The Interplay between Fasting Glucose, Echocardiography, and Biomarkers: Pathophysiological Considerations and Prognostic Implications

Manan Pareek

This review has been accepted as a thesis together with four previously published papers by the University of Southern Denmark on February 28, 2017 and defended on March 3, 2017.

Tutor(s): Michael Hecht Olsen, Poul Flemming Høilund-Carlsen, Axel Cosmus Pyndt Diederichsen, Lars Melholt Rasmussen, Jes Sanddal Lindholt

Official opponents: Henrik Wiggers, Olle Melander

Correspondence: Department of Endocrinology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark

E-mail: mananpareek@dadlnet.dk

Dan Med J 2017;64(9):B5400

1. LIST OF PAPERS

The thesis is based on the following papers:

I. Pareek M, Aharaz A, Nielsen ML, Gerke O, Leósdóttir M, Møller JE, Andersen NH, Nilsson PM, Olsen MH. Untreated diabetes mellitus, but not impaired fasting glucose, is associated with increased left ventricular mass and concentric hypertrophy in an elderly, healthy, Swedish population. IJC Metab Endocr. 2015 Dec;9:39-47.

II. Pareek M, Nielsen ML, Gerke O, Leósdóttir M, Møller JE, Hindersson P, Sehestedt TB, Wachtell K, Nilsson PM, Olsen MH. Worsening diastolic function is associated with elevated fasting plasma glucose and increased left ventricular mass in a supra-additive fashion in an elderly, healthy, Swedish population. Int J Cardiol. 2015 Apr 1;184:466-72.

III. Pareek M, Vaduganathan M, Bhatt DL, Leósdóttir M, Olsen MH. Prognostic implications of fasting plasma glucose in subjects with subclinical echocardiographic abnormalities Int J Cardiol. 2017 Aug 15;241:423-9.

IV. Pareek M, Bhatt DL, Vaduganathan M, Biering-Sørensen T, Qamar A, Diederichsen AC, Møller JE, Hindersson P, Leósdóttir M, Magnussen M, Nilsson PM, Olsen MH. Traditional and Novel Cardiovascular Biomarkers in the General Population: Echocardiographic Correlates and Prognostic Abilities. Eur J Prev Cardiol. 2017 Jan 1:2047487317717065. [Epub ahead of print]

2. ABBREVIATIONS

ARIC: Atherosclerosis Risk In the Community Study
BNP: brain natriuretic peptide
CI: confidence interval
C-index: concordance index
DHS: Dallas Heart Study
DT: E-wave deceleration time
FHS: Framingham Heart Study
FPG: fasting plasma glucose
$HbA1_c$: hemoglobin $A1_c$ (glycosylated hemoglobin)
HR: hazard ratio
Hs-TnT: high-sensitivity (cardiac) troponin T
ICD: International Classification of Diseases
IFG: impaired fasting glucose
IQR: interquartile range
LV: left ventricle / left ventricular
LVEF: left ventricular ejection fraction
LVH: left ventricular hypertrophy
LVM: left ventricular mass
LVMI: left ventricular mass index
MESA: Multi-Ethnic Study of Atherosclerosis
MPP: Malmö Preventive Project
MPP-RES: Malmö Preventive Project Re-Examination Study
NFG: normal fasting glucose
NT-proBNP: N-terminal prohormone of brain natriuretic peptide
RWT: relative wall thickness
SCORE: Systematic COronary Risk Evaluation
SHS: Strong Heart Study
TnI: (cardiac) troponin I
TnT: (cardiac) troponin T

3. RESEARCH IN CONTEXT

Despite declining age-adjusted mortality rates, cardiovascular disease is still the leading cause of death worldwide (1). Traditional cardiovascular risk stratification tools that employ clinical risk factors, including *Systematic COronary Risk Evaluation (SCORE)* and *Framingham Risk Score*, although easily applied, are limited by their modest discriminative abilities (2-5). As such, robust cardio-

vascular risk assessment, including our understanding of the complex interplay between risk factors, in the primary preventive setting, remains incomplete. Phenotypical heterogeneity may be even greater among subjects with hyperglycemic conditions, i.e., prediabetes and diabetes, which is troublesome, given the dramatic global rise in mean fasting glucose levels, and the strong association with adverse cardiovascular outcomes (6-12). The unmet need for refinement or restratification of risk based on these conventional prediction models is further emphasized by our entrance into the era of precision medicine after the realization that one size simply does not fit all (13-15). Potential tools for closing these gaps and increasing our understanding of the pathways from risk factors through subclinical changes to manifest disease include imaging modalities and circulating biomarkers (16-20).

4. BACKGROUND

4.1 Glycemic Status and Cardiovascular Disease

Type 2 diabetes is a multifaceted, chronic disease, pathophysiologically characterized by a progressive decrease in pancreatic insulin secretion and a concomitant increase in peripheral insulin resistance, leading to hyperglycemia. The condition may be diagnosed based on fasting or random plasma glucose, the 2-hour plasma glucose during a 75 g oral glucose tolerance test, or glycated hemoglobin ($HbA1_c$) (21-23). In most cases, a confirmatory test is required. Many individuals do not meet the formal criteria for diabetes, but have glucose levels that cannot be considered normal. These conditions, i.e., impaired fasting glucose (IFG) and impaired glucose tolerance, are labeled prediabetes and are associated with a high risk of progression to manifest diabetes (21,23,24). Intermediate levels of $HbA1_c$ may be considered as prediabetes as well (25). Type 2 diabetes has reached epidemic proportions globally, and the burden continues to increase (26). This is worrisome, given the adverse contributions to health-related costs and disability-adjusted life years through its influence on multiple organ systems (12,27,28). The leading cause of death in diabetes is cardiovascular disease (29). There is a graded increase in cardiovascular risk with worsening glycemic status, and complications include coronary artery disease, heart failure, cerebrovascular disease, and peripheral artery disease (6-8,30-34). Therefore, diabetes is considered a major risk factor for, or perhaps even a risk equivalent to, cardiovascular disease (35-37).

4.2. Left Ventricular Structure and Function

Since the course from risk factors to manifest cardiovascular disease is highly variable, subclinical, i.e., asymptomatic anatomical and functional, alterations may resemble intermediate mechanistic links connecting the two, and as such, potentially improve risk discrimination (38). The presence of subclinical cardiovascular damage significantly raises the likelihood of developing symptomatic cardiovascular disease (39-42). Two such examples include left ventricular hypertrophy (LVH) and diastolic dysfunction, both of which can be evaluated using transthoracic echocardiography. LVH is defined as an inappropriately increased left ventricular mass (LVM), whereas diastolic dysfunction is the inability of cardiac myofibrils to rapidly or completely return to their resting length and is characterized by delayed active relaxation and increased LV stiffness. The conditions are interrelated as diastolic abnormalities are commonly observed among persons with LVH (43-46). Furthermore, both conditions are frequently encountered in the general population (47-53) and are predictive of cardiovascular morbidity and mortality in subjects with and without diabetes (54-57). The risk may be further modified by the magnitude of LVM and the LV geometric pattern, categorized according to the absence or presence of LVH and the relative wall thickness (RWT), a measure of the relationship between LV wall thickness and cavity diameter (58-61).

4.3. Potential Implications of Glycemic Status on Left Ventricular Structure and Function

One explanation for the poor prognosis among patients with diabetes is their susceptibility to develop a distinct primary myocardial condition, diabetic cardiomyopathy, predisposing them to an increased risk of heart failure (35). Diabetic cardiomyopathy is defined as ventricular dysfunction in patients with diabetes, occurring independently of hypertension, coronary artery disease, and other recognized causes and is characterized by increased LVM, concentric changes, and predominantly diastolic dysfunction (62-66). These cardiac abnormalities are common findings among patients with diabetes and may result from continuous metabolic stress, in line with the observation that their prevalence and severity seem directly related to the duration of diabetes (55,67-75). Indeed, the presence of subclinical cardiovascular damage in diabetes may act as a significant risk modifier and translates to a substantially increased event risk (76-78). However, it remains controversial whether there is a graded association between glycemic status, particularly when assessed in the fasting state, and LV structural and functional abnormalities, i.e., whether the risk increases along the diabetic continuum, from normal glycemic status through prediabetes to manifest diabetes (79-86). Importantly, although abnormal glycemic status accentuates risk in patients with known heart failure, its prognostic impact on subclinical cardiac abnormalities in apparently healthy subjects is unknown (87-90).

4.4. Cardiovascular Biomarkers

Despite the high prevalence of subclinical cardiac abnormalities, routine echocardiographic screening among asymptomatic patients with diabetes is not recommended (91,92). The same applies to asymptomatic individuals without diabetes. The availability of circulating cardiovascular biomarkers, e.g., natriuretic peptides and cardiac troponins, and their link to key pathophysiological processes, structural and functional myocardial alterations among others, makes their use as risk modifiers across the spectrum of cardiovascular risk theoretically attractive, even in subjects who have been stratified according to their echocardiographic findings (93-106). Brain natriuretic peptide (BNP) is released predominantly from ventricular myocytes in response to increased wall stress, i.e., volume expansion with resultant pressure overload, and has vasodilatory and diuretic properties (107). Circulating levels of the physiologically inert N-terminal fragment of its prohormone (NT-proBNP) may be measured instead (108). Cardiac troponins I (TnI) and T (TnT) form part of the contractile apparatus in myocytes and are released upon disruption of normal cell membrane integrity (109). Their myocardial specificity makes them the preferred markers of ischemia and necrosis; however, the introduction of high-sensitivity troponin (hs-Tn) assays has facilitated detection of circulating levels in a considerable proportion of individuals without established cardiovascular disease as well (110-112). Finally, natriuretic peptides and troponins may be independent predictors of adverse outcomes in subjects both with and without diabetes, but their overall contribution to risk prediction models, particularly in low risk, apparently healthy subjects, is less clearly established (16,17,113-131).

