in rest or during exercise [5]. Generally HFpEF is characterized by increased LV filling pressures that are caused by concentric remodeling and reduced filling, whereas HFrEF is characterized by a lack of contractility and eccentric remodeling [6]. HFpEF is rising in prevalence, but it's precursor left ventricular diastolic dysfunction (LVDD) is even more prevalent and can also eventually lead to HFrEF or HF with mid-range ejection fraction (HFmrEF) with a LVEF 40-49% [7]. Important risk factors for developing LVDD and eventually HFpEF are hypertension, overweight, diabetes mellitus and previous ischaemic heart disease [8]. Within four to five years 12 to 25% of patients with established LVDD progress to symptomatic HFpEF [9–12]. However, there is still a knowledge gap as to who will progress from LVDD to HFpEF (or other types of HF), and which drivers are involved in this deterioration [13].
Interestingly, the prevalence of LVDD is similar in men and women [14,15], but women with LVDD seem prone to more often develop HFpEF, while men more often develop HFrEF [16–20]. This sex difference in progression from LVDD to HFpEF is currently poorly understood and warrants closer attention, especially in the view of early identification of patients at risk for worsening LVDD [21,22]. Sex differences in underlying mechanisms may partially explain the observed difference in HFpEF prevalence. Women more often present with coronary microvascular dysfunction (CMD) [23]. CMD may lead to myocardial stiffening and LV filling problems, both features of LVDD and HFpEF. Men more often present with pronounced coronary macrovascular disease, a hallmark of HFrEF [23].
To expand the current knowledge about LVDD and HFpEF, it is important to better understand this underlying heterogeneity [24]. One promising method to differentiate heterogeneous groups within HFpEF is by detailed 'mapping' of the different phenotypes using both clinical information and biomarkers. Ideally, these biomarkers reflect different pathophysiological processes at the tissue level. Another method may be the application of "omics" studies [25]. Identification of patients prone to progression of LVDD to HFpEF may aid the development of new treatment options for patients with HFpEF. While effective treatment options are available for HFrEF and some show effectiveness in patients with HFmrEF [26,27], these treatments are ineffective for patients with HFpEF [28], although spironolactone might yet prove to be beneficial [29–31]. At the moment only aggressive preventive treatment focused on managing hypertension, overweight, diabetes mellitus and a more active lifestyle seem to be effective in reverting or slowing the progression of LVDD to HFpEF [7].

The aim of the HELPFul study is to discover sex-specific biomarkers for LVDD and HFpEF using several approaches such as multi-marker panels and "omics" studies in combination with extensive additional coronary phenotyping with cardiac magnetic resonance (CMR) imaging and

coronary computed tomography angiography (CCTA) in high risk individuals.

Methods and analysis

Study design

HELPFul is a single center, prospective, case-cohort study conducted at a cardiology outpatient clinic in Utrecht, the Netherlands. All patients aged 45 years and older, without previous cardiac interventions or congenital heart disease, who are referred by the general practitioner (GP) to this outpatient clinic are eligible for inclusion. On three of the four inclusion days, only patients with elevated LV filling pressures, defined as an E/e' ≥ 8.0 are eligible for inclusion. On the fourth day, 25% of all patients attending that day are invited to participate regardless of their echocardiography results (Table 1). The case-cohort design results in a group of 'cases' that have slightly elevated LV filling pressures, of whom a percentage may eventually deteriorate in diastolic function. Part of the patients in the case group may also already have LVDD. The random sample will reflect the distribution of exposure and also serve as a pool for the selection of healthy controls. With a case-cohort design the distribution of LVDD and HFpEF in the source population is accurately reflected in the random sample, while simultaneously creating a pool for the selection of controls [32]. A flow chart of the study design and procedures is presented in supplemental figure S1.

Study population

Participants are enrolled at the Cardiology Center Utrecht (CCU), one of the outpatient clinics of the Cardiology Center Netherlands. Recruitment of participants started 19 September 2016 and will continue until July 2019. CCU covers the area of the city of Utrecht and neighboring cities and towns, and on average receives 10 to 20 newly referred patients per day. The study population comprises adults in the Netherlands aged 45 years and older referred for cardiac evaluation by their GP. Only patients without previous cardiac surgery, a previous cardiac intervention, or congenital heart disease are eligible for inclusion. The following cardiac surgical procedures or interventions are considered exclusion criteria; angioplasty, bypass surgery, heart valve surgery or intervention, implantable cardiac defibrillator and/or cardiac resynchronization therapy, radiofrequency ablation, left ventricular assist device, heart transplantation and pacemaker. Patients referred for pre-operative screening or by other specialists than the GP, such as insurance physicians or company physicians, are also excluded from participation.

Rationale for study setting

The CCU cardiology outpatient clinic is positioned between the GP and the hospital and is intended for quick referral and fast diagnostics to serve the GP, which results in a population at this center with fewer symptoms and lower cardiovascular disease risk than the population often seen in a similar setting at the hospital. Within this population we expect large variety in diastolic function, ranging from normal diastolic function to definite LVDD and HFpEF. HFpEF is a syndrome that often presents with intermittent complaints of dyspnea and/or other less typical symptoms, which can be difficult to detect, especially in elderly patients in the community. GPs are usually the first clinicians that see these patients with unexplained symptoms. Due to the efficient workflow of the cardiac outpatient clinic it is possible to perform this diagnostic work-up for 10-20 new patients each day. There is no waiting list and patients can often be seen within days, even if their complaints are not urgent. This makes referral to this cardiac outpatient clinic a fast and convenient option for the GP. Due to this unique setting the source population of the HELPFul

study is different from patients that are referred to the hospital. It therefore provides a unique opportunity to study risk factors and biomarker levels in patients that have not developed LVDD or HFpEF yet, or are still in the early stages of LVDD or HFpEF.

Study endpoints
The primary endpoint is a diagnosis of LVDD or HFpEF. The primary endpoint is adjudicated by a panel of three experts based on all available diagnostic information and the current recommendations from the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure [5,33–36]. The expert panel will comprise two of four available cardiologists (MC, AT, RM, LS) and a GP specialized in HF (FR). Adjudicating the endpoint by an expert panel is considered the preferred method as a sufficiently reliable reference standard for HFpEF is lacking [37]. If the diagnostic criteria for LVDD or HFpEF change over time we will incorporate these new criteria in the classification of LVDD or HFpEF in the HELPFul study population.
Secondary endpoints are (i) hospitalization for HF, (ii) a composite end-point of cardiovascular death (due to myocardial infarction, stroke, HF, peripheral arterial disease, and sudden death of unspecified cause) and (iii) all-cause mortality.

Definition of LVDD/HFpEF
HFpEF is initially defined according to recommendations of the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (Table 2). Participants with (i) symptoms or signs typical of HF and/or brain natriuretic peptide (BNP) > 35 pg/mL, (ii) in combination with an LVEF > 50%, and (iii) objective echocardiographic evidence of LVDD will be classified as having HFpEF [5]. The presence of these criteria but with an LVEF between 40-49% or an LVEF < 40% will result in participants being classified as having HFmrEF and HFrEF, respectively (Table 2). LVDD is defined as E/e' ratio > 13 or E/e' between 8 and 13 with other structural abnormalities, such as left atrial volume index (LAVi) > 34 ml/m2, or left ventricular mass index (LVMi) > 95 g/m2 for women and > 115 g/m2 for men and/or functional abnormalities, such as e' lateral < 10 m/s or e' septal < 7 m/s or tricuspid regurgitation (TR) velocity > 2.8 m/s [5].

Standard care measurements at enrolment
Standard care measurements consist of history taking, physical examination, electrocardiography (ECG) (Welch Allyn Cardioperfect Pro recorder), laboratory blood measurements (Roche Reflotron Sprint system), an exercise test on a watt bike (Lode Corival Eccentric) with simultaneous blood pressure measurements (Medtronic BL-6 Compact) and ECG recordings (Welch Allyn Cardioperfect recorder), and transthoracic echocardiography (with a General Electric Vivid E6 or E7 cardiovascular echocardiography device). In addition, co-morbidities and current medication use will be registered. Physical examination includes measuring height and weight, blood pressure (two readings at least on a Microlife WatchBP), pulse rate, and calculation of the respiratory rate. A standard 12-lead ECG (Welch Allyn Cardioperfect Pro recorder) will be recorded in supine position and interpreted by a cardiologist. The standard laboratory test returns plasma and serum levels of potassium, glucose, hemoglobin, creatinine, total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides.

Echocardiography
Comprehensive transthoracic echocardiographic examinations were performed by trained sonographers and interpreted by a cardiologist in accordance with the European Association of Cardiovascular Imaging 2016 recommendations for chamber quantification [38]. The LVEF was assessed quantitatively (Teichholz), or semi-quantitatively (eye-balling). Multiple diastolic

parameters were measured, including pulsed-wave Doppler of the mitral and pulmonary venous inflow and tissue Doppler imaging of the mitral annulus motion. The ratio of peak early (E) diastolic filling velocity to peak atrial (A) contraction filling velocity was calculated to derive the E/A ratio. The early diastolic mitral annular recoil velocity (e') was determined at both the septal and lateral wall. The E/e' ratio was calculated by dividing E with the average of septal and lateral e'. LAVi was derived from tracing the left atrium during maximal atrial filling in the apical two chamber and apical four chamber views and subsequently indexing by body surface area (BSA). LVMi was calculated according to the formula validated by Devereux and subsequently indexed by BSA [39]. The sonographers assessed TR in the parasternal right-ventricular (RV) inflow, parasternal short-axis and apical 4-chamber views. A minimum of five sequential complexes were recorded. The peak velocity of the TR signal was measured with continuous-wave Doppler and the systolic pulmonary artery pressure was calculated with the modified Bernoulli's equation [40].

Cardiologist consult
The standard care protocol is for the CCU cardiologist to perform an assessment of all information that is collected during diagnostic work-up. The cardiologist may wish to extend beyond the standard diagnostic work-up procedure when there is a medical indication to do so. Additional information on symptoms may be collected, or the cardiologist may perform additional physical examinations in accordance with the appropriate guidelines [5]. All data collected during the standard care pathway is recorded in the electronic health database of CCU and will be extracted for HELPFul patients. Aside from the data collected during diagnostic work-up, the electronic health database of CCU may contain information on follow-up visits and on results of procedures performed at other locations than CCU.

Specific HELPFul measurements
Eligible patients are invited to participate in the HELPFul study by their CCU cardiologist at the end of the visit. After obtaining informed consent, a study physician or a trained research nurse takes a detailed questionnaire of the patient at the baseline visit. Data was collected on symptoms (including questions adapted from the Minnesota Living with Heart Failure questionnaire, New York Heart Association classification and Medical Research Council dyspnea scale), cardiovascular risk factors, general and cardiovascular medical history, family history for cardiovascular events (positive if a first degree relative had a cardiovascular event at age 65 years or younger), pregnancy history and menopausal status, and medication use.

Study specific blood sampling
Approximately 70 mL of venous blood is collected at baseline immediately after obtaining informed consent. After ultracentrifugation, serum, ethylenediaminetetraacetic acid (EDTA), citrate and sodium-heparin plasma are aliquoted and frozen at -80 C. Peripheral blood mononuclear cells (PBMCs) are isolated from EDTA blood and stored in a CoolCell freezing container to ensure freezing at a standardized controlled rate of -1 C/minute cell in a -80 C freezer. Whole blood EDTA aliquots are frozen at -80 C for the purpose of storing genetic subgroups that can be used for biomarker discovery studies.

HELPFul study follow-up
All participants will be followed up for occurrence of any cardiac event (fatal and non-fatal myocardial infarction, proven unstable angina, coronary revascularization, hospitalization for heart failure, stroke, peripheral arterial disease, sudden death of unspecified cause and death

from any cause) by means of

1. linkage with regional (Julius GPs Network)[41] and national registries (National Hospital Discharge Registry and Statistics Netherlands (i.e. National Causes of Death Registry))[42].
2. questionnaires sent through e-mail or letter 2 years after enrolment in HELPFul, after which a yearly questionnaire will be sent. The \ questionnaires will enquire after status of symptoms of cardiovascular disease and specifically of heart failure and hospitalization for cardiac disease.

Case-control selection within the case-cohort

For the case-cohort, we consider cases to be patients with echocardiographic-defined E/e'≥8. Cohort refers to the total population sample (which could also include patients with E/e'≥8). In this way we create a case-cohort design. For a nested diagnostic case-control study, we take samples from this case-cohort study in which the cases are patients with HFpEF, and controls (no HFpEF) are sampled from the cohort. For the power calculations, we use the 'Harrell's rule of thumb' applicable to diagnostic research. For the aforementioned calculation, we speculate that around 15% of the patients will be diagnosed with HFpEF; the true cases for the nested case-control design. Thus we can evaluate one diagnostic predictor in multivariable logistic regression analysis per 10 HFpEF cases. As we aim to analyse at least 15 determinants/biomarkers, we therefore would need at least 150 patients with HFpEF. Hence we require the inclusion of around 1000 patients in total.

Statistical analyses

Descriptive data will be presented as frequencies with proportions for categorical variables and either as means with corresponding standard deviations or medians with corresponding interquartile range for continuous variables depending on the distribution. We will use the appropriate statistical tests for differences at baseline, such as Pearson Chi-square for frequencies, Mann-Whitney for non-normally distributed continuous variables and student's t-test for normally distributed variables. In case of possible interaction of sex, interaction terms will be created for sex and for each variable of interest. The interaction terms will then be tested for significance using logistic regression models.

Logistic regression will be used to analyze the association of various determinants with LVDD and HFpEF status at baseline. Survival analyses will be used to evaluate the relationship between baseline determinants and the primary and secondary study outcomes. All models will be adjusted for suspected confounders. All data analyses will be performed using appropriate statistics software.

Data analysis prediction algorithm

We will develop a prediction model using state of the art methodology as described in the TRIPOD statement [43]. Missing data will be imputed to minimize bias and loss of precision. The choice of imputation technique will depend on the extent and type of missing data. The linearity assumption will be tested using restricted cubic splines and transformations will be applied where necessary. A backstep model will be used to eliminate redundant predictors, using the likelihood ratio test with a p-value of 0.157 (equal to Akaike's Information Criterion for predictors with one degree of freedom). Eliminating redundant predictors reduces the risk of overfitting the prediction model and makes the model easier to use.

The discrimination and calibration of both models will be compared between the overall and final (reduced) prediction model to evaluate their performance. Discrimination is defined as the ability of the model to distinguish between patients that have LVDD and/or HFpEF from those that do not

have the outcome and is quantified with the area under the curve (AUC) of a receiver operating characteristic plot. Calibration refers to the agreement between the predicted absolute risks of HFpEF being present and the observed HFpEF frequencies. This is expressed by comparing the observed incidence of HFpEF per predicted risk category.
Prediction models are known for overestimated regression coefficients, which result in too extreme (optimistic) predictions when applied in new patients. Therefore, we will (internally) validate our model with bootstrapping techniques where in each bootstrap sample the entire modeling process (including the variable selection process) is repeated. The regression coefficients of the final model are then adjusted for overfitting by multiplying it with the estimated shrinkage factor, yielded from the bootstrap. The bootstrap procedure is also used to correct the AUC for overfitting, which can be considered as an estimate of discriminative ability that is expected in future patients. These analyses will be performed using the appropriate R version.

Discussion
The HELPFul study is currently recruiting men and women at a cardiology outpatient clinic with the double aim of studying LVDD and HFpEF and providing sufficient power for sex-stratified biomarker research. We expect the prevalence of LVDD and HFpEF in the HELPFul study to be similar to the prevalence in other studies that screened patients at the GP practice [3,35,44,45]. Biomarkers panels derived from discoveries made in the HELPFul study may help to direct screening both at the GP practice and (outpatient) cardiology clinics.
To the best of our knowledge, the evidence on (prediction of) LVDD deterioration is rather limited. While information is available on risk factors for and biomarkers associated with development of HFpEF [10,11,46], the few studies investigating the development of LVDD did not include biomarkers [11,12,47]. These studies have shown that diastolic function deteriorates in around 25% of patients with LVDD over the course of five years [11,12] and that LVDD is an independent risk factor for development of HF [11,47]. Preventing the development of LVDD in this population is therefore highly relevant, because it may prevent many new cases of HF as well. However, current international guidelines on HF do not provide any recommendations on early detection of LVDD and subsequent prevention of HFpEF. As a consequence, current treatment is focused on reduction of symptoms and management of risk factors in patients with LVDD who have already progressed to HFpEF. However, it is generally acknowledged that (drug) interventions could be more effective in the very early phases of HFpEF or LVDD underscoring the relevance of early biomarkers and mechanistic insight [7].
One of the aims of the HELPFul study is to fill this knowledge gap by focusing on biomarkers that may aid the prediction of LVDD deterioration. We will use follow-up echocardiography measurements to investigate drivers associated with progression of LVDD and development of HFpEF in the participants of the HELPFul study. In addition, linkage to nationwide hospitalization registers and death registers will enable the assessment of the clinical consequences of LVDD and HFpEF.
To investigate the possible connection between microvascular disease and LVDD and HFpEF, the prevalence of (non-) obstructive CAD and CMD will be assessed using CMR and CCTA imaging. A meta-analysis of international variations in angina prevalence across 31 countries showed a slightly higher prevalence of angina in women with a pooled sex ratio of 1.20 [48]. Other studies have suggested that this could be driven by CMD instead of obstructive CAD of the epicardial vessels [49,50]. Furthermore, in a cohort of women with chest pain suspected for obstructive CAD, those who were hospitalized for HF at 6 year follow-up suffered predominantly from HFpEF [51].

The HELPFul study is designed to accommodate changes in the definitions of LVDD and HFpEF, HFrEF and HFmrEF, which have occurred frequently over the past 10 years. At the moment

multiple guidelines for HF [5,52] provide different criteria and cut-offs for LVDD and HFpEF [53,54]. This has resulted in varying recommendations over the last decades, which hampers the comparison of diagnostic studies of LVDD and HFpEF [17].

Limitations

1. The cases as defined in the study design are not necessarily patients with LVDD or HFpEF by current diagnostic criteria, but were selected for having slightly elevated LV filling pressures on echocardiography. As explained in the discussion, there is a knowledge gap on which patients with a possible early form of LVDD will eventually progress towards actual LVDD. Therefore we consider sampling these patients to investigate biomarker levels and risk factors involved in progression to LVDD of high value. However we are sampling relatively many participants with no definitive diagnosis of LVDD or HFpEF by current diagnostic criteria. However this will predominantly lead to a lower efficiency for selection of patients with LVDD or HFpEF, whereas it does provide the opportunity to efficiently study patients most at risk of eventually developing LVDD or HFpEF.
2. Initial analyses indicate that the HELPFul study population has a high prevalence of hypertension, but a low prevalence of chronic inflammatory comorbidities that are associated with LVDD and HFpEF, such as diabetes mellitus and overweight. Furthermore chest pain is a common complaint, hinting toward the importance of possible CMD in this study population. The external validity could be affected when the generalizability to the population at risk of developing LVDD or HFpEF in the community is lower. However hypertension and CMD are known to be important in the development of LVDD and HFpEF. Therefore we consider the HELPFul study population to be representative of, for instance, community based elderly individuals of 65 years and older. Even so prudence is appropriate when generalizing results to community based or hospital based patients with LVDD or HFpEF, particularly in the context of chronic inflammatory comorbidities.
3. Patients are referred to this center when the GP considers referral to be indicated. However the cardiology outpatient clinic does not record the indication for referral in their electronic patient database. Therefore we have no data on the indication for referral. As mentioned previously patients that are referred often do not have acute/severe complaints of cardiac problems. This could lead to referral bias, which is a form of selection bias usually affecting the comparison of cases and controls and generalizability of the results. Due to our study design we do not expect referral bias to be a problem, because cases and participants of the random sample are selected from the same source population. Furthermore, if future results are generalized within the context of the study we do not see a problem with external validity.

In conclusion, HELPFul is an ongoing study recruiting men and women at a cardiology outpatient clinic with the aim of studying LVDD and HFpEF, that offers unique opportunities for well powered biomarker research in a sex-stratified manner.

Ethics and dissemination

The study protocol is approved by the Institutional Review Board of the University Medical Center Utrecht. The study is conducted according to the principles of the Declaration of Helsinki October 2013 and in accordance with the Medical Research Involving Human Subjects Act. The study does not interfere with routine patient care, and all patients will be treated at the discretion of their cardiologist or GP according to the appropriate guidelines. Participants have given informed consent for extra venous blood collection and storage, and for additional questionnaires. We will present our findings at national and international conferences and in peer-reviewed journals in cardiovascular disease.

Patient and public involvement
No patients were involved in the design of the study. A Dutch patient group, the 'Hart- en Vaatgroep', has been involved in the 'Queen of Hearts' consortium, which funded the HELPFul study. This patient group is involved in knowledge dissemination to the public. A patient information evening for participants of the HELPFul study was organized in 2018, where some of the first results were presented and a forum for questions and discussion was held. At the moment we are organizing a focus group consisting of and for patients that wish to be more involved in knowledge dissemination for the HELPFul study.

Author contributions
G.B. Valstar: acquisition of data, analysis and interpretation of data, drafting and revising the manuscript. S.H. Bots: acquisition of data, revising the manuscript. F. Groepenhoff: addition of imaging to HELPFul study, acquisition of data, revising the manuscript. A. Gohar: acquisition of data, revising the manuscript. F.H. Rutten: conception and study design, interpretation of data, participation in expert panel, drafting and revising the manuscript. T. Leiner: addition of imaging to HELPFul study, revising the manuscript. M.J. Cramer: interpretation of data, participation in expert panel, revising the manuscript. A.J. Teske: participation in expert panel, revising the manuscript. L.P. Suciadi: participation in expert panel, quality control of raw echocardiography data, revising the manuscript. R. Menken: addition of imaging to HELPFul study, participation in expert panel, revising the manuscript. G. Pasterkamp: conception and study design, revising the manuscript. F.W. Asselbergs: conception and study design, interpretation of data, revising the manuscript. L. Hofstra: conception and study design, revising the manuscript. M.L. Bots: conception and study design, analysis and interpretation of data, drafting and revising the manuscript. H.M. Ruijter: conception and study design, analysis and interpretation of data, addition of imaging to HELPFul study, drafting and revising the manuscript. All authors have read and given final approval of the submitted manuscript.

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Competing interests
The authors have no competing interests to declare.

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Data safety and monitoring board
An independent Data and Safety Monitoring Board (DSMB) was not installed.

Table 1. Inclusion and exclusion criteria for the HELPFul study

Inclusion: a patient must meet criteria 1, 2 and either 3 or 4
1. Age ≥ 45 years 2. Written informed consent 3. E/e' ≥8.0 (selectively for those included as a case) 4. Consultation on a random sample day
Exclusion: a patient cannot be included in case of any of the criteria below
1. Any past cardiac intervention 2. Congenital heart disease

Table 2. Definition of subtypes of heart failure*

Type of HF		HFrEF	HFmREF	HFpEF
Criteria	1	Symptoms and/or Signs[a]	Symptoms and/or Signs[a]	Symptoms and/or Signs[a]
	2	LVEF < 40%	LVEF 40-49%	LVEF ≥ 50%
	3	-	1. Elevated levels of BNP[b] 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LA enlargement), b. Diastolic dysfunction	1. Elevated levels of BNP[b] 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LA enlargement), b. Diastolic dysfunction

BNP = B-type natriuretic peptide; HF = heart failure, HFrEF = heart failure with reduced ejection fraction; HFmREF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; LA = left atrial ; LVH = left ventricular hypertrophy.

*Adapted from 2016 ESC guidelines for acute and chronic heart failure[5].

[a]Signs may not be present in early stage of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP > 35pg/mL

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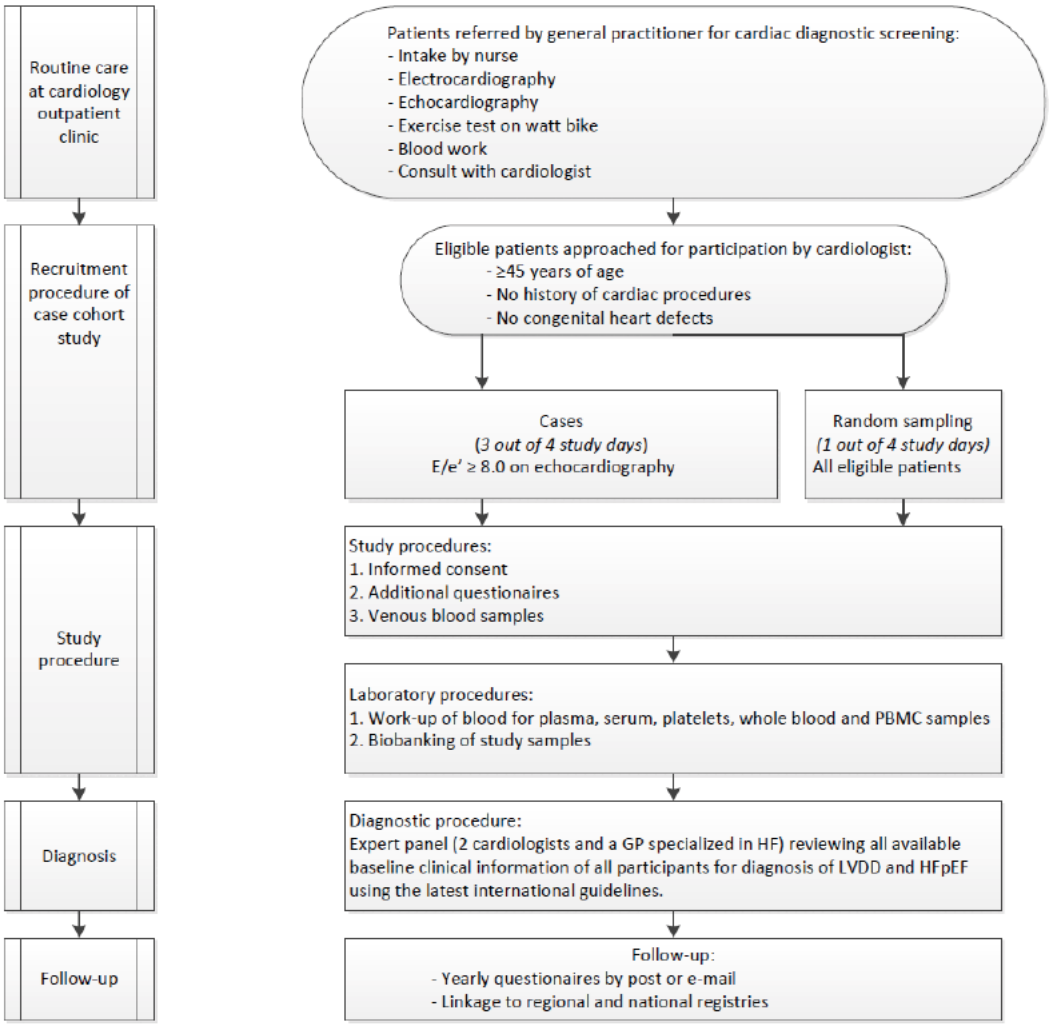
Supplemental figure S1. Flowchart of HELPFul study



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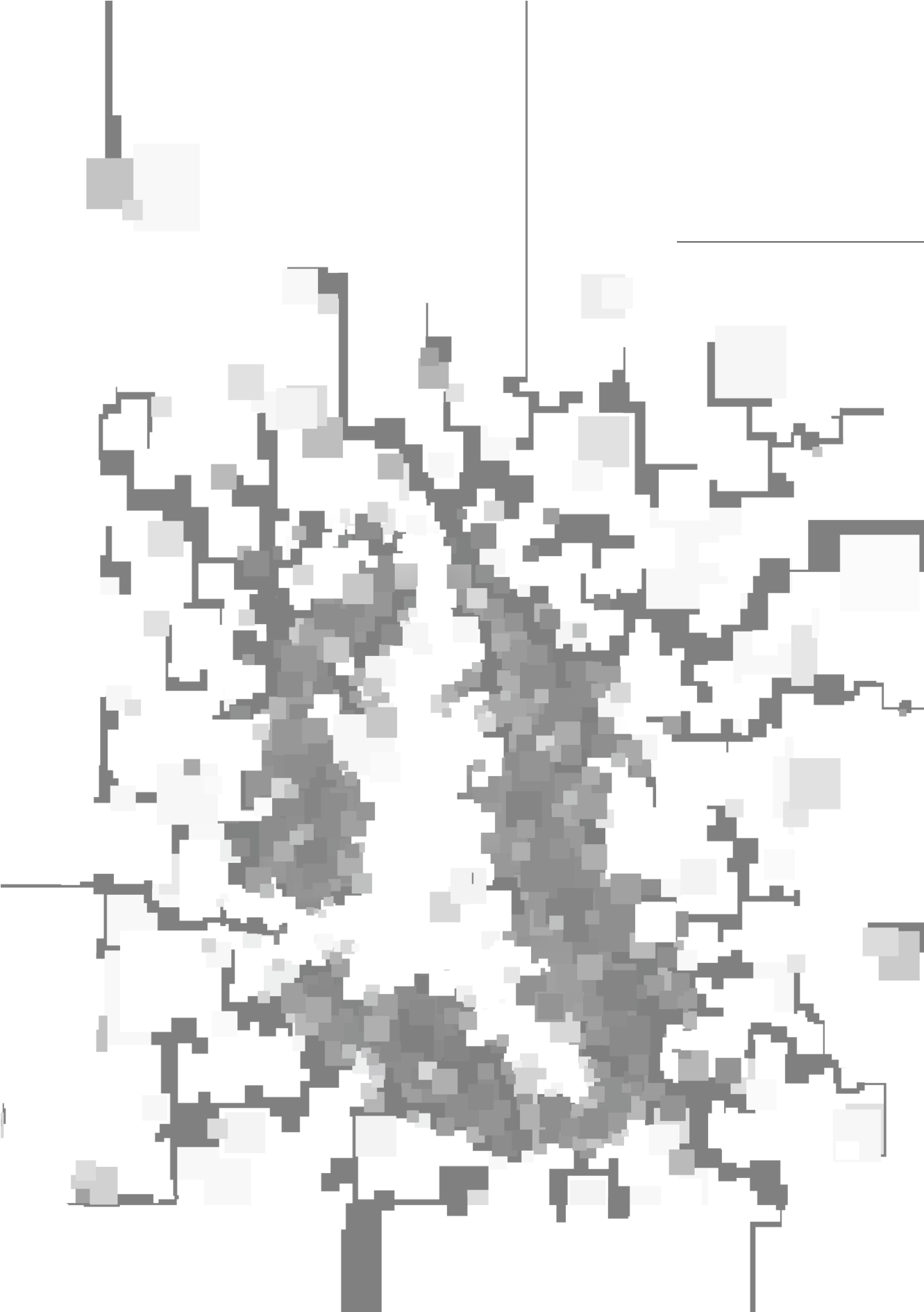

Chapter 4

The relation between renal dysfunction and left ventricular diastolic dysfunction in men and women is driven by age.

Submitted

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2

ABSTRACT

Introduction
Renal disease is often concomitant with heart failure with preserved ejection fraction (HFpEF), but the relation with left ventricular diastolic dysfunction (LVDD) is uncertain. We assessed the association between renal dysfunction and LVDD in men and women referred to an outpatient cardiology clinic by the general practitioner (GP).

Methods
We measured creatinine and cystatin-c in a case-cohort study of patients referred to a specialized outpatient cardiology clinic by their GP for a diagnostic cardiac assessment. Routine cardiovascular work-up consisted of history taking, physical examination, electrocardiography (ECG), exercise-ECG, blood tests and trans thoracic echocardiography.
The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration formula based on either creatinine (eGFRscr), or both creatinine and cystatin-C (eGFRcys). An expert panel consisting of 2 cardiologists and an experienced GP decided on LVDD based on all diagnostic variables and with guidance of current guidelines. We performed multivariable logistic regression analyses to assess the relation between renal parameters and LVDD.

Results
Of the 601 patients (mean age 63.1 (SD 9.4) years, 66% women), 216 (36%) had LVDD. Renal dysfunction (eGFRcys<60 mL/min/1.73m2) was more common among patients with LVDD than in those without LVDD (11% vs. 5%,), with lower median eGFRscr (84.0 vs. 91.0 mL/min/1.73m2) and eGFRcys (77.2 vs. 86.3 mL/min/1.73m2). Renal dysfunction was univariably associated with LVDD (Odds Ratio (OR) 2.07 [95% Confidence Interval (CI) 1.15-3.83]), but not after correction for age (OR 1.11, [95% CI 0.57-2.16]). The association was not different between men and women.

Conclusion
The association between renal dysfunction and LVDD seems to be driven by age, and no longer existed among men and women after correction for age.

4

Introduction

In patients with heart failure with preserved ejection fraction (HFpEF) impaired renal function is common (1–3) and a risk factor for mortality (4,5), at any level of renal dysfunction (6,7). Current treatment options for HFpEF are limited (8), and therefore prevention of HFpEF is important. Left ventricular diastolic dysfunction (LVDD) can progress to HFpEF (9–12), but also to HF with reduced or mid-range ejection fraction (HFrEF and HFmrEF) (13). LVDD is thus an important target for early intervention. Previous studies reported a positive relation between renal dysfunction and single echocardiographic parameters of diastolic function (14,15), and renal dysfunction has been related to worsening of LVDD in some studies, but not in others (9–12,16).

There is still an ongoing debate about how best to establish LVDD with the result that international HF guidelines recommend different combinations of echocardiographic parameters and cut-points for diagnosing LVDD and HFpEF (17). This hampers comparability of studies of drivers of LVDD and HFpEF and results in large differences in prevalence estimates of LVDD and HFpEF possibly involved (18,19). In the absence of an internationally accepted reference standard ('gold standard') for LVDD and HFpEF, diagnosis by an expert panel based on consensus is an acceptable alternative (20,21). However, diagnosis by consensus should be based on (i) the assessment of all available diagnostic information including B-type natriuretic peptide levels (BNP) and echocardiography, and (ii) guided by available guidelines recommendations for the diagnosis.

Previous studies have mostly used estimated glomerular filtration ratio (eGFR) calculated from serum creatinine levels with the Modification of Diet in Renal Disease (MDRD) formula as a measure of renal function. However the MDRD formula is a suboptimal reflection of renal function compared to eGFR calculated with the Chronic Kidney Disease Epidemiology (CKD-EPI) formula (22). Inker et al. in addition showed that the precision of the CKD-EPI formula could be further improved by adding blood levels of cystatin-C (23). However studies reporting the eGFR, that incorporates cystatin-c, in patients with LVDD are limited (15).

We aimed to assess the relation of markers of renal function, including creatinine, cystatin-C, and eGFR, with LVDD in men and women to clarify whether early signs of renal dysfunction are related with the structural and/or functional cardiac abnormalities that define LVDD. We therefore investigated patients referred to an outpatient cardiology clinic for a diagnostic cardiac assessment for the relation of renal function with LVDD.

Methods

Study population

Study design and procedures of the "Discovery of biomarkers for the presence and progression of left ventricular diastolic dysfunction and HEart faiLure with Preserved ejection Fraction in patients at risk for cardiovascular disease" (HELPFul) study have been published in more detail (24). Briefly, HELPFul is a Dutch case cohort in which patients participated, who were referred by their GP to a outpatient cardiology clinic for a diagnostic cardiac assessment. Patients who had a previous cardiac intervention, or who were known with congenital cardiac disease were excluded from participation. Patients that had a ratio of the peak early (E) diastolic filling velocity and early

diastolic mitral annular velocity (e') (average of septal and lateral) (E/e') ≥ 8 with tissue Doppler echocardiography were considered as 'a case', because these patients were considered to have a higher probability of having LVDD. 'Cohort' patients were randomly sampled from all patients aged 45 years or older, striving to include 25% of eligible participants. For the current analyses we used data of participants included until June 20th 2018.
The HELPFul study adheres to the principles of the declaration of Helsinki.The institutional review board of the University Medical Center Utrecht approved the study (reference number: NTR6016). Written informed consent was obtained from all participants.

Clinical variables
Information on co morbidities, medical history, and medication use was collected. The diagnostic assessment further consisted of physical examination, blood testing of standard cardiovascular biomarkers, electrocardiogram (ECG), bycicle exercise ECG, and transthoracic echocardiogram. A structured case record form was used to assess symptoms suggestive of cardiac pathology. Hypertension was determined by (I) patient self report, or (II) prescription of blood pressure lowering medication, or (III) a mean (of at least two) systolic blood pressure measurements > 140mmHg. Type 2 diabetes was determined by (I) patient self
report, or (II) prescription of blood glucose lowering medication. Hypercholesterolemia by (I) patient self report or (II) prescription of lipid lowering medication. Atrial fibrillation was determined by (I) patient self report or (II) documented history with atrial fibrillation, or (III) atrial fibrillation on the 12 lead electrocardiography. Body weight and height were measured and body mass index (BMI) was calculated by dividing weight (kg) by height squared in meters (m2). Waist/hip ratio was calculated from the waist circumference measured around the belly button in centimeters (cm) divided by hip circumference, which was measured around both greater trochanters (cm).

Echocardiographic parameters
Comprehensive transthoracic echocardiographic examinations were performed with a General Electric (GE) Vivid E6 or E7 device (GE Healthcare, United Kingdom) by trained sonographers and interpreted by an experienced cardiologist in accordance with the European Association of Cardiovascular Imaging 2016 recommendations for chamber quantification (25). The left ventricular ejection fraction (LVEF) was assessed quantitatively (Teichholz), or semi-quantitatively (eye-balling). Diastolic parameters that were measured included pulsed-wave Doppler of the mitral valve inflow velocities and pulmonary venous inflow and tissue Doppler imaging of the mitral annulus motion. The ratio of peak early (E) diastolic filling velocity to peak atrial (A) contraction filling velocity was calculated to derive the E/A ratio. The early diastolic mitral annular velocity (e') was determined at both the septal and lateral wall. The E/e' ratio was calculated by dividing E with the average of septal and lateral e'. Left atrial volume index (LAVi) was derived from tracing the left atrium during maximal atrial filling in the apical two and four chamber views and indexing by body surface area (BSA). Left ventricular mass index (LVMi) was calculated with the Devereux formula and subsequently indexed by BSA (26). The sonographers assessed tricuspid regurgitation (TR) in the parasternal right-ventricular (RV) inflow, parasternal short-axis and apical 4-chamber views. A minimum of five sequential complexes were recorded. The peak velocity of the TR signal was measured with continuous-wave Doppler and used for calculating the systolic pulmonary artery pressure (SPAP) with the modified Bernoulli's equation (27).