4.5. Potential Implications of Glycemic Status on Cardiovascular Biomarkers

Patients with diabetes are prone not only to heart failure, but also coronary artery disease, which is often silent (6-8,35). In fact, adverse cardiac alterations may already be present at the time of diagnosis of diabetes (132,133), making NT-proBNP and hs-TnT rational candidates for biomarkers in this setting. Nevertheless, glycemic status may affect the strength of the association between biomarkers and echocardiographic findings, perhaps implying that this should be taken into account when attempting biomarker-based risk prediction (134,135). The proportion of individuals with elevated concentrations of cardiovascular biomarkers may further be higher in the presence of diabetes, but seems to be influenced by diabetes duration and risk factor burden (98,116,121,123,128,136-139), and, similar to that noted for echocardiographic abnormalities, it is unclear whether hyperglycemia and biomarker concentrations exhibit a graded relationship (139-143). Finally, it is uncertain whether the predictive capabilities of NT-proBNP and hs-TnT differ across the glycemic spectrum, in apparently healthy subjects.

5. OBJECTIVES

1. To examine whether greater fasting plasma glucose (FPG) levels were independently associated with LVM and/or geometric pattern, in apparently healthy, elderly subjects with preserved LV ejection fraction (LVEF).

2. To examine whether greater FPG levels were associated with LV diastolic dysfunction, independently of increased left ventricular mass index (LVMI), in apparently healthy, elderly subjects with preserved LVEF.

3. To examine whether FPG levels modified the prognostic role of abnormal LVM, geometric pattern, and diastolic dysfunction, in predicting cardiovascular morbidity and mortality, in apparently healthy, elderly subjects with preserved LVEF.

4. To examine whether greater FPG levels were independently associated with concentrations of NT-proBNP and hs-TnT, in apparently healthy, elderly subjects with preserved LVEF.

5. To define the incremental prognostic value of NT-proBNP and hs-TnT for predicting incident cardiovascular outcomes, beyond traditional risk factors and subclinical echocardiographic abnormalities, in apparently healthy, elderly subjects with preserved LVEF. Additionally, to explore the associations of NT-proBNP and hs-TnT with key echocardiographic measures of LV structure and function, including effects of FPG, in these subjects.

6. To examine whether greater FPG levels modified the prognostic abilities of NT-proBNP and hs-TnT in predicting cardiovascular morbidity and mortality, in apparently healthy, elderly subjects with preserved LVEF.

6. METHODS

6.1. Study Population

The study population was derived from the echocardiography subsample (n=1,792) of the *Malmö Preventive Project Re-Examination Study (MPP-RES)* (2002-2006, n=18,238) (82). *MPP-RES* was the second phase of the *Malmö Preventive Project (MPP)* (1974-1992, n=33,346), a population-based screening program that included inhabitants from Malmö, Sweden, who belonged to prespecified birth cohorts between 1921-1949 (144). All participants answered a computer-based, self-administered questionnaire on lifestyle and medical history, including medication. Blood pressure and heart rate were recorded twice after 5 minutes of supine rest, with values averaged for the analyses. Height, weight, waist and hip circumferences were measured, and body mass index and body surface area (DuBois formula) were calculated. Blood samples were drawn after an overnight fast for analysis of plasma glucose, plasma lipids, and biobank storage for genetic analysis. Additional blood samples for cardiovascular biomarker assessments were drawn at the time of echocardiography, approximately 6 months after the initial screening visit. Samples were stored at -20°C.

Subjects, who underwent echocardiography, were randomly chosen from the three categories defined by baseline FPG, i.e., normal fasting glucose (NFG), IFG, and diabetes, including use of anti-diabetic medication, with oversampling in the two latter groups. The original echocardiography subsample was stratified into patients (defined as individuals with known cardiovascular disease (n=300), those who were on cardiovascular (n=864), anti-diabetic (n=329), or lipid-lowering medication (n=464), or had a reduced LVEF < 50% (n=99)) and apparently healthy subjects, the latter being the focus of this thesis. Slight between-paper sample size variations were due to certain additional exclusion criteria, including missing echocardiographic variables (n=158), missing biomarkers (n=31), or incomplete follow-up (n=6), but comprised of 670-693 subjects.

MPP-RES was approved by the *Regional Ethical Review Board* and conducted in accordance with the *Declaration of Helsinki*. All participants provided written informed consent.

6.2. Fasting Plasma Glucose

The majority of analyses took into account the aforementioned FPG-based selection of study subjects. Excluding those already on anti-diabetic medication, the definitions of NFG, IFG, and diabetes resembled the *World Health Organization* criteria (21): NFG: a single FPG ≤ 6.0 mmol/L; IFG: a single FPG between 6.1-6.9 mmol/L, or one measurement 7.0-11.0 mmol/L and a separate measurement ≤ 6.9 mmol/L; newly diagnosed diabetes: a single FPG ≥ 11.1 mmol/L or two separate measurements ≥ 7.0 mmol/L. Given the age-range of the study population, it was presumed that all cases comprised of type 2 diabetes, and no clear distinction was made throughout this thesis or its related publications.

6.3. Echocardiography

Six experienced technicians (biomedical scientists) performed all echocardiograms using either a 3V2c transducer (Acuson Sequoia, Mountain View, CA, USA) or an S3 transducer (Sonos 5500 Philips, Andover, MA, USA) and further did offline analyses of the images, using a mean of 3-5 cycles. Intra- and interobserver variabilities have been reported previously (82).

LVEF estimates were based on visual quantification. For LVM assessment, end-diastolic, 2-dimensional linear measurements in the parasternal long-axis view, at the tips of the mitral valve leaflets, perpendicular to the LV long axis, were used (46). Calipers were positioned on the interface between myocardial wall and cavity and the interface between myocardial wall and pericardium, respectively, obtaining the thickness of the interventricular septum, LV internal diameter, and thickness of the posterior wall. The Devereux formula was used for LVM calculation, with LVMI obtained by indexing for body surface area. Cut-offs employed for LVH were LVMI > 95 g/m^2 (females) and > 115 g/m^2 (males). LV geometric characterization was achieved by combining LVMI and relative wall thickness (RWT, (2*posterior wall thickness)/LV internal diameter): normal: absence of LVH and RWT ≤ 0.42; concentric remodeling:

absence of LVH and RWT > 0.42; eccentric LVH: presence of LVH and RWT ≤ 0.42; concentric LVH: presence of LVH and RWT > 0.42.

For evaluation of LV diastolic function, transmitral pulsed Doppler flow with a 1-3 mm sample volume placed between the tips of the mitral valve leaflets and tissue Doppler imaging with the sample volume positioned within 1 cm of the septal and lateral borders of the mitral annulus, both in the apical four-chamber view, were used (44). E, A, and E-wave deceleration time (DT) were obtained by pulsed Doppler imaging, and septal and lateral é by tissue Doppler imaging. Age-appropriate partitions of these parameters were then used for classification: normal diastolic function: septal é ≥ 8 cm/s and/or lateral é ≥ 10 cm/s; diastolic dysfunction: septal é < 8 cm/s and lateral é < 10 cm/s; grade 1 dysfunction: diastolic dysfunction + DT ≥ 240 ms, E/A ratio < 0.8, averaged E/é ratio ≤ 12; grade 2 dysfunction: diastolic dysfunction + DT 140-240 ms, E/A ratio 0.8-1.5, averaged E/é ratio ≥ 9; grade 3 dysfunction: diastolic dysfunction + DT < 140 ms, E/A ratio > 1.5, averaged E/é ratio ≥ 13. All cases of E/é ratio < 9 were classified as normal (DT < 240ms and E/A ratio ≥ 0.8), or grade 1 dysfunction (the remainder). In case of E/é ratio ≥ 9 and ≤ 12, subjects were only categorized as grade 1 or grade 2 dysfunction if both DT and E/A ratio fitted the same category, with the remainder labeled undetermined diastolic dysfunction. If E/é ratio was > 12, subjects were categorized as grade 2 or 3 diastolic dysfunction, which were grouped together for the analyses, due to the low number of subjects with grade 3 dysfunction. Finally, planimetri in the apical four-chamber view during end-systole allowed for estimation of left atrial area.

6.4. Biomarkers

NT-proBNP was measured with an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland) at the Department of Clinical Chemistry, Akershus University Hospital, Lorenskog, Norway. An elevated concentration was defined as ≥ 15 pmol/L. Hs-TnT was analyzed at the Department of Clinical Biochemistry, Regional Hospital of Northern Jutland, Hjørring, Denmark, between May-June 2013, using an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland). A concentration ≥ 14 ng/L (99^{th} percentile of a healthy reference population) was used as partition.

6.5. Outcomes

In papers III-IV, a composite of coronary events (myocardial infarction, stable ischemic heart disease, percutaneous coronary intervention, coronary artery bypass grafting), heart failure, stroke, and all-cause mortality constituted the primary clinical outcome. Nonfatal events were defined according to *International Classification of Diseases* (*ICD-9* and *ICD-10*) codes, with validities in the *Swedish National Inpatient Register* previously reported (145). Mortality data were obtained through the *National Registry on Causes of Mortality* at the *Swedish Central Bureau of Statistics*. Follow-up was terminated on December 31, 2014.

6.6. Statistical Methods

The statistical software packages IBM SPSS Statistics versions 22-23 (IBM, Armonk, NY, USA) and Stata/IC versions 13-14 (StataCorp LP, College Station, TX, USA) were used for all analyses.

6.6.1. Summary Statistics

Continuous variables were plotted as histograms, and distributions were visually inspected. Means, medians, skewness, and kurtosis were examined as well. Summary statistics were presented as means and standard deviations (variables with a clear or approximate Gaussian distribution) or medians and interquartile ranges (IQR) (variables with a clear non-Gaussian distribution). Categorical variables were presented as counts with corresponding percentages. Group-wise comparisons were performed using independent samples t-test, one-way analysis of variance, Mann-Whitney U test, Kruskal-Wallis test, Pearson's χ^2-test, and Fisher's exact test, as appropriate.

6.6.2. Cross-Sectional Analyses

In papers I-II, associations between echocardiographic variables and risk factors were examined using multivariable linear regression, binary logistic regression, and ordinal logistic regression models. In all cases, potential explanatory variables underwent univariable analysis. Variables that were statistically significant or deemed clinically appropriate, including FPG category, were entered into the final multivariable regression models, with application of stepwise backward elimination for optimization (P-retention < 0.20 except for FPG category, which was kept in the models regardless of its P-value). Correlations between LV structure (mass and geometry) and diastolic function were further tested with Pearson's product moment correlation (r) or Kendall's tau-b (τ). In paper IV, associations between biomarkers and echocardiographic variables were assessed using sex- and age-adjusted multivariable linear regression models or binary logistic regression models. Moderately to severely positively skewed variables (DT, E/A ratio, averaged E/é ratio, NT-proBNP, and hs-TnT) were natural logarithmically transformed before inclusion in the regression models.

6.6.3. Survival Analyses

In papers III-IV, the risk associated with abnormal LV structure and function, and abnormal biomarker levels, respectively, were tested using Cox proportional-hazards regression models, with time to first composite endpoint as the underlying timescale. The proportional-hazards assumption was examined using Schoenfeld residuals. Possible covariates included *SCORE* variables (age, sex, smoking status, systolic blood pressure, total cholesterol), kidney function (cystatin C), FPG category, and presence of LVH and/or grade 2 or 3 diastolic dysfunction. For biomarkers, hazard ratios (HR) were reported for both the assay-specific cut-offs and the upper quartile versus the three lower quartiles.

6.6.4. Discrimination and Reclassification

In paper IV, discrimination abilities for prediction models, with and without addition of the biomarkers as continuous variables, were described and compared using Harrell's concordance index (C-index), with the assumption that in case of two simultaneously terminating lifetimes, neither could be said to have survived the other (uncensored policy) (146). The ability of each biomarker to improve prognostication was also tested with the continuous (category-free) net reclassification improvement, which is not affected by category cut-offs and event rates (147).

6.6.5. Interaction Analyses

Interactions (effect modifications) were tested using the likelihood-ratio test for regression models with and without the interaction term and most often displayed using Forest plots.

6.6.6. Statistical Significance

A two-sided P-value < 0.05 was considered statistically significant. No adjustments for multiple comparisons were made, and all findings are to be considered exploratory (hypothesis-generating).

7. RESULTS

7.1. Paper I

7.1.1. Left Ventricular Mass Index

LVMI was significantly greater among subjects with diabetes than in subjects with NFG or IFG (mean 90 +/- 26 g/m^2 vs. 85 +/- 20 g/m^2; P = 0.01), but there was no significant difference between subjects with IFG versus NFG (mean 87 +/- 21 g/m^2 vs. 84 +/- 19 g/m^2; P = 0.08). Although FPG category was not a significant predictor of LVMI on multivariable analysis (**Table 1**), greater LVMI was only associated with higher NT-proBNP levels among subjects with IFG or diabetes (P < 0.001 for interaction) (**Figure 1**). There was a weak correlation between LVMI and diastolic function (r = 0.171; P < 0.001).

7.1.2. Left Ventricular Hypertrophy and Geometry

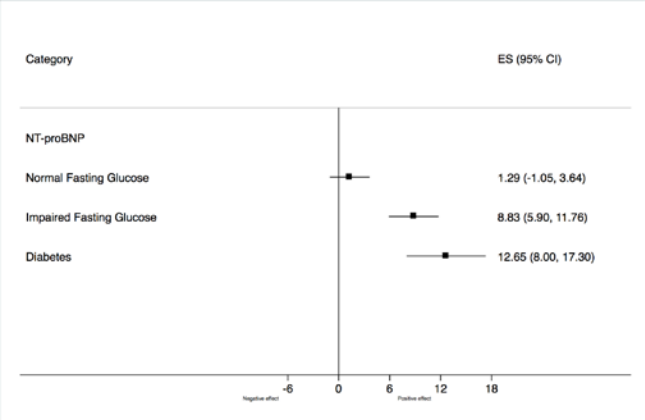
LVH in its entirety was not more commonly observed among subjects with diabetes than those without (14% vs. 12%, P = 0.60). The adjusted multivariable regression model is shown in **Table 2**. As such, FPG category was not associated with LVH on multivariable analysis, but significantly interacted with the association between LVH and NT-proBNP (P = 0.01 for interaction) (**Figure 2**). LVH and diastolic function were weakly, albeit significantly, correlated (τ = 0.185; P < 0.001). Of note, concentric LVH was significantly more prevalent among subjects with diabetes (11% vs. 6%, P = 0.03) and also displayed the strongest correlation with grade 2 or 3 diastolic dysfunction (τ = 0.280; P < 0.001), with a significant interaction analogous to that described for LVH (P = 0.02 for interaction).

Table 1. Multivariable linear regression model for prediction of left ventricular mass index (adjusted r^2 = 0.204).

Risk factor	β-coefficient (95% confidence interval)	P-value
Age, per year	0.25 (-0.04 to 0.55)	0.10
Female sex	-11.03 (-14.49 to -7.57)	< 0.001
Body mass index, per kg/m^2	0.91 (0.44 to 1.39)	< 0.001
Systolic blood pressure, per mmHg	0.20 (0.13 to 0.28)	< 0.001
Pulse rate, per min^{-1}	-0.26 (-0.38 to -0.13)	0.001
Log(NT-proBNP), per log(pmol/L)	5.59 (3.71 to 7.48)	< 0.001
Fasting plasma glucose category		
Normal fasting glucose (reference)		
Impaired fasting glucose	1.94 (-1.34 to 5.23)	0.25
Diabetes	1.17 (-3.26 to 5.61)	0.60

Abbreviation: NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Figure 1. The association between NT-proBNP and left ventricular mass index, according to fasting plasma glucose category.



P < 0.001 for interaction.

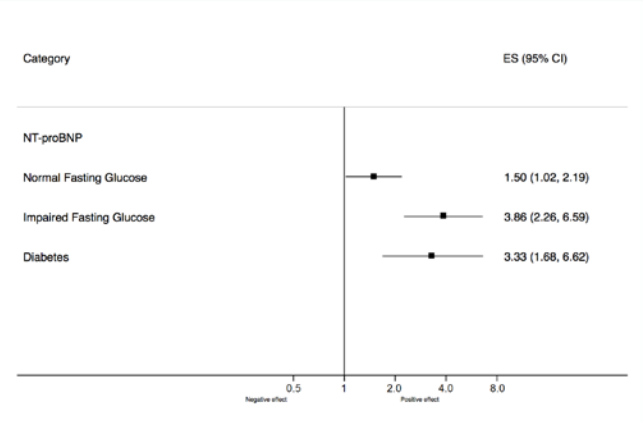
Abbreviations: ES = estimate; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table 2. Binary logistic regression model for prediction of left ventricular hypertrophy (pseudo-r^2 = 0.126).

Risk factor	Odds ratio (95% confidence interval)	P-value
Age, per year	1.05 (0.999 to 1.11)	0.05
Female sex	1.46 (0.87 to 2.47)	0.15
Body mass index, per kg/m^2	1.08 (1.01 to 1.16)	0.04
Systolic blood pressure, per mmHg	1.02 (1.004 to 1.03)	0.009
Log(NT-proBNP), per log(pmol/L)	1.88 (1.39 to 2.56)	< 0.001
Fasting plasma glucose category		
Normal fasting glucose (reference)		
Impaired fasting glucose	1.26 (0.72 to 2.21)	0.42
Diabetes mellitus	0.86 (0.41 to 1.80)	0.69

Abbreviation: NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Figure 2. The association between NT-proBNP and left ventricular hypertrophy, according to fasting plasma glucose category.



P = 0.01 for interaction.

Abbreviations: ES = estimate; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

7.2. Paper II

7.2.1. E/é

E/é was significantly greater among subjects with diabetes than those without (median 8 (IQR: 6-11) vs. 7 (IQR: 6-10); P = 0.03), but lower among subjects with IFG than those with NFG (median 7 (IQR: 6-9) vs. 8 (IQR: 6-10); P = 0.04). Moreover, FPG category was not a significant determinant of E/é on multivariable analysis (**Table 3**), but did interact with the association between E/é and systolic blood pressure (P = 0.001 for interaction), E/é and NT-proBNP (P < 0.001 for interaction), and E/é and LVMI (P = 0.02 for interaction) (**Figure 3**). The direction of the interaction for LVMI was the opposite of what was seen for systolic blood pressure and NT-proBNP.

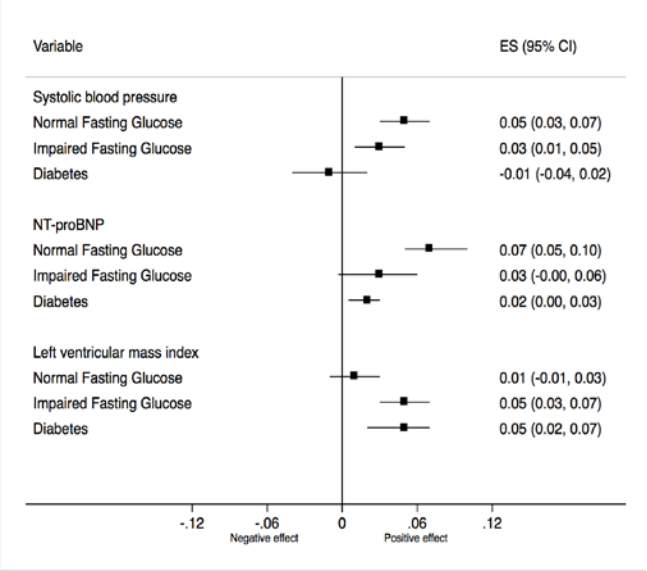
7.2.2. Diastolic Dysfunction

The prevalence of grade 2 or 3 diastolic dysfunction was significantly greater among subjects with diabetes than those without (25% vs. 16%; P = 0.02), and there was no significant difference between subjects with IFG versus those with NFG (13% vs. 18%; P = 0.08). As seen for E/é, FPG category was not a significant determinant of overall diastolic function on multivariable analysis (**Table 4**), but significantly interacted with the association between E/é and systolic blood pressure (P = 0.03 for interaction), and E/é and NT-proBNP (P = 0.005 for interaction) (**Figure 4**).