Left ventricular diastolic dysfunction
We applied consensus diagnosis for LVDD with an expert panel consisting of cardiologists (RM, MJC, AT) and a general practitioner specialized in heart failure (FR). This method is comparable to previous studies of our group (28,29). The expert panel used all available diagnostic information,

including patient reported symptoms, risk factors, electrocardiography, echocardiography, results from the exercise test, (cardiovascular) medication use and plasma B type natriuretic (BNP) levels. The panel based the diagnosis of LVDD on available diastolic function criteria and recommended cut points of recent international guidelines (17,30,31). The panel categorized patients into four groups; no LVDD, possible LVDD, probable LVDD, and definite LVDD. For the purpose of this study, we combined probable LVDD with definite LVDD into 'LVDD', and no LVDD and possible LVDD into 'no LVDD'.

Blood sampling procedures and renal parameters
Serum and plasma were obtained at baseline through venous blood sampling. Creatinine was measured in serum and cystatin-C, BNP and high-sensitivity troponin-I (hs-TnI) in plasma using the appropriate assay on the ARCHITECT i2000 analyzer (Abbott Park, Chicago, Illinois, USA). We calculated eGFR with the CKD-EPI formula both from creatinine alone (eGFRscr) and from creatinine and cystatin-c combined (eGFRcys) (22,23). Renal dysfunction was defined as an eGFR < 60 mL/min per 1.73m2 for both estimates of GFR (i.e. eGFRscr and eGFRcys).

Data analyses
Continuous variables are presented as mean ± standard deviation (SD), or median with interquartile range (IQR) if not normally distributed, and categorical variables as absolute numbers and percentages. Testing for significant differences in baseline characteristics between patients with and without renal dysfunction was performed with multivariable logistic regression models with each baseline variable and adjustment for age and sex. We applied univariable and multivariable logistic regression analyses to assess the association between renal parameters (determinant) and LVDD (outcome). The following clinical determinants were selected for multivariable adjustment in logistic regression models, based on their reported relation with LVDD in the literature: hypertension, atrial fibrillation, smoking, BMI and waist to hip ratio, C-Reactive Protein (CRP) and lipids (cholesterol, triglycerides, high density lipoprotein and low density lipid). The odds ratios (with 95% CI) from the regression models reflect the probability of the outcome (LVDD) per one unit increase in the determinant, e.g. creatinine level. We tested whether the association between LVDD and renal parameters differed by sex by using an interaction term, and by adjustment for sex of each investigated renal parameter in the logistic regression models. Finally we tested the association between renal dysfunction (determinant) and LVDD (outcome) with univariable and multivariable logistic regression analyses, with adjustment for age. All tests were two-sided and p-values <0.05 were considered statistically significant. Data analysis was performed using SPSS version 25 (SPSS INC., Chicago, IL, USA).

Results

The baseline clinical and echocardiographic characteristics of the study population stratified by LVDD are shown in Table 1. The mean age of the population was 63.1 (standard deviation (SD) 9.4) years, and 66% were women.
Patients with LVDD were older than patients without LVDD (66.4 vs. 61.2 years, p<0.001). The percentage of men and women was similar in those with LVDD and without LVDD. The prevalence of hypertension (p=0.001), diabetes (p=0.02) and the reporting of fatigue (p=0.035) were significantly different between patients with LVDD and no LVDD, after adjustment for age and sex. Renal dysfunction (eGFRcys<60 mL/min/1.73m2) was uncommon in the study population (n=45, 7%), but present more often in patients with LVDD than in those without LVDD (11% vs. 5%,

p=0.75). When renal dysfunction was based on eGFRscr <60 mL/min/1.73 m2 the difference was small (5% vs. 3%, respectively, p=0.48).

Differences between patients with renal dysfunction and normal renal function
Baseline differences in demographic and clinical variables stratified by renal dysfunction are presented in Table 2. Patients with renal dysfunction were significantly older than patients without renal dysfunction (73.2 vs. 62.3 years, p<0.001). Patients with renal dysfunction also significantly more often had ankle edema (32% vs. 17%, p=0.026) and were less often smokers (7% vs. 11%, p=0.046).

Associations between renal markers and LVDD
In Table 3 we show the univariable and multivariable relation of renal parameters with LVDD. The crude odds ratios (OR) after univariable analysis showed that higher cystatin-C (crude OR=3.17, [95% Confidence Interval (CI) 1.36-7.37]) and lower levels of eGFRscr (crude OR=0.98, [95% CI 0.97-0.99]) and eGFRcys (OR=0.98, [95% CI 0.97-0.99]) were significantly related to LVDD, but serum creatinine (crude odds ratio (OR)=1.002, [95% CI 0.99-1.01]) was not. After adjustment for age and other variables, the ORs attenuated and none of the relations between renal parameters and LVDD remained significant. Interaction terms of sex and renal parameters with LVDD showed no significant interactions. In all multivariable analyses, age had the strongest effect on the relation between renal parameters and LVDD.
Renal dysfunction (eGFRcys<60 mL/min/1.73m2) was significantly related to LVDD (crude OR 2.07, [95% CI 1.15-3.83], p=0.02), however, again not after adjustment for age (adjusted OR 1.11, [95% CI 0.57-2.16], p=0.76).

Discussion

Renal dysfunction (eGFRcys<60 mL/min/1.73m2) was present slightly more often in patients with LVDD than without LVDD, and the association between renal (dys)function and LVDD was driven by older mean age of those with LVDD. This finding was similar for men and women and independent of the parameter used to evaluate renal function. Our results in patients referred to a outpatient cardiology clinic do not confirm some previous studies suggesting that renal dysfunction is related to LVDD, which is an important precursor of HF with preserved ejection fraction.
There are previous studies that reported an attenuated association between renal function and LVDD after multivariable analyses that included (at least) age. In patients with coronary artery disease recruited from several outpatient clinics in the San Francisco Bay Area, the crude OR of eGFR <62 mL/min/1.73m2(with MDRD) for LVDD was 3.1 [95% CI 1.9–4.8]. However after adjustment for age, sex, race/ethnicity, tobacco use; history of myocardial infarction, coronary bypass, or diabetes mellitus; systolic blood pressure, anemia, low-density lipoprotein cholesterol, and CRP, the relation was no longer independent; adjusted OR 1.4 [95% CI 0.79-2.4] (14). In a completely different domain, that is patients known with chronic renal dysfunction, a multivariable adjusted relation of renal dysfunction (CKD-EPI) with LVDD was only observed in patients with an eGFR between 45-59 mL/min per 1.73 m2 (OR of 1.4 [95% CI 1.10-1.80]), after adjustment age, sex, race, site, hypertension, diabetes, LDL, high cholesterol, serum albumin, and BMI. In the same study however after multivariable adjustment for the above mentioned factors no significant association was found between eGFR of 30-44 ml/min/1.73m2 or < 30 ml/min/1.73m2.
We found that renal dysfunction (eGFRcys<60ml/min/m2) is present in 11% of patients with LVDD (5% with eGFRscr<60ml/min/1.73m2), which is similar to the observed prevalence of

renal dysfunction in an opportunistic screening study of 581 Dutch patients with type 2 diabetes 60 years and over (eGFR with MDRD 6.8%, with mean age 72 years) (34) and to the prevalence of 5.7-6.4% in a screening study investigating preclinical and clinical heart failure in an elderly Italian population cohort (35). In addition we observed that using the CKD-EPI formula and adding cystatin-c to estimate eGFR leads to a 6% absolute increase in observed presence of renal dysfunction in patients with LVDD.
HFpEF is defined by the presence of symptoms suggestive of HF, e.g. shortness of breath, fatigue and ankle oedema (31). Interestingly, cross-sectional studies among patients with HFpEF show a clear relation between renal dysfunction and HFpEF (4,35). In populations with HFpEF, renal dysfunction is more common than in populations with LVDD (3,4), and has mainly been shown to be an important prognostic factor for developing HF in general (9) and HFpEF (3,13), as well as for mortality in patients with HFpEF (4). Our results show no relation between renal dysfunction and LVDD when adjusted for age. This is at first glance counter-intuitive given the role of LVDD in defining HFpEF. However, we have to realize not all patients with LVDD develop HFpEF (9–12,16). Furthermore some of those with some degree of LVDD may recover, or may remain stable over many years (9–12,16). Second, other studies have similarly shown no or inconsistent associations between LVDD and renal function when investigated in patients that have not developed HFpEF, and after multivariable adjustment for age and other relevant factors (14,15). Lastly, the strong relation between older age and renal dysfunction is well known and also seen in the general population (36). Therefore renal dysfunction might not be an important factor in LVDD, but renal dysfunction might be an important contributing factor in development of HFpEF and prognosis of HFpEF.
Given that renal dysfunction is not related to LVDD, but seems to be a major comorbidity among patients with HFpEF (LVDD plus symptoms suggestive of HF and an EF ≥ 50%) suggests that HFpEF seems to induce kidney function (the kidney follows the heart) than the other way around (the heart follows the kidney). A phenomenon well known in HFrEF, and related to (periods of) insufficient filtration pressure in the kidneys. Thus, the heart seems to be dominant in the cardio-renal interaction in HF, without a clear interaction in an important precursor of HF, namely LVDD. However, longitudinal studies are needed to better unravel the relation between renal function and LVDD and the development of HF, notably HFpEF.

Limitations
We report the relation of renal function with consensus based diagnosis of LVDD. The observed relation between renal function and LVDD might be different when diagnosis of LVDD is based on a different definition. Furthermore our findings will not be directly comparable to other studies investigating renal function, but using a different definition for LVDD.

Conclusion

The association between renal dysfunction and LVDD seems to be driven by age, and no longer existed among men and women after correction for age.

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Conflict of interest: The authors have no competing interests to declare.

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Table 1. Baseline characteristics of 601 participants seen at the cardiology outpatient center divided into those with LVDD and no LVDD .

	No LVDD (n=385)	*LVDD (n=216)*	*All (n=601)*
Mean age in years (SD)	61.2 (9.1)	66.4 (9.1)	63.1 (9.4)
Women (%)	254 (66%)	144 (67%)	398 (66%)
Mean BMI in kg/m^2 (SD)	26.8 (4.2)	27.1 (9.9)	26.9 (6.8)
Mean Waist/hip ratio (SD)	0.91 (0.08)	0.93 (0.09)	0.92 (0.08)
Hypertension (%)	202 (52%)	151 (70%)	353 (59%)
Hypercholesterolaemia (%)	146 (38%)	93 (43%)	239 (40%)
History of diabetes (%)	23 (6%)	27 (13%)	50 (8%)
History of atrial fibrillation (%)	11 (3%)	9 (4%)	20 (3%)
Current smokers (%)	42 (11%)	22 (10%)	64 (11%)
History of CVD (%)	22 (6%)	27 (13%)	49 (8%)
Family history of CVD (%)	214 (65%)	130 (67%)	344 (66%)
Shortness of breath (%)	175 (45%)	118 (55%)	293 (49%)
Chest pain (%)	230 (60%)	122 (56%)	352 (59%)
Reduced exercise tolerance (%)	124 (32%)	83 (38%)	207 (34%)
Fatigue (%)	139 (36%)	87 (40%)	226 (38%)
Ankle oedema (%)	59 (15%)	48 (22%)	107 (18%)
Median E/e' ratio (IQR) [a]	8.6 (7.5-9.7)	10.8 (9.4-14.0)	9.1 (8.1-10.5)
Median septal e' cm/sec (IQR) [a]	7.0 (6.0-9.0)	6.0 (5.0-7.0)	7.0 (6.0-8.0)
Median lateral e' cm/sec (IQR) [a]	9.0 (8.0-11.0)	7.0 (6.0-9.0)	8.0 (7.0-10.0)
Median LAVi in cm^2/m^2 (IQR) [a]	22.0 (18.2-26.8)	33.7 (27.8-41.5)	24.1 (19.5-30.7)
Mean LVMi in g/m^2 (SD) [a]	71.3 (15.8)	85.3 (22.1)	76.3 (19.5)
Median relative wall thickness (IQR) [a]	0.40 (0.36-0.46)	0.45 (0.40-0.53)	0.42 (0.37-0.48)
Mean LV ejection fraction (SD) [a]	68.0 (8.0)	66.8 (9.3)	67.6 (8.5)
Median creatinine in µmol/L (IQR)	66.3 (60.1-76.2)	67.3 (60.9-78.0)	66.4 (60.3-75.6)
Median eGFRscr (mL/min/1.73m^2) (IQR)	91.0 (82.2-96.9)	84.0 (77.3-92.4)	89.9 (81.2-96.3)
Renal dysfunction (eGFRscr<60 mL/min/1.73m^2) (%)	13 (3%)	11 (5%)	24 (4%)
Median cystatin-c in mg/L (IQR)	0.94 (0.83-1.04)	1.01 (0.90-1.16)	0.95 (0.84-1.06)
Median eGFRcys (mL/min/1.73m^2) (IQR)	86.3 (76.0-96.7)	77.2(66.6-87.3)	84.5 (74.6-94.8)
Renal dysfunction (eGFRcys<60 mL/min/1.73m^2) (%)	21 (5%)	23 (11%)	44 (7%)
Median hs-TnI pg/mL (IQR)	2.3 (1.6-3.7)	4.6 (2.6-9.2)	2.6 (1.8-4.4)
Median BNP in pg/mL (IQR) [a]	15.5 (10.0-26.7)	45.9 (19.6-83.2)	19.2 (10.0-37.0)

BMI= body mass index; BNP = Brain-type natriuretic peptide; CVD=cardiovascular disease; cys= cystatin-c; eGFR=estimated glomerular filtration rate; hs-TnI = high sensitivity Troponin-I; IQR=interquartile range; LAVI=left atrial volume index; LVDD=left ventricular diastolic dysfunction; LVMi=left ventricular mass index; TR velocity=tricuspid regurgitation velocity; scr = serum creatinine; SD =standard deviation.

[a] Diastolic function parameter used by the expert panel for categorization of LVDD.

Table 2. Baseline characteristics of the 601 participants stratified by renal dysfunction (eGFRcys<60mL/min/1.73m2) and no renal dysfunction (≥ 60mL/min/1.73m2).

	Renal dysfunction (n=44)	*No renal dysfunction (n=557)*	*P-value#*
Mean age in years (SD)	73.2 (9.2)	62.3 (8.9)	<0.001
Women (%)	29 (66%)	369 (66%)	0.51
Mean BMI in kg/m^2 (SD)	25.0 (20.0)	27.1 (4.3)	0.38
Mean waist/hip ratio (SD)	0.93 (0.09)	0.92 (0.08)	0.89
Hypertension (%)	33 (75%)	320 (57%)	0.16
Hypercholesterolaemia (%)	16 (36%)	223 (40%)	0.14
History of diabetes (%)	7 (16%)	43 (8%)	0.11
History of atrial fibrillation (%)	4 (9%)	16 (3%)	0.11
Current smokers (%)	3 (7%)	61 (11%)	0.046
History of CVD (%)	5 (11%)	44 (8%)	0.39
Family history of CVD (%)	27 (69%)	317 (66%)	0.33
Shortness of breath (%)	26 (59%)	267 (48%)	0.32
Chest pain (%)	21 (48%)	331 (59%)	0.31
Reduced exercise tolerance (%)	14 (32%)	193 (35%)	0.15
Fatigue (%)	16 (36%)	210 (38%)	0.21
Ankle oedema (%)	14 (32%)	93 (17%)	0.026
Median E/e' ratio (IQR)	10.0 (8.5-13.6)	9.0 (8.0-10.3)	0.24
Median septal e' m/sec (IQR)	6.0 (5.0-7.0)	7.0 (6.0-8.0)	0.68
Median lateral e' m/sec (IQR)	7.0 (5.8-10.0)	8.0 (7.0-10.0)	0.79
Median LAVi in cm^2/m^2 (IQR)	26.4 (20.0-33.4)	24.0 (19.4-30.5)	0.36
Mean LVMi in g/m^2 (SD)	86.0 (23.5)	75.5 (18.9)	0.12
Median relative wall thickness (IQR)	0.43 (0.39-0.49)	0.42 (0.36-0.47)	0.29
Mean LV ejection fraction (SD)	66.5 (12.0)	68.0 (8.2)	0.24
LV diastolic dysfunction (%)	23 (52%)	193 (35%)	0.66
Median eGFRcys (mL/min per 1.73m^2) (IQR)	53.8 (44.3-57.4)	86.3 (76.5-95.5)	[a]
Median eGFRscr (mL/min per 1.73m^2) (IQR)	57.4 (50.0-68.4)	90.9 (83.3-96.7)	[a]
Median creatinine in umol/L (IQR)	94.1 (79.0-105.4)	65.6 (59.9-73.3)	[a]
Median cystatin-c in mg/L (IQR)	1.38 (1.27-1.51)	0.93 (0.83-1.03)	[a]
Median hs-TnI pg/mL (IQR)	5.1 (3.1-7.9)	2.5 (1.7-4.1)	0.31
Median BNP in pg/mL (IQR)	36.8 (12.8-82.0)	17.9 (10.0-35.4)	0.054

BMI= body mass index; BNP = Brain-type natriuretic peptide; CVD=cardiovascular disease; cys= cystatin-c; eGFR=estimated glomerular filtration rate; hs-TnI = high sensitivity Troponin-I; IQR=interquartile range; LAVI=left atrial volume index; LV = left ventricular; LVMi=left ventricular mass index; TR velocity=tricuspid regurgitation velocity; scr = serum Creatinine; SD =standard deviation.

[a] No p-value calculated for variable, because these variables were used for classifying renal dysfunction.

P-value is a two sided p value based on a multivariable logistic regression model with adjustments for age and sex. See for definition the methods paragraph.

Table 3: The relation between renal parameters and LVDD from logistic regression analyses.

Outcome LVDD vs. no LVDD Crude and after adjustment	OR[a] (95% CI)
Creatinine per umol/L	1.002 (0.99 ; 1.01)
+ age	0.99 (0.98 ; 1.01)
+ sex	1.003 (0.99 ; 1.02)
+ age & sex	0.99 (0.98 ; 1.01)
+ age & sex & hypertension	0.99 (0.98 ; 1.01)
+ age & sex & diabetes	0.99 (0.98 ; 1.01)
+ age & sex & atrial fibrillation	0.99 (0.98 ; 1.01)
+ age & sex & smoking	0.99 (0.98 ; 1.01)
+ age & sex & BMI & waist/hip ratio	0.99 (0.98 ; 1.01)
+ age & sex & CRP & lipids	0.99 (0.98 ; 1.01)
Cystatin-c per mg/L	3.17 (1.36 ; 7.37)
+ age	1.09 (0.43 ; 2.78)
+ sex	3.32 (1.41 ; 7.79)
+ age & sex	1.14 (0.44 ; 2.93)
+ age & sex & hypertension	0.97 (0.37 ; 2.52)
+ age & sex & diabetes	1.06 (0.41 ; 2.73)
+ age & sex & atrial fibrillation	1.12 (0.43 ; 2.89)
+ age & sex & smoking	1.12 (0.43 ; 2.89)
+ age & sex & BMI & waist/hip ratio	0.97 (0.36 ; 2.59)
+ age & sex & CRP & lipids	1.17 (0.43 ; 3.15)
eGFRscr per mL/min/1.73m^2	0.98 (0.97 ; 0.99)
+ age	1.006 (0.99 ; 1.02)
+ sex	0.98 (0.97 ; 0.99)
+ age & sex	1.006 (0.99 ; 1.02)
+ age & sex & hypertension	1.008 (0.99 ; 1.03)
+ age & sex & diabetes	1.008 (0.99 ; 1.02)
+ age & sex & atrial fibrillation	1.006 (0.99 ; 1.02)
+ age & sex & smoking	1.006 (0.99 ; 1.02)
+ age & sex & BMI & waist/hip ratio	1.006 (0.99 ; 1.02)
+ age & sex & CRP & lipids	1.004 (0.99 ; 1.02)
eGFRcys per mL/min/1.73m^2	0.98 (0.97 ; 0.99)
+ age	1.001 (0.99 ; 1.01)
+ sex	0.98 (0.97 ; 0.99)
+ age & sex	1.001 (0.99 ; 1.01)
+ age & sex & hypertension	1.003 (0.99 ; 1.02)
+ age & sex & diabetes	1.002 (0.99 ; 1.02)
+ age & sex & atrial fibrillation	1.001 (0.99 ; 1.01)
+ age & sex & smoking	1.001 (0.99 ; 1.01)
+ age & sex & BMI & waist/hip ratio	1.002 (0.99 ; 1.02)
+ age & sex & CRP & lipids	0.99 (0.99 ; 1.01)

BMI = body mass index; CRP = c-reactive protein; cys= cystatin-c; eGFR=estimated glomerular filtration rate; scr = serum Creatinine; 95% CI = 95% confidence interval.
a Beta reflects the difference in the outcome, e.g. Creatinine, between the intermediate group or the LVDD and the reference group (no LVDD). Further details on definitions and the applied statistical procedures are provided in the methods paragraph.

Supplemental table 1. Sex stratified baseline characteristics of patients with LVDD and no LVDD.

	Men			***Women***		
	No LVDD n=131)	LVDD (n=72)	All (n=203)	No LVDD (n=254)	LVDD (n=144)	All (n=398)
Mean age in years (SD)	61.6 (10.1)	67.3 (9.3)	63.6 (10.2)	61.0 (8.5)	66.0 (8.9)	62.8 (9.0)
Mean BMI in kg/m^2 (SD)	26.8 (3.6)	26.3 (15.5)	26.6 (9.6)	26.9 (4.4)	27.4 (5.3)	27.1 (4.8)
Mean Waist/hip ratio (SD)	0.96 (0.07)	0.98 (0.07)	0.97 (0.07)	0.89 (0.07)	0.91 (0.09)	0.90 (0.08)
Hypertension (%)	70 (53%)	50 (69%)	120 (59%)	132 (52%)	101 (70%)	233 (59%)
Hypercholesterolaemia (%)	44 (34%)	31 (43%)	75 (37%)	102 (40%)	62 (43%)	164 (41%)
History of diabetes (%)	11 (8%)	10 (14%)	21 (10%)	12 (5%)	17 (12%)	29 (7%)
History of atrial fibrillation (%)	3 (2%)	6 (8%)	9 (4%)	8 (3%)	3 (2%)	11 (3%)
Current smokers (%)	18 (14%)	6 (8%)	24 (12%)	24 (9%)	16 (11%)	40 (10%)
History of CVD (%)	5 (4%)	10 (14%)	15 (7%)	17 (7%)	17 (12%)	34 (9%)
Family history of CVD (%)	61 (58%)	39 (68%)	100 (61%)	153 (69%)	91 (66%)	244 (68%)
Shortness of breath (%)	45 (34%)	33 (46%)	78 (38%)	130 (51%)	85 (59%)	215 (54%)
Chest pain (%)	75 (57%)	32 (44%)	107 (53%)	155 (61%)	90 (63%)	245 (62%)
Reduced exercise tolerance (%)	34 (26%)	20 (28%)	54 (27%)	90 (35%)	63 (44%)	153 (38%)
Fatigue (%)	37 (28%)	20 (28%)	57 (28%)	102 (40%)	67 (47%)	169 (42%)
Ankle oedema (%)	8 (6%)	15 (21%)	23 (11%)	51 (20%)	33 (23%)	84 (21%)
Median E/e' ratio (IQR) [a]	8.4 (6.6-9.4)	9.8 (8.1-10.8)	8.6 (7.3-10.0)	8.8 (8.0-9.0)	10.5 (9.3-12.9)	9.3 (8.2-10.6)
Median septal e' cm/sec (IQR) [a]	7.0 (6.0-9.0)	6.0 (5.0-7.0)	7.0 (6.0-8.0)	7.0 (6.0-9.0)	6.0 (5.0-7.0)	7.0 (6.0-8.0)
Median lateral e' cm/sec (IQR) [a]	9.0 (8.0-11.0)	7.0 (6.0-9.0)	8.0 (7.0-10.0)	9.0 (8.0-11.0)	7.0 (6.0-8.0)	8.0 (7.0-10.0)
Median LAVi in cm^2/m^2 (IQR) [a]	22.9 (18.3-26.6)	31.0 (24.9-35.5)	24.8 (20.0-30.9)	21.8 (18.1-27.0)	29.3 (22.0-35.7)	24.0 (19.2-30.5)
Mean LVMi in g/m^2 (SD) [a]	71.3 (15.8)	71.3 (15.8)	83.2 (21.8)	68.7 (14.8)	79.7 (18.7)	72.7 (17.1)
Median relative wall thickness (IQR) [a]	0.41 (0.36-0.47)	0.44 (0.41-0.50)	0.42 (0.37-0.48)	0.40 (0.36-0.45)	0.46 (0.39-0.52)	0.42 (0.37-0.48)
Mean ejection fraction (SD) [a]	68.0 (8.0)	68.0 (8.0)	66.8 (9.0)	68.0 (8.1)	67.9 (8.5)	68.0 (8.3)
Median creatinine in µmol/L (IQR)	77.0 (69.4-87.1)	76.8 (66.3-85.9)	77.0 (68.5-86.8)	63.5 (57.9-68.6)	63.8 (58.8-69.3)	63.6 (58.1-68.8)
Median eGFRscr (mL/min/1.73m^2) (IQR)	89.7 (82.4-97.3)	90.9 (79.4-95.5)	90.4 (81.1-96.9)	91.7 (81.9-96.8)	86.6 (77.7-93.3)	89.1 (81.1-95.7)
Renal dysfunction (eGFRscr<60 mL/min/1.73m^2) (%)	4 (3%)	5 (7%)	9 (4%)	9 (4%)	6 (4%)	15 (4%)
Median cystatin-c in mg/L (IQR)	0.99 (0.89-1.08)	1.01 (0.88-1.16)	1.00 (0.89-1.11)	0.91 (0.80-1.03)	0.95 (0.84-1.07)	0.92 (0.81-1.04)
Median eGFRcys (mL/min per 1.73m^2) (IQR)	84.9 (76.7-94.1)	82.5 (71.8-93.3)	83.8(74.6-93.6)	87.3 (75.7-97.9)	81.2 (72.1-90.9)	84.8 (74.6-95.6)
Renal dysfunction (eGFRcys<60 mL/min/1.73m^2) (%)	5 (4%)	10 (14%)	15 (7%)	16 (6%)	13 (9%)	29 (7%)
Median hs-TnI pg/mL (IQR)	3.2 (2.0-5.1)	4.6 (3.1-9.8)	3.7 (2.4-6.0)	2.0 (1.5-3.1)	2.6 (1.9-4.5)	2.3 (1.6-3.5)
Median BNP in pg/mL (IQR) [a]	12.9 (10.0-25.2)	36.3 (11.6-68.1)	16.9 (10.0-37.4)	16.0 (10.0-27.6)	32.4 (15.0-52.9)	19.5 (10.0-37.0)

BMI= body mass index; BNP = Brain-type natriuretic peptide; CVD=cardiovascular disease; cys= cystatin-c; eGFR=estimated glomerular filtration rate; hs-TnI = high sensitivity Troponin-I; IQR=interquartile range; LAVI=left atrial volume index; LVDD=left ventricular diastolic dysfunction; LVMi=left ventricular mass index; TR velocity=tricuspid regurgitation velocity; scr = serum Creatinine; SD =standard deviation.

[a] Diastolic function parameter used by expert panel for categorization of LVDD.

Supplemental table 2. Sex stratified baseline characteristics of groups with vs. without renal dysfunction (eGFRcys < 60 mL/min per 1.73m^2).

	Men		***Women***	
	Renal dysfunction (n=15)	No renal dysfunction (n=188)	Renal dysfunction (n=29)	No renal dysfunction (n=369)
Mean age in years (SD)	73.2 (9.2)	62.7 (9.7)	71.9 (9.8)	62.1 (8.5)
Mean BMI in kg/m^2 (SD)	18.9 (32.9)	27.2 (3.7)	28.1 (6.4)	27.0 (4.6)
Mean Waist/hip ratio (SD)	0.97 (0.07)	0.97 (0.07)	0.90 (0.08)	0.92 (0.09)
Hypertension (%)	8 (53%)	112 (60%)	25 (86%)	208 (56%)
Hypercholesterolaemia (%)	3 (20%)	72 (38%)	13 (45%)	151 (41%)
History of diabetes (%)	4 (27%)	17 (9%)	3 (10%)	26 (7%)
History of atrial fibrillation (%)	4 (27%)	5 (3%)	0 (0%)	11 (3%)
Current smokers (%)	1 (7%)	23 (12%)	2 (7%)	38 (10%)
History of CVD (%)	2 (13%)	13 (7%)	5 (11%)	44 (8%)
Family history of CVD (%)	5 (33%)	95 (62%)	22 (76%)	222 (67%)
Shortness of breath (%)	9 (60%)	69 (37%)	17 (59%)	198 (54%)
Chest pain (%)	6 (40%)	101 (54%)	15 (52%)	230 (62%)
Reduced exercise tolerance (%)	2 (13%)	52 (28%)	12 (41%)	141 (38%)
Fatigue (%)	5 (33%)	52 (28%)	11 (38%)	158 (43%)
Ankle oedema (%)	3 (20%)	20 (11%)	11 (38%)	73 (20%)
Median E/e' ratio (IQR)	9.7 (7.7-12.7)	8.6 (7.1-9.9)	10.1 (8.6-14.0)	9.2 (8.2-10.5)
Median septal e' m/sec (IQR)	6.0 (4.8-7.3)	7.0 (6.0-8.0)	6.0 (4.5-7.5)	7.0 (6.0-8.0)
Median lateral e' m/sec (IQR)	8.0 (4.8-10.3)	8.0 (7.0-10.0)	7.0 (6.0-9.8)	8.0 (7.0-10.0)
Median LAVi in cm^2/m^2 (IQR)	26.4 (20.0-33.7)	24.7 (19.8-30.4)	26.4 (18.9-31.2)	23.8 (19.2-30.6)
Mean LVMi in g/m^2 (SD)	94.7 (25.1)	82.3 (21.3)	86.0 (23.5)	75.5 (18.9)
Median relative wall thickness (IQR)	0.41 (0.39-0.47)	0.42 (0.37-0.48)	0.45 (0.39-0.53)	0.42 (0.37-0.47)
Mean ejection fraction (SD)	58.1 (11.2)	67.5 (8.4)	69.4 (8.9)	67.8 (8.2)
LV diastolic dysfunction (%)	10 (67%)	62 (33%)	13 (45%)	131 (36%)
Median eGFRcys (mL/min per 1.73m^2) (IQR)	54.6 (48.7-58.3)	85.8 (77.5-94.2)	53.4 (44.1-57.4)	86.5 (76.0-97.1)
Median eGFRscr (mL/min per 1.73m^2) (IQR)	56.5 (52.6-69.0)	91.1 (83.6-97.1)	60.3 (48.3-67.8)	90.7 (83.2-96.3)
Median creatinine in umol/L (IQR)	100.6 (93.8-115.7)	76.2 (68.0-84.5)	86.2 (76.1-102.0)	62.7 (57.8-67.2)
Median cystatin-c in mg/L (IQR)	1.42 (1.30-1.52)	0.99 (0.88-1.07)	1.36 (1.27-1.51)	0.91 (0.80-1.02)
Median hs-TnI pg/mL (IQR)	6.2 (5.0-16.1)	3.5 (2.3-5.8)	3.9 (2.6-6.9)	2.2 (1.6-3.3)
Median BNP in pg/mL (IQR)	50.8 (12.0-211.1)	16.3 (10.0-34.5)	31.6 (13.5-76.2)	19.3 (10.0-35.7)

BMI= body mass index; BNP = Brain-type natriuretic peptide; CVD=cardiovascular disease; cys= cystatin-c; eGFR=estimated glomerular filtration rate; hs-TnI = high sensitivity Troponin-I; IQR=interquartile range; LAVI=left atrial volume index; LV = left ventricular; LVMi=left ventricular mass index; TR velocity=tricuspid regurgitation velocity; scr = serum Creatinine; SD =standard deviation.

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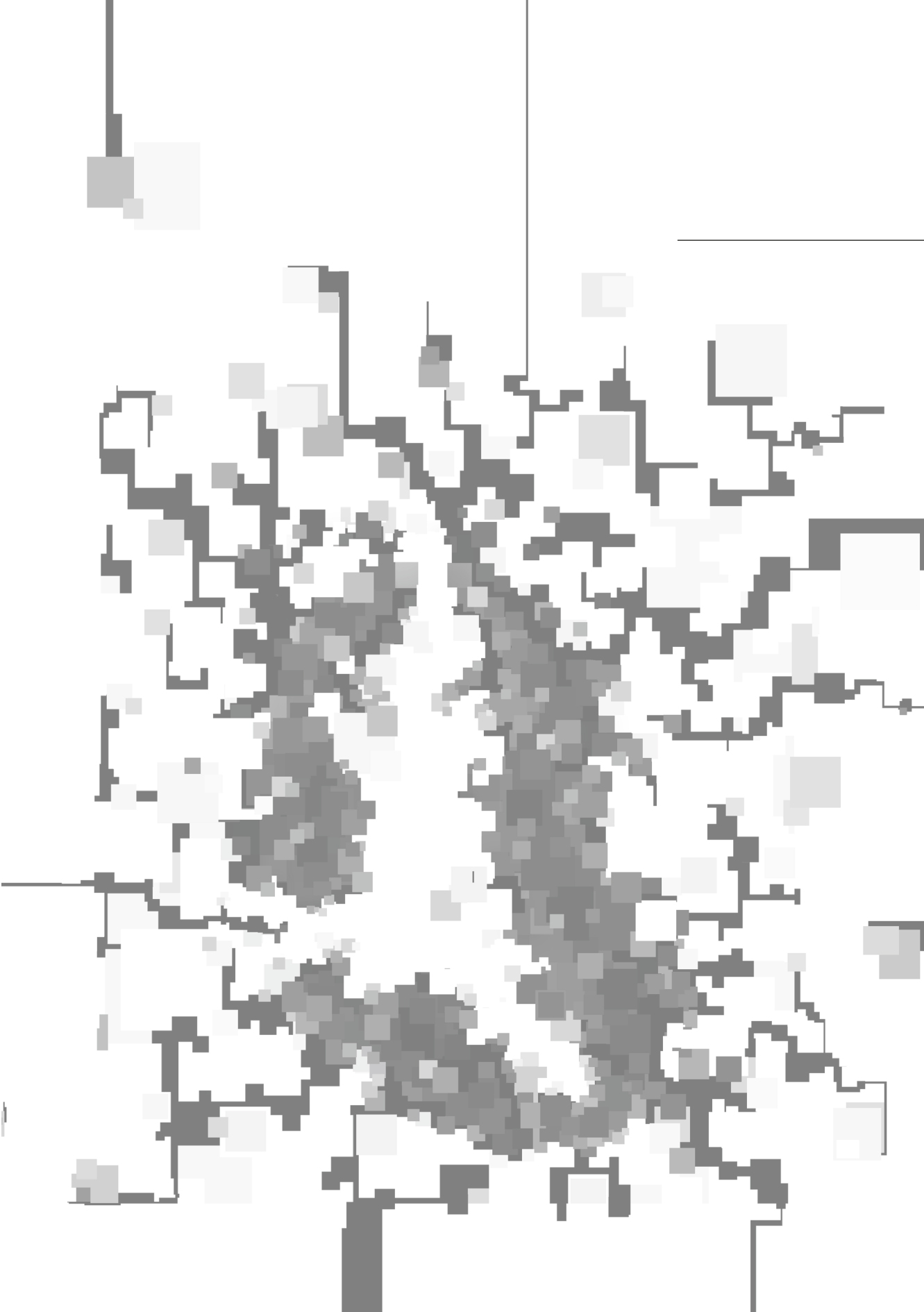

Chapter 5

The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis

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2

ABSTRACT

Aims
Type 2 diabetes (T2D) is a risk factor for the development of left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction (HFpEF). Our aim was to provide a summary estimate of the prevalence of LVDD and HFpEF in T2D patients and investigate sex disparities.

Methods and results
A systematic search of the databases Medline and Embase was conducted for studies reporting the prevalence of LVDD or HFpEF among T2D patients. Studies were only included if echocardiography was performed. Prevalence estimates were pooled using random-effects meta-analysis. Twenty-eight studies were included. Data on the prevalence of LVDD was available in 27 studies. The pooled prevalence for LVDD in the hospital population (2,959 T2D participants) and in the general population (2,813 T2D participants) was 48% (95%CI: 39-58%) and 35% (95%CI: 24-46%), respectively. Heterogeneity was high in both populations, with estimates ranging from 19% to 81% in the hospital population to 28% to 54% in the general population. For women and men the pooled prevalence estimates of LVDD were 47% (95%CI: 37-58%) and 46% (95%CI: 37-55%), respectively. Only two studies presented the prevalence of HFpEF; 8% (95%CI: 5-14%) in a hospital population and 25% (95%CI: 21-28%) in the general population (18% in men (mean age 73.8 SD 8.6) and 28% in women (mean age 74.9 SD 6.9)).

Conclusion
The prevalence of LVDD among T2D patients is similarly high in men and women, while HFpEF seems to be more common in women than men, at least in community people with T2D.