Table 3. Multivariable linear regression model for prediction of log(E/é) (adjusted r^2 = 0.317).

Risk factor	β-coefficient (95% confidence interval)	P-value
Age, per year	0.03 (0.02 to 0.03)	< 0.001
Female sex	0.13 (0.07 to 0.18)	< 0.001
Body mass index, per kg/m²	0.006 (-0.002 to 0.01)	0.14
Systolic blood pressure, per mmHg	0.001 (0.0003 to 0.003)	0.01
Left ventricular mass index, per g/m²	0.002 (0.001 to 0.003)	< 0.001
Fasting plasma glucose category		
Normal fasting glucose (reference)		
Impaired fasting glucose	-0.006 (-0.06 to 0.04)	0.81
Diabetes mellitus	0.05 (-0.02 to 0.12)	0.18

Figure 3. The associations between risk factors and E/é, according to fasting plasma glucose category. For visual purposes, the β-coefficients are shown for every 10-unit increase.

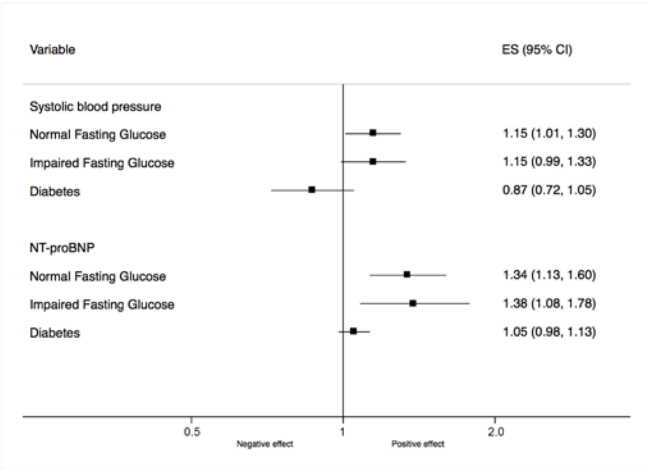


Systolic blood pressure: P = 0.001 for interaction; NT-proBNP: P < 0.001 for interaction; LVMI: P = 0.02 for interaction.
Abbreviations: ES = estimate; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table 4. Ordered logistic regression model for prediction of worse diastolic function (pseudo-r^2 = 0.158).

Risk factor	Odds ratio (95% confidence interval)	P-value
Age, per year	1.20 (1.16 to 1.25)	< 0.001
Female sex	1.45 (0.97 to 2.17)	0.07
Left ventricular mass index, per g/m²	1.01 (1.01 to 1.02)	0.002
Fasting plasma glucose category		
Normal fasting glucose (reference)		
Impaired fasting glucose	0.82 (0.54 to 1.25)	0.36
Diabetes mellitus	1.12 (0.67 to 1.87)	0.67

Figure 4. The associations between risk factors and worse diastolic function, according to fasting plasma glucose category. For visual purposes, the odds ratios are shown for every 10-unit increase.



Systolic blood pressure: P = 0.03 for interaction; NT-proBNP: P = 0.005 for interaction.
Abbreviations: ES = estimate; CI = confidence interval; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

7.3. Paper III

7.3.1. Fasting Plasma Glucose

Although a graded, positive relationship between FPG category and outcome was indicated, this was not statistically significant: unadjusted analyses; NFG: baseline; IFG: HR, 1.14 (95% CI: 0.79-1.66), P = 0.47; diabetes: HR, 1.32 (95% CI: 0.83-2.10), P = 0.25 (P = 0.23 for trend) (**Table 5** and **Figure 5**).

7.3.2. Left Ventricular Mass and Geometry

LVMI was not significantly associated with cardiovascular event risk (HR, 1.05 (95% CI: 0.97-1.14) per 10 g/m² increase, P = 0.20). Similar results were observed for LVH (HR, 1.36 (95% CI: 0.85-2.09), P = 0.21) and for the individual geometric patterns (P ≥ 0.09 for all) (**Table 5** and **Figure 6**). However, a significant interaction was found between FPG category and concentric LVH (P < 0.001 for interaction), i.e., concentric LVH only predicted risk among subjects with IFG or diabetes (**Figure 7**).

7.3.3. Diastolic Dysfunction

Greater E/é (HR, 1.06 (95% CI: 1.01-1.11), P = 0.02), any diastolic dysfunction (HR, 1.66 (95% CI: 1.18-2.32), P = 0.003), grade 1 dysfunction, and grade 2 or 3 dysfunction (P ≤ 0.01 for both) were all significantly associated with an increased event risk on univariable analysis, whereas undetermined dysfunction was not (P = 0.97) (P = 0.002 for trend) (**Table 5** and **Figure 8**). FPG category significantly interacted with the association between adverse risk and any diastolic dysfunction, grade 2 or 3 dysfunction, and undetermined dysfunction (P ≤ 0.04 for all interactions), with diastolic dysfunction being a better predictor of adverse risk among subjects with hyperglycemia (**Figure 7**).

Table 5. Unadjusted and adjusted hazard ratios for fasting plasma glucose and echocardiographic measures of left ventricular structure and function (composite of coronary events, heart failure, stroke, and all-cause mortality).

Variable / risk group	Unadjusted HR (95% CI)	P-value	Adjusted[a] HR (95% CI)	P-value
Fasting plasma glucose				
Fasting plasma glucose, per mmol/L	1.02 (0.93-1.11)	0.72	1.01 (0.93-1.11)	0.75
Impaired fasting glucose[b]	1.14 (0.79-1.66)	0.47	1.12 (0.76-1.66)	0.56
Diabetes mellitus[b]	1.32 (0.83-2.10)	0.25	1.26 (0.78-2.03)	0.35
Left ventricular mass and geometric pattern				
Left ventricular mass index, per 10 g/m²	1.05 (0.97-1.14)	0.20	0.98 (0.90-1.06)	0.59
Left ventricular hypertrophy[c]	1.36 (0.85-2.09)	0.21	1.10 (0.69-1.74)	0.70
Relative wall thickness, per 0.1 unit	1.17 (0.96-1.41)	0.11	1.01 (0.82-1.24)	0.92
Concentric remodeling[d]	1.38 (0.95-1.99)	0.09	1.12 (0.77-1.64)	0.55
Eccentric hypertrophy[d]	1.49 (0.79-2.83)	0.22	1.39 (0.72-2.68)	0.32
Concentric hypertrophy[d]	1.48 (0.80-2.75)	0.21	0.95 (0.50-1.82)	0.89
Diastolic function				
E/é, per unit	1.06 (1.01-1.11)	0.02	1.02 (0.96-1.08)	0.50
Any diastolic dysfunction[e]	1.66 (1.18-2.32)	0.003	1.13 (0.78-1.64)	0.53
Grade 1 diastolic dysfunction[e]	1.84 (1.17-2.88)	0.008	1.23 (0.76-1.98)	0.40
Grade 2 or 3 diastolic dysfunction[e]	1.71 (1.13-2.57)	0.01	1.26 (0.80-1.96)	0.32
Undetermined diastolic dysfunction[e]	1.02 (0.44-2.35)	0.97	0.54 (0.23-1.27)	0.16

[a]Adjusted for *SCORE* variables (age, sex, smoking status, systolic blood pressure, total plasma cholesterol)
[b]Reference category = normal fasting glucose
[c]Reference category = absence of left ventricular hypertrophy
[d]Reference category = normal geometric pattern
[e]Reference category = normal diastolic function
Abbreviations: HR = hazard ratio; CI = confidence interval.

Figure 5. Kaplan-Meier survival curves for the composite of coronary events, heart failure, stroke, and all-cause mortality, according to fasting plasma glucose category.

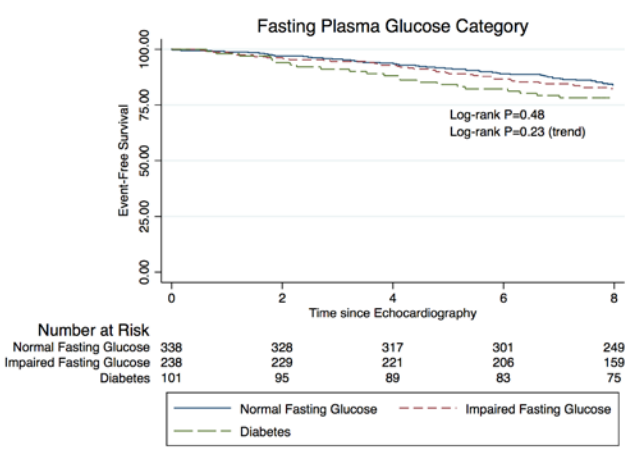


Figure 6. Kaplan-Meier survival curves for the composite of coronary events, heart failure, stroke, and all-cause mortality, according to the absence or presence of left ventricular hypertrophy.

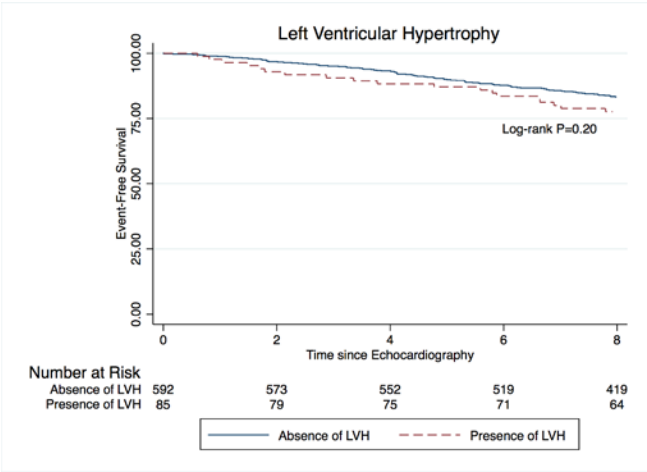
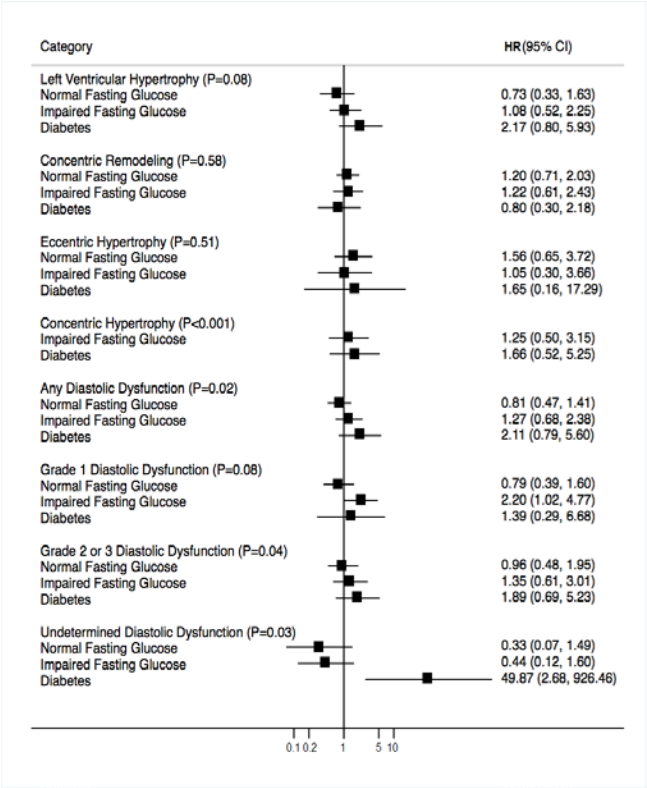
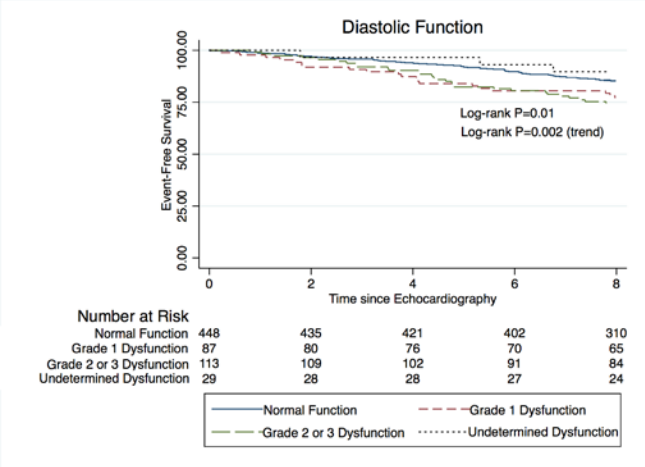


Figure 7. The associations between echocardiographic measures and the composite of coronary events, heart failure, stroke, and all-cause mortality, according to fasting plasma glucose category.



All hazard ratios are adjusted for *SCORE* variables (age, sex, smoking status, systolic blood pressure, total plasma cholesterol). No events occurred in the group of subjects with NFG and concentric LVH (n=16); therefore, that subgroup is not depicted in the figure.
Abbreviations: HR = hazard ratio; CI = confidence interval.

Figure 8. Kaplan-Meier survival curves for the composite of coronary events, heart failure, stroke, and all-cause mortality, according to left ventricular diastolic function.



7.4. Paper IV

7.4.1. N-terminal Prohormone of Brain Natriuretic Peptide

NT-proBNP concentrations did not significantly differ between subjects with and without diabetes (median 8 (IQR: 5-16) pmol/L vs. 8 (IQR: 5-15) pmol/L; P = 0.46), but were significantly lower among subjects with IFG (median 7 (IQR: 4-13) pmol/L) than among those with NFG (median 10 (IQR: 5-18) pmol/L; P < 0.001 for difference) or diabetes (median 8 (IQR: 5-16) pmol/L; P = 0.009 for difference). However, IFG did not remain significantly associated with NT-proBNP on multivariable analysis (**Table 6**), and there were no significant interactions.

7.4.2. High-Sensitivity Troponin T

Hs-TnT concentrations were significantly greater among subjects with diabetes than those with NFG or IFG (median 9 (IQR: 6-11) ng/L vs. 7 (IQR: 5-9) ng/L; P < 0.001), but there was no difference between subjects with IFG and NFG, respectively (median 7 (IQR: 5-9) ng/L vs. 7 (IQR: 5-9) ng/L; P = 0.87). Furthermore, hs-TnT was significantly greater among subjects with diabetes on multivariable analysis, although without any significant interactions (**Table 7**).

7.4.3. Echocardiographic Correlates

Both NT-proBNP and hs-TnT displayed significant associations with several echocardiographic measures, particularly those of LV structure, although effect sizes were generally unimpressive. Associations with concentric LVH were stronger than those for eccentric LVH. Among measures of diastolic function, the most consistent results were observed for grade 2 or 3 diastolic dysfunction. **Table 8** shows an extract of these associations. The effects of FPG on associations between NT-proBNP and echocardiographic measures have been addressed in previous sections. In addition, FPG significantly interacted with the association between hs-TnT and LVMI (P = 0.02 for interaction) and LVH (P = 0.04 for interaction), but not E/é (P > 0.99 for interaction) and diastolic function (P = 0.73 for interaction) (**Figures 9 and 10**).

7.4.4. Prediction of Cardiovascular Events

Subjects with high concentrations (upper quartile) of NT-proBNP or hs-TnT were at greater risk compared to those with low concentrations (lower three quartiles) (**Figures 11 and 12**). The addition of NT-proBNP to traditional risk factors, fasting glucose, cystatin C, and echocardiography provided a significant discrimination improvement for prediction of cardiovascular events (C-index: 0.721 vs. 0.714, P = 0.045) and a positive net reclassification improvement. However, no such isolated benefit was found for hs-TnT (C-index: 0.715 vs. 0.714; P = 0.82) (**Table 9**).

7.4.5. Prognostic Impact of Fasting Plasma Glucose on N-terminal Prohormone of Brain Natriuretic Peptide

Although the prognostic ability of NT-proBNP seemed stronger among subjects with diabetes, no significant interactions were detected (P ≥ 0.24) (**Figure 13**).

7.4.6. Prognostic Impact of Fasting Plasma Glucose on High-Sensitivity Troponin T

Similar to NT-proBNP, a stronger prognostic ability of hs-TnT among subjects with diabetes was indicated, but without any significant interactions (P ≥ 0.23) (**Figure 13**).

Table 6. Multivariable linear regression model for prediction of log(NT-proBNP) (adjusted r^2 = 0.290).

Risk factor	β-coefficient (95% confidence interval)	P-value
Age, per year	0.06 (0.05 to 0.07)	< 0.001
Female sex	0.37 (0.23 to 0.50)	< 0.001
Body mass index, per kg/m²	-0.02 (-0.04 to -0.01)	0.002
Systolic blood pressure, per mmHg	0.01 (0.002 to 0.01)	< 0.001
Pulse rate, per min⁻¹	-0.01 (-0.01 to -0.004)	0.001
Fasting plasma glucose category		
Normal fasting glucose (reference)		
Impaired fasting glucose	-0.11 (-0.24 to 0.02)	0.10
Diabetes	0.08 (-0.10 to 0.26)	0.38

Abbreviation: NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table 7. Multivariable linear regression model for prediction of log(hs-TnT) (adjusted r^2 = 0.260).

Risk factor	β-coefficient (95% confidence interval)	P-value
Age, per year	0.03 (0.03 to 0.04)	< 0.001
Female sex	-0.28 (-0.36 to -0.21)	< 0.001
Body mass index, per kg/m²	0.01 (0.001 to 0.02)	0.03
Systolic blood pressure, per mmHg	0.003 (0.002 to 0.005)	< 0.001
Cystatin C, per mg/L	0.36 (0.19 to 0.54)	< 0.001
Fasting plasma glucose category		
Normal fasting glucose (reference)	0.01 (-0.07 to 0.08)	0.89
Impaired fasting glucose	0.11 (0.01 to 0.21)	0.04
Diabetes		

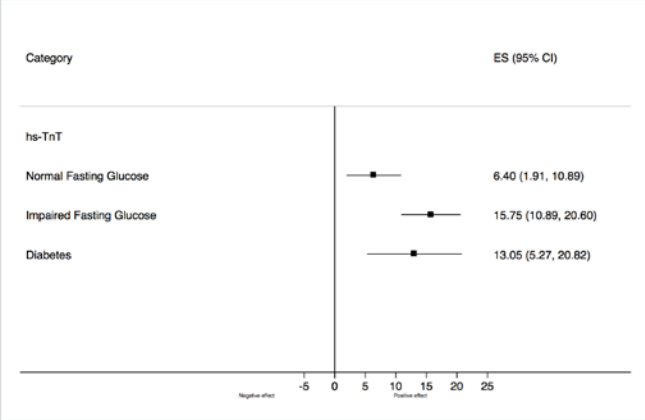
Abbreviation: hs-TnT = high-sensitivity troponin T.

Table 8. Age- and sex-adjusted associations between biomarkers and echocardiographic variables.