Introduction

Heart failure (HF) and type 2 diabetes are both major public health concerns and impose a considerable burden on the health budget for Western societies. Mortality and hospitalization rates are much higher among individuals with both type 2 diabetes and HF than in individuals suffering from HF alone 1, 2. It is well recognized that type 2 diabetes is a significant risk factor for HF. In the Framingham Heart study it was shown that HF was twice as common among men and five times as common among women with than without diabetes 3.
Until recently, HF was most often categorized into HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) with the single left ventricular cut-point 45%, but currently three categories are used, and cut-points changed; HFrEF (left ventricular EF<40%), HFpEF (EF≥50%), and a grey area in between (EF 40-49%) now categorized as mid-range (HFmrEF) 4. A recent systematic review showed that in the general Western population aged 60 years or over, HFpEF with a prevalence of 4.9% is now more common than HFrEF with a prevalence of 3.3% 5. Longitudinal data from the USA suggest that over the last ten years, the incidence of HFrEF seems to be decreasing, while the incidence of HFpEF is increasing 6, 7. A reduction in myocardial infarction, notably ST-elevation myocardial infarction, over the last decades may be the major cause behind the relative reduction of HFrEF, while the worsening epidemic of overweight and type 2 diabetes affecting western societies may be one of the major explanations behind the increasing trend in HFpEF 8-10. As such type 2 diabetes seems to be more strongly associated with the development of HFpEF than with HFrEF 11, 12. In line with these finding, left ventricular diastolic dysfunction (LVDD), the preclinical stage of HFpEF, is also more prevalent among type 2 diabetes patients than in those without diabetes 13-15. Although type 2 diabetes is a known risk factor of LVDD and HFpEF, the use of echocardiography is in general not considered in existing type 2 diabetes primary care disease management programs. Sex-differences in prevalence of LVDD and HFpEF in patients with type 2 diabetes are generally unclear so far. Although some studies suggest that women more often have LVDD and HFpEF than men, some argue this to be related to an average older age of women 6, 16. A systematic review and meta-analysis could help to clarify whether differences in prevalence of HFpEF or LVDD exist between women and men with type 2 diabetes.
Given the large impact of both type 2 diabetes and HFpEF for patients, but also for the community, it is important to know the exact prevalence of LVDD in patients with type 2 diabetes as this can be helpful to target prevention and intervention strategies for both LVDD and early stages of HFpEF. The prevalence of both HF and LVDD in type 2 diabetes patients has been studied previously 3, 17, 18. However, most of these studies did not distinguish between HFrEF and HFpEF, nor assessed LVDD adequately with echocardiography 17, 19. Moreover, many studies on LVDD were exclusively performed in type 2 diabetes patients managed in secondary care, and thus are not representative of type 2 diabetes patients from the population at large 20, 21. A systematic review of studies on the prevalence of LVDD and/or HFpEF in type 2 diabetes patients is lacking. Therefore, we reviewed the existing literature to estimate the prevalence of LVDD and HFpEF in type 2 diabetes patients in both the hospital setting and in the general population. Furthermore, we examined whether these prevalence estimates differed between men and women.

2

Methods

Data Sources and Searches

A search using the Medline and Embase databases was conducted up to and including May 2016. We used the search terms and synonyms of 'heart failure', 'diastolic ventricular dysfunction', 'systolic ventricular dysfunction', 'diabetes mellitus, type 2', 'prevalence' and 'incidence'. For the exact search strategy, see Supplementary Table 1. Of the studies retrieved for full text assessment, reference lists were screened for other relevant studies.

Study Selection

Only studies published in English were considered. Letters, editorials, case reports, practical guidelines and animal or in vitro studies were excluded. The following predefined inclusion criteria were applied: i) The study reported the prevalence of HFpEF and/or LVDD in patients with type 2 diabetes, ii) The study population was derived from the population at large or from the hospital population, iii) Only studies were included that used echocardiography to establish or confirm the diagnosis of previously undetected HFpEF and/or LVDD, iv) type 2 diabetes defined by one of the following criteria: documentation in medical record, physician's diagnosis, self-reported history, use of anti-diabetic agents and random serum glucose ≥200 mg/dL (or ≥11.1 mmol/L) or serum fasting glucose ≥ 126 mg/dL (or ≥ 7.0 mmol/L).

LVDD was defined as an ejection fraction of ≥ 45% and diastolic abnormalities on echocardiography such as an E/A ratio <0.75 or >1.50, E/e' ratio >13, and LA volume indexed >34 ml/m2. HFpEF was defined as having an ejection fraction of ≥ 45% and clinical symptoms and signs suggestive of HF (i.e. shortness of breath, fatigue, pulmonary congestion and/or peripheral edema), and objective evidence of diastolic dysfunction measured with echocardiography.

If multiple studies were based on the same study population, we selected the study with the largest population for data extraction. Selection of publications and data extraction was done independently by two reviewers (SB and GV). Consensus was used to resolve disagreement. If consensus could not be reached, a third reviewer (FR) was consulted.

Data Extraction and Quality Assessment

A methodological quality assessment of each of the included studies was performed independently by two authors (SB and GV). In case of discrepancies, consensus was reached after discussion between the two assessors. If disagreement remained, a third assessor was asked and the majority of votes counted. As there is no formal checklist available specifically designed to appraise risk of bias in prevalence studies, we based our assessment on the risk of bias tool of Hoy et al 22. This is a new risk of bias tool for prevalence studies based on a modification of an existing tool, and on the approach of the QUADAS-2 (Tool for the Quality Assessment of Diagnostic Accuracy Studies) 23. Signaling questions were used to identify potential problems in the design, conduct and analysis of a study that might introduce bias or raise concerns about the applicability of the findings. The following signaling questions were used:

a) Do the included patients and setting match what is intended by the review question (type 2 diabetes patients from the general population, referral centers, hospital center)?
b) Is the sampling frame a true or close representation of the population intended by the review question?
c) Is an unselected (random/consecutive) sample of patients invited to participate?
d) Is the response rate ≥75% or did a non-response analysis show no

difference between participants and nonparticipants?
e) Is an acceptable case definition for LVDD and/or HFpEF used in the study?
f) Is the instrument to measure LVDD and/or HFpEF valid?
g) Is the same mode of data collection used for all subjects?
h) Is it unlikely that the handling of missing (endpoint) data introduced bias?
i) Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

All signaling questions were scored with either low or high risk of bias. Studies had an overall risk of bias which was classified as low if ≤ 1 question had a risk of bias, a medium risk of bias if 2-3 questions had a high risk bias, or finally a high risk of bias if > 3 questions had a high risk of bias).

Data Synthesis and Analysis

Information on study characteristics was collected with a data extraction form and comprised of first author's name, publication year, source population and setting, age, number of participants, duration of type 2 diabetes, exclusion criteria, echocardiographic measurements used, LVEF threshold used and prevalence estimates of HFpEF and/or LVDD. Prevalence numerators and denominators were extracted from the studies.

Individual study prevalence and corresponding 95% confidence intervals (95% CI) were calculated for all the included studies. To perform meta-analysis, the prevalence data were logit transformed so that the data followed a normal distribution. A random-effects model was used to obtain pooled estimates (with corresponding 95% CI) of the logit transformed prevalence data, as this model takes the between-study heterogeneity into account better than a fixed effects model. Heterogeneity was assessed using the Cochrane Q test and the I2 statistic 24. The pooled prevalence estimate was calculated for all of the included studies, and separately for studies concerning the general population and hospital population. If we could not recalculate prevalence estimates, because of missing information on the number of individuals suffering from LVDD or HFpEF, they were not included in the meta-analysis.
Results of the meta-analysis are presented as Forest plots showing prevalence proportions with corresponding 95% CIs for each study and the overall random-effects pooled estimate. Publication bias was first assessed by visually inspecting the distribution of observed studies on a funnel plot. To quantify the degree of bias illustrated in the funnel plot, the Begg's rank correlation test and Egger's linear regression were used 25, 26. A p-value <0.05 was considered significant. All statistical analyses were performed in R by using the 'metafor' package 27.

Results

Search results and characteristics

In total, our search resulted in 5,410 unique studies. These studies were first screened on title and then on abstract for eligibility. We additionally screened the full text article of 165 studies for more detailed information. The main reasons for exclusion included: no echocardiographic measurements, missing information on type 2 diabetes, HFpEF or diastolic dysfunction or studies had another domain of interest, for instance hypertensive patients with diabetes 28. Finally, 28 studies were included in this review. Details of the selection process are provided in Figure 1.

Study characteristics and quality assessment of all the 28 included studies are shown in Table 1. Of all included studies, the majority of studies included participants derived from a hospital setting (n=18) 13-15, 20, 21, 29-41, six studies recruited their participants from the population at large 18, 42-46 and four studies failed to report where they had selected their participants from 47-50. Data on the prevalence of LVDD was available in 27 studies and data on HFpEF in two studies (Table 1). Data on prevalence numbers was available from 16 different countries; four from Africa, two from Australia, eleven from Europe, four from the USA, and three from Asia (Table 1). Of the 28 studies analyzed, 24 reported the age of their participants, with only 5 studies reporting sex-specific mean age. The mean age ranged from 44±6 years (in an American cohort with an upper age limit of 65) to 71.5±7.5 years of age in a European cohort. Duration of type 2 diabetes was reported in 19 of the 28 studies and ranged from new onset diabetes to a mean duration of more than 18 years. Different parameters were used to assess LVDD and included: the ratio between early (E) and late (A) ventricular filling velocity over the mitral valve (E/A ratio), E-wave deceleration time (DT), isovolumetric relaxation time (IVRT), the ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity (E/e' ratio). See Table 1 for the exact cut-off values of the different parameters and the classification of LVDD used in the included studies. The LVEF cut-point ranged from 45% to 55%, with most studies using 50% (n=15). Most articles had a medium risk of bias (n=19), five had a high risk of bias and four had a low risk of bias. Most studies scored a high risk of bias on item b concerning the sampling frame.

Prevalence of LVDD and HFpEF

Of the 27 studies, three studies did not report the number of individuals diagnosed with LVDD, but only reported prevalence estimates 29, 37, 44. These studies were not included in the meta-analysis, as these prevalence estimates could not be manually verified and 95% confidence intervals could not be reliably calculated. Pooled prevalence estimates for LVDD are presented for all of the included studies (n=24 including a total of 6,061 individuals), and separately for studies including the hospital population (n=15) including 2,959 participants, and the general population (n=5) including 2,813 participants (Figure 2-4). These meta-analyses yielded a summary prevalence of LVDD of 46% (95%CI: 39-54%), 48% (95%CI: 38-59%) and 35% (95%CI: 24-46%), respectively. Estimates ranged from 23% to 54% in the general population and from 19% to 81% in the hospital population (Figure 3 and 4) and there was a high level of study heterogeneity (hospital population: Q=326.87, p<0.001, I2=96.3%, general population: Q=104.58, p<0.001, I2=96.7%). The pooled prevalence estimate of the four studies with an unknown setting was 55% (95%CI: 46-63%). Two funnel plots were constructed: one for the general population studies and one for the hospital population studies (Supplementary Figure S1 and S2). Although visual inspection revealed slight asymmetry, both Begg's test (p= 0.48 and p= 0.56, respectively) and Egger's test (p=0.39 and p=0.30, respectively) showed no potential risk of publication bias. Sex-specific data was available in 12 studies (including 3,609 individuals), and separately for studies including the hospital population (n=3) including 2,570 participants, and the general population (n=7) including 1,039 participants. For two studies the settings were unknown. One study had only information about the prevalence in men. Sex specific pooled prevalence estimates of LVDD revealed a prevalence of 47% (95%CI:37-58%) for women and 46% (95%CI:37-55%) for men (Figure 5 and 6) and there was a high level of heterogeneity (men: Q=224.87, p<0.001, I2=91.5%, women: Q=128.89, p<0.001, I2=92.5%), with prevalence estimates ranges from 24%-78% in women and 19%-63% in men. Only 5 studies reported sex-specific mean ages with differences between men and women of 1-3 years. This did not explain differences in sex-specific prevalence in those studies.

The prevalence of HFpEF was only available in two studies including a total of 765 individuals, one from the general population and one from the hospital population, and were therefore not

pooled. The prevalence of HFpEF found in the general population (605 individuals with type 2 diabetes) was 25% (95%CI: 21-28%) and 8% (95%CI: 5-14%) in the hospital population (160 individuals with type 2 diabetes) 18, 41. The general population study by Boonman-de Winter et al was the only study presenting also sex-specific prevalence of (previously undetected) HFpEF: 18% in men (mean age 73.8 SD 8.6 years) and 28% in women (mean age 74.9 SD 6.9 years) 18.

Discussion

Our review is the first to provide pooled estimates of the prevalence of LVDD among type 2 diabetes patients and demonstrates that LVDD is an important problem among men and women with type 2 diabetes, affecting on average 35% (95%CI: 24-46%) of type 2 diabetes patients in the community and 48% (95%CI: 38-59%) of type 2 diabetes patients in the hospital population. This review, however, demonstrates a wide variation in prevalence of LVDD among type 2 diabetes patients and therefore the pooled prevalence estimates need to be interpreted with caution. Only two studies provided prevalence estimates of HFpEF among type 2 diabetes patients; among 605 type 2 diabetes patients from the general population, aged 60 years or over, the prevalence of HFpEF was 24.8% (95%CI: 21-28%), and in a hospital population among 160 type 2 diabetes patients the prevalence was 8% (95%CI: 5-14%). The prevalence estimates of HFpEF in type 2 diabetes from the general population are high compared to a prevalence of 4.9% of HFpEF in community dwellers 60 years or over, as presented in a recent review 5
By definition, the denominator of the prevalence is (a sample of) the population at large. As such, studies investigating type 2 diabetes patients from the general population provide better estimates than studies that calculate a prevalence in a hospital population with only a selection of patients with type 2 diabetes, in generally more diseased patients. Nevertheless, for clinical practice prevalence data from the hospital setting are especially useful for specialists, while the prevalence data from the community are of interest for the general practitioner.
LVDD is a risk factor for developing heart failure, notably HFpEF, but likely HFrEF as well, and it is associated with an increase in all-cause mortality compared to people (age- and gender adjusted) without LVDD 51, 52. HFpEF is increasingly considered to be important 6, 51, and is known for its high mortality rates. Studies reporting comparisons in mortality rates between HFrEF and HFpEF are conflicting, with some studies showing that HFpEF patients have a somewhat lower mortality rate than HFrEF patients, while others suggest similar mortality rates 53-55. Unfortunately though, as compared with HFrEF, clear mortality-reducing therapies for HFpEF have not yet been identified 56. Furthermore debate remains ongoing regarding the criteria of LVDD and the cut-points to be used for echocardiographic parameters. Also the exact pathophysiology underlying LVDD and HFpEF has not yet been unravelled 11, 12. It has been well-recognized that HFpEF typically occurs in patients with comorbidities including type 2 diabetes, which is in line with our findings in this review showing very high prevalence rates of LVDD among type 2 diabetes patients 5, 11, 12. Only one study so far has shown, with longitudinal data, that 9% of patients with LVDD improves to a better diastolic function in 4 years' time in contrast to 23% worsening and the remainder having a similar grade of diastolic dysfunction 57. It is currently unknown whom with LVDD will eventually become symptomatic, i.e. develop HFpEF, and after how many years. For that longitudinal studies need to be performed, also among patients with type 2 diabetes. Such studies could help focus identifying those type 2 diabetes patients with LVDD at high risk of developing HFpEF, and in order to optimize cardiovascular risk prevention, including optimal blood pressure control 58, 59. Another important prospective research area lies in the development of prognostically effective treatment strategies of HFpEF. There have been some suggestions for

targeting specific subgroups of HFpEF, however these treatment strategies need to be further developed 60, 61.

Previous research suggested that women are more likely to develop HFpEF than men based on a bimodal distribution for sex and ejection fraction in heart failure, with female sex as a risk factor for HFpEF 53, 54, 62. One study in our review clearly showed in a general population setting that women with type 2 diabetes (mean age 74.9 (SD 6.9) years) had a higher prevalence of HFpEF than men with type 2 diabetes (mean age 73.8 (SD 8.6) years): 28% vs. 18% 18. Interestingly, however, in this same population study, the prevalence rates of LVDD were similar among women and men (24% vs. 26%)18. Also in our systematic review, based on 12 studies providing such data, the prevalence of LVDD was similar between women and men (47% vs 46%). An explanation may be that women with LVDD develop HFpEF more easily than men do. However, we could not completely account for the effect of age, as only 6 studies reported sex-specific mean age.

Many studies included in this review used a relatively young and healthy study population by excluding several comorbidities. However, the pathophysiology of HFpEF and diastolic dysfunction is complicated by a host of comorbidities, as well as, by age and sex, with a different impact on cardiac function and remodeling 63. As has been recently proposed in a review by Dunlay, part of the explanation for the female predominance for developing HFpEF could lie in their older age at time of detection 64. The general lack of studies examining the natural progression of diastolic dysfunction to HFpEF make it difficult to state if the difference in HFpEF prevalence between men and women is largely attributable to ageing, or a combination of sex-differences in cardiac remodeling and ageing. Given, however, the results of Boonman-Winter et al it seems that the difference between men and women with type 2 diabetes in prevalence of HFpEF is not driven by differences in age because they were of similar age 18.

The higher prevalence of diastolic dysfunction and HFpEF in type 2 diabetes patients seems to show the impact of diabetes in the development of these conditions. Diabetes is associated with changes in cardiac metabolism, structure and function. Mechanisms contributing to myocardial dysfunction in diabetes include hyperglycemia, lipotoxicity and insulin resistance 11, 12. Perhaps these factors differed between men and women in the studies included and may thus impact the underlying pathophysiology of diastolic dysfunction and hence the prevalence rates. However, more research is necessary to confirm this finding and to unravel possible underlying pathways.

A number of limitations of this review need to be addressed. First of all we noted significant heterogeneity between the included studies, a common finding in meta-analyses concerning prevalence estimates 65-67. Many hospital population studies in this review excluded patients with a history of cardiovascular diseases, hypertension, atrial fibrillation, valvular diseases and renal diseases, which was in contrast to the general population studies (except for the study by Pareek et al), and resulted in very select study populations 45. So it is highly plausible that the prevalence of LVDD (and HFpEF) is much higher among unselected hospitalized type 2 diabetes patients than what the results from this review suggest 68. Other important reasons for different prevalence rates in our review are differences in case definition and echocardiographic criteria for diastolic dysfunction. There is no uniform agreement on the definition of diastolic dysfunction, and it has only been agreed upon that multiple echocardiographic measurements should be used. However, because a reference standard is lacking, an algorithm of echocardiographic parameters variables is not generally accepted nor could be validated 51, 69. Tissue Doppler Imaging (TDI), widely available since 2002, is considered crucial in the diagnosis of diastolic dysfunction, notably the use of the parameter E/e', but we also included studies performed after 2002 that did not incorporate the use of TDI. Importantly, we conducted sensitivity analyses by only including studies using similar case definitions for LVDD, but again prevalence rates largely varied (data not shown), suggesting that more factors may have influenced the results, including differences in source population, study setting, variation in age and gender distribution, duration

of type 2 diabetes and different cut-off points for ejection fraction. In addition, survey year, study design and sample size may have had an influence on the prevalence of LVDD. Unfortunately, we only identified five studies conducted in the community at large. They were of reasonable quality, ranging from low (n=2) to medium (n=3) risk of bias. The quality of the 15 hospital population studies included in this review was of a moderate standard with the majority having a medium risk of bias, but one study had a low risk of bias, and another a high risk of bias.

CONCLUSIONS

The prevalence of LVDD among type 2 diabetes patients is similarly high in men and women, while HFpEF seems to be much more common in women than men in community people with type 2 diabetes. More general population studies should be performed for an improved understanding of the prevalence of undetected LVDD and HFpEF. In addition there is a need for more longitudinal studies to identify whom with type 2 diabetes and LVDD will develop HFpEF, after how much time, and whether this differs between men and women, so strategies for better management of these at risk groups can be developed.

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Conflicts of interest
The authors declare no conflicts of interest.

Contributions
S.B. conceived of the study, performed the systematic search, screened articles, performed the meta-analysis and wrote the manuscript. G.V. screened articles and wrote the manuscript. A.G. contributed to the results and reviewed/edited the manuscript. H.R. reviewed/edited the manuscript. J.R. contributed to the methods. A.H. reviewed/edited the manuscript. F.R. conceived of the study, contributed to the methods and results and reviewed/edited the manuscript.

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Figure 1. Flow chart of the process for selection of relevant articles

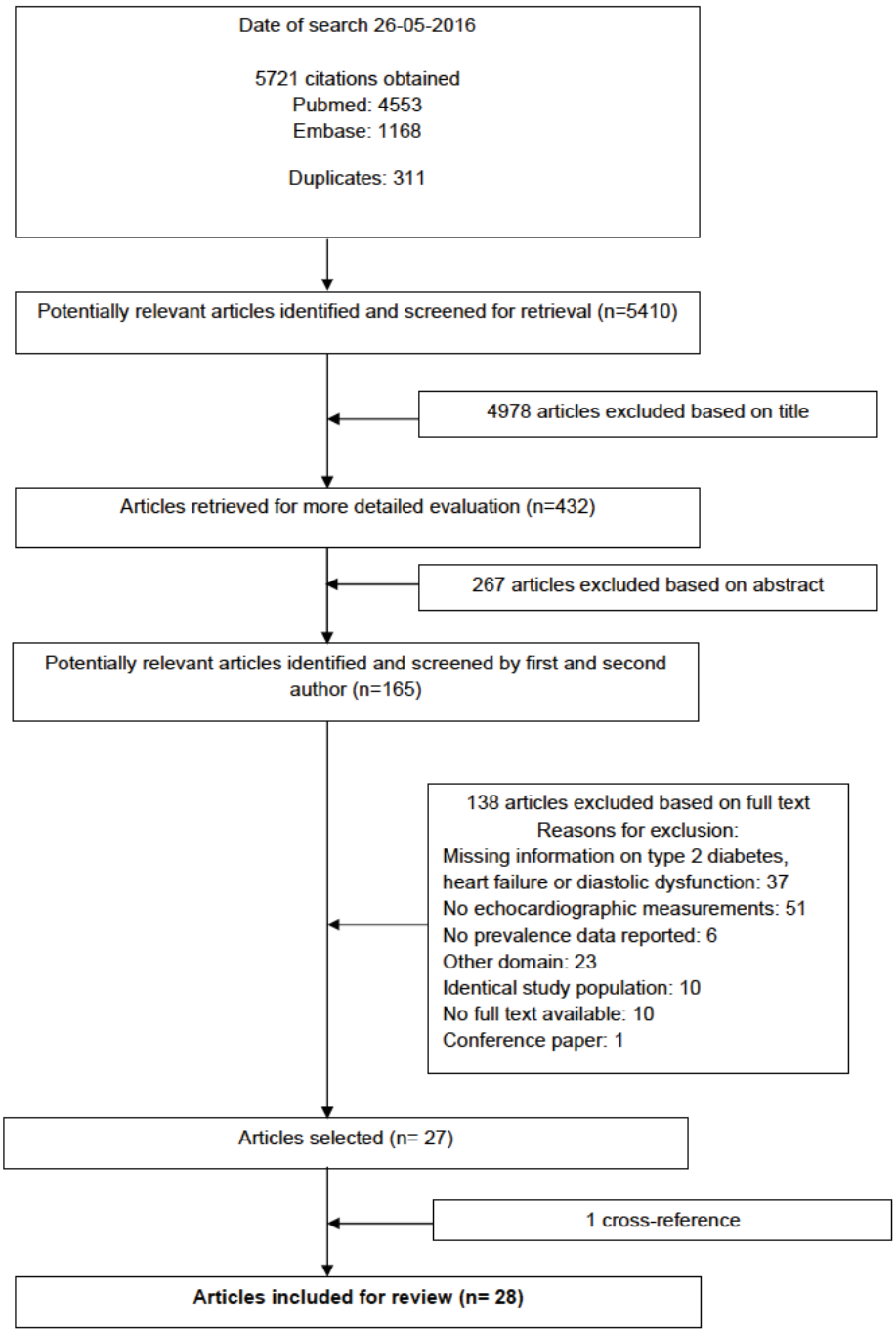


Table 1. General characteristics and quality assessment of included studies

Author (year of publication)	Source population and setting	Age in years[1]	Participants (male)	type 2 diabetes duration (years) (means ±SD or median (range))	Exclusion criteria	Echocardiographic measurements (methods)		Heart failure (yes/no)	Risk of bias (Low/High)									Overall risk (Low/medium/high)
						Cut-point LVEF to separate LVSD from LVDD	Classification of LVDD		a	b	c	d	e	f	g	h	i	
Poirier (2001)	Consecutive Caucasian sedentary men, setting not reported	38-67	46 (100%)	Normal LVDD: 4 (1-10) Impaired relaxation: 2.5 (0.25-32) Pseudo-normalized pattern: 6.5 (1.5-30)	Cardiovascular or respiratory disease, hypertension, not well-controlled DM during 3 months before enrollment, retinopathy, neuropathy and macro-albuminuria	Normal LVEF, no cut-point reported	Classified according to Canadian consensus on LVDD (impaired, pseudonormal, restrictive) Pseudonormal: two of the three criteria: E/A <1 after Valsalva maneuver E/A ratio decrease≥25% Pulmonary A wave duration longer than mitral A wave duration	no	H	H	L	H	L	L	L	L	L	Medium
Zabalgoitia (2001)	Source population and setting not reported	38-59 46±NA	86 (57%)	Normal LVDD: 4.6 (1-10) Impaired relaxation: 4.5 (0.5-12) Pseudo-normalized pattern: 6.5 (1-10)	Ischemic heart disease, congestive heart failure, hypertension, insulin therapy, uncontrolled diabetes < 1 month before enrollment, retinopathy, neuropathy and nephropathy	not reported	Divided into impaired, pseudonormal and restrictive. Pseudonormal: E/A ratio >1 and DT 160-240, but E/A ratio <1 after Valsalva maneuver	no	H	H	H	H	H	L	L	L	L	High
Annonu (2001)	Patients attending the Diabetic Center of Cairo University hospital, Egypt	39-64 57±6.8	66 (53%)	Not reported	Insulin use, alcoholism, clinical or electrocardiographic evidence of heart diseases and hypertension	50%	E/A ratio <1	no	L	H	H	H	L	L	L	L	L	Medium
Boyer (2004)	Consecutive asymptomatic, normotensive patients, setting not reported	49 (31-59)	57 (47%)	Normal LVDD: 4.7±3.3 Abnormal LVDD: 5.8±5.5	Hypertension, coronary artery disease, valvular heart disease and congestive heart failure, > 60 years of age	Not reported	One of the following findings by conventional echo: E/A ratio <1 or >2 DT <150 or >220 IVRT <60 or > 100 Pseudo-normal: Change in E/A ratio >40% after Valsalva maneuver TDI: septal and lateral walls<8cm/s Color M-mode: propagation velocity <45	no	H	H	L	H	L	L	L	L	L	Medium
Fang (2005)	Asymptomatic patients from the ambulatory Diabetes Clinic at Princess Alexandra Hospital, Australia.	No age range or overall mean age reported	101 (Not reported)	Not reported	History of complaints of cardiac disease, history of coronary artery disease, valvular disease, atrial fibrillation, severe arrhythmias and congenital heart disease	50%	Resting basal segmental myocardial peak diastolic velocity (Em)	no	L	H	L	H	H	L	L	H	H	High

Bajraktari (2005)	Consecutive patients from the Clinic of Internal Medicine, University Clinical Centre, Kosovo	56±8.3	228 (114 male)	Not reported	Arterial hypertension, ischemic heart disease, cardiac arrhythmias, congenital or acquired valvular heart disease, chronic renal failure, age > 75, insulin therapy and poor echocardiographic window	not reported	E/A ratio<1 Pseudo-normal: E/A ratio ≥1 and VP>55	no	L	H	L	H	L	L	L	L	L	Medium
Dawson (2005)	Random volunteers from the Diabetes Centre, Ninewells Hospital, Scotland	63.8±10.6	500 (61.6%)	6.0±5.5	Frailty and inability to give written informed consent	45%	E/A ratio, E wave DT, IVRT according to European Study Group on Diastolic Heart Failure: LVEF≥45% and E/A ratio <50y<1·0 and DT<50y>220 ms, E/A ratio >50y<0·5 and DT>50y>280 ms and/or IVRT<30y>92 ms, IVRT30–50y>100 ms, IVRT>50y>105 ms	no	L	L	L	L	L	L	L	H	H	Medium
Albertini (2008)	Consecutive asymptomatic patients admitted at the Avicenne Hospital endocrinology unit, France	59.8±1.5 Male: 60±14 Female: 61±15	91 (54%)	13±1.1	Previous or suspected history of heart disease, intrinsic lung or overt renal disease, incomplete echocardiographic data or poor echogenicity	50%	Impaired: E/A ratio<1 or >1, E/e' ratio >10 Restrictive: E/A ratio >2 or EA ratio 1-2 with DT≤130 Pseudo-normal: E/A ratio 1-2 With DT 150-220	no	L	H	L	H	L	L	L	L	L	Medium
Henry (2008)	Participants from the Hoorn Study and Hoorn Screening Study, both population-based studies, the Netherlands	66.9±8.2	746 (298 DMII patients, 54%)	Not reported	none	55%	One of the following criteria: Peak A velocity ≥ 97 Difference between A_{pv} and A_{mv} duration ≥ 41 Left atrial volume ≥ 57	no	L	L	L	L	L	L	L	L	H	High
Srivastava (2008)	Patients referred for echocardiography as part of a routine complications surveillance programme, mainly by general practitioners (80%) and 20% from the hospital, at the Diabetic Clinic at Austin Health, Australia.	62±1	229 (58%)	10±1	none	50%	Divided into impaired, pseudo-normal and restrictive. Pseudo-normal: evidence of increased LV filling pressures with three of four of the following criteria: E/e' ratio >10 Depressed Vp (<50) Pulmonary A duration > mitral A duration PulAVmax >0.35 and positive Valsalva maneuver	no	L	L	H	H	L	L	L	H	L	Medium
From (2010)	Participants from Olmsted County	60±14	1760 (49%)	Not reported	Diagnosis of HF before echocardiogram or made within	Not reported	E/e' ratio >15	no	L	L	H	L	L	L	L	L	L	Low

	population, USA				30 days after echocardiogram													
Poulsen (2010)	Patients referred, for the first time, for diabetes education or poorly regulated diabetes to the Diabetes Clinic at Odense University Hospital, Denmark	58.6±11.3	305 (54%)	4.5±5.3	History of CVD, malignancy or end-stage kidney disease, pregnancy, body weight >150kg, physical or mental disability, not able to provide inform consent	50%	Grade I: DT >240, E/A ratio <0.7, Vp ≤45 and e_{septum}'<8 Grade II: DT 140-240, E/A ratio 0.7-1.5, Vp ≤45 and e_{septum}'<8 Grade III: DT <140, E/A ratio >1.5, Vp ≤45 and e_{septum}'<8	no	L	H	L	H	L	L	L	L	Medium
Kazlauskaite (2010)	Consecutive adults from ethnic minority groups (African-American, Hispanic, other immigrant) with newly diagnosed type 2 diabetes attending a diabetes clinic at a large urban public hospital in Chicago, USA	No age range or overall mean age reported	126 (48%)	Not reported	History of cardiovascular diseases, creatinine >141 umol/l, current or chronic infectious disease, prolonged cocaine or heroin use or alcoholism	Not reported	Grade I: DT >240, E/A ratio ≤0.75, IVRT>90 Grade II (pseudo-normal filling): DT >140, 0.75<E/A ratio <1.5, E/e' ratio ≥10 Grade III and IV: not reported	no	L	H	L	H	L	L	L	L	Medium
Patil (2011)	Normotensive patients with > 5 years DMII at the Krishna Institute of Medical Sciences, Karad, India	Male: 51±9 Female: 49±10	227 (127 cases, 55% male)	Male: 11±5 Female: 10±4	Evidence of coronary artery disease, valvular disease, hypertension or antihypertensive medication, poor transthoracic echo window	50%	One of the following findings: E/A ratio <1 or >2 DT <150 or >220 IVRT <60 or > 100 E/e' ratio > 15	no	L	H	H	H	L	L	L	L	Medium
Ernande (2011)	Consecutive patients referred to the outpatient clinical department of diabetology of Louis Pradel Hospital, Lyon, France	52±4.5	200 (114 cases, 61% male)	11±7	Absence of sinus rhythm, coronary and valvular heart diseases, severe renal failure, severely uncontrolled DM and uncontrolled blood pressure (SBP>180 mm Hg and/or DBP > 100 mm Hg), DM I, echo images unsuitable for quantification	55%	Septal e' <8 and lateral e' <10 and LA volume > 34, then they were further categorized into grade I, II or III according to ASE and EAE recommendations using E/A ratio, mDT, E/e' ratio and Ar-A time interval	no	L	H	L	H	L	L	L	L	Medium

Aigbe (2012)	Randomly selected patients at the University Teaching Hospital, Nigeria	26-80 55.4±11.6	300 (150 cases, 43% male)	4.5±4.5	Hypertension, pregnancy, sickle cell disease and structural heart disease	50%	Impaired: E/A ratio <1 or>1, DT>120 Pseudo-normalization: E/A ratio 1-2, IVRT 80-110, DT 150-220 and S/D<1 Restrictive: E/A ratio >2 and DT <150	no	L	H	L	H	L	L	L	L	H	Medium
Boonman-de Winter (2012)	Patients enrolled in the Diabetes Care programme of the Center for Diagnostic Support in Primary Care, the Netherlands	71.5±7.5 Male: 71.9±7.5 Female: 71.4±7.4	605 (54%)	Not reported	none	45%	E/e' ratio ≥15 or E/e ratio' 8-15 and septal e' <8. Then further categorized as: Grade I: E/A ratio ≤0.75, DT≥180, S/D≥1 Grade II: 0.75<E/A ratio <1.5, 140<DT<320, S/D <1 Grade III: E/A ratio >1.5, DT<140, S/D<1	yes	L	L	L	H	L	L	L	L	L	Low
Cioffi (2012)	Non-institutionalized subjects>45 years of age participating in the Dysfunction in DiAbetes' (DYDA) study recruited in 37 diabetes referral centers, Italy	61±7	751 (61%)	7 (3-13)	Myocardial infarction, myocarditis, HF, coronary heart disease, alcoholic cardiomyopathy, primary hypertrophic cardiomyopathy, asymptomatic known LVD, prior myocardial revascularization, valvular heart disease, atrial fibrillation, electrocardiographic findings of myocardial ischaemia, DMI and severe systematic disease with life expectancy <2 years	50%	All conditions different from normal LVDD defined as: E/A ratio 0.75-1.5 and DT of E-wave >140msec according to Redfield	no	L	H	L	L	L	L	L	L	L	Low
Utrera-Lagunas (2013)	Patients attending the Internal Medicine Service at Nacional de Ciencias Medicas y Nutricion, Mexico	No age range or overall mean age reported	160 (45%)	With HF: 17.4±8.5 Without HF: 19.4±9.7	Pancreatitis, liver failure, end-stage renal failure, recent (<3 months) acute coronary syndrome and/or myocardial revascularization, congenital heart disease, myocarditis, valvular heart disease, myocardial dysfunction secondary to radio-chemotherapy	45%	LAD>45mm, ventricular septal thickness >12 mm, posterior wall thickness>12 and characteristic pattern of transmitral Doppler flow (slow, inverted, pseudonormal or restrictive)	yes	L	H	H	H	L	L	L	L	H	High

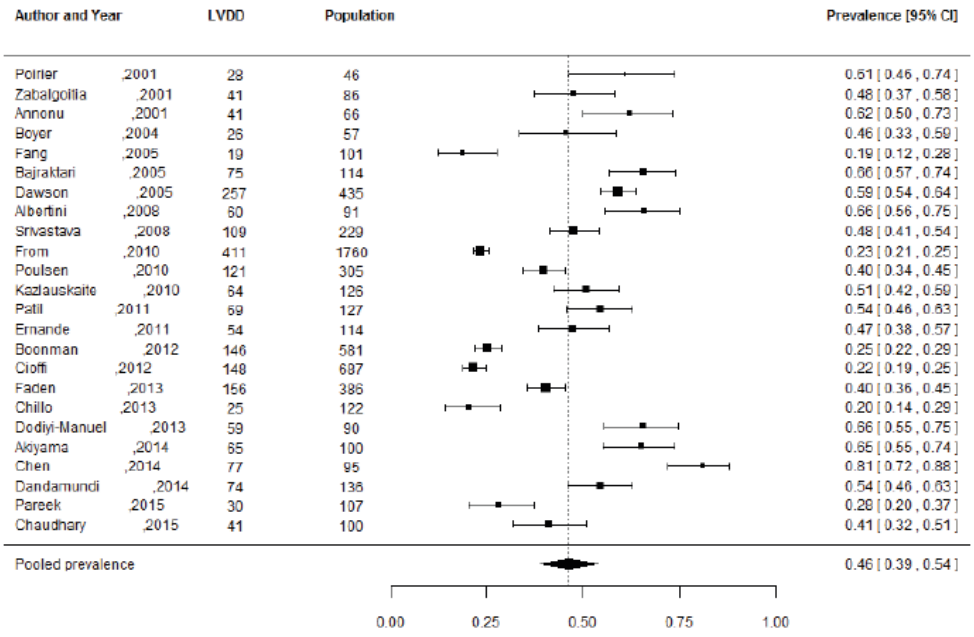
Faden (2013)	Consecutive non-institutionalized subjects>18 years of age attending a prospective, multicenter study, (SHORTWAVE) in cardiology and diabetes referral centers in 4 hospitals, Italy	69±10	386 (57%)	5 (2-10)	Myocardial infarction, dilated cardiomyopathy or HF, primary hypertrophic cardiomyopathy, prior myocardial revascularization, valvular disease, atrial fibrillation, chronic pulmonary disease, DMI	Not reported	Mild: E/A ratio≤0.75, ΔE/A ratio<0.5. E/é ratio<10, S>D Moderate: E/A ratio 0.75-1.5, DT>140, ΔE/A≥0.5. E/é ratio ≥10, S<D Severe: E/A ratio>1.5, DT<140, 0.5<ΔE/A≥0.5. E/é ratio≥10, S<D according to Redfield (2003)	no	L	H	L	H	L	L	L	L	L	Medium
Chillo (2013)	Patients who participated in a survey to determine prevalence of microalbuminuria attending the outpatient clinic of Muhimbili National Hospital in Dar es Salaam, Tanzania	55±9	180 (122 DMII patients, sex not reported)	11±6	None (reported)	50%	E/e' ratio ≥ 15	no	L	H	H	L	L	L	L	L	L	Medium
Dodiyi-Manuel (2013)	Patients attending the Medical Outpatient Department of the University of Port Harcourt Teaching Hospital, Nigeria	36-65 50.8±9.1	180 (90 DMII patients, 43% male)	3.4±2.9	Hypertension (>140/90 mm Hg), anti-hypertensive medications, valvular abnormalities and wall motion abnormalities	55%	Impaired relaxation: E/A ratio<1 Pseudo-normal using Valsalva method Restrictive: E/A ratio >2	no	L	H	H	H	L	L	L	L	L	Medium
Akiyama (2014)	Asymptomatic outpatients, setting not reported	61.6±9.7	100 (55%)	Not reported	Overt heart failure, LVEF<50, history of CAD, severe valvulopathy and chronic atrial fibrillation	50%	E/A ratio<0.75, or ≤0.75 and E/e' ratio≥10 according to definition of Redfield	no	L	H	H	H	L	L	L	L	L	Medium
Chen (2014)	Consecutive patients treated with stable hypoglycemic medication for at least 3 months recruited from the medical outpatient clinic of Queen Mary Hospital, Hong Kong, China	62±9	95 (39%)	10±8	History or clinical symptoms of cardiovascular disease, including CAD, MI, stroke or peripheral vascular disease, renal impairment (eGFR<30ml/min/1.73m^2), liver failure, SLE, rheumatoid arthritis, systemic sclerosis	50%	Septal e' <8 and lateral e' <10 and LA volume > 34, then further categorized into: Grade I: E/A ratio<0.8, DT>200, E/é ratio ≤8, Ar-A<0 Grade II: E/A ratio 0.8-1.5, DT160-200, E/é ratio 9-12, Ar-A≥30 Grade III: E/A ratio ≥2, DT<160, E/é ratio ≥13, Ar-A≥30 According to Nagueh (2009)	no	L	H	L	H	L	L	L	L	L	Medium