Echocardiographic variable	N-terminal prohormone of brain natriuretic peptide	High-sensitivity troponin T
Left ventricular mass index	0.214 (< 0.001)	0.213 (< 0.001)
Left ventricular hypertrophy	0.517 (< 0.001)	0.424 (0.001)
Concentric remodeling	-0.006 (0.96)	-0.049 (0.64)
Eccentric hypertrophy	0.510 (0.02)	0.206 (0.25)
Concentric hypertrophy	0.588 (0.002)	0.509 (0.002)
Averaged E/é	0.047 (0.22)	0.060 (0.10)
Diastolic dysfunction	0.110 (0.32)	0.264 (0.02)
Grade 1 dysfunction	-0.069 (0.64)	0.173 (0.21)
Grade 2 or 3 dysfunction	0.332 (0.03)	0.339 (0.02)
Undetermined dysfunction	-0.038 (0.88)	0.648 (0.007)

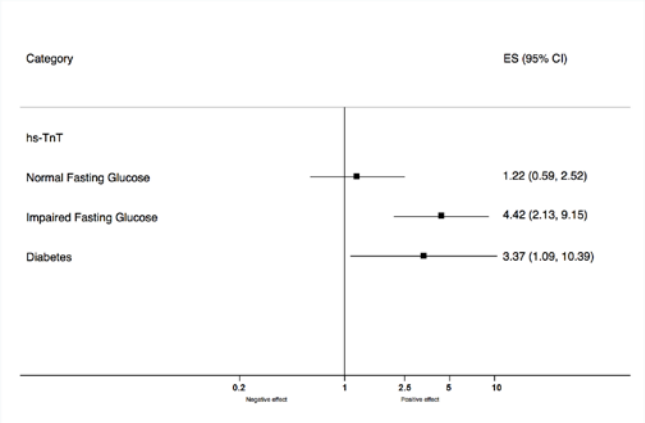
For associations between two continuous variables, standardized β-coefficients (P-values in brackets) are reported.
For associations between one categorical (echocardiography) and one continuous (biomarker) variable, β-coefficients for standardized values of biomarkers (P-values in brackets) are reported.

Figure 9. The association between hs-TnT and left ventricular mass index, according to fasting plasma glucose category.



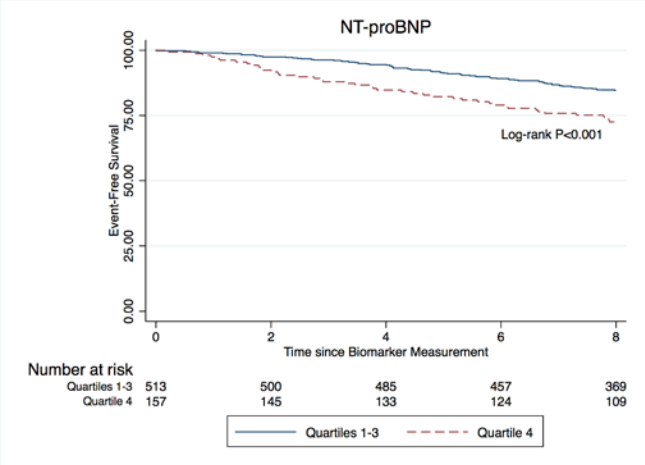
P = 0.02 for interaction.
Abbreviations: ES = estimate; CI = confidence interval; hs-TnT = high-sensitivity troponin T.

Figure 10. The association between hs-TnT and left ventricular hypertrophy, according to fasting plasma glucose category.



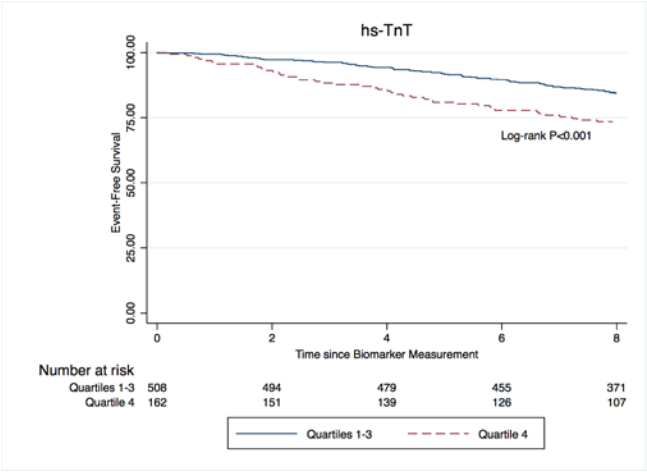
P = 0.04 for interaction.
Abbreviations: ES = estimate; CI = confidence interval; hs-TnT = high-sensitivity troponin T.

Figure 11. Kaplan-Meier survival curves for the composite of coronary events, heart failure, stroke, and all-cause mortality, according to NT-proBNP concentrations.



Abbreviation: NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Figure 12. Kaplan-Meier survival curves for the composite of coronary events, heart failure, stroke, and all-cause mortality, according to hs-TnT concentrations.



Abbreviation: hs-TnT = high-sensitivity troponin T.

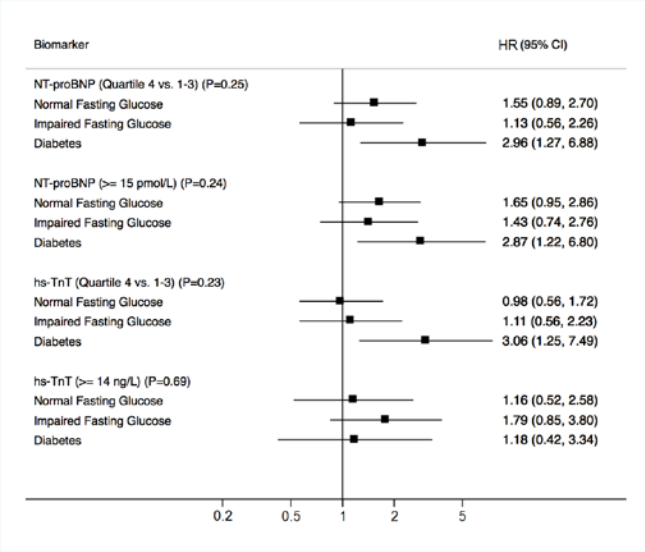
Table 9. Hazard ratios, C-indices, and net reclassification improvement for NT-proBNP and hs-TnT (composite of incident coronary events, heart failure, stroke, and all-cause mortality).

	Hazard ratio[a] (95% CI)	P-value	Hazard ratio[b] (95% CI)	P-value	C-index[c]	P-value for difference	Net reclassification improvement[d] (95% CI)
N-terminal prohormone of brain natriuretic peptide							
Model 1	1.58 (1.10-2.29)	0.01	1.51 (1.04-2.18)	0.03	0.690 vs. 0.685	0.12	0.270 (0.039-0.457)
Model 2	1.58 (1.09-2.29)	0.02	1.47 (1.01-2.14)	0.04	0.720 vs. 0.713	0.03	0.238 (-0.033-0.447)
Model 3	1.57 (1.07-2.29)	0.02	1.46 (0.99-2.13)	0.053	0.720 vs. 0.714	0.07	0.177 (-0.088-0.410)
Model 4	1.57 (1.08-2.28)	0.02	1.47 (1.01-2.14)	0.045	0.720 vs. 0.714	0.047	0.212 (-0.054-0.425)
Model 5	1.55 (1.06-2.27)	0.02	1.45 (0.99-2.12)	0.06	0.721 vs. 0.714	0.045	0.179 (-0.082-0.389)
High-sensitivity cardiac troponin T							
	Hazard ratio[a] (95% CI)	**P-value**	**Hazard ratio[b] (95% CI)**	**P-value**	**C-index[c]**	**P-value for difference**	**Net reclassification improvement[d] (95% CI)**
Model 1	1.42 (0.88-2.27)	0.15	1.36 (0.95-1.95)	0.09	0.688 vs. 0.685	0.43	0.044 (-0.145-0.246)
Model 2	1.46 (0.90-2.36)	0.12	1.27 (0.88-1.83)	0.21	0.715 vs. 0.713	0.61	0.010 (-0.198-0.218)
Model 3	1.44 (0.89-2.33)	0.14	1.26 (0.87-1.83)	0.22	0.715 vs. 0.714	0.66	-0.034 (-0.212-0.229)
Model 4	1.38 (0.85-2.25)	0.19	1.23 (0.85-1.78)	0.28	0.715 vs. 0.714	0.58	-0.064 (-0.245-0.182)
Model 5	1.36 (0.83-2.21)	0.22	1.22 (0.84-1.77)	0.29	0.715 vs. 0.714	0.82	-0.079 (-0.259-0.199)

[a] For prespecified cut-off
[b] For quartile 4 versus quartiles 1-3
[c] With versus without biomarker (continuous)
[d] For biomarker (continuous), bootstrapped confidence interval (1,000 replications)
Model 1: Adjusted for age and sex
Model 2: Adjusted for *SCORE* variables (age, sex, smoking status, systolic blood pressure, total plasma cholesterol)
Model 3: Adjusted for *SCORE* variables, left ventricular hypertrophy and/or diastolic dysfunction
Model 4: Adjusted for *SCORE* variables, fasting plasma glucose category, and cystatin C
Model 5: Adjusted for models 3+4

Abbreviations: NT-proBNP = N-terminal prohormone of brain natriuretic peptide; hs-TnT = high-sensitivity troponin T; CI = confidence interval.

Figure 13. The associations between biomarker concentrations and the composite of coronary events, heart failure, stroke, and all-cause mortality, according to fasting plasma glucose category.



Additional interaction analyses for absence versus presence of diabetes were non-significant (P = 0.06 for both biomarkers (quartile 4 versus quartiles 1-3)).