Dandamundi (2014)	Random sample of residents participating in the Rochester Epidemiology Project, Olmsted County, USA	No age range or overall mean age reported	2042 (136 DMII patients, 60% male)	Not reported	Missings on systolic or diastolic assessments	50%	Mild (impaired relaxation without increased filling pressures): E/A ratio ≤0.75 and E/e' ratio <10 Moderate (impaired relaxation with moderately elevated filling pressures of pseudo-normal filling): 0.75<E/A ratio <1.5 and E/e' ratio ≥10 Severe (reversible of fixed restrictive filling): E/A ratio>1.5 and E/e' ratio ≥10	no	L	L	L	H	L	L	L	L	L	Low
Habek (2014)	Patients were recruited from the Center for Diabetes Clinic of Internal Medicine, University Hospital Osijek, and the cardiac and diabetic outpatient 'Sunce' policlinic, Zagreb, Croatia	60.2±NA Male: 63±NA Female: 58.5±NA	202 (61%)	8.9±NA	LVEF<50%, AF, pacemaker or ICD, history of MI, AP, left bundle branch block, chronic congestive HF, serious valvular of congenital cardiac disease, active myocarditis, severe hepatic of renal disease and type I DM	50%	Septal e' <8 and lateral e' <10 and LA volume > 34, then further categorized into: Grade I: E/A ratio <0.8, DT>200, E/é ratio ≤8, Ar-A<0 Grade II: E/A ratio 0.8-1.5, DT160-200, E/é ratio 9-12, Ar-A≥30 Grade III: E/A ratio ≥2, DT<160, E/é ratio ≥13, Ar-A≥30 According to Nagueh (2009)	no	L	H	H	H	L	L	L	L	H	High
Pareek (2015)	Subjects derived from a population-based cohort study (Mälmo Preventive Project), Sweden	66 (IQR 60-70)	691 (107 with DMII, 79% male)	New onset	Cardiovascular disease and/or cardiovascular, anti-diabetic or lipid-lowering therapy	50%	Grade I (mild): septal é < 8, lateral é <10, DT≥240, E/A ratio <0.8, E/é ratio ≤12 Grade II (moderate): septal é < 8, lateral é <10, DT 140-240, E/A ratio 0.8-1.5, E/é ratio ≥9 Grade III (severe): septal é < 8, lateral é <10, DT <140, E/A ratio >1.5, E/é ratio ≥13	no	L	H	L	H	L	L	L	L	H	Medium
Chaudhary (2015)	Normotensive patients with newly diagnosed (within 1 month) DMII recruited from the SVBP Hospital, LLRM Medical College, Meerut, India	30-60 50.1±6.3 Male: 50.7±5.7 Female: 48.9±7.0	100 (65%)	New onset	Hypertension >130/80, abnormal ECG, already diagnosed DMII, antidiabetic treatment, valvular heart disease, ischemic and hypertensive heart disease, congestive HF, cardiomyopathy, renal failure, COPD, severe anemia and haemoglobinopathies	50%	Any of the following criteria: E/A ratio <1 or >2 DT <150 or >220 IVRT <60 or > 100 E/e' ratio >15	no	L	H	H	H	L	L	L	L	L	Medium

[1]Values indicate the age range, mean ± standard deviation or median (range)

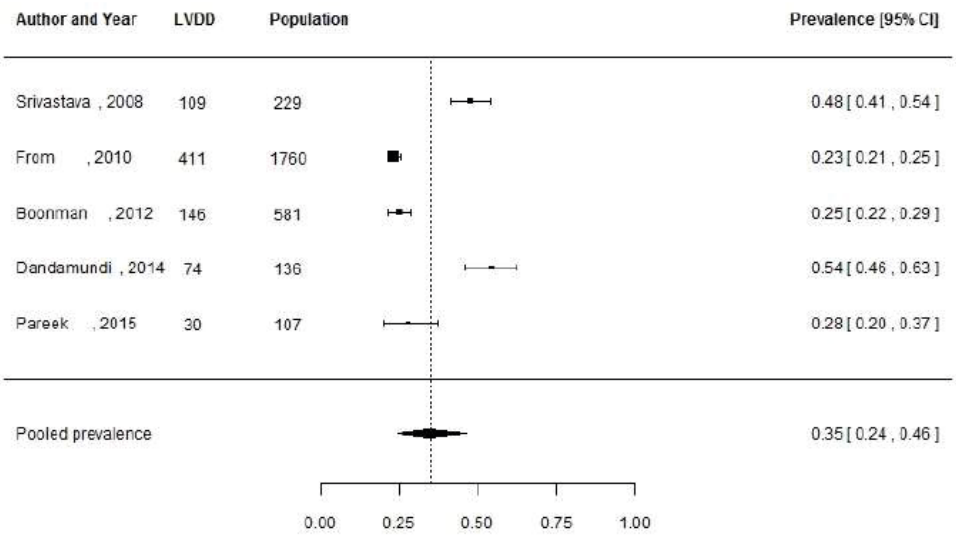
Abbreviations: type 2 diabetes Type 2 diabetes, SD standard deviation, LVEF left ventricular ejection fraction, LVSD left ventricular systolic dysfunction, LVDD left ventricular diastolic dysfunction, DM diabetes mellitus, (DT E-wave deceleration time, IVRT iso-volumetric relaxation time, TDI tissue doppler imaging, VP flow propagation velocity, PulAVmax pulmonary venous atrial reversal maximal velocity, CVD cardiovascular disease, LVD left ventricular dysfunction, HF heart failure, LAD left atrial diameter, CAD coronary artery disease, MI myocardial infarction, eGFR estimated glomerular filtration ratio, SLE systemic lupus erythematosus, ECG electrocardiogram, COPD chronic obstructive pulmonary disease, LA volume left atrial volume, AF atrial fibrillation, ICD internal cardiac defibrillator, AP angina pectoris, NA not available, E (wave) peak early diastolic mitral inflow velocity, A (wave) peak late mitral inflow velocity, E/A (ratio) ratio of peak early and peak late mitral inflow velocity, M-mode motion mode, E/e' (ratio) peak early mitral inflow velocity divided by peak mitral annular velocity, Apv pulmonary vein flow A wave duration, Amv mitral valve A wave duration, Eseptum peak septal mitral annular velocity , mDT E-wave deceleration time, Ar-A time difference between atrial reversal velocity waveform and mitral late filling duration, S/D ratio peak systolic velocity divided by peak anterograde diastolic velocity in the pulmonary vein, ASE American Society of Echocardiography, EAE European Association of Echocardiography.

Figure 2. Prevalence of left ventricular diastolic dysfunction among type 2 diabetes patients in both general and hospital population



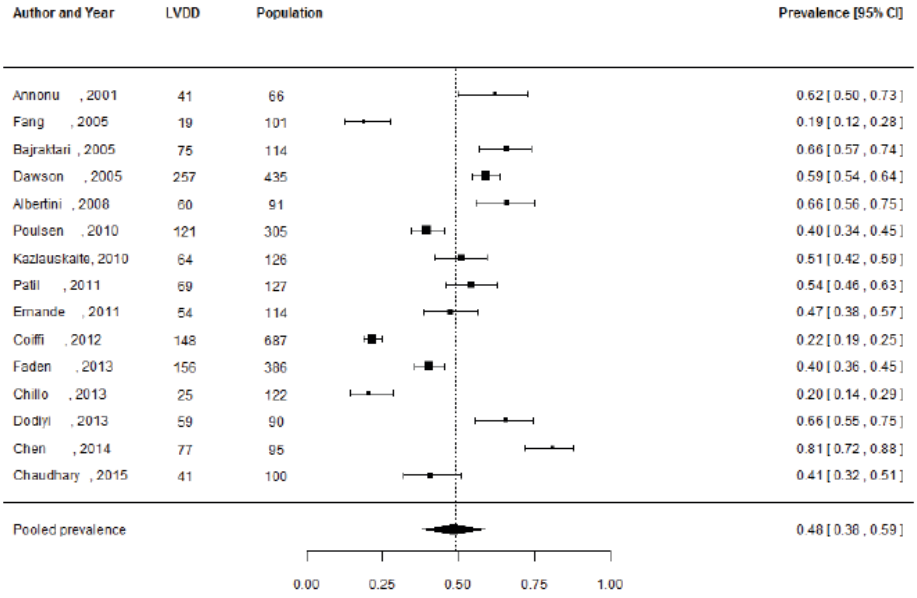
*Prevalence proportions with 95% confidence interval of left ventricular diastolic dysfunction among type 2 diabetes patients in both general and hospital population and pooled prevalence estimate with 95% confidence interval.

Figure 3. Prevalence of left ventricular diastolic dysfunction among type 2 diabetes patients in the general population



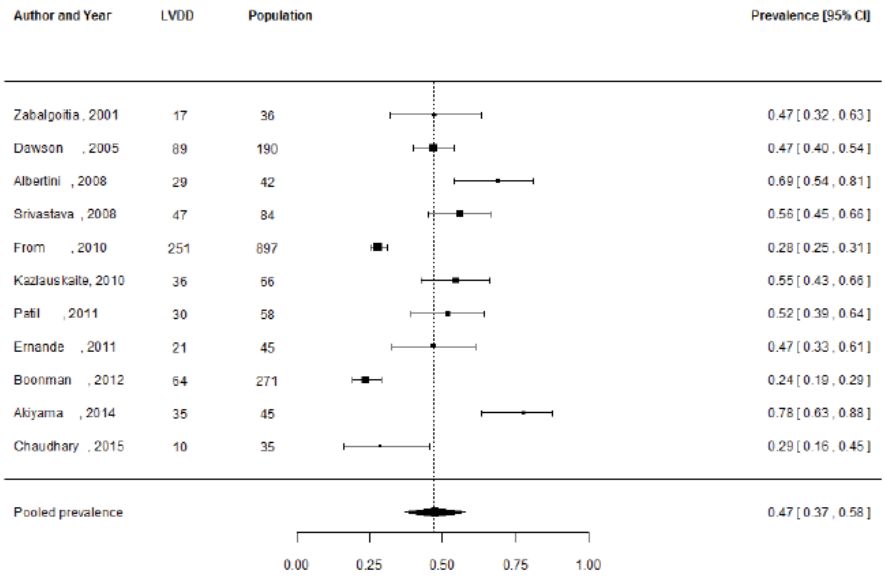
*Prevalence proportions with 95% confidence interval of left ventricular diastolic dysfunction among type 2 diabetes patients in the general population and pooled prevalence estimate with 95% confidence interval.

Figure 4. Prevalence of left ventricular diastolic dysfunction among type 2 diabetes patients in the hospital



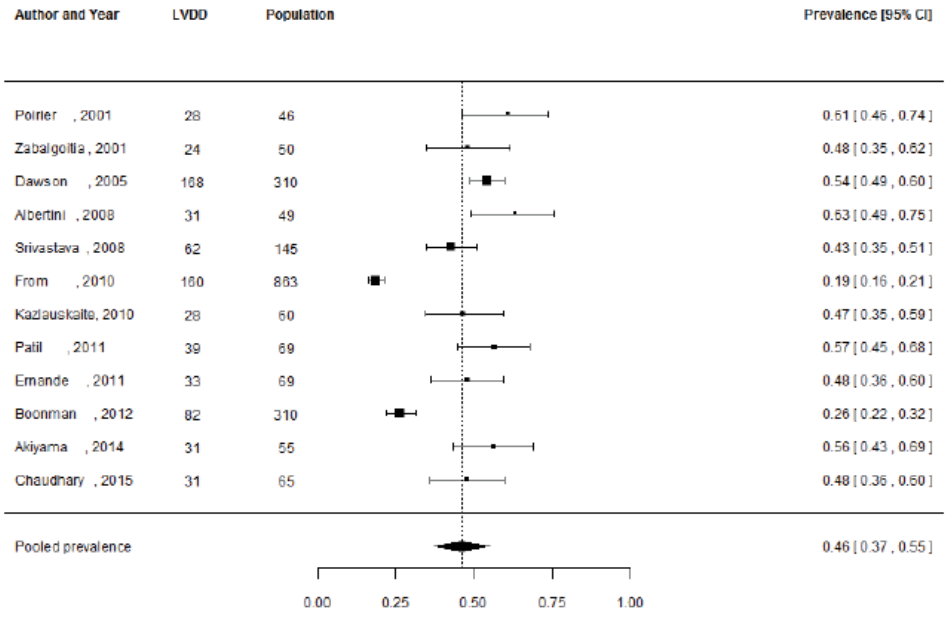
*Prevalence proportions with 95% confidence interval of left ventricular diastolic dysfunction among type II diabetes patients in the hospital population and pooled prevalence estimate with 95% confidence interval.

Figure 5. Prevalence of left ventricular diastolic dysfunction among women with type 2 diabetes



*Prevalence proportions with 95% confidence interval of left ventricular diastolic dysfunction among women with type 2 diabetes and pooled prevalence estimate with 95% confidence interval

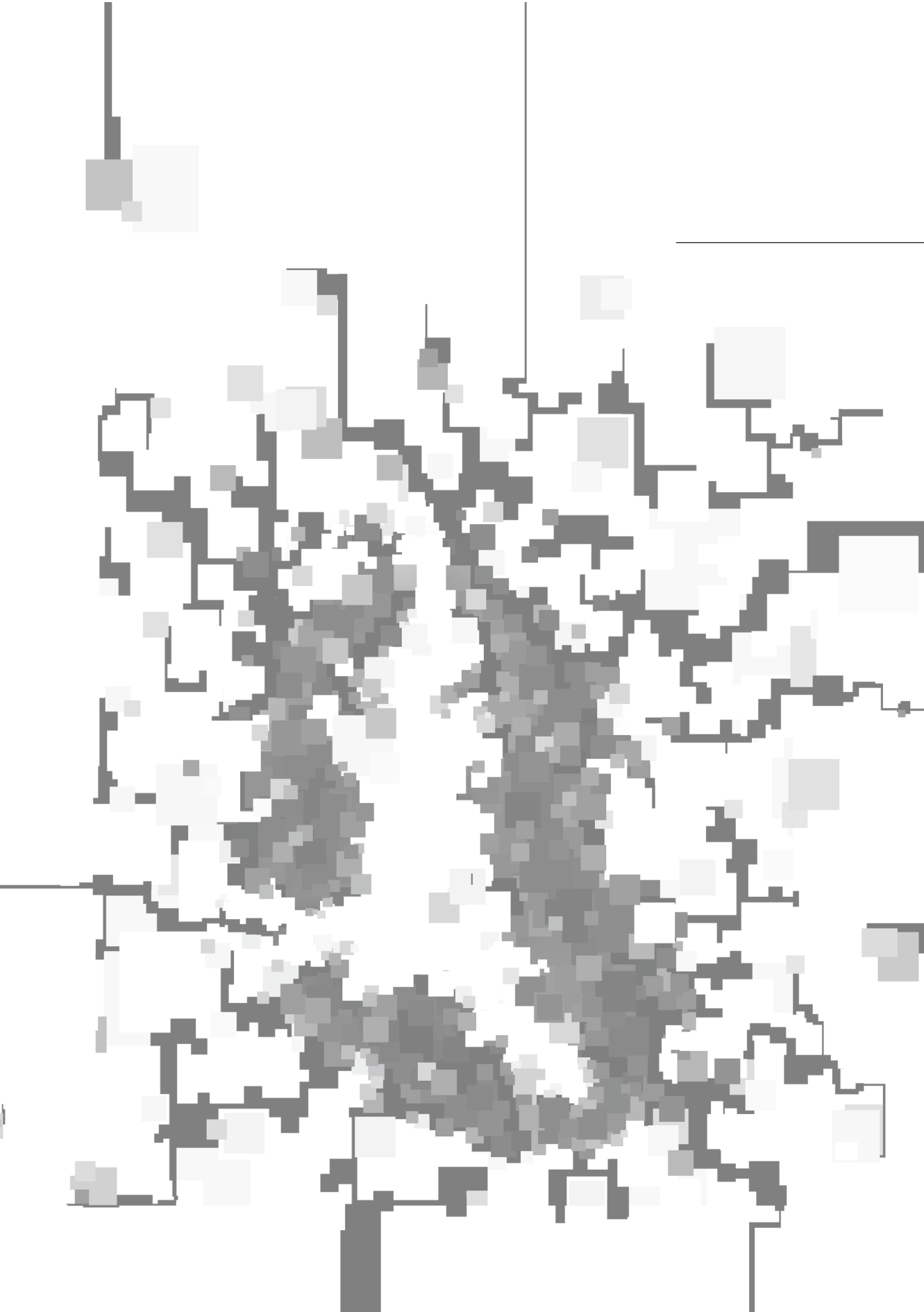
Figure 6. Prevalence of left ventricular diastolic dysfunction among men with type 2 diabetes



*Prevalence proportions with 95% confidence interval of left ventricular diastolic dysfunction among men with type 2 diabetes and pooled prevalence estimate with 95% confidence interval

PART THREE

Diagnosis of LVDD and HFpEF



Chapter 6

Comparison of three recommendations to detect left ventricular diastolic dysfunction in men and women referred to a outpatient cardiology clinic

Submitted

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3

ABSTRACT

Aims
Currently, multiple sets of criteria for left ventricular diastolic dysfunction (LVDD) exist. Therefore no unambiguous diagnosis can be made. We assessed the impact of three recent recommendations on the prevalence of LVDD in men and women referred to a outpatient cardiology clinic.

Methods and Results
The study population comprised of 697 consecutive individuals referred to an outpatient cardiology clinic by the general practitioner for a diagnostic cardiac assessment. We compared three LVDD criteria: (1) the 2019 Heart Failure Association (HFA
PEFF) recommendations with (2) those of the 2016 European Society of Cardiology (ESC) guidelines and (3) the 2016 American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines. Cardiac evaluation included echocardiography and natriuretic peptides. The LVDD criteria of the three guidelines were assessed in 550 subjects, mean age 62.6 (SD 9.3) years, and 67% were women. The prevalence of LVDD was 5.5% with 'HFA PEFF 2019', 24.5% with 'ESC 2016', and 1.8% with 'ASE/EACVI 2016'.There were no sex differences in prevalence of LVDD. Agreement in classification of 'HFA PEFF 2019' with 'ESC 2016' and 'ASE/EACVI 2016' was 23.5%, and 29.5%, respectively. Applying the 'HFA PEFF 2019' resulted in 76.3% of the study population being classified as "intermediate".

Conclusion
The three current prevailing guidelines identify different populations with LVDD. Therefore, when different guidelines were used results from previous studies on etiology, diagnosis, prognosis and treatment options are rather difficult to compare and interpret, thus more uniformity is required.

Introduction

Left ventricular diastolic dysfunction (LVDD) is common in the general population [1], especially among elderly women [2]. LVDD is considered present when there is echocardiographic evidence of abnormally elevated filling pressures and impaired relaxation. It is a condition that occurs partly due to aging, but its progression can be exacerbated by co
morbidities like hypertension, obesity and diabetes mellitus amongst others. LVDD deteriorates over time to a more severe degree of dysfunction in 12 25% of individuals [3,4], and around 12% will eventually develop heart failure with preserved ejection fraction (HFpEF) within 5 years [3,5,6]. LVDD can be present as a separate entity before development of heart failure, but it is also an important part of the HFpEF diagnosis in patients presenting with symptoms and signs suggestive of heart failure (HF) [7].Although both spironolactone and irbesartan may be beneficial, especially in patients with elevated but still relatively low levels of natriuretic peptides [8 10], treatment for HFpEF is lacking. Therefore, LVDD as an early hallmark of HFpEF may provide a crucial target for prevention. However, before the usefulness of preventive treatment for LVDD and HFpEF can be investigated and thereafter widely implemented, consensus on the diagnosis of LVDD is warranted.

Until now, several guidelines have proposed different diagnostic criteria and cut offs for LVDD and HFpEF [7,11 13]. In these diagnostic criteria similar echocardiographic parameters are incorporated, focusing on surrogate measures of left ventricular (LV) filling pressure, impaired relaxation, left atrial enlargement, LV remodeling and pulmonary (or vascular) pressures. Yet, these measures are used in different combinations and, more importantly, using different cut off values. As a result of differences in proposed diagnostic criteria and cut off values, prevalence estimates of both LVDD and HFpEF differ strongly among studies, hampering both comparison of studies as well as elucidating risk factors involved in deterioration of LVDD towards HFpEF [14,15].

Recently, a new diagnostic algorithm for HFpEF was proposed by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) [16]. The work up includes a score system for LVDD that ranges from zero to six points based on cut off values for echocardiographic parameters and levels of natriuretic peptides in either sinus rhythm or the presence of atrial fibrillation. This score system classifies LVDD in three categories (i.e.: no LVDD, intermediate LVDD, and LVDD). For patients with symptoms and/or signs suggestive of HF it is proposed to aid in the diagnosis of HFpEF. Before the introduction of this new algorithm the prevailing diagnostic criteria for LVDD were formulated in the guidelines of the European Association of Cardiovascular Imaging (EACVI) and American Society for Echocardiography (ASE) in 2016 [13] and in the ESC guidelines on heart failure for 2016 [7].

We investigated whether the prevalence of LVDD differed when comparing the latest HFA-PEFF 2019 diagnostic algorithm to the two previous recommendations for diagnosis of LVDD defined by the EACVI/ASE and the ESC. Furthermore, we assessed the concordance between the new diagnostic algorithm and the prevailing recommendations. For the present study we used a case cohort study of individual referred to a outpatient cardiology clinic by the general practitioner (GP) for diagnostic cardiac assessment.

3

Methods

Study population

Study design and procedures of the "Discovery of biomarkers for the presence and progression of left ventricular diastolic dysfunction and HEart faiLure with Preserved ejection Fraction in patients at risk for cardiovascular disease" (HELPFul) study have been published in more detail [17]. Briefly, HELPFul is a Dutch case cohort in which patients participated who were referred by their GP for a diagnostic cardiac assessment. Patients who had a previous cardiac intervention, , or who were known with congenital cardiac disease were excluded from participation. Patients that had a ratio of the peak early (E) diastolic filling velocity and early diastolic mitral annular velocity (e') (average of septal and lateral) (E/e') ≥ 8 with tissue Doppler echocardiography were considered as 'a case', because these patients were considered to have a higher probability of having LVDD. 'Cohort' patients were randomly sampled from all patients aged 45 years or older, striving to include 25% of eligible participants. The study adheres to the principles of the declaration of Helsinki. Written informed consent was obtained from all participants. The ethics committee of the University Medical Center Utrecht approved the study (reference number: NTR6016).

Assessment; Clinical variables

Information on co morbidities, medical history, and medication use was collected. The diagnostic work up further consisted of physical examination, blood testing of standard cardiovascular biomarkers, electrocardiogram (ECG), bycicle exercise ECG, and transthoracic echocardiogram. A structured case record form was used to assess symptoms suggestive of cardiac pathology. Hypertension was determined by (i) self reporting, (ii) use of blood pressure lowering medication, or (iii) a mean (of at least two measurements) systolic blood pressure > 140mmHg at the outpatient center. Type 2 diabetes was determined by self
reporting or use of blood glucose lowering medication. Hypercholesterolemia was determined by self reporting or use of lipid lowering medication. Atrial fibrillation was determined by self reporting or atrial fibrillation on ECG at the outpatient center. Body mass index (BMI) was calculated from dividing weight (kg) by squared height in meters (m2). Waist to hip ratio was calculated from dividing waist circumference (cm) by hip circumference (cm). The estimated glomerular filtration rate (eGFR) was calculated from both creatinine and cystatin c with the validated CKD EPI formula [18].

Assessment; Echocardiography

Comprehensive transthoracic echocardiographic examinations were performed with a General Electric (GE) Vivid E6 or E7 device (GE Healthcare, United Kingdom) by trained sonographers and interpreted by experienced cardiologists in accordance with the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) 2016 recommendations for chamber quantification [19]. The left ventricular ejection fraction (LVEF) was assessed quantitatively (Teichholz), or semi quantitatively (eye balling), in case an LVEF was considered abnormal the LVEF was calculated using the Simpsons biplane method of disk. Diastolic parameters that were measured, included pulsed wave Doppler of the mitral valve inflow velocities and pulmonary venous inflow and tissue Doppler imaging of the mitral annulus motion. The ratio of peak early (E) diastolic filling velocity to peak atrial (A) contraction filling velocity was calculated to derive the E/A ratio. The early diastolic mitral annular recoil velocity (e') was determined at both the septal and lateral wall. The E/e' ratio was calculated by dividing E with the average of septal and lateral e'. Left atrial volume (LAV) was derived from tracing the left atrium during maximal atrial filling in the apical two chamber and apical four chamber views, and indexed (LAVi) by body surface area (BSA). Left ventricular mass was calculated according

to the formula that was validated by Devereux, and indexed (LVMi) by BSA [20]. Relative wall thickness (RWT) was calculated by multiplying posterior wall thickness at end diastole by two and dividing the sum by left ventricular end diastolic dimension. The sonographers assessed tricuspid regurgitation (TR) in the parasternal right ventricular (RV) inflow, parasternal short axis and apical 4 chamber views. Continuous wave Doppler sampling of the peak TR velocity was used and a minimum of five sequential complexes were recorded. The peak velocity of the TR signal was measured with continuous wave Doppler and used to calculate the systolic pulmonary artery pressure (SPAP) with the modified Bernoulli's equation [21].

Definition of LVDD

All three definitions of LVDD were applied separately in participants with a LVEF above (>=) 50% on echocardiography. A flow diagram of the procedure described below is provided in Figure 1. LVDD classification with the 2019 diagnostic algorithm of the ESC/HFA working group ('HFA PEFF 2019') was performed as follows; those with zero or one point were classified as 'normal', 2 to 4 points as 'intermediate' and patients with 5 or 6 points as 'LVDD' [16]. As the 2016 ESC guidelines ('ESC 2016') do not provide a diagnostic algorithm [7], but only recommend criteria and cut offs, we used the interpretation proposed by Reddy et al. [22]. The 'adapted' classification with the ESC 2016 guidelines was as follows; patients with E/e' ratio >13 plus (i) an average of lateral and septal e' < 9 cm/s, (ii) or LAVi > 34 ml/m2, or (iii) LVMi >95 g/m2 for women and > 115 g/m2 for men were classified as LVDD, the others as 'no LVDD' [7]. The classification with the ASE/EACVI 2016 guidelines ('ASE/EACVI 2016') [13] was as follows; patients with (i) E/e' ratio > 14, (ii) lateral and septal e' velocities of < 10 cm/s and 7 cm/s , (iii) TR velocity > 2.8m/s and (iv) LAVi > 34 ml/m2 were classified as LVDD if three or four items were fulfilled, as 'intermediate' if two items were fulfilled and as normal if one or no item was above the cut off.

Data analyses

We excluded individuals in whom not all three recommendations could be compared from further analysis. We were able to apply the diagnostic criteria to all 697 individuals for the HFA PEFF 2019 recommendations, to 620 (89%) individuals for the ESC 2016 recommendations and to 613 (88%) individuals for the ASE/EACVI 2016 recommendations. In 550 subjects (79%) all three diagnostic sets of criteria could be applied, and this subset of patients was used for direct comparisons.

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables as absolute numbers and percentages. To investigate possible effects of age on (re)classification, age was divided in quartiles of equal width. Prevalence and concordance was calculated. Data analysis was performed using SPSS version 25 (International Business Machines INC., Chicago, IL, USA).

Results

The baseline clinical and echocardiographic characteristics of the study population are shown in Table 1. The mean age of the 550 individuals was 62 years (SD 9.2) and 371 (68%) were women. An overview of classification and reclassification is provided in Figure 1. The percentage of classification as LVDD was 5.5% (n=30) according to the 'HFA PEFF 2019', 24.5% (n=135) according to the 'ESC 2016' and 1.8% (n=10) according to the 'ASE/EACVI 2016'. The 'HFA PEFF 2019' and the 'ASE/EACVI 2016' classified 74.9% (n=412) and 11.1% (n=61) patients as intermediate, respectively.
In Table 2, comparing the 'HFA PEFF 2019' to the 'ESC 2016' showed a concordance of 23.5% (129/550). Upward classification of patients with no LVDD with the 'ESC 2016' towards intermediate or LVDD by the 'HFA PEFF 2019' was observed in 74.5% of the 415 patients: from no LVDD to intermediate (n=306 (73.7%)), or from no LVDD to LVDD (n=5 (1.2%)). Of 135 patients that were classified as having LVDD with the 'ESC 2016', 110 (81.5%) were classified downwards with the 'HFA PEFF 2019', either to intermediate cases (n=106 (78.5%)) or to having a normal function (n=4 (3.0%)).
In Table 3 the data are presented of the comparison between the 'HFA PEFF 2019' and the 'ASE/EACVI 2016' ,which was concordant in 29.5% (162/550). Compared with the ASE/EACVI 2016 recommendations 383 (69.6%) patients were classified up and 5 (0.9%) patients were classified down with the 'HFA PEFF 2019'. Of 479 patients previously classified as 'normal' for diastolic function with the 'ASE/EACVI 2016', 371 (77.5%) were classified up with the 'HFA PEFF 2019' either as intermediate cases (n=358 (74.7%)) or as cases with LVDD (n=13 (2.7%)). Of 61 patients that were classified as intermediate cases with the 'ASE/EACVI 2016', 12 (19.7%) were classified up as having LVDD with the 'HFA PEFF 2019', but none were classified down to a normal function. Of 10 patients previously classified as having LVDD with the 'ASE/EACVI 2016', 5 (50.0%) were classified down as intermediate cases with the 'HFA PEFF 2019'.

Subgroups of age and sex

Because the development of LVDD is strongly related to age and sex, we performed subgroup analyses with age quartiles and by sex. A classification table comparing age quartiles is shown in Table 4. The concordance between recommendations is highest in the youngest age quartile (<55.4 years) with 37.7% of patients (n=52) classified the same with the 'HFA-PEFF 2019' as the 'ESC 2016' and 45.7% (n=63) with the 'HFA PEFF 2019' compared with the 'ASE/EACVI 2016'. Classification tables comparing the three recommendations stratified by sex are presented in supplemental tables S1 S4. There were small, but not statistically or clinically significant differences in prevalence and concordance between women and men. The percentage of LVDD in women in the HELPFul study was 5.1% (n=19) with the 'HFA PEFF 2019', 25.7% (n=96) with the 'ESC 2016' and 2.4% (n=9) with the 'ASE/EACVI 2016', for men the percentages were 6.1% (n=11), 21.8% (n=39) and 0.6% (n=1) respectively. Concordance between the 'HFA PEFF 2019' and 'ESC 2016' was 20.9% (n=78) for women and 28.5% (n=51) for men. For the 'HFA PEFF 2019' and 'ASE/EACVI 2016' concordance was 28.6% (n=106) for women and 31.3% (n=56) for men.

Discussion

We compared the prevalence of LVDD using the recently proposed HFA PEFF 2019 diagnostic algorithm (i.e. the second step of the diagnostic work up proposed for HFpEF) to the ESC 2016 heart failure guideline recommendations and to the ASE/EACVI 2016 heart failure guideline recommendations. First, the prevalence of LVDD varies widely in our cohort of patients referred for cardiovascular screening at a cardiology outpatient center and concordance in classification was low between all the compared international recommendations. Importantly, the HFA PEFF 2019

algorithm resulted in a large intermediate group with inconclusive evidence to diagnose LVDD. Second, we investigated differences between men and women and observed that women have a slightly higher prevalence of LVDD with all three LVDD criteria, but that the concordance between the diagnostic sets of criteria was similarly low in both women and men.
The ESC/HFA working group for heart failure has put large efforts into a new comprehensive, step wise diagnostic algorithm for suspected HFpEF. Their work has already been validated in three cohorts of patients with HFpEF [23] and showed promising diagnostic performance, with a positive predictive value of a high HFA PEFF score (≥ 5 points) of 98%. Our cohort is less selected than the clinical cohorts used in the validation study of the HFA PEFF score and differs from clinical and community cohorts that have more selectively included individuals with certain symptoms, for instance unexplained dyspnea, or one comorbidity, for instance hypertension.In this heterogeneous population of patients referred for evaluation of non-acute symptoms we observed several surprising consequences of the use of the HFA PEFF score in detecting LVDD, which are the large intermediate group, the small percentage of patients classified with definite LVDD and the low percentage of patients that is classified the same as with previous recommendations for the diagnosis of LVDD.
Prevalence and concordance in previous studies
The large variation in prevalence of LVDD when comparing different diagnostic recommendations for LVDD within one study population has been described previously, but none have compared recent recommendations with the new HFA PEFF score [14,15,24 26]. Among 1.485 participants of the community based (STANISLAS) cohort, mean age 47 years and 58% women, applying the ASE/EACVI 2016 criteria resulted in an overall lower prevalence of LVDD than with (I) ASE/EACVI 2009 criteria and two recommendations made by (II) Appleton [27] and by (III) Paulus [28] (1.3% versus 5.7 8.8%) [15]. Similarly, among participants of the (EPIPorto) community cohort, mean age 62 years and 63% women, a prevalence of LVDD of 1.4% was shown with the 2016 ASE/EACVI recommendations and 38.1% with the 2009 ASE/EACVI recommendations [14]. Likewise, Rasmussen et al. compared four different diagnostic sets of criteria (two different interpretations of the 2009 ASE/EACVI recommendations, one by Redfield et al. [1] and one from the (VALIDD) trial [29]) in 3474 participants of the (CARDIA) community cohort, which also resulted in the prevalence of LVDD ranging from 2% to 32% [24]. Additionally, the ASE/EACVI 2009 criteria have been shown to have led to at least 25 different interpretations, which upon testing in a single community cohort yielded prevalence estimates of LVDD varying from 12% to 84% [26]. Finally, a study in 885 patients of the GRADO study, in a primary care outpatient setting, showed that concordance between the ASE/EACVI 2009 recommendations and the Olmstead county classification or the Canberra study classification ranged from 59% to 73% [25]. Our findings are in line with these previous observations (varying prevalence estimates and low concordance) and underscore a persisting want: The use of a single prevailing diagnostic algorithm in cohort studies and trials should be encouraged to increase the comparability of results derived from any type of study involving LVDD and HFpEF.

The newly proposed intermediate group
The new HFA PEFF 2019 recommendations introduce an intermediate group that is recommended to undergo additional exercise echocardiography or invasive hemodynamics to detect increased (filling) pressures for the final diagnosis of LVDD in patients suspected of HFpEF. However even in a recent validation study of the HFA PEFF 2019 recommendations, 36% of patients were classified to the intermediate category [23]. In our study the intermediate group was even larger (76.4%), possibly due to the fact that we did not apply the recommended pre selection based on brain type natriuretic peptide (BNP) levels and symptoms of HF. In routine clinical practice cardiologists and general practitioners (GP's) will have a high suspicion of HF in patients that present with clear HF

symptoms and/or signs, or increased levels of natriuretic peptides. These patients will likely be referred or given further diagnostic work up regardless of their score, suggesting the HFA PEFF 2019 algorithm is of little benefit to this patient group.. The difficulty at the moment lies in the elderly population who do not have clear symptomatology nor clear elevated natriuretic peptides, but are at risk of developing more pronounced symptoms and could benefit from preventive treatment [30 33]. The algorithm may be most useful in these patients that might also benefit from referral for further diagnostic work up [31 33]. If other community based cohort studies confirm that use of the diagnostic algorithm results in a (too) large intermediate group, then the algorithm might benefit from modification, for instance by re defining which point score leads to classification as no LVDD, intermediate or LVDD.

Prognosis of LVDD towards HFpEF

Only a small number of studies investigated progressive LVDD or development of HF in patients with LVDD and showed that risk factors related to progression of LVDD can be different from those related to development of HF [3,5,34 36]. Patients with LVDD are heterogeneous with different profiles of cardiovascular and non cardiovascular comorbidities, such as hypertension, coronary artery disease, dyslipidemia, diabetes [37]. These comorbidities have been suggested to induce different disease specific changes in cardiovascular structure and function, hence influencing further progression of LVDD differently [38]. Further research is required to elucidate the specific relationship between LVDD and progression to HFpEF, and how the different risk factors are involved [6]. It is vital that future studies extending on this issue use similar diagnostic criteria and cut offs for the diagnosis of LVDD. Otherwise the risk factors that potentially drive the development of LVDD and the strength of their association could be different depending on the diagnostic criteria and cut offs that were applied [24].