8. DISCUSSION

8.1. Impact of Glycemic Status on Left Ventricular Structure

Manifest diabetes is generally regarded as an independent risk factor for increased LVMI (67-69,72); however, in accordance with the magnetic resonance imaging based results from the *Multi-Ethnic Study of Atherosclerosis (MESA)* (81), we did not see a graded association between FPG category and LV structure. Conversely, traditional markers of hyperglycemia were associated with LVMI and RWT in both the *Strong Heart Study (SHS)* (79,84,85) and the *Framingham Heart Study (FHS)* (80). For example, *De Marco et al.* found progressively greater LVMI and RWT among obese adolescents and young adults with IFG or diabetes (84), *Capaldo et al.* observed greater LVMI and RWT in persons with isolated IFG or combined IFG and impaired glucose tolerance (85), and independent associations for impaired glucose tolerance were demonstrated in *FHS* (80). There are several possible methodological explanations for these inconsistencies. Despite IFG and impaired glucose tolerance being equally predictive of incident type 2 diabetes, the concordance between these two categories is limited, and postload glucose may better predict cardiovascular morbidity and mortality than fasting glucose (24). The development of adverse myocardial changes is temporally related to hyperglycemia (73,75), and the time spent with glycemic disturbances in our study was presumably short as we excluded subjects on anti-diabetic medication at the time of screening. In addition, data from *SHS* referred to a specific ethnic cohort, i.e., American Indians. Lastly, the importance of hyperglycemia may decrease with age, and the subjects in the present study were on average older than those examined in *SHS*. Further adding to the premise that the mode of assessment for glucose metabolism and selected partitions are important factors to consider when attempting to demonstrate cardiovascular differences across the hyperglycemic spectrum, is a recent report from the *Atherosclerosis Risk In the Community (ARIC) Study*, which showed graded associations between LV abnormalities and glycemic category, based on $HbA1_c$, for some, but not all markers of LV structure, i.e., septal wall thickness and RWT were greater and LV internal diameter smaller, but LVMI was not significantly different in subjects with prediabetes versus those with normal glycemic status (86).

In our study, diabetes was primarily associated with concentric LVH, and concentric LVH further displayed the strongest correlation with diastolic dysfunction. Concentric changes are more prevalent in the setting of hyperglycemia (67-69,79,80), and concentric LVH may further be associated with a higher risk of morbidity and mortality than the other LV geometric patterns (59-61). Additionally, the effects of antihypertensive treatment on LVH regression seem attenuated among patients with diabetes (148,149), and the cardiovascular role of isolated, strict glucose-lowering is also unclear (150-155). Formation of advanced glycation end products and their cross-linking with collagen may in part account for these treatment failures (156). All things considered, the presence of LVH in diabetes may represent a more harmful type of LVH than that seen in other conditions.

8.2. Impact of Glycemic Status on Left Ventricular Function

Evidence regarding the association between glycemic status and LV diastolic function is less abundant than that for LV structure. Similar to the observations for LV structure, and in line with *SHS* (84), we did not find a graded effect of FPG category on diastolic function. In contrast, in the *Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure*, the prevalence and severity of diastolic dysfunction increased along the diabetic continuum (83). However, in the latter study, all individuals without known diabetes were subjected to an oral glucose tolerance test, the implications for which have been described in the previous section, and the study population was further enriched by selecting subjects with risk factors for or even manifest heart failure. Finally, in *ARIC*, the majority of measures of diastolic function did not significantly differ between individuals with normal glycemic status and prediabetes, whereas significant changes were reported for most measures when comparing patients with diabetes versus those without (86). Since diabetes per se is considered a risk factor for diastolic dysfunction, we speculate that the significant differences observed between subjects with diabetes and those without might be due to a threshold effect of hyperglycemia on myocardial stiffening.

Higher systolic blood pressure was predominantly associated with worse diastolic function among subjects without diabetes, strengthening the idea of an independent effect of diabetes, whereas greater LVMI showed a significantly stronger association with worse diastolic function among patients with abnormal glycemic status. It is likely that hyperglycemia augments the myocardial stiffening caused by LVH, possibly through a reduction in coronary flow reserve, which has proven associations with LVH, diastolic dysfunction, and diabetes (157). Nevertheless, whether the lower coronary flow reserve among patients with diabetes is a direct consequence of hyperglycemia or due to insulin resistance, endothelial dysfunction, or increased sympathetic activity, is not known. Although the absence of an association between systolic blood pressure and diastolic function among subjects with diabetes disagrees with previously demonstrated synergistic effects of diabetes and hypertension (158), an explanation may be provided by the

Cardiovascular Continuum paradigm, i.e., ageing, whether physiological or pathological, brought on by cardiovascular risk factors, including diabetes, ultimately results in the same adverse cardiovascular alterations, and accelerated effects are seen in the presence of multiple risk factors (159-161). This theory and our findings are supported by the strong relationship between age and diastolic function in this elderly cohort, a presumed late onset of hyperglycemia, and a probable dominating effect of diabetes over other cardiovascular risk factors. Lastly, a theoretical framework, complementing the *Cardiovascular Continuum*, has been proposed, in which diastolic dysfunction can be considered the final common pathway for various conditions, including overweight, hypertension, and diabetes, which induce a state of inflammation, coronary microvascular endothelial dysfunction, and cardiomyocyte hypertrophy and stiffening (162).

8.3. Prognostic Impact of Glycemic Status on Left Ventricular Structure and Function

Several studies have examined the cross-sectional relationships between prediabetes, diabetes, and LV structural and functional alterations; however, we have demonstrated for the first time that glycemic status, in a graded fashion, modifies the risk of incident events associated with subclinical echocardiographic abnormalities. Specifically, concentric LVH and diastolic dysfunction were more strongly associated with an adverse prognosis in subjects with IFG or diabetes compared to subjects with NFG. These observations fit well the aforementioned *Cardiovascular Continuum* concept (159-161), including the tendency towards risk factor clustering in diabetes (12), not all of which can be adjusted for. Moreover, we used a composite endpoint, including all-cause mortality, and even non-cardiovascular mortality may be elevated among patients with diabetes (163). Still, the underlying mechanisms, specifically on the cardiac level, remain speculative. As alluded to previously, the presence of LVH in diabetes may represent a more deleterious form of LVH, due to its often-concentric nature and strong association with hypertension and diastolic dysfunction, but notably, the results were independent of systolic blood pressure. These findings are also consistent with previously proposed theories regarding the etiology and pathogenesis of structural and functional echocardiographic alterations in patients with diabetes, including inflammation and endothelial dysfunction (162), decreased coronary flow reserve (157), and formation of advanced glycation end products (156).

8.4. Impact of Glycemic Status on Cardiovascular Biomarker Concentrations

Prior studies have shown higher hs-TnT concentrations among patients with diabetes compared to subjects without (98,116,121,137,138,142,143). Examples include the *Dallas Heart Study (DHS)*, in which the proportion of patients with diabetes increased across hs-TnT categories (98), and the *Women's Health Study*, in which hs-TnT concentrations and the fraction with detectable hs-TnT concentrations, but not elevated above the upper reference limit, i.e., the 99th percentile, were significantly higher among women with a history of diabetes versus those without (116). Our results confirmed these observations in older, low risk individuals, but hs-TnT did not vary between subjects with NFG and IFG. Although such a difference was seen in *ARIC* (142), only glycemic status defined by means of $HbA1_c$, not FPG, was significantly associated with hs-TnT. Further supporting our results, and the prior notion that the method for measuring and defining glycemic status should be taken into consideration when exploring associations with subclinical cardiovascular disease, significant differences between subjects with diabetes versus those without, but not between normal glycemic status and prediabetes, defined as IFG or impaired glucose tolerance, were shown by *Zheng et al.* (143). Finally, the relationship between $HbA1_c$ and hs-TnT may be steepest in the narrow range that defines prediabetes, providing a rationale for the more robust findings for diabetes (142). Potential underlying mechanisms for the increased hs-TnT levels in non-acute settings largely mimic those proposed for hyperglycemia-related LV structural and functional alterations, including microvascular dysfunction or damage (164), advanced glycation end products (156), low grade inflammation (165), myocardial fibrosis (166), or perhaps even silent epicardial coronary artery disease (167).

The case may be more complicated for NT-proBNP since concentrations were lowest in the IFG group, and without any measurable difference between subjects with diabetes and NFG. Indeed, previous results concerning glycemic status have been somewhat inconsistent (136,139-141,168-172), while inverse relationships of natriuretic peptides with body mass index and other metabolic risk factors have been consistently shown in population-based studies, including *FHS* (168,171) and *DHS* (170). *Wang et al.* showed additive, negative effects of obesity and diabetes on BNP levels (168), whereas *Das et al.* found inverse associations between both BNP and NT-proBNP with body mass index and a closer correlation with lean mass than with fat mass (170). This suggests that the presence of natriuretic peptide clearance receptors in adipose tissue, which are believed not to bind NT-proBNP, is not the only explanation (173). Altered cardiac synthesis and/or secretion seems more probable (174), and sex may play an additional role (141,168). Finally, and in agreement with its hemodynamic properties, NT-proBNP is elevated in the presence of subclinical cardiac damage (95-97,99-102,104-106,134,135), which is more common in the presence of diabetes. Although it is difficult to draw definite conclusions regarding the influence of isolated hyperglycemia on NT-proBNP, lower concentrations should generally be expected, and interpretation in relation to the overall metabolic profile seems reasonable.

8.5. Impact of Glycemic Status on the Associations between Echocardiography and Cardiovascular Biomarkers

Significant, albeit modest, correlations between biomarkers and echocardiography were expected in this apparently healthy cohort (98,100,134,135). This highlights the beliefs that individual biomarkers cannot be recommended as screening tools solely for LV dysfunction due to limited sensitivity (94,97,98,101,175), that risk estimates based on imaging studies and circulating biomarkers should be considered complimentary (100,105), and further fits the said clinical and pathophysiological complexities associated with circulating levels of NT-proBNP and hs-TnT. We found stronger correlations with LV structure than with diastolic function, perhaps due to the inherent challenges associated with non-invasive assessment of diastolic function (44,176).