Future implications

Ideally, the diagnosis of LVDD would be based on a validated diagnostic algorithm that can be used in different types of studies and study populations. The new diagnostic algorithm for LVDD creates an opportunity to improve the generally poor situation regarding standardization of diagnosis of LVDD in diagnostic, etiologic, prognostic and intervention research. A large individual participant data (IPD) meta analysis may aid in defining globally applicable diagnostic algorithms of LVDD, as within this design one can pool participants of a number of existing cohort studies and explore optimal diagnostic criteria and cut off values for LVDD. Preferably, these are chosen based on prognostic information such as incident hospitalizations and mortality. Furthermore, such an approach is able to explore subgroups in a valid manner, and therefore may also show that the 'one size fits all' does not hold for a diagnostic algorithm for LVDD. With such an IPD algorithm for the diagnosis of LVDD screening in populations at risk of developing HFpEF could be implemented, possibly combined with preventive treatment and more aggressive treatment of important co
morbidities, such as hypertension, diabetes and obesity.

Limitations

The new HFA PEFF 2019 diagnostic algorithm for LVDD presented by the HFA at the 2018 ESC HF congress in Munich is only one step in a four step approach to diagnose patients with HFpEF. The authors explicitly mention that the four step approach is for diagnosing HFpEF and therefore symptoms and/or signs suggestive of HF and a LVEF>50% is a prerequisite [16]. Evidence of LVDD is generally regarded as vital for the diagnosis of HFpEF, but in the absence of symptoms and signs of HF, i.e., isolated, LVDD can be regarded as a separate entity. Therefore we applied

only the second step of the four step approach, which is an algorithm for the diagnosis of LVDD, as previous work has shown that it is highly likely the algorithm for diagnosis of LVDD could be used in isolation by other investigators [26]. However this approach could have resulted in an overestimation of the relative size of the intermediate group in our study.

Conclusion

Different LVDD guidelines identify different populations with LVDD. This indicates that results from previous studies on etiology, diagnosis, prognosis and treatment options are rather dif-ficult to compare and interpret, thus more uniformity is required.

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Conflicts of interest
none declared

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Figure 1. Overview of application of LVDD recommendations and (re)classification.

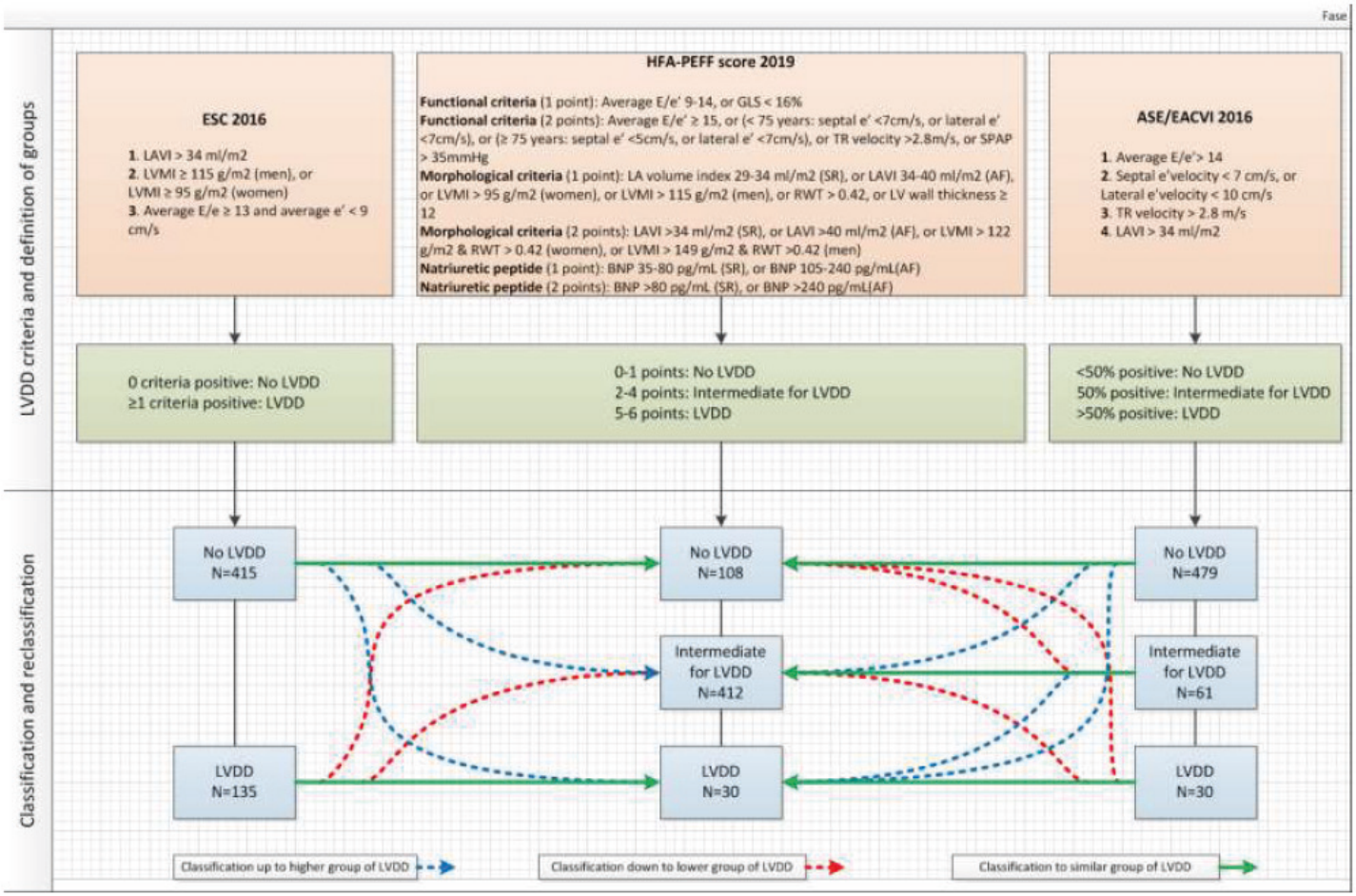


Table 1. Clinical and echocardiographic characteristics of the 550 participants in the HELPFul study

Clinical characteristics	**HELPFul subjects (n= 550)**
Mean age in years (SD)	62.6 (9.2)
Women (%)	371 (68)
Mean BMI in kg/m^2 (SD)	27.2 (4.4)
Hypertension (%)	321 (58)
Hypercholesterolaemia (%)	224 (41)
Median eGFR (ml/min/1.73m^3) (IQR)	84.8 (74.8-94.2)
History of diabetes (%)	47 (9)
Current smokers (%)	61 (11)
COPD (%)	69 (13)
Atrial fibrillation (%)	13 (2)
Mean Waist/hip ratio[b] (SD)	0.92 (0.08)
Echocardiographic measurements of diastolic function	
Median E/e' ratio (IQR)	9.0 (8.1- 10.5)
Median e' septal in m/sec (IQR)	7.0 (6.0-8.0)
Median e' lateral in m/sec (IQR)	8.0 (7.0-10.0)
Median LAVi in cm^2/m^2 (IQR)	24.3 (19.5-30.4)
Mean LVMi in g/m^2 (SD)	75.7 (19.1)
Mean RWT (SD)	0.43 (0.09)
Median Ejection fraction (IQR)	67.0 (63.0-73.0)
Biomarkers	
Median BNP in pg/mL (IQR)	18.3 (10.0-36.0)
Median hs-TnI in pg/mL (IQR)	2.6 (1.8-4.1)

BNP = B-type natriuretic peptide, BMI=body mass index, COPD = chronic obstructive pulmonary disease, eGFR=estimated glomerular filtration rate, ESC=European Society of Cardiology, ASE/EACVI=America Society of Echocardiography/European Assocation of CardioVascular Imaging, hs-TnI= high sensitivity-Troponin I, LAVi = left atrial volume indexed for BSA, LVDD=left ventricular diastolic dysfunction, LVMI = left ventricular mass indexed for BSA, RWT = relative wall thickness, TR velocity = Tricuspid valve regurgitation velocity.

Table 2. Classification of diastolic dysfunction of 550 participants in the Helpful study comparing the HFA-PEFF 2019 recommendations and the ESC 2016 HF guideline recommendations.

		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ESC 2016 recommendations	Normal	**104**	306	5	415
	LVDD	4	106	**25**	135
	Total	108	412	30	550

Table 3. Classification of diastolic dysfunction of 550 participants in the Helpful study comparing the HFA-PEFF 2019 recommendations and the ASE/EACVI 2016 guideline recommendations.

		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ASE/EACVI 2016 recommendations	Normal	**108**	358	13	479
	Intermediate	0	**49**	12	61
	LVDD	0	5	**5**	10
	Total	108	412	30	550

Table 4. Classification table of patients according to age quartiles.

		Age quartiles			
		< 55 years (n=138)	56-63 years (n=137)	63-69 years (n=136)	>69 years (n=139)
Mean age in years (SD)		51.1 (3.1)	59.0 (2.1)	65.7 (1.9)	74.6 (4.6)
Women (%)		94 (68)	92 (67)	97 (71)	88 (63)
Reclassification from ESC 2016 to 'HFA-PEFF 2019'	Down classified by applying 'HFA-PEFF' 2019(%)	22 (15.9)	22 (16.1)	32 (23.5)	34 (24.5)
	Concordant classification (%)	52 (37.7)	33 (24.1)	20 (14.7)	24 (17.3)
	Up classified by applying 'HFA-PEFF 2019'(%)	64 (46.4)	82 (59.9)	84 (61.8)	81 (58.3)
Reclassification from ASE/EACVI 2016 to 'HFA-PEFF 2019'	Down classified by applying 'HFA-PEFF 2019'(%)	1 (0.7)	0 (0)	2 (1.5)	2 (1.4)
	Concordant classification (%)	63 (45.7)	42 (30.7)	26 (19.1)	31 (22.3)
	Up classified by applying 'HFA-PEFF 2019'(%)	74 (54.6)	95 (69.3)	108 (79.4)	106 (76.3)

Supplemental table S1. Classification of diastolic dysfunction *in women* using the HFA-PEFF 2019 recommendations and ESC 2016 recommendations.

		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ESC 2016 recommendations	Normal	**63**	208	4	275
	LVDD	3	78	**15**	96
	Total	66	286	19	371

Supplemental table S2. Classification of diastolic dysfunction *in men* using the HFA-PEFF 2019 recommendations and ESC 2016 recommendations.

		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ESC 2016 recommendations	Normal	**41**	98	1	140
	LVDD	1	28	**10**	39
	Total	42	126	11	179

Supplemental table S3. Classification of diastolic dysfunction prevalence *in women* using the HFA-PEFF 2019 recommendations and ASE/EACVI 2016 recommendations.

		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ASE/EACVI 2016 recommendations	Normal	**66**	245	8	319
	Intermediate	0	**36**	7	43
	LVDD	0	5	**4**	9
	Total	66	286	19	371

Supplemental table S4. Classification of diastolic dysfunction prevalence *in men* using the HFA-PEFF 2019 recommendations and ASE/EACVI 2016 recommendations.

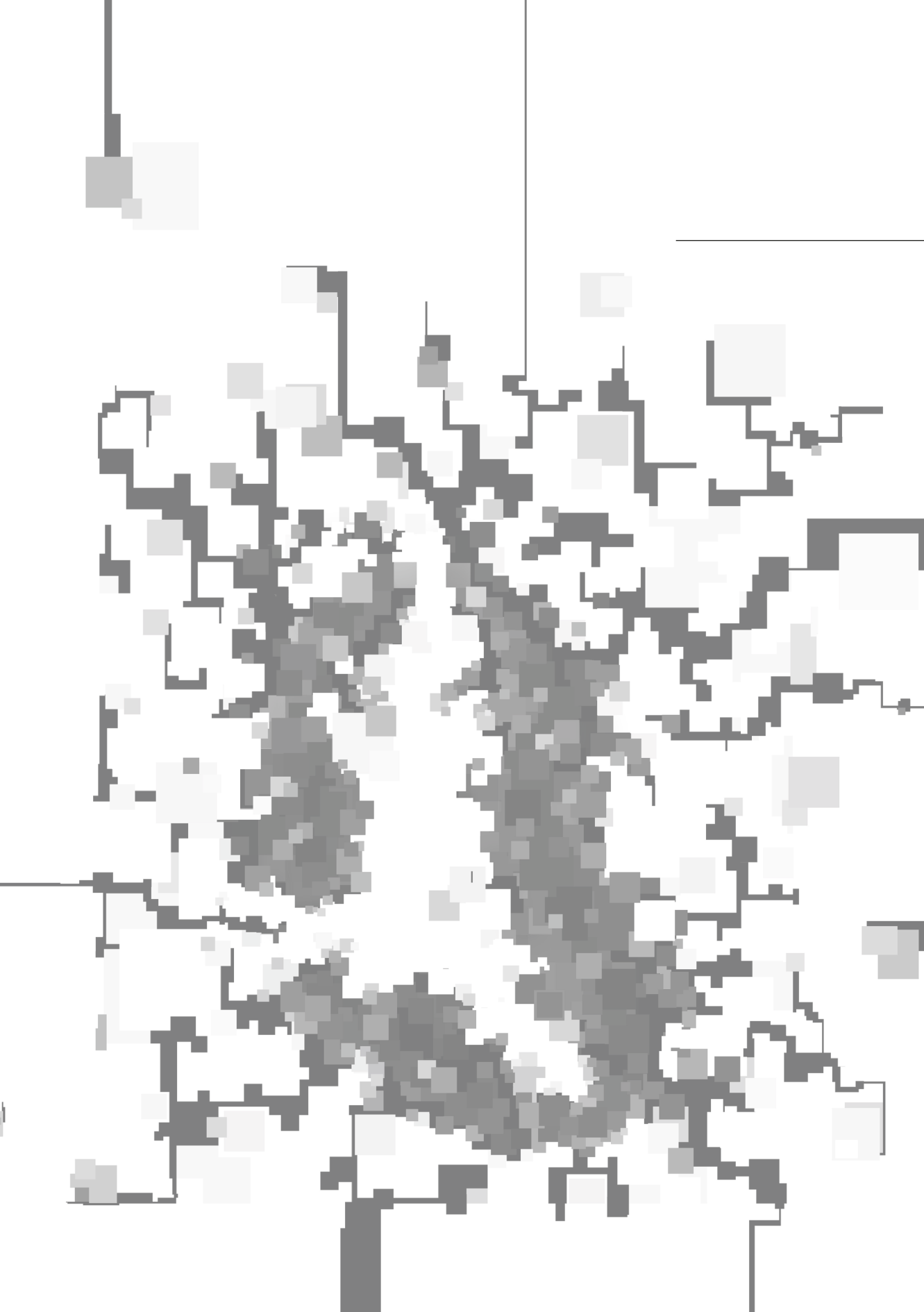
		HFA-PEFF 2019 recommendations			
		Normal	Intermediate	LVDD	Total
ASE/EACVI 2016 recommendations	Normal	**42**	113	5	160
	Intermediate	0	**13**	5	18
	LVDD	0	0	**1**	1
	Total	42	126	11	179

Supplemental table S5. Overview of criteria and cut-points used for diagnosing LVDD.

	HFA-PEFF 2019	ESC 2016	ASE/EACVI 2016
Septal e' cm/s < 7 cm/s *	√		√
Lateral e' cm/s < 10 cm/s *	√		√
Septal e' cm/s < 5 cm/s (age ≥ 75 years)	√		
Lateral e' cm/s < 7 cm/s (age ≥ 75 years)	√		
Average E/e' ≥ 13 and average e'< 9 cm/s		√	
Average E/e' ≥ 15	√		
Average E/e' 9-14	√		
Average E/e' >14			√
TR velocity m/s > 2.8 m/s	√		√
Global longitudinal strain < 16 %	√		
LAVI > 34 ml/m^2 with SR	√	√	√
LAVI 29-34 ml/m^2 with SR	√		
LAVI > 40 ml/m^2 with AF	√		
LAVI 29-34 ml/m^2 with AF	√		
LVMI ≥ 149 g/m^2 & RWT> 0.42 (Men)	√		
LVMI ≥ 122 g/m^2 & RWT> 0.42 (Women)	√		
LVMI ≥ 115 g/m^2 for men	√	√	
LVMI ≥ 95 g/m^2 for women	√	√	
RWT > 0.42	√		
LV wall thickness ≥ 12 mm	√		
NT-proBNP > 220 pg/mL with SR	√		
NT-proBNP > 660 pg/mL with AF	√		
NT-proBNP 125-220 pg/mL with SR	√		
NT-proBNP 365-660 pg/mL with AF	√		
BNP > 80 pg/mL with SR	√		
BNP > 240 pg/mL with AF	√		
BNP 35-80 pg/mL with SR	√		
BNP 105-240 pg/mL with AF	√		
Sinus rhythm	√		
Atrial fibrillation	√		
LVEF > 50%	√	√	√

TR velocity = Tricuspid valve regurgitation velocity, LAVI = left atrial volume indexed for BSA, LVMI = left ventricular mass indexed for BSA, RWT = relative wall thickness, NT-proBNP = N-terminal propeptide of B-type natriuretic peptide, BNP = B-type natriuretic peptide, LVEF = left ventricular ejection fraction.

* For HFA-PEFF 2019 diagnostic algorithm for LVDD an age cut-off is applied < 75 years.



Chapter 7

Opportunistic screening models for high-risk men and women to detect diastolic dysfunction and heart failure with preserved ejection fraction in the community

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ABSTRACT

Background
The prevalence of undetected left ventricular diastolic dysfunction (LVDD) is high, especially in the elderly with comorbidities. LVDD is a prognostic indicator of heart failure, in particularly heart failure with preserved ejection fraction (HFpEF) and of future cardiovascular and all-cause mortality. Therefore we aimed to develop sex-specific diagnostic models to enable the early identification of men and women at high-risk of LVDD with or without symptoms of HF who require more aggressive preventative strategies.
Design Individual patient data from four primary care HF-screening studies were analysed (1371 participants (excluding patients classified as HF and LVEF <50%)).

Methods
Eleven candidate predictors were entered into logistic regression models to be associated with the presence of LVDD/HFpEF in men and women separately. Internal-external cross-validation was performed to develop and validate the models.

Results
Increased age and -blocker therapy remained as predictors in both the models for men and women. The model for men additionally consisted of increased body mass index, moderate to severe shortness of breath, increased pulse pressure, and history of ischaemic heart disease. The models performed moderately and similarly well in men (c-statistics range 0.60 to 0.75) and women (c-statistics range 0.51 to 0.76) and the performance improved significantly following the addition of NTproBNP (c-statistics range 0.61 to 0.80 in women and 0.68 to 0.80 in men).

Conclusions
We provide an easy to use screening tool for use in the community, which can improve the early detection of LVDD/HFpEF in high-risk men and women and optimise tailoring of preventive interventions.

Introduction

Left ventricular diastolic dysfunction (LVDD), a functional cardiac abnormality, is characterised by the impairment of LV relaxation and increased LV stiffness and is the dominant underlying feature of heart failure with preserved ejection fraction (HFpEF).
The prevalence of undetected LVDD is high in the community with estimates exceeding 30% in population based studies among adults.[1,2] Recognising LVDD is important as not only is it known to be independently associated with the development of HF[3,4], but it is also known to be predictive of cardiovascular and all-cause mortality.[5,6] Therefore early recognition and implementation of management strategies could potentially play a major role in improving prognosis. To assess LVDD, the latest European Society of Cardiology (ESC) guidelines suggest the use of various structural/functional echocardiographic measures including the left atrial volume index (LAVI), E/e' and longitudinal strain.[6] However such measurements are not feasible in all community-dwelling men and women due to high costs and time pressures. Currently, there are models available for the prediction of all-type HF, highlighting the importance of history taking and physical examination as well the use of NTproBNP.[7] A practical model to predict LVDD (with or without symptoms (HFpEF)) does not exist; previous studies that examined predictors of LVDD lacked clinical variables and only included echocardiographic parameters, and are therefore not applicable for use in the community as a risk assessment tool to assess who should undergo echocardiography or not.[1,8]
Previous HF-screening trials focused on a combination of high-risk patients from the community such as the STOP-HF trial which included participants with at least one risk-factor such as hypertension and hypercholesterolemia.[9] This trial demonstrated a reduction in newly diagnosed HF and LV dysfunction (both diastolic and systolic) following intervention with cooperative cardiological management and intensified use of renin-angiotensin blockers and -blocker therapy. Therefore given the relevance of screening high-risk populations, we aimed to develop and validate a risk prediction model for LVDD/HFpEF using four HF-screening studies performed in high-risk individuals from the community aged 60 or 65 years and over. Given that evidence is accumulating regarding determinants of LVDD/HFpEF differing according to sex, this was performed separately for men and women. With this information, preventative strategies within the community can be tailored towards these high-risk individuals.

Methods

Study population

Four previously published studies performed in a primary care setting among high-risk community people aged 60 or 65 years or older (STRETCH, TREE, UHFO-COPD, and UHFO-DM) were combined into one individual patient dataset (IPD).[10–13] For a description of the four cohorts see Supplementary Figure 1. All of these studies had a common aim to screen for previously unknown, all-type HF. The studies consisted of older people with either (i) symptoms of shortness of breath on exertion [10], (ii) multimorbidity or polypharmacy [11], (iii) chronic pulmonary obstructive disease (COPD) [12], or T2D.[13] The data in all cross-sectional diagnostic studies was collected from all participants using the same uniform case record form with questions regarding symptoms, drug use, and medical history, evaluation of physical signs, and additional investigations with electrocardiography, B-type natriuretic peptide testing, and echocardiography.

Outcome, diagnostic predictors and model development

The outcome of HF or no HF, was established by an expert panel as described previously.[10–13] In cases with HF, the panel chose between HFpEF, HFrEF, and isolated right-sided HF, primarily based on ejection fraction (cut point 45%) and estimated pulmonary artery pressures. Natriuretic peptide measurements were used as an inclusion criterion for echocardiography in the STRETCH cohort, applying a cut-off point of N-terminal pro b-type natriuretic peptide (NTproBNP) level above 125 pg/mL (≈15 pmol/L).[6] The panel also assessed NTproBNP levels in the TREE cohort prior to diagnosis. The panels were not privy to the NTproBNP levels in the UHFO-COPD and UHFO-DM cohorts, thereby preventing incorporation bias for this variable in these two cohorts.[14] The reproducibility of this panel consensus method has been shown to be high (mean inter-agreement with re-evaluation of a random sample of 10% of the cases; K = 0.84 (Rutten K = 0.90, Mourik K = 0.74, van Riet K = 0.89, Boonman K = 0.82)). Only patients who underwent TDi were selected for the current study (Supplementary Figure 1). All studies measured the early diastolic lengthening velocities (e') at the septal and lateral side and took the average, except the UHFO-DM study which only examined the septal side. We redefined patients with HF according to the recent 2016 ESC guidelines on HF into HFrEF, HFmrEF, and HFpEF using the cut points of left ventricular ejection fraction (LVEF) of 40% and 50%. According to this definition, patients diagnosed with HFrEF (n=36, HF symptoms and LVEF <40%) and HFmrEF (n=52, HF symptoms LVEF 40-49%) were removed leaving 1371 patients in the current study.

LVDD was assessed non-invasively by echocardiography including measurements with TDi. LVDD was defined, using recommendations from the 2016 ESC guidelines, [6] as an E/e' above 13 or an E/e' between 8 and 13 with one or more of the following:

- LAVI > 34 ml/ m2
- Left ventricular mass index (LVMI) >115 mg/m2 for males or >95 mg/m2 for females
- Atrial fibrillation (AF) on the ECG
- NTproBNP level >125 pg/ml

Those defined as having LVDD therefore have a LVEF ≥50% and contain asymptomatic participants as well as individuals with HF symptoms and thus may also be identified as HFpEF. The outcome was subsequently defined as those who fulfilled the criteria for LVDD (including those with symptoms of HF and thus HFpEF according to an expert panel) versus those without LVDD (and in view of the exclusion criteria) without LVSD/HFrEF/HFmrEF).

We evaluated, in a multivariable manner, eleven potential diagnostic predictors from previous literature, known to predict at least univariably, diastolic dysfunction.[1,5,8,15,16] These were; age, a history of IHD, AF, hypertension, T2D, angina pectoris, shortness of breath at least when walking at a normal pace (MRC ≥3), ankle oedema, pulse pressure, body mass index (BMI), and the use of -blocker therapy.

Data analysis

We aimed to derive four diagnostic models: first a clinical model for men and women separately with all the aforementioned variables and excluding NTproBNP, and a second, extended model, again separately for men and women, including all independent variables with the addition of NTproBNP. From the candidate diagnostic predictors, we selected those that were important in predicting the presence of LVDD/HFpEF in men and women separately following the Akaike information criteria (AIC) in a multivariable logistic regression model. NTproBNP was log transformed for all analyses.

A summary of the missing values is displayed in Supplementary Table 2. Missing values in each dataset set were imputed five times separately for men and women using the MICE algorithm in R [17].

In all analyses a linear relationship between the outcome LVDD/HFpEF and the continuous predictors age, BMI and log NTproBNP value was assumed and checked. There was no collinearity between variables. Data was analysed using R version 3.3.2.[18]
The Internal-External Cross Validation (IECV) method was used for model development and validation. Further details can be found in the supplementary material.
The performance of the models was quantified by examining discrimination and calibration.
A risk score was constructed for both men and women separately from the final models multiplying the shrunken coefficients by two and then rounding to the nearest integer. A dummy variable was added representing whether a participant came from the TREE cohort, the highest risk population, i.e with three or more chronic or vitality threatening diseases and/or using five or more prescribed drugs daily during the past year in people aged 65 years, to account for differences in prevalence and therefore baseline risk of LVDD/HFpEF. The risk of LVDD/HFpEF was then calibrated using logistic regression modelling according to the scores, resulting in a corresponding risk for each score, which was presented graphically. The total range of scores was divided by three to create different risk groups; mild, moderate and high. The participants were then allocated a particular group depending on their summed score.

Results

The baseline characteristics of the 1371 patients included in the study from the four participating cohorts stratified by sex are displayed in Table 1. Overall more women (n=706, 51.5%) than men (n=665, 48.5%) participated in the studies. Mean age was comparable across the four cohorts (range 71.0 to 75.5 years), although somewhat lower in the UHFO-DM cohort because of the age cut-point of 60 years, and there were no mean age differences between sexes within each cohort. BMI was generally higher in women (mean BMI 28.2 (standard deviation 4.9)) than in men (27.2 (standard deviation 3.7)) across all cohorts. Women were more likely to suffer from hypertension (67.4% vs. 56.4%), whereas men were more likely to suffer from T2D than women (23.4% vs. 18.4%) in the three cohorts excluding UHFO-DM (as all participants have T2D). Men were also more likely to suffer from IHD (21.1% vs. 7.4%), and more often had a history of AF (11.6% vs. 4.4%) than women. The prevalence of previously unrecognised LVDD/HFpEF was higher in women than men (72.2% vs. 55.6%)(Table 1).
From the eleven candidate predictors in the clinical model, age and -blocker therapy were important predictors in a minimum of three out of the four datasets for the presence of LVDD/HFpEF in women (Table 2). In men, increased age, increased BMI, shortness of breath when walking at a normal pace or worse (MRC ≥3), increased pulse pressure, a history of IHD and also -blocker therapy were important predictors in a minimum of three out of the four datasets. Beta coefficients and odds ratios for each of the final predictors for men and women were additionally calculated for only the individuals with NTproBNP levels >125pg/ml (Supplementary Table 3).
Discrimination of the models was similar between men and women. Discrimination of the male model (consisting of increased age, increased BMI, shortness of breath when walking at a normal pace or worse (MRC ≥3), increased pulse pressure, a history of IHD and -blocker therapy) ranged at cross-validation from AUC 0.60 to 0.75 (Supplementary Table 4). Discrimination of the female model (consisting of only age and -blocker therapy) ranged at cross-validation from AUC 0.51 to 0.76. The addition of NTproBNP to the models improved the performance in both men and women with AUCs in men ranging from 0.68 to 0.80 and in women from 0.61 to 0.80.
Calibration of the models, as displayed by the OE ratios (Supplementary Table 4) and visualised with calibration plots (Supplementary Figure 2) was better in women than men but improved in

both men and women following the addition of NTproBNP to the models..
The corresponding bootstrap corrected c-statistic of the final model for all four cohorts combined in men was 0.66 (95% CI 0.62-0.69) for the clinical model and 0.80 (95% CI 0.77-0.84) for the extended model with the addition of NTproBNP. For women, the corresponding bootstrap corrected c-statistic of the final model was 0.58 (95% CI 0.54-0.62) for the clinical model and 0.78 (95% CI 0.74-0.81) for the extended model with the addition of NTproBNP.
From these final models a scoring rule was constructed, separately for men and women with and without NTproBNP (Table 3). This scoring rule can be used to extrapolate the absolute risk of an individual having LVDD/HFpEF by first summing up the score and then applying it to the predicted probability figures represented in Supplementary Figure 3 and Supplementary Figure 4.
The performance of the female model using the additional male specific predictors in addition to age and -blocker therapy (increased BMI, shortness of breath when walking at a normal pace or worse (MRC ≥3), increased pulse pressure, a history of IHD), as assessed by the bootstrap corrected c-statistic was 0.60 (95% CI 0.56-0.63) and with the addition of NTproBNP 0.78 (95% CI 0.74-0.81). Hence adding the additional predictors did not improve the performance significantly. The performance of male model using only the predictors remaining in the female model which were also present in the male model (age and -blocker therapy) i.e excluding the additional male-specific predictors, was 0.62 (95% CI 0.59-0.66) and with the addition of NTproBNP 0.80 (95% CI 0.76-0.83).
Using the risk scores to categorise men and women into low, moderate and high-risk categories (Table 4), we show that with a cut-point of 22 or above, 34.7% of men are at high-risk of having LVDD/HFEF and thus should undergo echocardiography. Of these men, 88.8% will actually have confirmed LVDD/HFpEF. With a cut-point of above 14, 21.4% of women are categorised as being at high-risk of having LVDD/HFpEF so should also undergo echocardiography. Of these women, 97.4% will have confirmed LVDD/HFpEF.

Discussion

We developed and validated the first sex-specific models for the prediction of LVDD/HFpEF among high-risk men and women over the age of 60 or 65 in four opportunistic HF screening cohorts in the community. The multivariable logistic models performed similarly in men and women and both sexes shared overlapping predictors, albeit with the model in women only containing two of the six independent predictors making up the male model (increased age and -blocker therapy). The male model also consisted of history of IHD, shortness of breath when walking at a normal pace or worse (MRC ≥3), increased pulse pressure and increased BMI. Nevertheless, after applying the male model in females and visa versa, it is evident that age, -blocker therapy and NTproBNP are the most important predictors in both men and women for predicting LVDD/HFpEF. The model accurately categorises 88.3% of high-risk men and 94.4% of high-risk women, according to the constructed risk scores, as having confirmed LVDD/HFpEF on echocardiography.
Age is a well known determinant of LVDD/HFpEF and also all-type HF.[15] Echocardiographic parameters used to define LVDD are affected by the effect of ageing on myocardial stiffness.[21] Also increased BMI and IHD have previously been shown to be independently predictors of LVDD.[22,23] Interestingly, we showed that these variables remained as independent predictors in a reduced model with backward regression only in men. -blocker therapy remained an independent predictor in both men and women. We subsequently evaluated a model containing only hypertension, angina, AF, history of IHD, as possible indications for -blocker therapy use in addition to -blocker therapy, and still showed an independent association between -blocker therapy and LVDD/HFpEF in both men (odds ratio (OR) 2.45 [95% CI 1.64-3.66]) and women

(OR 1.74 [95% CI 1.14-2.64), although these values were lower than with univariable analysis (OR 3.32 [95% CI 2.33-4.75] in men, OR 2.17 [95% CI 1.48-3.18] in women). However, whether the use of -blockers is related to LVDD/HFpEF or their use is merely representative of the many indications, including a history of IHD, angina pectoris, AF and other tachycardias, and hypertension, remains unclear.
The addition of NTproBNP to the models significantly improved the performance of the models in both men and women. This highlights the importance of NTproBNP, not only in diagnosing HFpEF but also for LVDD and, as previously shown, for all-type HF.[6,7]
We present the first models of their kind. Previous screening studies have generally, not looked at LVDD/HFpEF in men and women separately from the community. Previous models also lacked external validation and incorporated echocardiographic parameters into the models and thus, because of logistic reasons and the costs involved, cannot be used in the community.[1,8] A study by Ho et al. compared the prediction of HFrEF and HFpEF and found that increased age, increased BMI, antihypertensive treatment, and IHD were independent predictors of HFpEF in multivariable analyses in four combined general population studies.[16] Increased age, sex, increased systolic blood pressure, increased BMI, smoking status, antihypertensive treatment, LV hypertrophy, left bundle branch block, T2D, and previous myocardial infarction were predictive of HFrEF. It is not known how the antihypertensive treatment was defined and whether or not it included -blocker therapy. They applied 45% as a cut point between HFrEF and HFpEF thus not considering HFmrEF. Although not clear, the authors may have analysed HFpEF vs. no HF plus HFrEF, and HFrEF vs. no HF plus HFpEF. It is important to highlight that we evaluated LVDD/HFpEF vs. no LVDD/HFpEF in a population excluding LVSD/HFrEF and HFmrEF. Despite the differences in methodology, the results of the study by Ho et al. do show an overlap with our results concerning antihypertensive treatment as an independent predictor of LVDD/HFpEF in both men and women.
With applying state-of-the art regression analysis we present models that have been externally validated representing the "real world" population as our cohorts involve older men and women from the community who have a variety of different risk profiles, which is representative of the patients attending general practitioner clinics at high-risk of LVDD/HFpEF. Once patients have been identified at risk of having HF/LVDD, management including treatment and preventative strategies can be implemented such as risk factor management, as recommended by the guidelines to prevent progression of the disease and to prevent LVDD from entering into the symptomatic phase, i.e HFpEF.[6] These models can also be used to help identify low risk patients who do not require echocardiography limiting unnecessary cardiology and echocardiography referrals, reducing health care costs and reducing demands on resources. Treatment with spironolactone has shown promise in reducing cardiovascular events in patients with HFpEF in the TOPCAT post-hoc analysis results of the American sub-set population, and in those with elevated natriuretic peptide levels.[24,25] Thus it is not only extremely helpful in relieving symptoms in these patients suffering from congestion, which is one of the primary goals of such patients, but it may also help improve outcomes. Other drugs such as Empagliflozin show potential but the effect on cardiovascular outcomes will be determined in the near future following results of clinical trials. Therefore our models will be able to identify patients who would benefit from not only risk factor control, symptomatic relief with diuretics but also improve morbidity and prognosis of these patients.[26]

Strengths and limitation

Our study consists of cohorts from the general population and are applicable to primary care settings. By excluding LVSD/HFmrEF/HFrEF instead of combining them with no HF we provide better predictions as we are able to discriminate between subjects with HFpEF and no HF. However an outcome ideally consisting of three categories; no HF, HFrEF and HFmrEF, and

HFpEF would likely lead to a more informed clinical applicability. A limitation of our study is that participants of the STRETCH study only underwent echocardiography examination if they had an abnormal ECG and/or an NTproBNP >125 pg/mL. This criterium may have resulted in missing some participants with LVDD/HFpEF that were erroneously considered to have no structural or functional cardiac abnormalities. The prevalence estimate in that study may therefore be a little bit too high, but this is unlikely to affect the modelling and the related ORs, especially not when combining this study with the other three studies without such an exclusion criterion. Another limitation is that E/e' was used to diagnose diastolic dysfunction although evidence backing up the use of resting E/e' for left ventricular filling pressure remains limited.[27] Incorporation bias has been mentioned previously, as the expert panel on two out of the four cohorts were aware of the NTproBNP results when deciding on the diagnosis. It is important to realise that incorporation bias is inevitable in diagnostic modelling studies.[14] However avoiding the use of the NTproBNP results in the panel diagnosis may lead to a worse problem; misclassification of patients.[14] It is also important to note that in our study the information obtained from echocardiography was not used in the formulation of the prediction models. Trials previously focusing on at-risk cohorts, such as the STOP-HF trial have found a reduction in HF onset therefore our high-risk cohorts provide a valid basis to screen for HF/LVDD. However it is important to note that translation of such risk management strategies into routine primary care practices may be challenging.
In summary, we developed and externally validated sex-specific models for the prediction of LVDD/HFpEF in community based high-risk older men and women.This early detection will help to optimise tailoring of the required preventative interventions for LVDD/HFpEF.

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Conflicts of interests
All four studies were investigator-driven research projects, and Roche diagnostics was not involved in the design, execution or analysis of the study. None of the authors received personal payment from any industrial partner.

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Table 1. Baseline patient characteristics of the 1371 elderly participants divided over each cohort and stratified by sex

	STRETCH (≥65 years)			TREE (≥65 years)			UHFO-COPD (≥65 years)			UHFO-DM (≥60 years)		
	Male	Female	p	Male	Female	p	Male	Female	p	Male	Female	p
n	157	191		146	187		73	68		289	260	
Age (mean (sd))	74.9 (6.0)	75.5 (6.5)	0.37	75.2 (5.8)	74.5 (6.0)	0.31	73.2 (4.5)	72.7 (6.2)	0.64	71.0 (7.1)	71.8 (7.4)	0.2
Current Smoker, n (%)	32 (20.4)	19 (9.9)	0.01	20 (13.7)	15 (8.0)	0.14	17 (23.3)	14 (20.6)	0.86	45 (15.6)	31 (11.9)	0.27
Past medical history												
Hypertension, n (%)	76 (48.4)	117 (61.3)	0.02	98 (67.1)	146 (78.1)	0.03	23 (31.5)	25 (36.8)	0.63	178 (61.6)	188 (72.3)	0.01
IHD, n (%)	37 (23.6)	13 (6.8)	<0.001	51 (34.9)	25 (13.4)	<0.001	6 (8.2)	1 (1.5)	0.15	46 (15.9)	13 (5.0)	<0.001
AF, n (%)	21 (13.4)	12 (6.3)	0.04	26 (17.8)	17 (9.1)	0.03	4 (5.5)	3 (4.4)	1	26 (9.0)	13 (5.0)	0.1
Diabetes mellitus, n (%)	26 (16.6)	24 (12.6)	0.37	54 (37.0)	56 (29.9)	0.22	8 (11.0)	2 (2.9)	0.13	289 (100.0)	260 (100.0)	-
PAD, n (%)	13 (8.3)	10 (5.2)	0.36	22 (15.1)	10 (5.3)	0.01	2 (2.7)	1 (1.5)	1	22 (7.6)	12 (4.6)	0.2
COPD/asthma, n (%)	94 (59.9)	94 (49.2)	0.06	37 (25.3)	51 (27.3)	0.79	73 (100.0)	68 (100.0)	-	35 (12.1)	31 (11.9)	1
Symptoms												
MRC ≥3, n (%)	41 (26.1)	62 (32.5)	0.24	48 (32.9)	74 (40.0)	0.22	27 (37.0)	37 (54.4)	0.06	110 (38.1)	119 (45.8)	0.08
Orthopnoea +/or PND, n (%)	16 (10.2)	34 (17.8)	0.06	15 (10.3)	14 (7.5)	0.48	14 (19.2)	19 (27.9)	0.3	24 (8.3)	32 (12.3)	0.16
Swollen ankles, n (%)	41 (26.1)	78 (40.8)	0.01	27 (18.5)	60 (32.1)	0.01	14 (19.2)	20 (29.4)	0.22	62 (21.5)	87 (33.5)	0.002
Signs												
BMI (mean (sd))	27.3 (3.6)	28.3 (5.2)	0.05	27.6 (3.5)	28.5 (4.9)	0.04	25.3 (3.1)	26.5 (3.9)	0.05	27.5 (3.9)	28.3 (4.7)	0.04
SBP (mean (sd))	144.5 (16.5)	152.1 (19.1)	<0.001	139.0 (18.3)	139.2 (17.2)	0.94	155.6 (16.4)	152.8 (16.8)	0.32	156.5 (19.1)	161.9 (19.5)	0.001
DBP (mean (sd))	76.6 (10.5)	78.0 (11.2)	0.23	75.1 (9.2)	75.7 (8.5)	0.54	84.4 (8.8)	84.7 (11.2)	0.8	87.2 (9.7)	90.3 (9.9)	<0.001
Pulse pressure (mean (sd))	68.0 (14.2)	74.1 (16.7)	<0.001	63.9 (15.8)	63.5 (15.1)	0.79	71.3 (14.7)	68.1 (14.4)	0.2	69.3 (15.3)	71.5 (16.9)	0.11
HR (mean (sd))	71.6 (15.4)	74.3 (11.1)	0.06	68.5 (11.1)	70.2 (11.3)	0.19	74.3 (14.0)	73.9 (13.2)	0.86	69.0 (11.7)	70.3 (11.0)	0.17
Pulmonary crepitations, n (%)	37 (23.6)	37 (19.4)	0.41	17 (11.6)	10 (5.3)	0.06	11 (15.3)	3 (4.5)	0.07	21 (7.3)	27 (10.4)	0.25
Displaced apex, n (%)	11 (7.0)	3 (1.6)	0.02	17 (11.6)	12 (6.5)	0.14	16 (21.9)	14 (20.6)	1	39 (13.5)	30 (11.5)	0.57
Raised JVP, n (%)	17 (10.8)	12 (6.3)	0.18	12 (8.2)	13 (7.0)	0.82	9 (12.3)	8 (11.8)	1	8 (2.8)	10 (3.8)	0.64
Medications												
β-blocker, n (%)	47 (29.9)	43 (22.5)	0.15	70 (47.9)	79 (42.2)	0.35	7 (9.6)	10 (14.7)	0.5	94 (32.5)	104 (40.0)	0.08
Additional tests												
NTproBNP, pg/ml (median [IQR])	169.1 [109.9, 298.1]	177.6 [126.9, 279.1]	0.61	135.7 [70.4, 306.4]	126.2 [66.9, 230.3]	0.35	114.8 [70.3, 177.7]	126.6 [84.7, 219.3]	0.1	76.1 [42.3, 135.3]	84.6 [50.7, 135.3]	0.08
Abnormal ECG, n (%)	103 (74.1)	101 (57.4)	0.003	106 (72.6)	97 (52.2)	<0.001	39 (53.4)	26 (38.2)	0.1	118 (40.8)	79 (30.4)	0.01
Outcome												
E/e' (median [IQR])	9.7 [8.1, 11.6]	11.4 [9.2, 14.0]	-	11.5 [9.2, 13.8]	12.0 [10.0, 14.2]	-	10.0 [8.5, 12.0]	11.0 [9.2, 12.3]	-	8.3 [7.0, 9.7]	9.7 [81, 11.3]	-
E/e' > 13, n (%)	21 (13.4)	60 (31.4)	-	51 (34.9)	69 (36.9)	-	12 (16.4)	13 (19.1)	-	6 (2.1)	35 (13.5)	-
LVDD/HFpEF, n (%)	107 (68.2)	160 (83.8)	-	126 (86.3)	163 (87.2)	-	41 (56.2)	47 (69.1)	-	96 (33.2)	140 (53.8)	-

The p-value indicates the difference between men and women for each cohort. Normally distributed continuous variables are presented as a mean plus standard deviation (sd); non-normally distributed continuous variables are presented as a median with the interquartile range [IQR]. Categorical variables are presented as total count (n) and percentages (%). IHD: ischaemic heart disease, AF: atrial fibrillation, PAD: peripheral arterial disease, COPD: chronic obstructive pulmonary disease, PND: paroxysmal nocturnal dyspnoea, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, JVP: jugular venous pressure, NTproBNP: N-terminal pro b-type natriuretic peptide, E/e': ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity. Displaced apex: a palpable apex outside the mid-clavicular line in decubital position, or broadened/sustained in left decubital position

Table 2. Selection of clinical predictors from the eleven candidate predictors for men and women

Men

Developed in	TREE, UHFO-COPD & UHFO-DM		STRETCH, UHFO-COPD & UHFO-DM		STRETCH, TREE & UHFO-DM		STRETCH, TREE & UHFO-COPD	
	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)
Clinical model								
Intercept STRETCH			-7.53		-8.12		-9.66	
Intercept TREE	-6.52				-7.18		-9.04	
Intercept UHFO-COPD	-7.65		-7.67				-9.65	
Intercept UFHO-DM	-8.87		-8.98		-9.58			
Age per 10 years increase	0.61 (0.19)	2.04 (1.39-2.98)	0.56 (0.17)	1.91 (1.36-2.70)	0.57 (0.17)	2.08 (1.36-2.73)	0.55 (0.24)	2.09 (1.36-3.22)
BMI per 5 unit increase	0.31 (0.16)	1.36 (1.03-1.78)	0.42 (0.15)	1.54 (1.19-1.99)	0.42 (0.15)	1.50 (1.16-1.94)	0.45 (0.21)	1.79 (1.26-2.54)
Dyspnoea (MRC >3)	0.62 (0.24)	2.01 (1.26-3.20)	0.60 (0.22)	1.99 (1.29-3.09)	0.48 (0.23)	1.69 (1.08-2.63)		
Angina	-0.51 (0.31)	0.57 (0.31-1.04)						
IHD	0.82 (0.34)	2.49 (1.28-4.80)	0.69 (0.30)	2.22 (1.24-3.98)	0.61 (0.27)	1.70 (1.00-2.87)		
Pulse pressure per 20 mmHg	0.23 (0.08)	1.68 (1.24-2.28)	0.17 (0.07)	1.54 (1.15-2.05)	0.27 (0.07)	1.76 (1.34-2.32)		
AF					0.48 (0.35)	1.97 (0.99-3.90)		
β-blocker therapy	0.75 (0.26)	2.29 (1.39-3.78)	1.01 (0.25)	3.23 (1.97-5.30)	0.85 (0.24)	2.55 (1.59-4.11)	0.81 (0.35)	3.40 (1.72-6.71)

Women

Developed in	TREE, UHFO-COPD & UHFO-DM		STRETCH, UHFO-COPD & UHFO-DM		STRETCH, TREE & UHFO-DM		STRETCH, TREE & UHFO-COPD	
	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)
Clinical model								
Intercept STRETCH			-4.28		-9.66		-9.66	
Intercept TREE	-5.06				-8.48		-9.56	
Intercept UHFO-COPD	-5.7		-4.76				-9.84	
Intercept UFHO-DM	-6.42		-5.45		-10.63			
Age per 10 years increase	0.87 (0.17)	3.21 (2.22-4.63)	0.74 (0.16)	3.05 (2.10-4.44)	0.63 (0.17)	3.65 (2.55-5.22)	0.28 (0.23)	2.70 (1.71-4.26)
β-blocker therapy	0.79 (0.24)	2.61 (1.63-4.17)	0.77 (0.25)	2.65 (1.63-4.31)	0.74 (0.24)	2.66 (1.68-4.21)		

Candidate predictors used to select the clinical predictors for the final model were: age, ischaemic heart disease, atrial fibrillation, history of hypertension, diabetes mellitus, angina, dyspnoea when walking at a normal pace or worse (MRC ≥3), ankle oedema, body mass index, increased pulse pressure and β-blocker therapy.

BMI: body mass index, IHD: ischaemic heart disease, AF: atrial fibrillation

Table 3. Clinical scoring rule for a) men and b) women with and without NTproBNP

a)

Rule score A: summation of points including NTproBNP	Points
Age (per 10 years)	1
History of ischaemic heart disease	1
Dyspnoea (MRC ≥3)	1
BMI (per 5 kg/m2)	1
Pulse pressure (per increase of 20)	1
β-blocker therapy	1
*High-risk because of multimorbidity and polypharmacy	4
NTproBNP in pg/mL per 100 pg/mL	2
Rule score B: summation of points excluding NTproBNP	
Age (per 10 years)	2
History of ischaemic heart disease	1
Dyspnoea (MRC ≥3)	1
BMI (per 5 kg/m2)	1
Pulse pressure (per increase of 20)	1
β-blocker therapy	1
*High-risk because of multimorbidity and polypharmacy	4

b)

Rule score A: summation of points including NTproBNP	Points
Age (per 10 years)	1
β-blocker therapy	1
*High-risk because of multimorbidity and polypharmacy	3
NTproBNP in pg/mL per 100 pg/mL	2
Rule score B: summation of points excluding NTproBNP	
Age (per 10 years)	2
β-blocker therapy	1
*High-risk because of multimorbidity and polypharmacy	2

*Multimorbidity and polypharmacy is defined as having three or more chronic or vitality threatening diseases and/or using five or more prescribed drugs daily during the past year in people aged 65 years

Use of the clinical scoring rule:

For example, a 70-year-old woman (14 points), with a history of ischaemic heart disease, type 2 diabetes and hypertension (2 points for being high-risk) who is taking a -blocker (1 point), has a score of 17 points. According to Supplementary Figure 4b this score corresponds to a risk of LVDD/HFpEF of approximately 85%. According to Table 4b(ii), if a GP decided that all high-risk individuals should be referred for echocardiography, the positive predictive value is 89.1%.

Table 4. Application of the clinical prediction rule for a) men and b) women with (i) and without (ii) NTproBNP

a) (i)

Summed score from scoring rule	Probability of HF estimated by the scoring rule	Percentage of participants	Sensitivity	Specificity	Positive predictive value	Negative predictive value
16	<12%	9.0%	0.99	0.19	60.5	98.9
17	<19%	18.1%	0.97	0.37	65.7	96.8
18	<38%	28.9%	0.91	0.54	71.3	91.1
20	<49%	47.8%	0.78	0.80	82.7	77.6
22	<69%	65.3%	0.55	0.91	88.3	55.1

Risk	Score range	Number of participants (%)	Number of patients with LVDD/HFpEF present (%)
Low	≤17	120 (18.1%)	12 (0.1)
Moderate	18-21	314 (47.2%)	154 (49.0)
High	≥22	231 (34.7%)	204 (88.3)

(ii)

Summed score from scoring rule	Probability of HF estimated by the scoring rule	Percentage of participants	Sensitivity	Specificity	Positive predictive value	Negative predictive value
22	<19%	11.6%	0.97	0.22	60.9	96.8
23	<31%	24.4%	0.91	0.43	66.8	90.8
24	<49%	37.6%	0.80	0.60	71.3	80.0
26	<62%	63.0%	0.55	0.85	82.5	54.9
28	<82%	81.4%	0.30	0.95	88.7	29.7

Risk	Score range	Number of participants (%)	Number of patients with LVDD/HFpEF present (%)
Low	<24	162 (24.4%)	34 (21.0)
Moderate	24-27	379 (57.0%)	226 (59.6)
High	≥28	124 (18.6%)	110 (88.7)

b) (i)

Summed score from scoring rule	Probability of HF estimated by the scoring rule	Percentage of participants	Sensitivity	Specificity	Positive predictive value	Negative predictive value
8	<38%	11.6%	0.95	0.30	78.0	95.5
9	<51%	22.8%	0.88	0.51	82.4	88.0
10	<56%	36.0%	0.78	0.72	87.8	77.8
12	<79%	61.3%	0.50	0.90	92.7	49.6
14	<70%	78.6%	0.29	0.98	97.4	28.8

Risk	Score range	Number of participants (%)	Number of patients with LVDD/HFpEF present (%)
Low	<9	161 (22.8%)	61 (37.9)
Moderate	9-14	394 (55.8%)	302 (76.6)
High	> 14	151 (21.4%)	147 (97.4)

(ii)

Summed score from scoring rule	Probability of LVDD/HFpEF estimated by the scoring rule	Percentage of participants	Sensitivity	Specificity	Positive predictive value	Negative predictive value
12.5	<31%	2.8%	0.99	0.08	73.8	99.2
13	<36%	7.4%	0.96	0.16	74.8	95.9
13.5	<56%	16.3%	0.90	0.33	77.8	90.2
14	<58%	23.9%	0.85	0.46	80.3	84.5
16	<76%	59.6%	0.50	0.84	89.1	49.8

Risk	Score range	Number of participants (%)	Number of patients with LVDD/HFpEF present (%)
Low	<13	52 (7.4%)	21 (40.4)
Moderate	13-16	369 (52.2%)	235 (63.7)
High	>16	285 (40.4%)	254 (89.1)

3

Supplementary Material

Supplementary Methods

The Internal-External Cross Validation (IECV) method was used for model development and validation. This method was recently recommended by Steyerberg and Harrell for use when combining individual patient data from multiple studies.[19] To explain the method briefly, the model is developed in all of the studies except one and the performance of this developed model is assessed in the omitted study; i.e. the validation study. A model is then developed in a different combination of studies omitting a different study from before and so on and so forth, until all of the studies have been omitted and used as the validation study.[20] The intercept used in the IECV is the estimated intercept from one of the development studies that is most similar in LVDD prevalence to the omitted study.[20]

Supplementary Table 1. Baseline patient characteristics of the combined 1371 elderly participants stratified by sex

	Male	Female	p
n	665	706	
Age (mean (sd))	73.1 (6.6)	73.6 (6.9)	0.14
Current Smoker, n (%)	114 (17.1)	79 (11.2)	0.002
Past medical history			
Hypertension, n (%)	375 (56.4)	476 (67.4)	<0.001
IHD, n (%)	140 (21.1)	52 (7.4)	<0.001
AF, n (%)	77 (11.6)	45 (6.4)	0.001
Diabetes mellitus, n (%)	377 (56.7)	342 (48.4)	0.003
PAD, n (%)	59 (8.9)	33 (4.7)	0.003
COPD/asthma, n (%)	239 (35.9)	244 (34.6)	0.63
Symptoms			
MRC ≥3, n (%)	226 (47.3)	294 (52.5)	0.11
Orthopnoea +/or PND, n (%)	69 (10.4)	99 (14.0)	0.05
Swollen ankles, n (%)	144 (21.7)	245 (34.7)	<0.001
Signs			
BMI (mean (sd))	27.2 (3.7)	28.2 (4.9)	<0.001
SBP (mean (sd))	149.7 (19.5)	152.3 (20.6)	0.02
DBP (mean (sd))	81.7 (11.1)	82.6 (11.9)	0.17
Pulse pressure (mean (sd))	68.0 (15.2)	69.8 (16.6)	0.05
HR (mean (sd))	70.1 (12.9)	71.7 (11.5)	0.02
Pulmonary crepitations, n (%)	86 (13.0)	77 (10.9)	0.28
Displaced apex, n (%)	83 (12.5)	59 (8.4)	0.02
Raised JVP, n (%)	46 (6.9)	43 (6.1)	0.61
Medications			
β-blocker, n (%)	218 (32.8)	236 (33.4)	0.84
Additional tests			
NTproBNP, pg/ml (median [IQR])	112.8 [55.3, 219.2]	126.9 [67.7, 215.4]	0.04
Abnormal ECG, n (%)	366 (56.6)	303 (43.9)	<0.001

Supplementary Table 2. Missing values in the data sets for the 1371 patients included in the study

Dataset (n)	Variable with missing values	Number of missing values	Percentage of missing values
STRETCH (348)	NTproBNP	2	0.57%
	Deceleration time	23	6.61%
	E/A	23	6.61%
	E/e'	12	3.45%
	LVMI	3	0.86%
	Left atrial volume index	5	1.44%
TREE (333)	Dyspnoea (MRC ≥3)	2	0.60%
	NTproBNP	3	0.90%
	Abnormal ECG	1	0.30%
	Deceleration time	13	3.90%
	E/A	28	8.41%
	E/e'	54	16.22%
	LVMI	31	9.31%
	Left atrial volume index	47	14.10%
UHFO-COPD (141)	BMI	1	0.71%
	Deceleration time	11	7.80%
	E/A	4	2.80%
	LVMI	12	8.51%
	Left atrial volume index	6	3.80%
UHFO-DM (549)	Pulse pressure	1	0.18%
	NTproBNP	40	7.29%
	Deceleration time	19	3.46%
	E/A	19	3.46%
	E/e'	25	4.55%
	LVMI	5	0.91%
	Left atrial volume index	67	12.20%

NTproBNP: N-terminal pro b-type natriuretic peptide, LVMI: left ventricular mass index, BMI: body mass index, E/e': the ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity, E/A: ratio between early (E) and late (A) ventricular filling velocity over the mitral valve

Supplementary Table 3. Selection of clinical predictors from the eleven candidate predictors for men and women with NTproBNP levels >125pg/ml

Men

Developed in	TREE, UHFO-COPD & UHFO-DM		STRETCH, UHFO-COPD & UHFO-DM		STRETCH, TREE & UHFO-DM		STRETCH, TREE & UHFO-COPD	
	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)
Clinical model								
Intercept STRETCH			-4.72		-5.69		-5.69	
Intercept TREE	-0.51				-3.77		-3.87	
Intercept UHFO-COPD	-1.18		-3.96				-4.50	
Intercept UFHO-DM	-1.43		-4.70		-5.68			
Age per 10 years increase	0.11 (0.38)	1.56 (0.59-4.14)	0.29 (0.26)	1.91 (1.36-2.70)	0.32 (0.26)	1.71 (0.94-3.13)	0.48 (0.31)	1.86 (1.08-3.20)
BMI per 5 unit increase	0.01 (0.33)	0.96 (0.48-1.90)	0.34 (0.24)	1.54 (1.19-1.99)	0.38 (0.23)	1.68 (1.07-2.64)	0.45 (0.28)	1.72 (1.07-2.75)
Dyspnoea (MRC >3)	0.28 (0.56)	2.37 (0.80-7.04)	0.32 (0.35)	1.99 (1.29-3.09)	0.23 (0.36)	1.37 (0.68-2.77)		
Angina	-0.11 (0.67)	0.71 (0.19-2.66)						
IHD	0.46 (0.80)	4.17 (0.87-19.96)	0.42 (0.42)	2.22 (1.24-3.98)	0.23 (0.42)	2.12 (0.92-4.86)		
Pulse pressure per 20 mmHg	0.24 (0.34)	2.38 (1.11-5.10)	0.24 (0.21)	1.54 (1.15-2.05)	0.41 (0.22)	1.83 (1.16-2.88)		
AF					0.54 (0.49)	1.37 (0.52-3.61)		
β-blocker therapy	0.04 (0.55)	1.15 (0.39-3.38)	0.58 (0.39)	3.23 (1.97-5.30)	0.84 (0.41)	3.20 (1.44-7.13)	1.68 (0.63)	10.84 (3.18-37.00)

Women

Developed in	TREE, UHFO-COPD & UHFO-DM		STRETCH, UHFO-COPD & UHFO-DM		STRETCH, TREE & UHFO-DM		STRETCH, TREE & UHFO-COPD	
	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)	Beta (SE)	OR (95% CI)
Clinical model								
Intercept STRETCH			0.64		-2.26		-2.26	
Intercept TREE	0.32				-1.44		-1.72	
Intercept UHFO-COPD	0.45		0.57				-2.12	
Intercept UFHO-DM	0.55		0.66		-2.37			
Age per 10 years increase	-0.9 (0.42)	3.00 (1.05-8.60)	-0.11 (0.26)	2.69 (1.53-4.76)	0.38 (0.27)	2.72 (1.51-4.89)	0.25 (0.31)	2.76 (1.52-5.01)
β-blocker therapy	-0.15 (0.65)	4.29 (1.21-15.25)	-0.11 (0.45)	2.48 (1.03-5.99)	0.49 (0.47)	3.22 (1.28-8.08)		

Supplementary Table 4. Discrimination of the models at cross-validation

a) Men

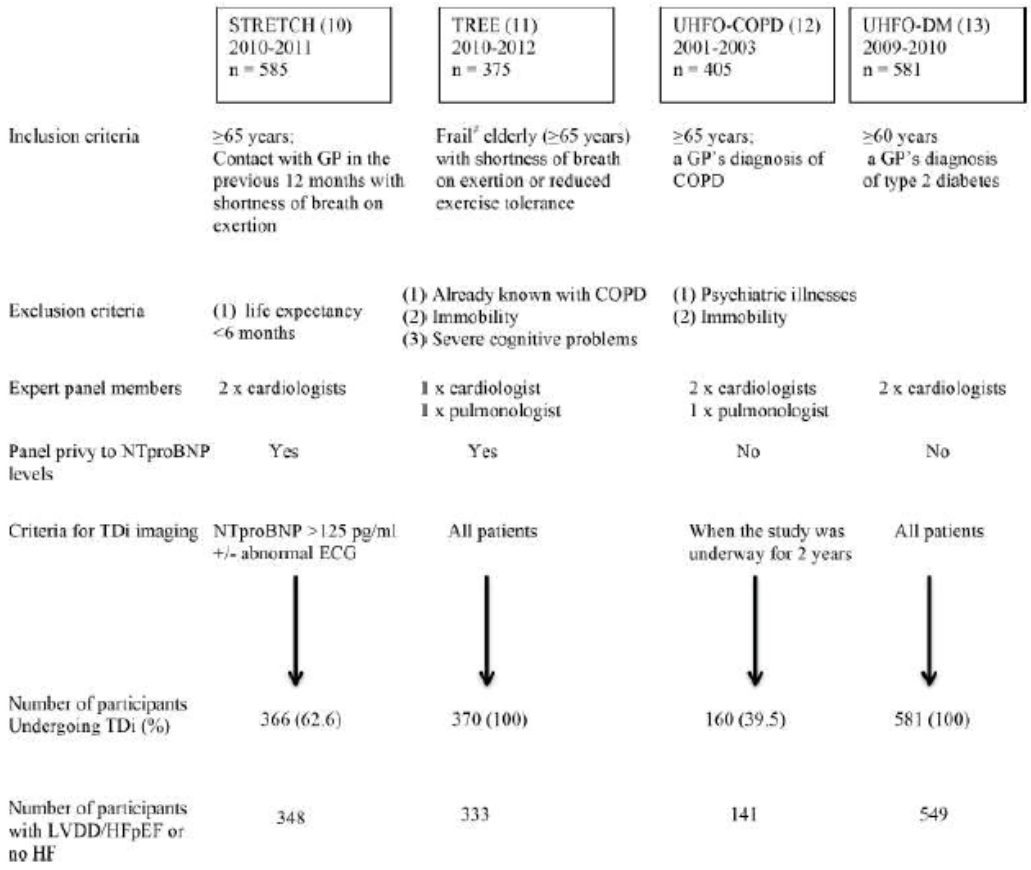
Developed in	Validated in	c-statistic clinical model (95% CI)	c-statistic clinical model & NTproBNP (95% CI)	Observed/Expected (OE) ration clinical model	Observed/Expected (OE) ration clinical model & NTproBNP
TREE, UHFO-DM & UHFO-COPD	STRETCH	0.75 (0.67-0.83)	0.80 (0.73-0.88)	3.10	2.63
STRETCH, UHFO-DM & UHFO-COPD	TREE	0.60 (0.48-0.73)	0.68 (0.60-0.80)	3.28	3.27
STRETCH, TREE & UHFO-DM	UHFO-COPD	0.66 (0.53-0.79)	0.76 (0.64-0.87)	3.30	3.04
STRETCH, TREE & UHFO-COPD	UHFO-DM	0.74 (0.68-0.80)	0.80 (0.74-0.85)	1.96	2.24

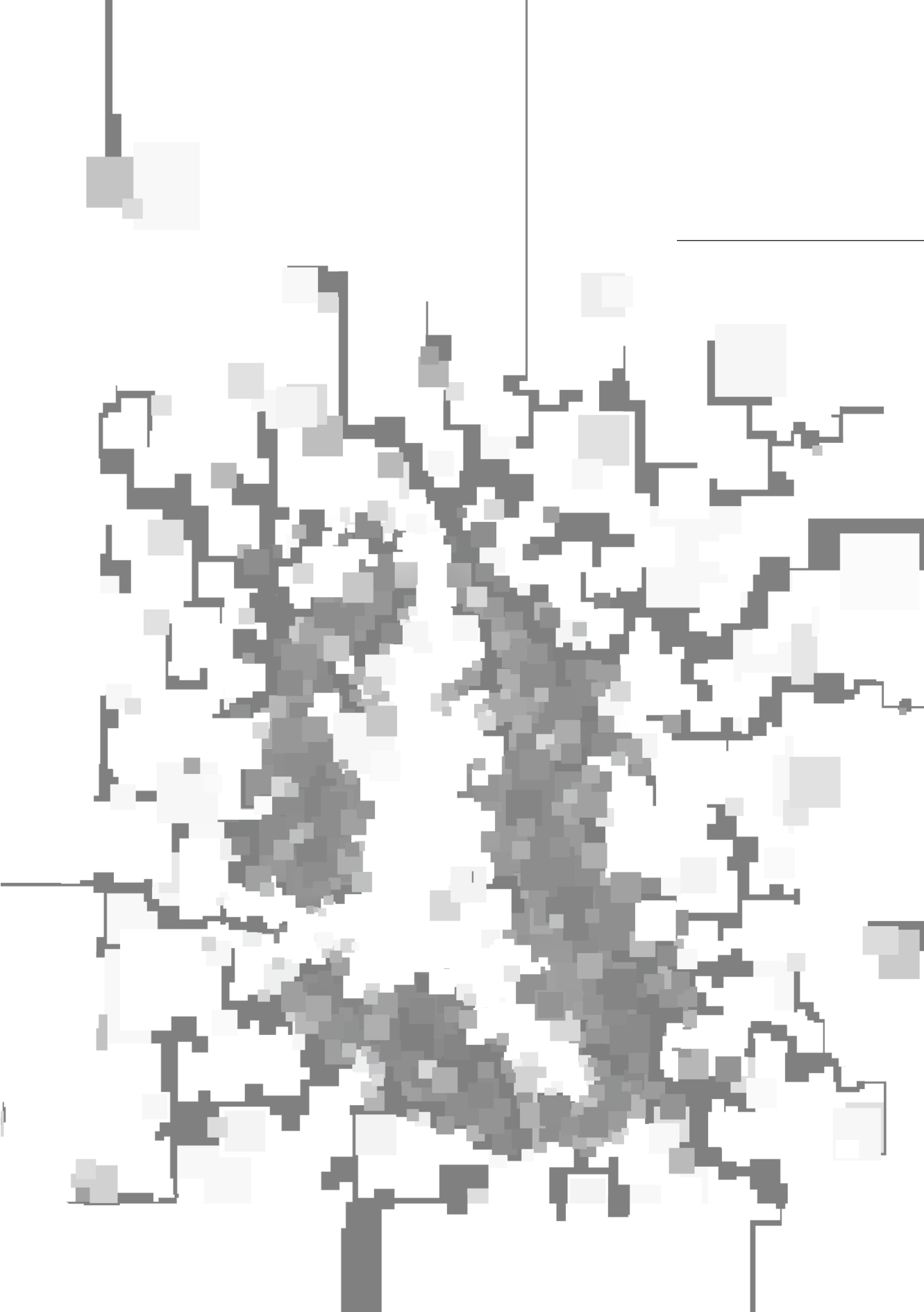
b) Women

Developed in	Validated in	c-statistic clinical model (95% CI)	c-statistic clinical model & NTproBNP (95% CI)	Observed/Expected (OE) ration clinical model	Observed/Expected (OE) ration clinical model & NTproBNP
TREE, UHFO-DM & COPD	STRETCH	0.69 (0.60-0.79)	0.77 (0.68-0.85)	2.60	2.37
STRETCH, UHFO-DM & COPD	TREE	0.76 (0.66-0.86)	0.80 (0.72-0.87)	2.61	2.69
STRETCH, TREE & UHFO-DM	UHFO-COPD	0.51 (0.37-0.64)	0.61 (0.48-0.75)	2.51	2.52
STRETCH, TREE & UHFO-COPD	UHFO-DM	0.75 (0.69-0.80)	0.76 (0.71-0.82)	1.93	2.08

Supplementary Figure Legends

Supplementary Figure 1. Summary and flow chart of the four opportunistic cohorts included in the individual participant data- meta-analysis set





Chapter 8

Validation of a diagnostic prediction rule for left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in patients referred to an outpatient cardiology clinic.

In preparation

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3

ABSTRACT

Introduction
Multiple diagnostic prediction models have been proposed for heart failure. Yet, few have been developed for HF with preserved ejection fraction (HFpEF) or left ventricular diastolic dysfunction (LVDD). Purpose: To validate a sex specific diagnostic model for LVDD and HFpEF, developed in primary care and to assess improvement with cardiovascular biomarkers.

Methods
The study population comprised 634 consecutive individuals (≥ 45 years and no history of a cardiac intervention) of the HELPFul case cohort study. Individuals were referred to an outpatient cardiology clinic for a diagnostic cardiac assessment. An expert panel established the diagnosis of LVDD and HFpEF. The prediction rule consisted of age, beta-blocker use and multimorbidity and/or polypharmacy in women, and additionally of history of ischemic heart disease, shortness of breath (MRC>3), BMI, pulse pressure in men. The following biomarkers were considered (Abbott assay): hs TnI, hs CRP, ASAT, albumin G, total cholesterol, creatinine, cystatin C, CK MB, lipoprotein (A), triglycerides, HDL and vitamin D.

Results
The c statistic of the recalibrated original model was 0.72 (95% CI 0.64 0.80) for men and 0.66 (95% CI 0.61 0.72) for women, and performed to similarly as in the primary care cohorts. Adding biomarkers did not significantly improve the model, but slightly raised the c-statistic to 0.74 (95% CI 0.67 0.81) for men and 0.69 (95% CI 0.63 0.74) for women. This was not statistically or clinically significant.

Conclusions
The sex specific diagnostic prediction model for LVDD/HFpEF performed modestly well in men and women referred to an outpatient cardiology clinic. There was no significant improvement in performance when cardiovascular biomarkers were added.

Introduction

Heart failure with preserved ejection fraction (HFpEF) may remain unrecognized in older community people (>60 years) at risk of heart failure, e.g. patients with dyspnea (1), with chronic obstructive pulmonary disease (COPD) (2), with type 2 diabetes (3), the elderly (4) and those with atrial fibrillation (5). A clinical decision rule may aid general practitioners in correctly identifying patients at risk of left ventricular dysfunction (LVDD) or HFpEF (LVDD plus a LVEF >50%, and symptoms suggestive of heart failure). Those at higher risk could be referred for additional diagnostic assessment, e.g. echocardiography. So far, only few such tools have been developed for HFpEF (6,7), and we recently developed and validated a sex
specific prediction rule for LVDD/HFpEF to be used in primary care setting (8).
External validation of diagnostic prediction algorithms is an important step in supporting generalizability (9 11). Another important aspect is the feasibility of use of the determinants in the prediction rule by the general practitioner, as some prediction models for HFpEF include echocardiography variables that are often unavailable in primary care (12 15). In recent years, development and implementation of biomarker panels for eventual use in clinical practice has rapidly been evolving (16,17). In heart failure, biomarkers have been proposed to have added value in diagnosis(18). For example, natriuretic peptides have shown to have independent added value in prediction models for heart failure, though often less in patients with HFpEF then patients with HFrEF (19). However, aside from natriuretic peptides other cardiovascular biomarkers often show no independent added value to diagnostic models for HFpEF (20,21).
Due to the heterogeneity within the syndrome of HFpEF, it is likely that only a panel of biomarkers reflecting different pathophysiological processes, such as cardiac remodeling, atherosclerosis and inflammation may improve a diagnostic model on top of clinical determinants (22,23).
We therefore aimed to externally validate our recently developed sex specific diagnostic prediction model for LVDD/HFpEF in an outpatient cardiology clinic. In addition, we assessed whether the sex specific models could be improved by cardiovascular biomarkers.

Methods

Study population

Study design and procedures of the "Discovery of biomarkers for the presence and progression of left ventricular diastolic dysfunction and HEart faiLure with Preserved ejection Fraction in patients at risk for cardiovascular disease" (HELPFul) study have been published in more detail(24). Briefly, the HELPFul study is a Dutch case cohort study in which patients participated, who were referred by their general practitioner to an outpatient cardiology clinic for a diagnostic cardiac assessment. Patients who had a previous cardiac intervention, or who were known with congenital cardiac disease were excluded from participation. Patients that had a ratio of the peak early (E) diastolic filling velocity to the early diastolic mitral annular velocity (e') (average of septal and lateral) (E/e') ≥ 8 with tissue Doppler echocardiography were considered as a 'case', because these patients were considered to have a higher probability of having LVDD than those with a E/e'<8. 'Cohort' patients were randomly sampled from all patients aged 45 years or older, striving to include 25% of eligible participants (25).
The study adheres to the principles of the declaration of Helsinki and the institutional review board of the University Medical Center Utrecht approved the study. HELPFul was registered in the

Dutch trial register (reference number NTR6016). Written informed consent was obtained from all participants. Data of patients from start of inclusion (16 September 2016) up to November 2018 has been used for the analysis.

Assessment of clinical variables
Information on co morbidities, medical history, and medication use was collected. The diagnostic assessment further consisted of physical examination, blood pressure measurements, blood testing of standard cardiovascular biomarkers, electrocardiography (ECG), bicycle exercise ECG, and transthoracic echocardiogram. A structured case record form was used to assess symptoms suggestive of cardiac pathology. Hypertension was determined by (I) patient self report, or (II) prescription of blood pressure lowering medication, or (III) a mean (of at least two) systolic blood pressure measurements ≥ 140mmHg. Type 2 diabetes was determined by (I) patient self report, or (II) prescription of blood glucose lowering medication. Hypercholesterolemia by (I) patient self report or (II) prescription of lipid lowering medication. Atrial fibrillation (AF) was determined by (I) patient self report or (II) documented history of AF, or (III) AF on the 12 lead electrocardiography during the assessment. Body weight and height were measured and body mass index (BMI) was calculated by dividing weight (kg) by height squared in meters (m2). Waist to hip ratio was calculated from the waist circumference measured around the belly button in centimeters (cm) divided by hip circumference, which was measured around both greater trochanters (cm). The estimated glomerular filtration rate (eGFR) was calculated from both creatinine and cystatin c with the validated CKD EPI formula (26). Ischemic heart disease was defined as history of coronary artery disease, acute myocardial infarction, a previous percutaneous coronary intervention or a coronary artery bypass grafting procedure. Multimorbidity and polypharmacy were defined as having three or more chronic or vitality threatening diseases and/or using five or more prescribed drugs daily during the past year in people aged 65 years (8).

Assessment of biomarkers
B-type natriuretic peptide (BNP), high sensitivity Troponin I (hs TnI), high sensitivity Creactive protein (hs CRP), aspartate aminotransferase (ASAT), albumin G, total cholesterol, creatinine, cystatin c, lipoprotein (A), triglycerides, high density lipoprotein (HDL) and vitamin D were measured using the appropriate assay on the ARCHITECT i2000 analyzer (Abbott Park, Chicago, Illinois, USA).

Echocardiographic assessment
Comprehensive transthoracic echocardiographic examinations were performed with a General Electronic (GE) Vivid E6 or E7 device (GE Healthcare, United Kingdom) by trained sonographers and interpreted by an experienced cardiologist in accordance with the EACVI 2016 recommendations for chamber quantification (27). The left ventricular ejection fraction (LVEF) was assessed quantitatively (Teichholz), or semi quantitatively (eye balling), in case an LVEF was considered abnormal, the LVEF was calculated using the Simpsons biplane method of disk. Diastolic parameters that were measured included pulsed wave Doppler of the mitral valve inflow velocities and pulmonary venous inflow and tissue Doppler imaging of the mitral annulus motion. The ratio of peak early (E) diastolic filling velocity to peak atrial (A) contraction filling velocity was calculated to derive the E/A ratio. The early diastolic mitral annular wall velocity (e') was determined at both the septal and lateral wall. The E/e ratio was calculated by dividing E with the average of septal and lateral e'. Left atrial volume (LAV) was derived from tracing the left atrium during maximal atrial filling in the apical two chamber and apical four chamber views, and indexed (LAVi) by body surface area (BSA). Left ventricular mass was calculated according to the formula that was validated by Devereux, and indexed (LVMi) by BSA (28). Relative wall

thickness (RWT) was calculated by multiplying posterior wall thickness at end diastole by two and dividing the sum by left ventricular end diastolic dimension. The sonographers assessed tricuspid regurgitation (TR) in the parasternal right ventricular (RV) inflow, parasternal short axis and apical 4 chamber views. Continuous wave Doppler sampling was used to measure the peak TR velocity after a minimum of five sequential complexes were recorded. The peak velocity of the TR signal was used to calculate the systolic pulmonary artery pressure (SPAP) with the modified Bernoulli's equation (29).

Adjudication of the diagnosis of LVDD and HFpEF

The primary endpoints were adjudicated by an expert panel consisting of cardiologists (RM, MJC, AT) and a general practitioner (FR) specialized in heart failure (FR). This method is comparable to previous studies of our group (30,31). Adjudicating the endpoint by an expert panel is considered an acceptable alternative when a sufficiently reliable reference standard is lacking (32,33). The expert panel used all available diagnostic information, including patient reported symptoms, risk factors, ECG, echocardiography, results from the exercise test, (cardiovascular) medication use and plasma BNP levels. The panel based the diagnosis of LVDD on available diastolic function criteria and recommended cut points of recent international guidelines (34 36). The panel categorized patients into two times four groups; no, 'possible', 'probable' and definite LVDD or HFpEF. First the expert panel assessed the presence of LVDD. LVDD was considered 'possible' if there was at least one echocardiographic structural or functional variable abnormal in the presence of LVEF >50%. 'Probable' LVDD if at least two variables were abnormal and/ or BNP levels above the exclusionary cut point 35 pg/mL. Patients were labeled LVDD if three or more echocardiographic variables were abnormal and/or BNP levels above the exclusionary cut-point 35 pg/mL. Patients without LVDD could not have HFpEF. HFpEF was classified absent if no symptoms suggestive of HF were present, classified 'possible' if some symptoms suggestive of HF were present and there was possible, probable, or definite LVDD. HFpEF was considered 'probable' if there were symptoms suggestive of HF and probable or definite LVDD. HFpEF was considered 'definite' if the patient had symptoms suggestive of HF and LVDD was also 'definite. If a patient had symptoms suggestive of HF and, either a LVEF between 40 and 49% then HF with mid range ejection fraction (HFmrEF) was considered present, or with a LVEF <40% HF with reduced ejection fraction (HFrEF) was considered present. For the purpose of this study we dichotomized patients into "no LVDD or HFpEF" and "LVDD or HFpEF". We did so by grouping patients with no and possible LVDD with no HFpEF and possible HFpEF in the first group, and probable and 'definite' LVDD with probable and definite HFpEF in the second group, respectively. Patients that were considered to have HFrEF or HFmrEF were not included in the analysis.

Data analyses

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) if not normally distributed, and categorical variables as absolute numbers and percentages. Differences between men and women were compared using a Pearson Chi square test, a student T test or a one way ANOVA, depending on the distribution of and type of variable. Missing data was less than 5%, therefore we chose to apply complete case analysis. The analyses were performed in a number of steps. First, the original prediction rule was applied in the HELPFul population. In a second step we recalibrated the prediction rule on the HELPFul data using two modelling approaches. The first approach was logistic regression modelling and the second approach involved modelling with penalized maximum likelihood estimation (PMLE). Both modelling approaches were performed separately for men and women. In both modelling approaches the models started out with all sex specific predictors from the original prediction rule of Gohar and coworkers (8). For men these predictors were age, history of ischemic heart disease,

shortness of breath (MRC>3), BMI , pulse pressure, beta blocker therapy, multimorbidity and/or polypharmacy. For women the predictors were age, beta blocker use and multimorbidity and/or polypharmacy. In the third step, we added the measured biomarkers to the sex specific models. Biomarkers that were added were hs TnI, hs CRP, ASAT, albumin G, total cholesterol, creatinine, cystatin C, lipoprotein (A), triglycerides, HDL, vitamin D. We tested if addition of all biomarkers to the sex specific recalibrated models resulted in significant improvement with the likelihood ratio test. Thereafter biomarkers were removed from the model with logistic regression modelling step by step if p value > 0.20 with the Wald test, until a model remained with all original sex specific predictors and biomarkers with p value < 0.20. Using PMLE, beta coefficients of possibly redundant predictors were reduced to 0 and thereafter automatically eliminated from the model. This process was repeated automatically until a final model remained with clinical predictors and biomarkers selected by the automated process of PMLE. To evaluate the performance of the newly created models, discrimination and calibration were compared with that of the recalibrated original model. Discrimination was based on the c statistic with 95% confidence intervals (95% CI). Calibration refers to the agreement between the predicted absolute risks of LVDD/HFpEF and the observed LVDD/HFpEF frequencies. Data analysis was performed using R studio (3.5.3).

Results

The baseline clinical and echocardiographic characteristics of the study population are shown in Table 1. The mean age of the 634 participants was 63.0 (SD 9.4) years and 421 (66%) participants were women. Mean BMI was 26.9 (SD 6.7). The percentage of participants with hypertension was 58% (n=369), 8% (n=53) had type 2 diabetes, and 3% (n=21) had atrial fibrillation.
In the primary care cohorts in which the prediction rule was developed and internally validated, patients had a higher mean age (range 71 to 76 years), were less often women (52% women), and had a higher BMI (28 kg/m2 in women, 27.2 kg/m2 in men), and more often type 2 diabetes (prevalence of 23.4% in women and 18.4% in men). Also, ischemic heart disease was more common (in women (21.1%) and men (7.4%)) as was atrial fibrillation (11.6% in women and 4.4% in men).
In the HELPFul study, the prevalence of LVDD was equal for women and men with 34% in women and 34% in men (p=0.86). For HFpEF, the prevalence of women was higher than that of men with 19% in women and 11% in men (p=0.01). In the cohorts where the prediction models were developed, the prevalence of LVDD and/ or HFpEF was higher and 72.2% in women and 55.6% in men.

Clinical parameters in men and women

The prediction rule (8)consisted of the following clinical predictors for women: age, beta blocker use and multimorbidity and/or polypharmacy. For men these predictors were age, history of ischemic heart disease, shortness of breath (MRC>3), BMI , pulse pressure, beta blocker therapy, multimorbidity and/or polypharmacy.
Clinical parameters for men and women are presented in Supplemental Table 1. Age was similar between men (64 years, SD 10.1) and women (63 years, SD 9.0), as were mean BMI, mean pulse pressure, use of beta blockers and prevalence of multimorbidity and polypharmacy. Women less often presented with a history of ischemic heart disease as compared to men (women, n=3, prevalence of 1% versus men, n=4, prevalence of 2%, p=0.02). Women more often reported complaints of dyspnea on the MRC dyspnea scale above 3 points (women, n=127, prevalence of

30% versus men n=45, prevalence of 21%, p=0.02).

Biomarkers
Differences in clinical characteristics and biomarker levels between men and women are presented in Supplemental Table 2. Men had similar median blood levels of BNP (17.1 pg/mL, IQR 10.0 36.8) as women (19.3 pg/mL, IQR 10.0 36.7), p=0.32. However women had a significantly lower median hs TnI (2.3 pg/mL, IQR 1.6 3.4) than men (3.6 pg/mL, IQR 2.3 6.0), p<0.01. Mean blood levels of cystatin c, CK MB, ASAT and triglycerides were significantly higher in men, while in women mean blood levels of vitamin D, total cholesterol and HDL were significantly higher.

Discrimination of original prediction rule
Figure 1 and 2 show the ROC curves of the original derivation prediction rule for men and women, respectively. The c statistic in men was 0.72 (95% CI 0.64 0.80) and the prediction rule consisted of age, beta blocker use, multimorbidity and/or polypharmacy, history of ischemic heart disease, shortness of breath (Medical Research council (MRC) scale ≥ 3), BMI > 30 kg/m2 and pulse pressure. In women, the c statistic was 0.66 (0.60 0.71) and the prediction rule consisted of age, beta blocker use and multimorbidity and/or polypharmacy.

Added value of biomarkers
Thereafter we recalibrated the original sex specific predictions rules and assessed if adding the complete set of biomarkers had added value beyond the recalibrated clinical model. Adding all biomarkers to the recalibrated model did not result in a significantly better model for both men (p=0.25) and women (p=0.21). To assess performance (i.e. discrimination and calibration), we continued using a conservative limit for p value <0.20. The following biomarkers had added value for men: albumin G (p=0.06) and hs CRP (p=0.13), and for women: CK MB (p=0.14), ASAT (p=0.05), total cholesterol (p=0.09) and triglycerides (p=0.046). We observed that PMLE modelling for women and men separately using the clinical predictors and adding all biomarkers resulted in selection of different predictors. The PMLE model for women included only age, eliminating all other clinical predictors and biomarkers from the model. While in the model for men, most clinical predictors, except beta blocker use, remained in the model, as did the biomarkers CK MB, ASAT, albumin G, cholesterol and hs CRP.

Discrimination
Figure 3 and 4 show the ROC curves of the recalibrated models for women and men, respectively. Table 2 shows the c statistic of various models for women and men separately. Recalibration of the models resulted in no increase of the c statistic in men (0.72, 95% CI 0.64 0.80), nor in women (0.66, 95% CI 0.61 0.72). Addition of biomarkers with logistic regression modelling resulted in an increase of the c statistic in men to 0.74 (95% CI 0.67
0.81), and in women the c statistic increased to 0.69 (95% CI 0.63 0.74). With PMLE the c statistic increased in men to 0.75 (95% CI 0.67 0.82), but decreased in women to 0.65 (95%CI 0.60 0.71). None of the increases in c statistic were statistically or clinically significant.

Calibration
Calibration of the sex specific models is presented in Table 3 and in Figure 5 and Figure 6.
With logistic regression modelling the likelihood of having LVDD/HFpEF among those with an estimated risk of ≥ 50% increased through biomarker measurement from 60% (24/60) to 64% (29/45), and from 55% (31/56) to 57% (39/68). When PMLE was used the likelihood of having LVDD/HFpEF among those with an estimated risk of ≥ 50% increased to 73% (19/26) in men and

to 63% (28/44) in women.

Sensitivity analyses
There were no differences in model performance (discrimination and calibration) when models were assessed only in men and women in the 'cohort' (i.e. patients included by random sampling).

Discussion
An existing sex specific clinical prediction rule developed for LVDD/HFpEF in primary care (8) was externally validated in patients referred to a cardiology outpatient clinic. The model consisted of clinical predictors that are available to the general practitioner and therefore useful in primary care for referral for echocardiography. We observed similar performance of the sex specific model in this outpatient setting with a c statistic of the 0.72 (95% CI 0.64
0.80) for men and 0.66 (95% CI 0.61 0.72) in women for diagnostic cardiac assessment. For women the relevant clinical predictors were age, beta blocker use and multimorbidity and/or polypharmacy, whereas in men the model additionally consisted of a history of ischemic heart disease, shortness of breath (MRC>3), BMI and pulse pressure. Furthermore we assessed the added value of biomarkers on top of the clinical model. The validated prediction rule and recalibrated models performed similarly to the original derivation model developed in high risk community men and women aged 60 to 65 years with either type 2 diabetes (37), COPD (2), shortness of breath (1), or that were frail (4). Extending the models with biomarkers improved the diagnostic performance only modestly given the small increase in c statistics and calibration. In men both traditional modelling and PMLE resulted in albumin
G and hs CRP remaining in the model. In women, with classic modelling CK MB, ASAT, total cholesterol and triglycerides remained in the model, while with PMLE only age remained in the model.
There are no other sex specific models for HFpEF/LVDD, however multiple models exist that were developed in community people suspected of heart failure by the GP (38). Other models were developed to distinguish (diagnostic) predictors relevant for HFrEF from (diagnostic) predictors relevant to HFpEF (7). We have chosen not to develop and present a new prediction model, but instead validate an existing sex specific one, and to investigate whether we can improve the model with cardiovascular biomarkers. We chose this approach because a myriad of HF prediction models already exist (10,11). With our approach, the usefulness of an existing model in a different setting and with a younger population was validated. The model proved to be robust, without clear overfitting in the initial derivation cohorts, given the similar results of (modest) performance in our validation cohort as shown in the derivation cohorts. However, given the difficulties of diagnosing LVDD/HFpEF, this may be considered a success (9).
Identifying individuals with LVDD/HFpEF is clinically relevant. Cardiovascular risk prevention, e.g. optimal blood pressure control and other risk factor modification, and lifestyle improvement can be initiated or intensified in an early stage of disease development (35,39). In those with HFpEF, symptom reduction may at least be achieved during periods of overfilling (35,39). Furthermore a diagnostic prediction model could be helpful for general practitioners to detect patients at increased risk for LVDD/HFpEF and select them for referral for echocardiography (40,41). A good example of the potentially large benefit of early risk stratification was shown in the STOP HF randomized trial comparing a BNP guided management strategy to usual care in 1374 community adults (mean age 64.8 (SD 10.2) years) with cardiovascular risk factors (notably type 2 diabetes and hypertension) who were recruited from 39 Irish general practices (42). In the intervention arm, those with marginally elevated BNP values > 50 pg/mL (≈15 pmol/L) at rest underwent echocardiography. Overall, patients in this arm received more intensified

cardiovascular preventive treatment, notably ACE inhibitors/ARBs and beta blockers than in the usual care group (42). After a mean follow up of 4.2 years the patients in the intervention arm had a lower incidence of LVDD with or without all type HF than patients in the control group (8.7% vs. 5.3%; odds ratio (OR) 0.55 (95%CI 0.37 0.82, p=0.003). The incidence rates of emergency hospitalization for major cardiovascular events were lower at 20.3 events per 1000 patient years in the intervention arm and 40.4 events per 1000 patient years in the usual care group (OR 0.60 (95% CI 0.45
0.81), p=0.002) (42). Early risk stratification that results in intensified treatment of risk factors can therefore prove crucial to reduce the rising prevalence of HFpEF.
A small study indicated that general practitioners regularly perform risk assessments. They rated the usefulness of risk scores as largely positive, but often still did not use them in clinical practice (43). General practitioners were hesitant towards implementation of these risk scores due to concerns on the accuracy and applicability of the risk scores to their patient population (43). This may be overcome when researchers show the validation of the models in various high risk populations. We did so by moving from the primary care setting to the outpatient cardiology clinic, and proved that this clinical diagnostic model performs well in both settings. In a next step these models might be embedded into a diagnostic intervention trial aimed at cooperative care with cardiologists for those patients with a high risk of LVDD and HFpEF.
We have assessed the added value of cardiovascular biomarkers that are often measured in patients with different cardiovascular diseases. We chose these biomarkers because they reflect cardiac tissue damage (hs TnI), inflammation (hs CRP), renal function (creatinine and cystatin c), atherosclerosis (HDL, total cholesterol, lipoprotein--(a), liver function/damage (albumin G and ASAT) and vitamin D due to its reported relation with cardiovascular disease (prognosis) (44). We observed no significant added value of the biomarkers that we assessed, but we did find small sex differences in the levels of these biomarkers. Interestingly, clinical predictors performed better in men than in women, even though we had an unbalanced population with underrepresentation of men. This may imply that women in our study were more heterogeneous in terms of disease as compared to men. It may also be that the known pathophysiological processes underlying LVDD and HFpEF are more pronounced in men as compared to women. This could be reflected by the higher levels of hs TnI, cystatin C, CK MB and hs CRP in men than in women have been reflected by the biomarkers in which the levels of cardiovascular markers were higher in men as compared to women. Overall, the biomarkers that we assessed might have better diagnostic value in patients in whom disease has already progressed further than in our study population in which overt HF was not common (22,23).

Limitations
Because of the difficulties with diagnosing LVDD and thus HFpEF, we used an expert panel applying existing guidelines on diagnosing LVDD/HFpEF. This is considered a valid approach when a accepted reference standard is missing, however it is not easily reproducible in another cohort study, nor in clinical practice. We did not incorporate BNP in our clinical models as it was part of assessment of the diagnosis (by the expert panel) and therefore it was part of the outcome that we used for the models.
Missingness was low (<5%) for the clinical determinants used in the models, therefore we chose not to impute missing values. However this could have resulted in a slight loss of power.
For this diagnostic study the study population was small with a low number of events for sex stratified modelling. This could have resulted in overfitting of the biomarkers. However we do not think that overfitting is likely, as we show that the biomarkers had no significant added value to the original prediction rule and the performance of the diagnostic models was improved only modestly.

3

Conclusion

The sex specific diagnostic prediction model for LVDD/HFpEF performed modestly well in men and women referred to an outpatient cardiology clinic. There was no significant improvement in performance when cardiovascular biomarkers were added.

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Table 1. Baseline characteristics of 634 participants in the HELPFul case-cohort study.

	HELPFul subjects (n= 634)
Clinical characteristics	
Mean age in years (SD)	63.0 (9.4)
Women (%)	421 (66)
Mean BMI in kg/m^2 (SD)	26.9 (6.7)
Hypertension (%)	369 (58)
Hypercholesterolaemia (%)	254 (40)
Median eGFR (ml/min/1.73m^3) (IQR)	84.7 (74.8-95.1)
Type 2 diabetes (%)	53 (8)
Current smokers (%)	66 (10)
COPD (%)	75 (12)
Atrial fibrillation (%)	21 (3)
Mean Waist/hip ratio (SD)	0.92 (0.08)
Echocardiographic measurements of diastolic function	
Median E/e' ratio (IQR)	9.0 (8.0- 10.4)
Median e' septal in m/sec (IQR)	7.0 (6.0-8.0)
Median e' lateral in m/sec (IQR)	8.0 (7.0-10.0)
Median LAVi in cm^2/m^2 (IQR)	23.0 (17.2-29.9)
Mean LVMi in g/m^2 (SD)	75.4 (18.5)
Mean RWT (SD)	0.42 (0.09)
Median Ejection fraction (IQR)	66.0 (60.6-71.9)
Biomarkers	
Median BNP in pg/mL (IQR)	18.7 (10.0-36.7)
Median hs-TnI in pg/mL (IQR)	2.6 (1.7-4.3)
Mean Lp (a) in mg/dL (SD)	26.2 (32.5)
Mean Cystatin-C in mg/L (SD)	0.9 (0.2)
Mean CK-MB in ng/mL (SD)	1.4 (0.9)
Mean Vitamin-D in ng/mL (SD)	24.7 (9.6)
Mean ASAT in U/L (SD)	24 (10)
Mean Albumin-G in g/L (SD)	42 (4)
Mean hs-CRP in mg/L (SD)	3.3 (7.2)
Mean Cholesterol in mmol/L (SD)	5.3 (1.2)
Mean Triglycerides in mmol/L (SD)	1.7 (1.1)
Mean HDL in mmol/L (SD)	1.4 (0.4)
Outcome	
LVDD (%)	216 (34)
HFpEF (%)	103 (16)

ASAT= aspartate aminotransferase, BNP = B-type natriuretic peptide, BMI=body mass index, CK-MB = Creatine kinase-MB, COPD = chronic obstructive pulmonary disease, hs-CRP=high sensitivity C-reactive protein, eGFR=estimated glomerular filtration rate, HDL=high density lipoprotein, HFpEF= heart failure with preserved ejection fraction, hs-TnI= high sensitivity-Troponin I, IQR=interquartile range, LAVi = left atrial volume indexed for BSA, Lp(a)=lipoprotein(a), LVDD=left ventricular diastolic dysfunction, LVMi = left ventricular mass indexed for BSA, RWT = relative wall thickness, SD=standard deviation.

Table 2. C-statistic (with 95% Confidence Interval) of the original prediction model and extended validation models for men and women

	Model	c-statistic	95% Confidence Interval
Men	Original prediction model	0.72	0.64-0.80
	Recalibrated model	0.72	0.64-0.80
	Recalibrated model with biomarkers	0.74	0.67-0.81
	PMLE model (with biomarkers in men only)	0.75	0.67-0.82
Women	Original prediction model	0.66	0.60-0.71
	Recalibrated model	0.66	0.61-0.72
	Recalibrated model with biomarkers	0.69	0.63-0.74
	PMLE model	0.65	0.60-0.71

PMLE=penalized maximum likelihood estimation

Table 3. Calibration table for men and women

Absolute Risk (%)	Recalibrated clinical model		Recalibrated clinical model + biomarkers		PMLE (+ biomarkers in men only)	
Men						
	N	LVDD/ HFpEF	N	LVDD/ HFpEF	N	LVDD/ HFpEF
< 25%	74	13 (18%)	74	13 (18%)	56	9 (16%)
25-49%	81	29 (36%)	77	24 (31%)	115	38 (33%)
≥50%	40	24 (60%)	45	29 (64%)	26	19 (73%)
Women						
	N	LVDD/ HFpEF	N	LVDD/ HFpEF	N	LVDD/ HFpEF
< 25%	100	17 (17%)	110	16 (15%)	88	15(17%)
25-49%	226	88 (39%)	204	81 (40%)	250	93 (37%)
≥50%	56	31 (55%)	68	39 (57%)	44	28 (63%)

PMLE= penalized maximum likelihood estimation, LVDD= left ventricular diastolic dysfunction, HFpEF= heart failure with preserved ejection fraction

Figure 1. Receiver operating characteristic curve of original prediction rule in men.

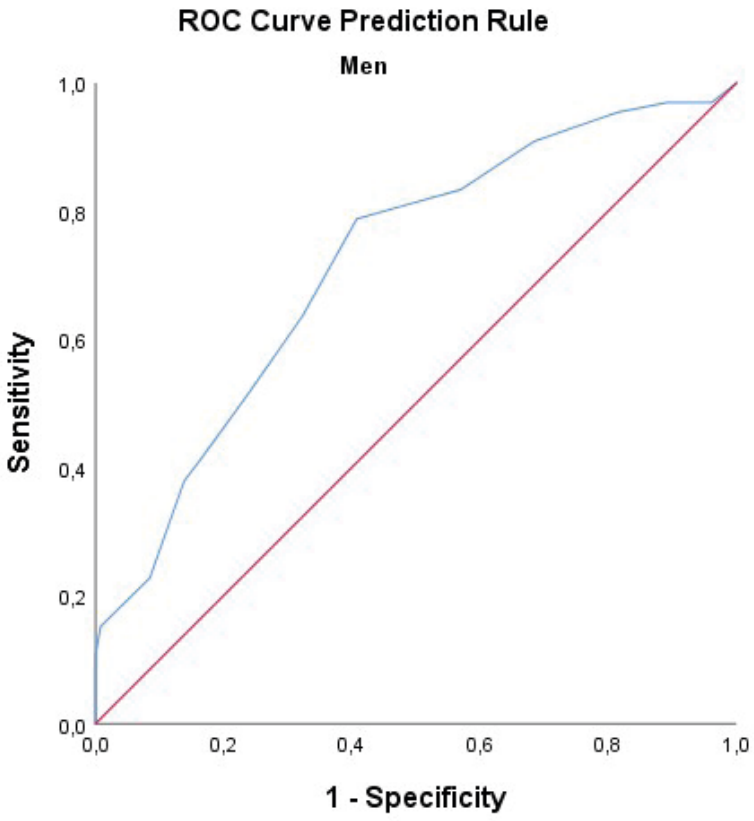


Figure 2. Receiver operating characteristic curve of original prediction rule in women.

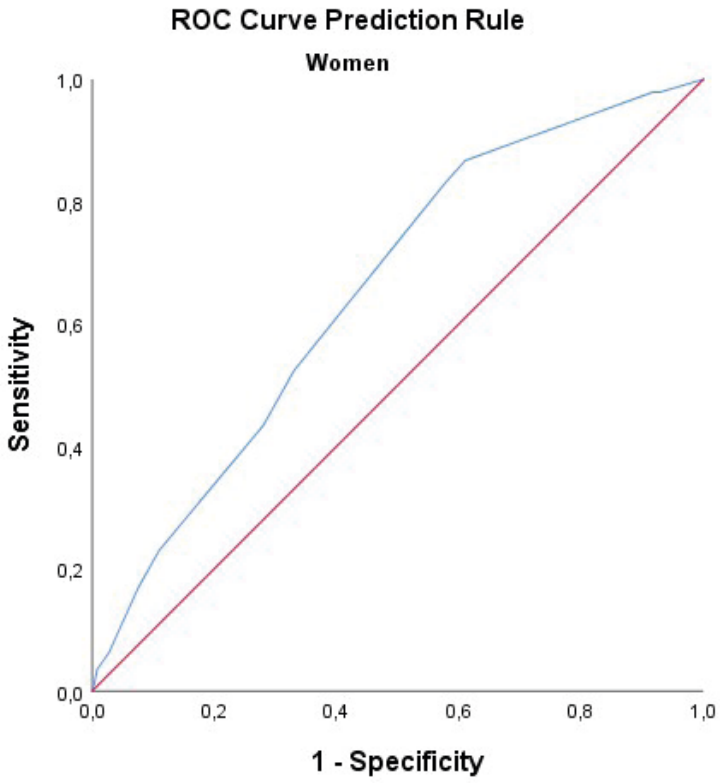


Figure 3. ROC curves diagnostic prediction models for LVDD/HFpEF for women.

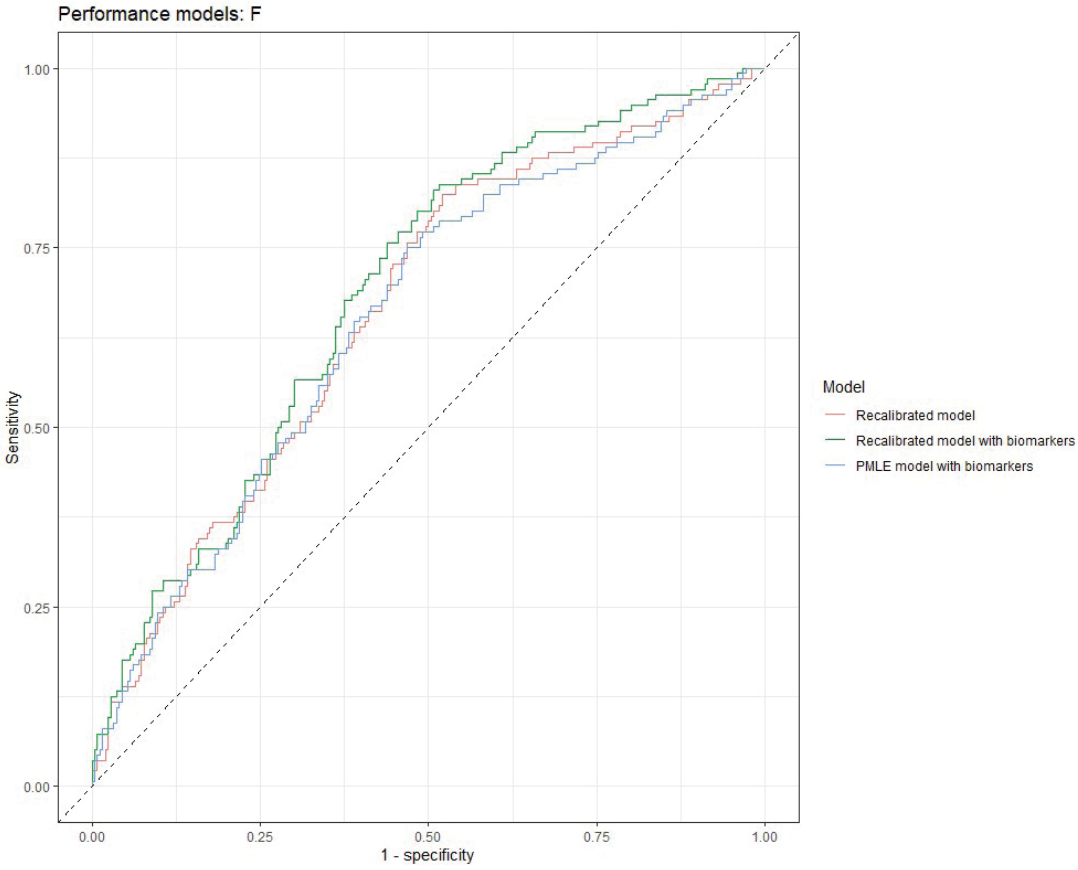


Figure 4. ROC curves diagnostic prediction models for LVDD/HFpEF for men.

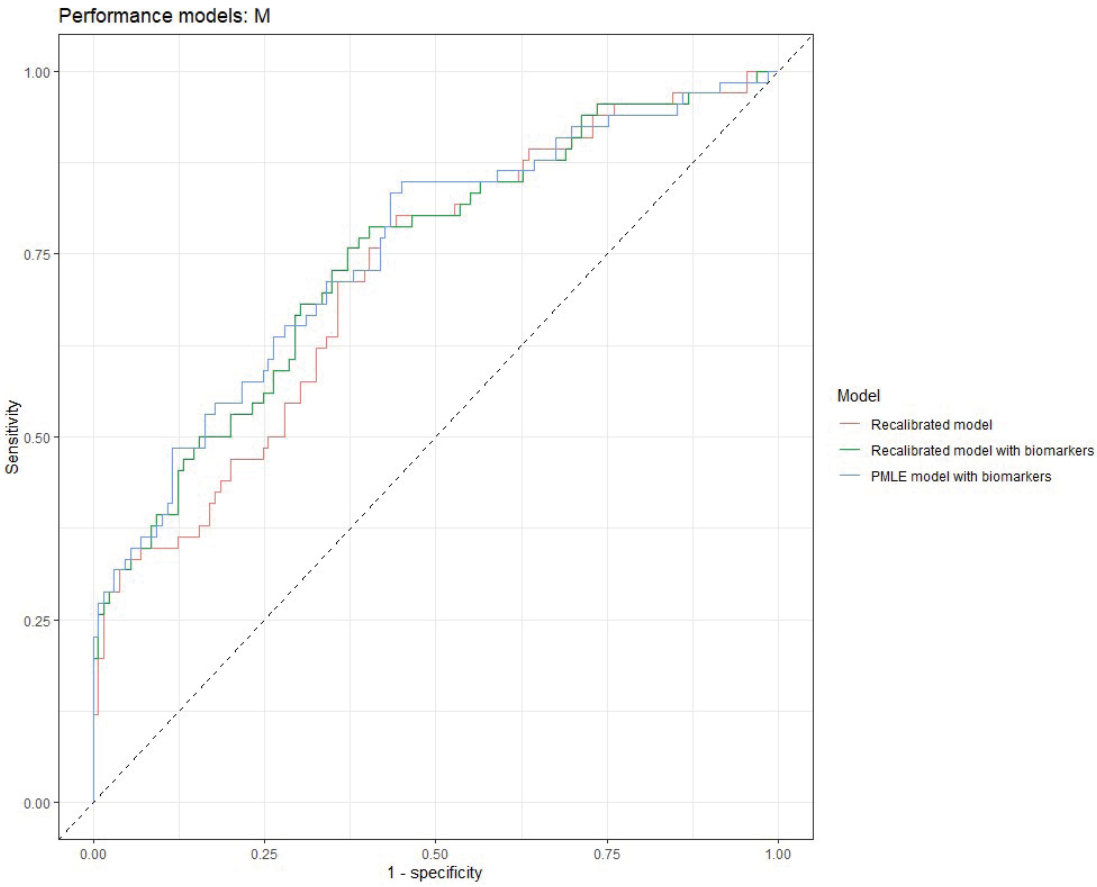


Figure 5. Calibration plot of diagnostic prediction models for LVDD/HFpEF in women.

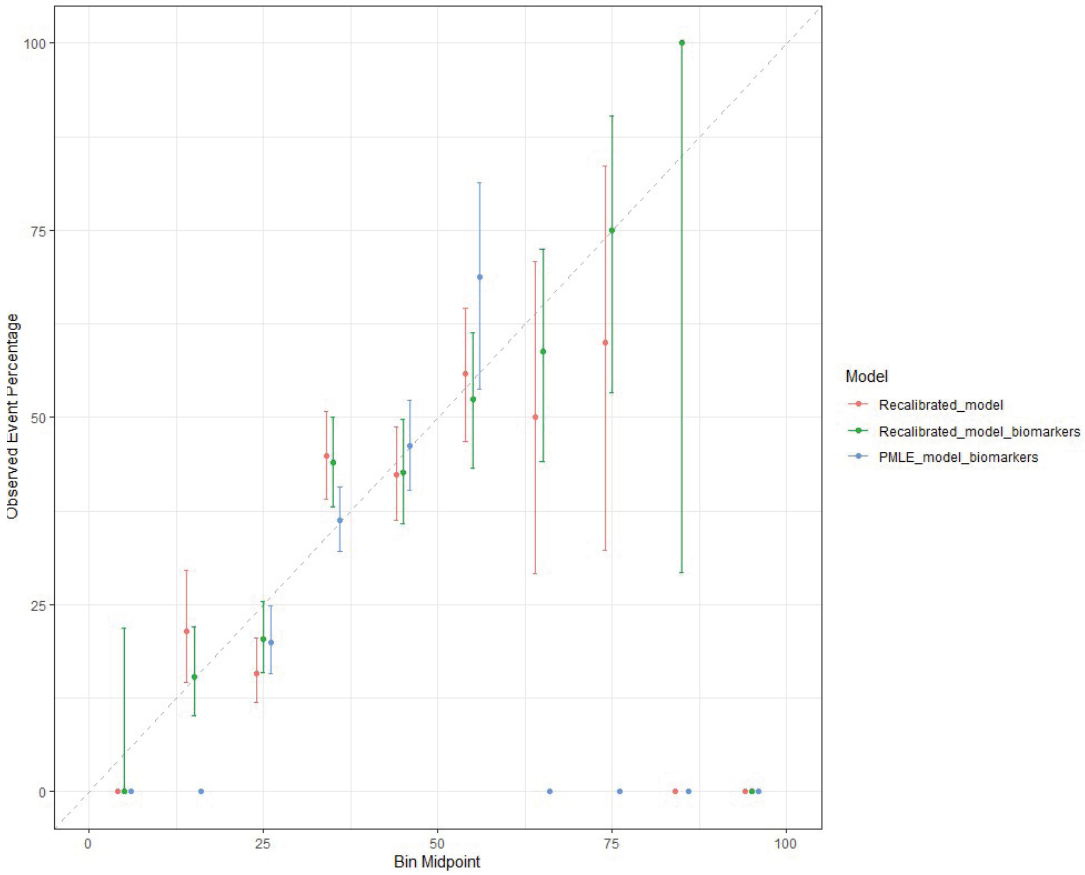
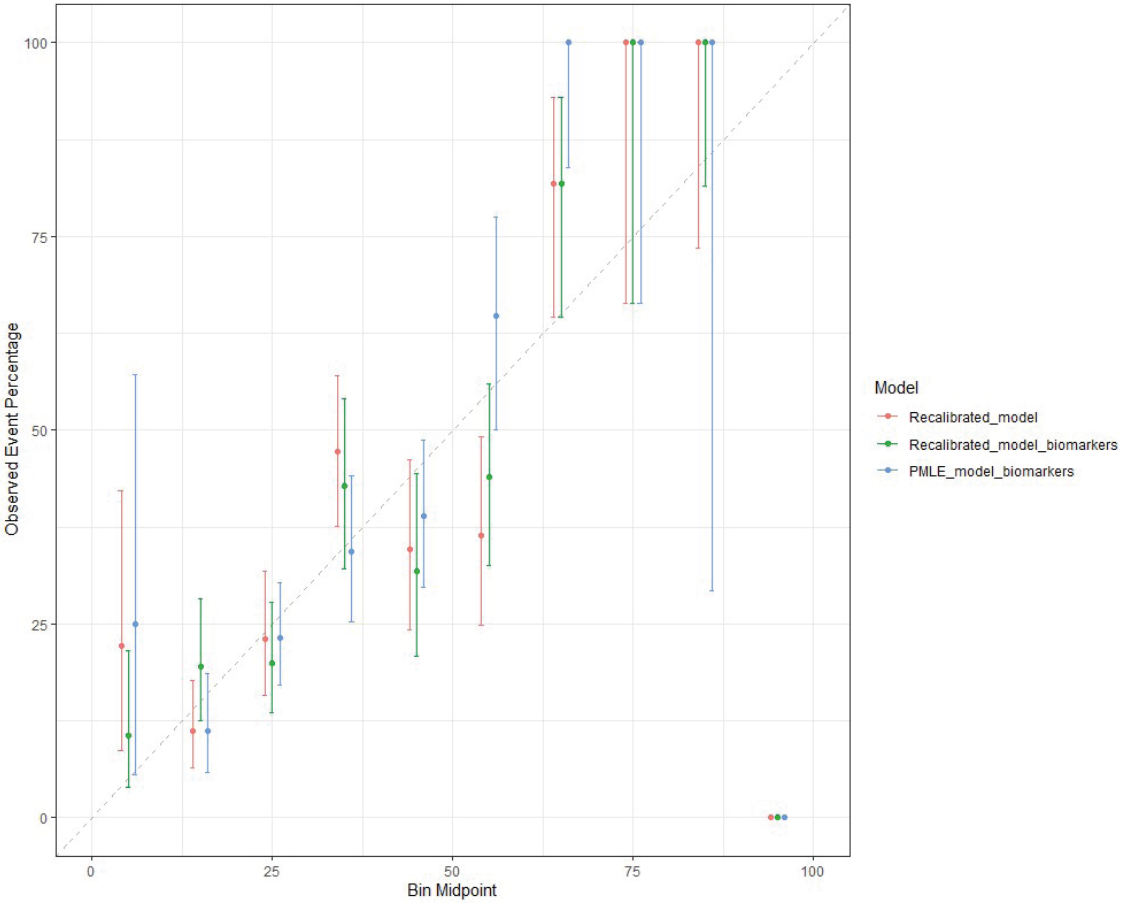


Figure 6. Calibration plot of diagnostic prediction models for LVDD/HFpEF in men.



Supplemental table 1. Clinical predictors in 634 men and women in the HELPFul case-cohort study stratified by sex.

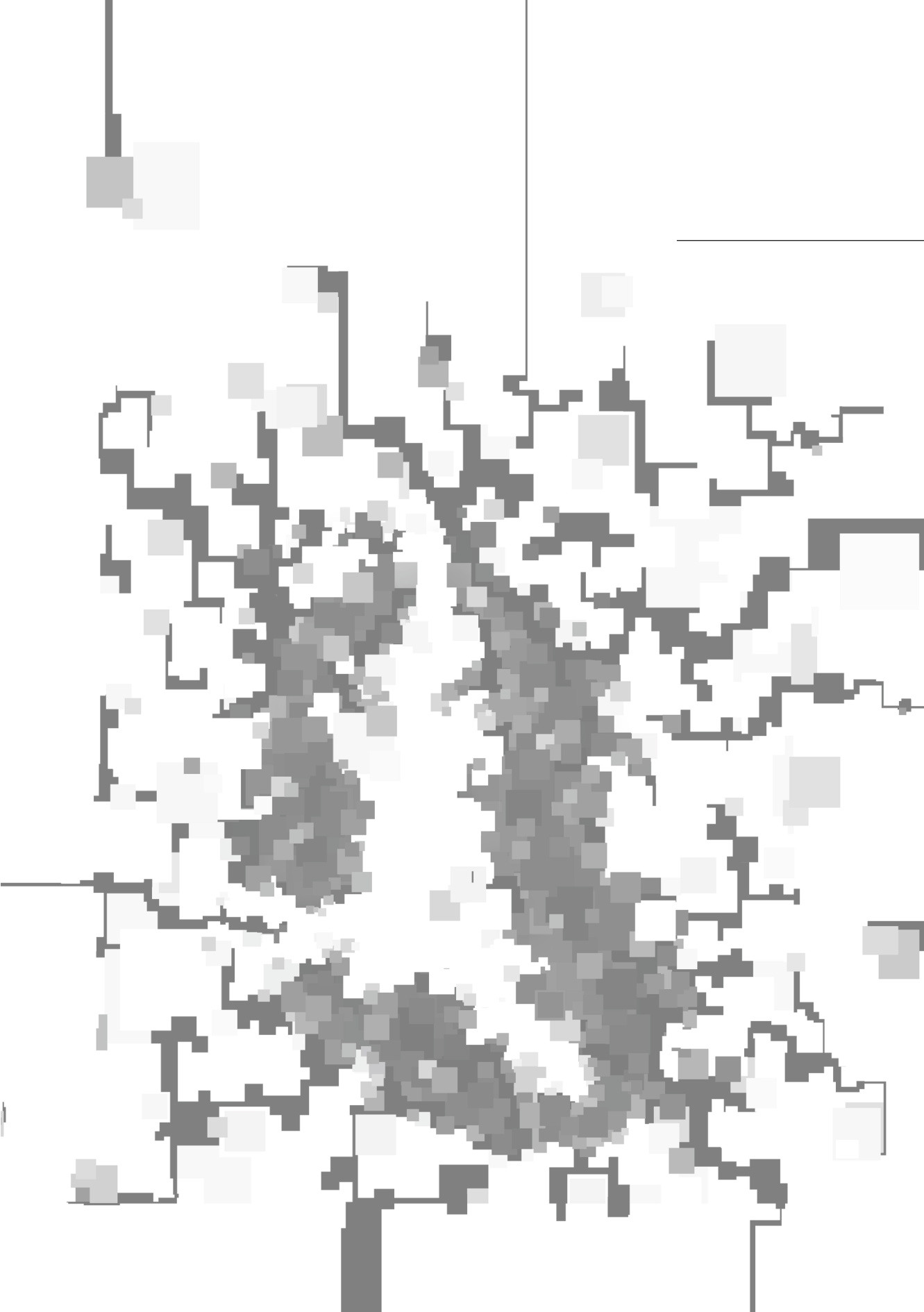
	Men (n=213)	*Women (n=421)*	*p-value*	*All (634)*
Original predictors				
Mean age in years (SD)	63.6 (10.1)	62.7 (9.0)	0.26	63.0 (9.4)
History of ischemic heart disease (%)	4 (2)	3 (1)	0.02	7 (1)
Dypnoea (MRC≥3) (%)	45 (21)	127 (30)	0.02	172 (27)
Mean BMI in kg/m^2 (SD)	26.8 (9.5)	27.0 (4.7)	0.72	26.9 (6.7)
Mean pulse pressure (SD)	61.4 (15.3)	59.7 (15.0)	0.20	60.3 (15.1)
Beta-blocker use (%)	28 (13)	73 (17)	0.17	101 (16)
Multi-morbidity and polypharmacy (%)	54 (25)	114 (27)	0.64	168 (26)

BMI=body mass index, MRC= medical research council, SD=standard deviation.

Supplemental Table 2. Baseline characteristics of 634 men and women in the HELPFul case-cohort study stratified by sex.

	Men (n=213)	*Women (n=421)*	*p-value*
Clinical characteristics			
Mean age in years (SD)	63.6 (10.1)	62.7 (9.0)	0.26
Mean BMI in kg/m^2 (SD)	26.8 (9.5)	27.0 (4.7)	0.72
Hypertension (%)	128 (60)	241 (57)	0.49
Hypercholesterolaemia (%)	80 (38)	174 (41)	0.36
Median eGFR (ml/min/1.73m^3) (IQR)	83.8 (74.7-93.6)	85.5 (74.9-96.7)	0.42
Type II diabetes (%)	24 (11)	29 (7)	0.06
Current smokers (%)	25 (14)	41 (11)	0.04
COPD (%)	23 (11)	52 (12)	0.82
Atrial fibrillation (%)	10 (5)	11 (3)	0.17
Mean Waist/hip ratio (SD)	0.97 (0.07)	0.90 (0.08)	<0.01
Echocardiographic measurements of diastolic function			
Median E/e' ratio (IQR)	8.6 (7.1- 10.0)	9.2 (8.2-10.6)	<0.01
Median e' septal in m/sec (IQR)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	0.53
Median e' lateral in m/sec (IQR)	8.0 (7.0-10.0)	8.0 (7.0-10.0)	0.45
Median LAVi in cm^2/m^2 (IQR)	24.0 (19.0-29.9)	22.9 (16.6-29.9)	0.26
Mean LVMi in g/m^2 (SD)	83.2 (21.9)	72.5 (16.9)	<0.01
Mean RWT (SD)	0.42 (0.09)	0.42 (0.09)	0.72
Median Ejection fraction (IQR)	65.3 (60.0-71.5)	66.2 (61.0-72.0)	0.47
Biomarkers			
Median BNP in pg/mL (IQR)	17.1 (10.0-36.8)	19.3 (10.0-36.7)	0.32
Median hs-TnI in pg/mL (IQR)	3.6 (2.3-6.0)	2.3 (1.6-3.4)	<0.01
Mean Lp (a) in mg/dL (SD)	24.0 (28.4)	27.4 (34.3)	0.22
Mean Cystatin-C in mg/L (SD)	1.0 (0.2)	0.9 (0.2)	<0.01
Mean CK-MB in ng/mL (SD)	1.8 (1.1)	1.3 (0.8)	<0.01
Mean Vitamin-D in ng/mL (SD)	22.7 (9.0)	25.8 (9.7)	<0.01
Mean ASAT in U/L (SD)	27 (13)	24 (8)	<0.01
Mean Albumin-G in g/L (SD)	42 (4)	42 (4)	0.28
Mean hs-CRP in mg/L (SD)	3.8 (10.1)	3.1 (5.1)	0.24
Mean Cholesterol in mmol/L (SD)	5.0 (1.2)	5.4 (1.1)	<0.01
Mean Triglycerides in mmol/L (SD)	2.0 (1.5)	1.6 (0.8)	<0.01
Mean HDL in mmol/L (SD)	1.2 (0.3)	1.5 (0.3)	<0.01
Outcome			
LVDD (%)	72 (34)	144 (34)	0.86
HFpEF (%)	23 (11)	80 (19)	0.01

ASAT= aspartate aminotransferase, BNP = B-type natriuretic peptide, BMI=body mass index, CK-MB = Creatine kinase-MB, COPD = chronic obstructive pulmonary disease, hs-CRP=high sensitivity C-reactive protein, eGFR=estimated glomerular filtration rate, HDL=high density lipoprotein, HFpEF= heart failure with preserved ejection fraction, hs-TnI= high sensitivity-Troponin I, IQR=interquartile range, LAVi = left atrial volume indexed for BSA, Lp(a)=lipoprotein(a), LVDD=left ventricular diastolic dysfunction, LVMi = left ventricular mass indexed for BSA, RWT = relative wall thickness, SD=standard deviation.



Chapter 9

3

Summary and General Discussion

The main objectives of this thesis were:

1. To address the impact of hospitalisation of heart failure over time in the Netherlands;
2. To assess the role of several potential determinants of left ventricular dysfunction and heart failure with preserved ejection fraction;
3. To quantify the effect of different published diagnostic guidelines on the classification of individuals suspected of LVDD;
4. To develop, validate and potentially update a diagnostic prediction algorithm for LVDD and HFpEF that can be used in general practice.

Main findings of this thesis

In **PART ONE**

- In **Chapter 2**, we showed that in the Netherlands, both short term (30-day, 1-year) and long term (5-year) survival after hospital admission for new-onset HF improved over time and did so equally in men and women. Nevertheless, mortality is still high with a 1-year risk of death of 36% in men and 36% in women in the time period 2000 to 2002, and 32% in men and 33% in women in the time period 2008 to 2010. The available data did not allow for differentiating between types of heart failure.

In **PART TWO**

- We first highlight the rationale and design of the HELPFul case-cohort s study in **Chapter 3**. We consider patients visiting a Dutch cardiology outpatient clinic as a good representation of adults from the community with symptoms such as chest discomfort, shortness of breath and palpitations, however, yet unknown with an established heart disease. These patients received a standardised work-up with history taking, physical examination, blood tests including B-type natriuretic peptide measurements, ECG, stress-ECG, and trans-thoracic echocardiography. From this study population extra blood samples were taken and stored t to investigate the role of biomarkers in the diagnostic assessment. An expert panel evaluated all diagnostic information and assessed the presence or absence of LVDD and HFpEF, resulting in a clinically well 'phenotyped' cohort of patients with and without LVDD or HFpEF.

- With our systematic review in **Chapter 4** among type 2 diabetes patients we showed that the prevalence of LVDD was similarly high in men and women (on average 46% and 47%, respectively). HFpEF was more common in women than man (28% vs 18%), though this was only reported in one study. There was large heterogeneity between studies possibly caused by the use of different diagnostic guidelines as well as differences in designs of the studies. Furthermore this

systematic review clearly shows that authors should put more effort in presenting age specific data for men and women separately.

- Biomarkers of renal function, e.g. eGFR and cystatin-C were only univariably related to LVDD in men and in women in **Chapter 5**. Renal dysfunction (defined as eGFR below 60 ml/min/1.73m2) was also not a very common finding (11% in those with LVDD and 5% in those without LVDD). Adjustment for age renal dysfunction was no longer statistically significantly related to LVDD and HFpEF. Further adjustment for sex, and either hypertension, diabetes, atrial fibrillation, smoking status, BMI & waist/hip ratio, and CRP & hyperlipidemia did not change this relationship further.

In **PART THREE**

- We first show in **Chapter 6** that application of different recent international recommendations for diagnosis of LVDD/HFpEF result in very different prevalence estimates and reclassification of the diagnosis was very common if applied to the HELPFul study population. Interestingly, we found this despite the similarities in echocardiographic parameters, and seems driven therefore by differences in how these criteria and cut-points are combined. Clearly these differences are fuel for confusion about classifying patients with LVDD or HFpEF. Who then are the truly HFpEF patients?
- We developed a sex-specific prediction rule in **Chapter 7** for LVDD/HFpEF in an individual patient data meta-analysis consisting of four community CV high-risk cohorts that performed well in these cohorts. Then in **Chapter 8**, we externally validated this prediction algorithm in the HELPFul study population. In addition, we evaluated the added value of kidney biomarkers (creatinine, cystatin-c), other blood biomarkers than BNP (hs-TnI, CKMB, Vitamin D, Lipoprotein (a), hs-CRP, lipids, albumin, ASAT). We performed logistic regression analysis and penalized maximum likelihood estimation modelling techniques for this evaluation. We show that original prediction model performed similarly in men and women of the HELPFul study. Furthermore the evaluated biomarkers did not significantly improve the model, nor performance of the sex-specific models.

3

Uncertainty in classifying LVDD or HFpEF: consequences for research and clinical practice

History and role of echocardiography

Transthoracic echocardiography remains important in the diagnostic assessment of all types of heart failure(1). Historically, focus has been on measuring the left ventricle ejection fraction (LVEF). LVEF is considered a surrogate for stroke volume in presence of a dilated left ventricle, typically seen months to years after an (large) acute myocardial infarction. Stroke volume cannot be measured with echocardiography. Thus the key element in heart failure, i.e., insufficient capacity (pump function) to deliver sufficient blood to the body, or only at the expense of increased filling pressures (1), cannot be directly measured by echocardiography. From the beginning of 2000 interest in HFpEF gradually increased, as it became clear that patients could have overt heart failure with a normal or preserved left ventricular ejection fraction (mostly defined as LVEF >45 50%). Furthermore developments after 2000 in tissue Doppler imaging enabled the measurement of mitral annular early diastolic velocities (e') of the LV lateral and septal wall. This made it possible to quantify stiffening of the cardiac wall and combined with early filling velocities (E), resulted in a new parameter to estimate filling pressures non invasively.

Role of LVEF measurements

Measurement of LVEF remains a key echocardiographic parameter, though it is well known that the measured LVEF can vary with approximately 5%. Even if the Simpson rule with tracking of the ventricle is applied with adequate correction for the volume of the papillary muscle there is still some degree of variation (1).

The importance of LVEF is also expressed by the classification of HF into two major (pathophysiologically) different entities; HFrEF and HFpEF. This occurred, irrespective of the knowledge that HF is (i) a clinical syndrome, (ii) with ejection fractions that may range from 10% to 90%, and (iii) the knowledge that LVEF is a rather imprecise measurement, and is not a surrogate of stroke volume in LV ejection fractions above 50%, nor in patients with normal or small LV volumes, as is often the case in concentric remodeled left ventricles.

The trend of subdividing HF based on LVEF continued over the years and remains ongoing. Different cut points for LVEF have been used in drug trials for both HFrEF and HFpEF, though most often LVEF <40% and LVEF ≥50%, respectively (2). In contrast in observational studies often a cut point of 45% is used. The use of LVEF cut points stems from the results of drug studies that showed that in those with HFrEF multiple drugs and also devices are effective in reducing morbidity and mortality, e.g. angiotensin converting enzyme (inhibitors or angiotensin receptor blockers (ARBs), beta blockers, mineral corticoid receptor inhibitors (MRIs) and angiotensin receptor neprilysin inhibitors (ARNIs), while these drugs were not clearly effective in reducing HF hospitalization or mortality in patients with LVEF >45 50%. It was suggested that the aforementioned drug categories are also effective in patients with HF and a LVEF 40 49%, however, less than in those with HF and a LVEF<40% (3 5). Recently, the PARAGON HF trial with sacubitril/valsartan vs. valsartan showed a significant small beneficial effect of this ARNI in patients defined as HFpEF in those with a LVEF 45% to 57%, and showed more effect in women (6). A new potential therapeutic class of drugs are inhibitors of sodium glucose transporter 2 (SGLT2 inhibitors) that was effective on the endpoint of HF hospitalizations in patients with HFrEF (LVEF ≤40%) and similarly in those known with type 2 diabetes and those without type 2 diabetes (7). RCTs with this drug in patients with HFpEF are ongoing and results are awaited with high expectations.

The nuanced role of B type natriuretic peptide measurements

Natriuretic peptides (B type natriuretic peptide (BNP) and N terminal pro BNP (NTproBNP)) are valuable for diagnosing all types of heart failure, although patients with HFpEF can have normal values, certainly when measured at a point in time when they are stable, i.e. not symptomatic, with normal fluid filling status. Moreover, elevated natriuretic peptide levels are part of the diagnostic algorithm for LVDD to diagnose HFpEF that was recently recommended by the ESC/HFA (8). Natriuretic peptides therefore have been and are still as important to the diagnosis of HFpEF as symptoms suggestive of heart failure (shortness of breath, fatigue and oedema) and echocardiographic signs of LVDD (1).

It is important to realize though that these natriuretic peptides are released by cardiac cells if wall tension is elevated. Considering Laplace's law (wall tension = pressure x radius/2x wall thickness) BNP or NTproBNP levels will be released substantially less from cardiac cells in concentric remodeled ventricles (as in HFpEF), than cardiac cells in eccentric remodeled ventricles (as in HFrEF) at the same LV pressures. Therefore natriuretic peptides will always be better biomarkers of HFrEF than for HFpEF. This is important knowledge as the HF syndrome is caused by pump failure (initially only during exercise), which goes along with elevated LV filling pressures. Nevertheless, new expert recommended criteria for LVDD include cut point values >220 pg/ml for NTproBNP, while 125 pg/ml is considered an exclusionary cut point for all type heart failure in the non acute setting (1,5).

The relation between LVDD and heart failure

Patients with LVDD may develop symptoms suggestive of heart failure. Regression of diastolic function does occur, but it is unclear yet what drives this change. To date a small number of population studies investigated the longitudinal change in patients with LVDD (10 14). In a large population based cohort of participants enrolled in the Olmsted County Heart Function Study in the United States, randomly selected 2042 participants 45 years or older that underwent three clinical evaluations and echocardiography (in 1997 2000, in 2002 2004 and 2004 2010) with complete data for 1402 participants. Between the first two time examinations, LVDD prevalence increased from 23.8% (95%CI 21.2 26.4%) to 39.2% (95%CI 7.1 10.5%), and worsened LVDD was associated with age 65 year or older (odds ratio 2.85 (95%CI 1.77 4.72). During 6.3 years of additional follow up, heart failure occurred in 2.6%, 7.8%, and 12.2% of persons whose diastolic function normalized or remained normal, remained or progressed to mild dysfunction, or remained or progressed to moderate or severe dysfunction, respectively ($p<0.001$). LVDD was associated with incident all type heart failure after adjustment for age, hypertension, diabetes and coronary artery disease (hazard ratio 1.81 (95%CI 1.01 3.48) (11). Thus, early detection of LVDD provides an opportunity for optimization of blood pressure and life style recommendations and thus prevention of heart failure (15).

Inconsistent use of criteria for LVDD

As already explained, HFpEF is defined as symptoms suggestive of HF plus structural and/or functional cardiac abnormalities related to LVDD. However there is ongoing discussion on how to define LVDD. In chapter 6, we have shown that the recommended criteria for the assessment of LVDD vary considerably between existing guidelines, with substantial reclassification as a result. The most recent definition for LVDD differs largely from previous definitions, and the same patient is differently classified if one or the other classification scheme is applied (1,8,16). New scores to classify patients suspected of HFpEF are the HFA

PEFF score from the ESC/HFA and the H2FPEF score from the Mayo Clinic (8,17). All scores for LVDD incorporate echocardiographic criteria, however many scores differ in what criteria to use and what exact cut points for those criteria. This leads to both similarities, i.e. the overlap, in

criteria and cut points and differences, for instance shown in Figure 1 of Chapter 6.
Older guidelines and the HFA PEFF score are expert opinion based, while the H2FPEF score is based on multivariable diagnostic prediction modeling with invasive cardiac pressure volume measurements including LV end diastolic pressure and mean pulmonary capillary wedge pressure as the reference test (8,9,16 19). However, both the derivation and validation cohort came from one hospital (Mayo Clinic, United States) and included relatively young patients (mean age 63 years, 60% female) with persistent shortness of breath that could not be explained by other causes than cardiac, and in whom echocardiography produced unclear results. According to pressure volume loop measurements (often considered the reference standard for LVDD) 64% of these patients had HFpEF (17), however as these results stem from a very selected subgroup of HFpEF patients the generalizability to the population of GPs and cardiology clinics is limited.
Hence after two decades, we still have to deal with multiple criteria for LVDD/HFpEF with substantial differences in echocardiographic parameters and their cut points, problems with the use of natriuretic peptides, and the use of clinical variables. Invasive pressure measurements and pressure volume loop recordings measured during rest and exercise that show abnormally elevated filling pressures are considered confirmatory evidence for LVDD (the reference standard). However, this diagnostic strategy is far from feasible to apply to all suspected cases given the prevalence of disease, the risks of invasive measurements, the workload and the burden it presents to patients.

Consequences of heterogeneity in populations caused by different criteria applied for LVDD

Depending on the criteria for LVDD used, there is very large heterogeneity among patients classified as LVDD. Therefore, comparing prevalence and incidence between different studies on LVDD and HFpEF is hampered, and any result of comparing populations may obscured by different definitions aside true biologic differences or similarities. Of course, also (comparison of) studies on diagnosis, etiology, prognosis, and therapy are severely hampered by potential differences due to use of different definitions. Differences between study populations in the field of LVDD and HFpEF essentially already exist. For studies on drugs, there is a tendency to depend heavily on having had an hospital admission for heart failure, but with a LVEF >50%, and (largely) elevated BNP/NTproBNP value. But as explained, this may easily result in excluding 'classic' HFpEF patients with concentric remodeled left ventricles after longstanding hypertension (20). Thus, the results of RCTs with drugs in the past and those that are ongoing may after conclusion of the trial present only a treatment effect in a population considered to have HFpEF, but assessed in patients that largely differ from community patients with HFpEF who have a different phenotype of HFpEF.
The ongoing drug studies in patients with HFpEF, thus only provide an answer for those selected patients ever hospitalized for heart failure and/or with relatively high BNP/NTproBNP values, and thus a very specific subgroup of the population of population of patients with HFpEF. This is an important reason for the difficulties in recruiting HFpEF patients for such studies. But even more important, failure or success of therapy, might be more dependent on the applied criteria, than on a treatment effect on the true underlying cause. Without any clearly effective therapy, and the lack of a universally accepted definition, HFpEF patients continue to be misdiagnosed or underdiagnosed, certainly at the early stages of disease, unless they have progressed to end stage heart failure necessitating hospitalisation.

Potential solutions to solve the lack of a feasible reference standard for LVDD

Any reference standard should preferably be based on the use of prognostic outcomes, e.g. (i) development of heart failure, (ii) heart failure hospitalization, or (iii) all cause or HF-related mortality with) heart failure. By developing an algorithm with echocardiographic parameters, clinical variables and blood biomarkers to diagnose LVDD that best predicts such prognostic

events, at least a prognostically relevant 'type' of LVDD may be defined. Such a new definition of LVDD will serve as good starting point for aetiological studies and therapeutic trials to clarify whether within this population there are subgroups that need specific treatments.
Currently, most classification algorithms for LVDD were authority based or developed in cohorts from a single hospital or a community based cohort. True external validation rarely occurs, and often only after an algorithm has already been published (21,22). The algorithms have often not necessarily been proven to be scalable to other populations (21,22).
It is therefore time to combine existing cohorts, that have been well phenotyped, to diagnose LVDD/HFpEF, and create a large individual patient data (IPD) set with relevant determinants and through IPD meta analysis provide a prediction model with as the outcome clinically relevant prognostic events. The potential of such a large scale IPD meta
analysis is substantial because it allows assessment of variation in determinants, of relevant cut points of determinants, but also of analysis in subgroups (for example age strata, men vs. women, ethnicity, comorbidities). Furthermore such an IPD meta analysis has the advantage that it is not dependent on the study specific diagnostic algorithms for LVDD. Instead, determinants and cut off values can be tested directly against prognosis.

Potential of an IPD meta analysis LVDD/HFpEF classification based on prognostic endpoints
With an IPD meta analyses existing and currently ongoing drug trials in patients with HFpEF could be re evaluated in post hoc analyses. Based on the new HFpEF diagnosis (IPD prognosis based) treatment effects can be compared in the treatment and placebo arm. Studies evaluating the same medication class could be combined, e.g. ACE inhibitors, ARB, beta blockers, ARNIs, and SGLT2 inhibitors. The result will be treatment effects that are easier to interpret as they are observed in a more homogeneous study population that has a clear poor prognosis. In effect the real treatment effects of a drug can be established, and no longer be obscured by misclassified patients, which could have been the case in the concluded drug trial studies. Newly initiated drug trials can also directly benefit from the results of such an IPD algorithm for LVDD/HFpEF as it offers the opportunity to clearly define the inclusion criteria, with the knowledge that patients included have a negative prognosis that is related to their diagnosis of HFpEF (2).

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Samenvatting in het Nederlands

Het Centraal Bureau voor Statistiek verwacht op basis van voorspellingen dat de Nederlandse populatie boven de leeftijd van 75 in de komende 20 jaar zal verdubbelen van 1.2 miljoen in 2011 naar 2.6 miljoen in 2040. Met de verdubbeling van deze leeftijdsgroep wordt verwacht dat ook de prevalentie van hartfalen zal stijgen. Deze stijging is niet alleen het gevolg van veroudering, maar ook van verbeterde overleving na een acuut coronair syndroom en van een toename in de prevalentie van belangrijke onderliggende co-morbiditeiten voor het ontwikkelen van hartfalen, zoals hypertensie, obesitas, type 2 diabetes en boezem fibrilleren.

Historisch gezien is er vooral onderzoek gedaan naar hartfalen met verminderde, ook wel reduced, ejectie fractie (HFrEF) met medicatie trials in voornamelijk jonge mannen met weinig tot geen co-morbiditeiten. De laatste jaren is echter toenemend aandacht voor hartfalen met behouden, ofwel preserved, ejectie fractie (HFpEF). Linker ventrikel diastolische dysfunctie (LVDD) is een afwijking met vertraagde relaxatie en verhoogde vullingsdrukken van de hartspier die gepaard gaat met veroudering, maar door verscheidene co-morbiditeiten sneller kan ontstaan en verergeren. Voor de diagnose van HFpEF is bewijs van LVDD in de vorm van functionele of structurele afwijkingen op echocardiografie een belangrijk onderdeel. LVDD en HFpEF hebben een hoge prevalentie in de oudere populatie met een hoger cardiovasculair risico door onder andere hypertensie en type II diabetes.

Kennis over HFpEF heeft zich traag ontwikkeld door een onduidelijk beeld over de ziekte zelf, als ook onduidelijkheid over hoe dit syndroom exact te definiëren. Er is geen gouden standaard voor LVDD en dus ook HFpEF waardoor verschillende studies hun eigen criteria hebben gehanteerd om patiënten te classificeren. In deze situatie is diagnose door een panel van experts het beste alternatief, echter is dit een arbeids intensief proces welk niet voor de kliniek haalbaar is. Een ander belangrijk probleem is onderdiagnose van hartfalen, met name HFpEF, welk onder andere het gevolg is van aspecifieke symptomen in vroege fase van HFpEF. Natriuretische peptides zijn biomarkers die voor HFrEF een belangrijke rol spelen in de diagnostiek. In het algemeen zijn deze natriuretische peptides echter lager in patienten met HFpEF. De natriuretische peptides worden namelijk uitgescheiden onder invloed van verhoogde wanddruk van de hartspier. Deze wanddruk is bij patienten met HFpEF lager door concentrische remodelering.

Tegenwoordig wordt meer aandacht besteed aan preventie van hart en vaatziekten, door middel van levenstijl aanbevelingen en vroege behandeling van hypertensie, verhoogd cholesterol en type 2 diabetes in de eerste lijn met intensievere, gestructureerde monitoring van het effect van behandeling. Daarnaast wordt in cardiologie buitenpoli klinieken meer one-stop shop gedaan.

Deze ontwikkelingen bieden de kan het proces van vroege diagnose van LVDD en HFpEF te onderzoeken. Gevalideerde diagnostische algoritmes kunnen ondersteuning bieden in de verwijzing van patienten met verhoogd risico op ontwikkelen van LVDD en HFpEF voor aanvullende diagnostiek. Tevens kan de rol van biomarkers in de verfijning van deze diagnostische algoritmes onderzocht worden. In deze thesis worden verscheidene van de bovengenoemde aspecten behandeld.

In **DEEL EEN**
laten we in **Hoofdstuk 2** zien dat in Nederland zowel de korte termijn (30-dagen, 1-jaar) en lange termijn (5-jaar) overleving verbeterde na ziekenhuis opname voor nieuw ontstane hartfalen en in gelijke mate voor mannen en vrouwen. Echter, de mortaliteit blijft hoog met een risico op overlijden na 1 jaar van 36% voor mannen en 36% voor vrouwen in de periode van 2000 tot 2002, en 32% voor mannen en 33% voor vrouwen in de periode van 2008 tot 2010. Met de beschikbare data was het niet mogelijk onderscheid te maken tussen de verschillende types van hartfalen.

In **DEEL TWEE**
belichten we eerst de rationale achter en de opzet van de HELPFul case-cohort studie in **Hoofdstuk 3**. We achten patiënten die een Nederlandse cardiologie buitenpoli bezoeken als een goede reflectie van volwassenen in de bevolking met pijn op borst, kortademigheid en hartkloppingen, die nog geen bewezen hart en vaatziekten hebben. Deze patiënten kregen een uitgebreide, gestandaardiseerde work-up met onder andere afnemen van ziekte voorgeschiedenis, lichamelijk onderzoek, bloed testen waaronder meten van B-type natriuretisch peptide, ECG, stress-ECG, and transthoracale echocardiografie. Extra bloed monsters werden afgenomen van deze studie populatie en opgeslagen om de rol van biomarkers in diagnostiek te onderzoeken. Een panel van deskundigen evalueerde alle beschikbare diagnostische informatie en beoordeelde de aan-, of afwezigheid van LVDD en HFpEF. Het resultaat is een klinisch goed gephenotypeerd cohort van patiënten met en zonder LVDD en HFpEF.

Met een systematic review in **Hoofdstuk 4** onder patiënten met type 2 diabetes laten we zien dat de prevalentie van LVDD onder mannen en vrouwen in gelijke mate hoog is (gemiddeld 46% en 47%, respectievelijk). HFpEF was vaker aanwezig onder vrouwen dan mannen (28% vs 18%), hoewel dit maar in één studie werd gerapporteerd. Tevens was sprake van grote heterogeniteit tussen de studies, welk mogelijk werd veroorzaakt door het gebruik van verschillende diagnostische richtlijnen, als ook verschillen in de opzet van de studies. Verder toont deze systematic review dat meer moeite moet worden gedaan voor het weergeven van leeftijds specifieke date voor mannen en vrouwen.

Biomarkers van nierfunctie, zoals eGFR en cystatin-C zijn enkel univariabel gerelateerd aan LVDD voor mannen en vrouwen in **Hoofdstuk 5**. Nier dysfunctie (gedefinieerd middels een eGFR onder de 60 ml/min/1.73m2) kwam niet vaak voor (11% onder individuen met LVDD en 5% onder individuen zonder LVDD). Na correctie voor leeftijd was renale dysfunctie niet langer statistisch significant gerelateerd met LVDD en HFpEF. Verdere correctie voor geslacht, en andere factoren; hypertensie, diabetes, boezem fibrilleren, rook gedrag, BMI & taille/heup ratio, en CRP & hyperlipidemie gaven geen verdere verandering van deze bevinding.

In **DEEL DRIE**
laten we in **Hoofdstuk 6** zien dat toepassing van verschillende recente internationale aanbevelingen voor de diagnose van LVDD/HFpEF op de HELPFul studie populatie resulteert in zeer verschillende prevalentie schattingen en reclassificatie van de diagnose voor patienten kwam vaak voor. Deze bevinding was er ondanks overeenkomst tussen de verschillende aanbevelingen van echocardiografische parameters en lijkt daarom gedreven door verschillen in hoe deze criteria en afkap waardes worden gecombineerd in de verschillende aanbevelingen. Deze verschillen kunnen een oorzaak voor de verwarring zijn over classificatie van patienten met LVDD of HFpEF. Welke patienten hebben nu echt HFpEF?

We hebben een geslachts-specifieke voorspel regel ontwikkeld voor LVDD/HFpEF in **Hoofdstuk 7** middels een individual patient data meta-analysis met vier cohorten van patiënten in de bevolking met hoog cardiovasculair risico. Vervolgens hebben we in **Hoofdstuk 8**, deze voorspelregel extern gevalideerd binnen de HELPFul studie populatie. Daarnaast hebben we de toegevoegde waarde van renale biomarkers (creatinine, cystatine-c), en andere bloed biomarkers dan BNP onderzocht; (hs-TnI, CKMB, Vitamine D, Lipoproteine (a), hs-CRP, lipiden, albumine, ASAT). We hebben logistische regressie analyse and penalized maximum likelihood estimation modellering toegepast voor

deze evaluatie. We laten zien dat de oorspronkelijke voorspel modellen vergelijkbaar presteren in zowel mannen en vrouwen van de HELPFul studie. Bovendien verbeteren de geëvalueerde biomarkers de geslachts specifieke modellen niet significant.

Conclusie

Transthoracale echocardiografie zal een belangrijk onderdeel blijven in de diagnostiek van alle types hartfalen, met een belangrijke rol voor meting van linker ventrikel ejectie fractie (LVEF) als surrogaat voor pompfunctie van het hart. Ook de onderverdeling van hartfalen in subtypes op basis van deze LVEF is een trend die voorlopig nog in gebruik zal blijven. Echter tonen we in dit proefschrift dat is sprake is van grote heterogeniteit in de classificatie van LVDD en HFpEF in patienten. Deze heterogeniteit wordt veroorzaakt door verschillen in het gebruik van criteria die voor LVDD worden gebruikt is. Tevens hebben we in dit proefschrift stappen gemaakt in ontwikkeling van voorspelmodellen voor patiënten in de eerste lijn gezondheidszorg. In de toekomst kan met voorspelmodellen gerichter preventief behandeld worden voor LVDD en HFpEF door bij hoog-risico patienten de onderliggende co-morbideiten in een vroeg stadium te behandelen en intensief te vervolgen in de eerste lijns zorg bij de huisarts. Hiervoor is echter wel een betere definitie van LVDD en HFpEF nodig. Het is tijd om met bestaande cohorten, die goed gephenotypeerd zijn, een grote individual patient data meta-analysis te verrichten voor een prognostisch relevante definitie van LVDD en HFpEF. Met een prognostische relevante definitie van LVDD en HFpEF kunnen verdere stappen worden gemaakt in onderzoek en behandeling van LVDD en HFpEF.

Appendix

Review committee

Prof. Dr. G. Pasterkamp
Prof. Dr. M.C. Verhaar
Prof. Dr. P.A. de Jong
Prof. Dr. M.H. Emmelot
Prof. Dr. F. Schellevis
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List of Publications

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Accepted for publication

*Buddeke J, ***Valstar GB**, van Dis I, Visseren FLJ, Rutten FH, den Ruijter HM, Vaartjes I, Bots ML; Queen of Hearts and RECONNECT investigators. Mortality after hospital admission for heart failure: improvement over time, equally strong in women as in men. BMC Public Health. 2020 Jan 10;20(1):36.

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Valstar G.B., Bots S.H., Cramer M.J., Teske A.J., Asselbergs F.W., Hofstra L., Menken R., Bots M.L., Den Ruijter H.M. Comparison of three recommendations to detect left ventricular diastolic dysfunction in men and women referred to an outpatient cardiology clinic

Patrick Rossignol, Daniela Dobre, Natalia Lopez-Andres, Stéphanie Grojean, Nicolas Girerd, Céline Leroy, Renaud Fay, Javier Diez, Arantxa González , Kenneth McDonald, Svend Aakhus, Giuseppe Ambrosio, Hans-Peter Brunner-La Rocca, Ricardo Fontes-Carvalho, Alan G. Fraser, Loek van Heerebeek, Gilles de Keulenaer, Paolo Marino, Alexandre Mebazaa, Zoltàn Papp, Riccardo Raddino, Carsten Tschöpe , **Gideon B. Valstar**, Hester M. den Ruijter, Saskia C.A. de Jager, Emma Robinson , Stephane Heymans, Walter J. Paulus, Faiez Zannad. Intercellular adhesion molecule 3 (ICAM3) in diastolic dysfunction and heart failure with preserved ejection fraction. Biomarker and experimental insight.

In preparation

Valstar G.B., Rutten F.H., Menken R.M., Cramer M.J., Teske A.J., Hofstra L., Bots M.L., Den Ruijter H.M. Validation of a diagnostic prediction rule for left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in patients referred to an outpatient cardiology clinic.

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Michiel Henkens, Emma Robinson. I had great fun setting up a collaborations with both of you on the Olink data and the cardiomyocyt experiments. I'm looking forward to the future and figuring

out these biomarkers and the pathophysiology with your involvement.

Selma Bouthoorn. Lekker door een kleine honderd tekst-screen ploeteren en samen nog het wiel uitvinden, ik als kersverse promovendus, jij als kersverse post-doc. Het was leuk om zo met jij mijn eerste gezamenlijke project te doen en een beetje te praten over de dingen des levens. Veel succes met de huisarts opleiding, als je niet al klaar bent inmiddels, en met je jonge gezin!

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Curriculum Vitae

Gideon Valstar was born on the 29th of May 1987 in Leiderdorp, the Netherlands to Marina Kneppers and Aat Valstar. The family moved to Meijel when Gideon was 7, where he spent his further youth. After completing the St. Willibrord Gymnasium he went to study Health Sciences for two years in Maastricht. These first two years in Maastricht were also his introduction to rowing, which he kept up for seven years.
After two years of Health Sciences Gideon was selected to study Medicine at the Erasmus University through the Decentral Selection program. In 2010 he had his first experience with science when he did research on the effects of smoking after a PCI procedure. In 2012 he along with a friend (Roderick Dulfer) got the opportunity to do four months of research on the best approach for blunt liver trauma at the trauma ward of the Groote Schuur Hospital in Cape Town. Thereafter medical internships started and Gideon found his interest drawn towards localization in neurology at first, but neurosurgery soon followed. After working at the neurosurgery department of the VUmc for half a year he thought it was time to expand his knowledge and skillset regarding medical research. He got the opportunity to work for Hester den Ruijter, Frans Rutten, Michiel Bots and Gerard Pasterkamp combining experimental cardiology with cardiovascular epidemiology as well as setting up a clinical study involving patients. Four years later the end result is this thesis, a successful end of the HELPFul study and a Postgraduate degree in (clinical) epidemiology to be obtained around May. On the 3rd of Februari Gideon will start at the cardiology department of the UMCU.