NT-proBNP concentrations were primarily related to LVMI and LVH among subjects with hyperglycemia, extending previous findings from the *Hoorn Study*, in which stronger cross-sectional associations between BNP and diastolic function, and BNP with temporally worsening diastolic function and increasing LVMI, were observed among patients with diabetes compared to those without (134,135). Possibly, the association between NT-proBNP and LV size only appeared stronger in subjects with IFG due to their lower NT-proBNP concentrations, whereas the robust association in patients with diabetes stemmed from relatively lower NT-proBNP

concentrations in relation to their higher prevalence of LV abnormalities (168,171,177-180). This lends support to the concept that similar NT-proBNP levels indicate a worse LV state and prognosis in diabetes. This could also apply to hs-TnT, despite its higher baseline levels among patients with diabetes as similar patterns for LVMI and LVH were observed. It has further been speculated that an increased production of natriuretic peptides might precede overt echocardiographic abnormalities, resembling damage by the mechanisms mentioned previously (157,181,182). The fact that the interaction between NT-proBNP and E/é followed a reverse pattern would support this concept as well as the hypothesis that LVH precedes diastolic dysfunction, i.e., the impact of hemodynamic measures on myocardial relaxation may fall beneath that of metabolic factors, once LVMI has been sufficiently increased. Although this contradicts the findings from the *Hoorn Study*, their lack of Doppler measurements for assessment of diastolic function obscures direct comparisons (134,135).

8.6. Prognostic Impact of Glycemic Status on Cardiovascular Biomarkers

Troponins and natriuretic peptides deliver incremental prognostic information among high risk individuals, particularly those with known cardiovascular disease (128,183,184), but the evidence for apparently healthy subjects is ambiguous, i.e., very large sample sizes have usually been needed to show minor improvements, if any, in risk stratification for individual biomarkers (115,127,130,185), and there is further evidence of reporting bias (186). The observed modest model improvement provided by NT-proBNP beyond clinical risk factors and structural and functional echocardiographic changes is intriguing and extends prior findings from *MESA* (99), *DHS* (100), and the *Cardiovascular Health Study* (105), in which LVH with concomitantly elevated concentrations of NT-proBNP and/or hs-TnT was associated with a more severe disease course. As an example, in *DHS*, which oversampled African Americans, NT-proBNP and hs-TnT provided incremental prognostic value beyond, and interacted with, LVH determined by magnetic resonance imaging (100). The findings were independent of LVM, leading the authors to propose that elevations of these biomarkers may represent adverse remodeling from LVH to manifest heart failure, not merely greater LVM in persons with higher biomarker concentrations. Furthermore, NT-proBNP and hs-TnT displayed distinct correlations with markers of LV structure. Likewise, in our study, hs-TnT seemed a better predictor of LV diastolic function than NT-proBNP and vice versa. However, hs-TnT showed no benefit as an individual marker in our sample in its entirety, possibly related to ethnicity, use of both LVH and diastolic dysfunction as the echocardiographic variable, and use of a composite endpoint, including all-cause mortality, which may not be accurately predicted by hs-TnT (127).

Despite the interaction terms between biomarkers and FPG category not reaching formal statistical significance, trends consistently favored a more robust predictive capability for both biomarkers among subjects with diabetes. Biomarker concentrations may further be stronger predictors of risk than a history of symptomatic cardiovascular disease in patients with diabetes (128), and *Zethelius et al.* found a greater discriminative ability for traditional risk factors, but lower utility of biomarkers, when comparing persons without established cardiovascular disease to those with (17). *Kroon et al.* showed a greater adjusted risk of adverse echocardiographic changes among patients with diabetes versus those without (135), and data from *ARIC* showed higher incidences of elevated hs-TnT among individuals with prediabetes and diabetes, and that such elevations were related to incident cardiovascular disease (121). In fact, associations with incident heart failure and mortality were stronger than with coronary artery disease, in line with the postulated etiological differences between acute versus chronic troponin release. Collectively, the prognostic properties of traditional risk factors and biomarkers may differ per a priori risk, including glycemic status.

Given the considerable interindividual differences in development and progression of adverse cardiovascular changes, concurrent measurement of biomarkers that resemble separate mechanistic pathways could, theoretically, enhance risk stratification. However, current data are less convincing for low risk subjects (16,17,113,115,128,183-185,187). Although slightly tangential to the objectives of this thesis, we tested a combination of three biomarkers, i.e., NT-proBNP, hs-TnT, and growth-differentiation factor 15, and demonstrated a stepwise increase in risk. Overall model performance was augmented modestly, but significantly, confirming prior findings from the *Uppsala Longitudinal Study of Adult Men* (17), the *Malmö Diet and Cancer Study* (115), and the *FINRISK97* cohort (185), among others. As such, there may be a role for multimarker models in lower risk populations, and the prognostic value seems to appear independently of echocardiographically determined LV structure and function.

9. LIMITATIONS

9.1. Study Population

Despite the relatively high participation rate of 72% in *MPP-RES*, it may be argued that the study subjects did not represent a truly random population sample, since individuals who agree to participate in such screening studies may be healthier than the general population. The applicability of the results in females may be limited by the fact that 70% of subjects in the present study were male, and the generalizability to groups other than elderly Caucasians is also unknown. Our exclusion of more than half of the original study population to obtain a cohort of apparently healthy subjects free from known cardiovascular disease and on no cardiovascular medications may have introduced another selection bias, i.e., healthy cohort effect. Additionally, the low event rate with associated low power to detect prognostic associations was a limitation and prompted us to use a composite endpoint. It should be noted, however, that these limitations would tend to decrease rather than increase the sensitivity of our analyses, thus highlighting the importance of the positive findings.

9.2. Fasting Plasma Glucose

The subgroup division was based on FPG, in most cases a single measurement. The addition of an oral glucose tolerance test or $HbA1_c$ measurements would have been desirable for several reasons. For instance, impaired glucose tolerance and diabetes defined by oral glucose tolerance testing are more common among women than men, whereas IFG is more often seen in men (24). FPG exhibits greater fluctuation than $HbA1_c$, which provides an estimate of the average glucose levels, and possibly sustained myocardial affection, over a 2-3-month period (22); however, the latter was not routinely measured during the screening process due to financial limitations. Furthermore, prognostic associations might have been affected by subjects having been captured early during hyperglycemia, and use of anti-diabetic medication, perhaps initiated soon after screening, could not be accounted for. Therefore, the use of FPG would tend to decrease the sensitivity, not specificity, of the analyses.

9.3. Echocardiography

2D-guided linear LV measurements have well-documented prognostic properties and are particularly useful for studying large populations. However, the method utilizes basal dimensions only, and LV changes that occur along the long axis of the chamber cannot be accounted for. The Devereux formula for calculating LVM assumes normal LV geometry and cubes the linear measurements (46). Consequently, even small errors may significantly influence the estimated mass. The exclusion of individuals with reduced LVEF < 50 % is likely to have accounted for distorted LV geometry except discrete upper septal thickening, which is particularly common in elderly, hypertensive subjects (188). It is possible that in our study population, this phenomenon may have attenuated the prognostic role of LVMI.

Preload increases é velocity in normal subjects, and as such, its utility in these individuals may be limited (189). In addition, lateral E/é may be better than septal E/é for estimation of LV filling pressures in subjects with preserved LVEF > 50%. However, we used the averaged E/é due to lack of information on regional dysfunction. Finally, a more robust grading of diastolic dysfunction could have been attained if we had been able to include the left atrial volume index (44). Nevertheless, we used strict criteria for E/é, and the uncertain prognostic differences between grade 1 dysfunction and grade 2 or 3 dysfunction in our cohort serve as a general reminder of the difficulties associated with echocardiographic diagnosis and grading of diastolic dysfunction (176).

Therefore, it may be argued, that these limitations pertaining to echocardiography, would, similar to what was noted for the study population and FPG, tend to increase the likelihood of false negative findings.

9.4. Biomarkers

Biomarkers were examined in blood samples which had been frozen for up to 10 years, potentially influencing concentrations and presumably leading to underestimation of their prognostic abilities (190).

10. CONCLUSIONS

1. Subjects with newly diagnosed diabetes had greater LVMI and a higher prevalence of concentric LVH, but only on univariable analysis.

2. Subjects with newly diagnosed diabetes had greater E/é and a higher prevalence of grade 2 or 3 diastolic dysfunction, but the associations were not independent of LVMI. FPG category significantly interacted with the association between E/é and LVMI, and LVMI was primarily associated with higher E/é in subjects with IFG or diabetes.

3. Subclinical echocardiographic abnormalities, par-ticularly those of LV diastolic function, were associated with an increased risk of incident cardiovascular events. FPG category was not by itself associated with the outcome, but modified the prognostic role of concentric LVH and diastolic dysfunction, i.e., these alterations were more strongly associated with adverse prognosis in subjects with IFG or diabetes.

4. Subjects with IFG had significantly lower NT-proBNP concentrations than subjects with NFG or newly diagnosed diabetes on univariable, but not multivariable, analysis. Diabetes was independently associated with higher hs-TnT concentrations on multivariable analysis.

5. Subjects with high concentrations of NT-proBNP and hs-TnT were at greater risk of incident cardiovascular events compared to those with low concentrations. NT-proBNP provided a significant discrimination improvement beyond traditional risk factors and subclinical echocardiographic abnormalities, whereas hs-TnT did not. NT-proBNP and hs-TnT were significantly associated with several echocardiographic parameters, particularly those of LV structure, and less so for diastolic function, but effect sizes were generally modest. Associations were modified by FPG category.

6. FPG category did not significantly modify the prognostic role of NT-proBNP and hs-TnT, but the totality of the data suggests that glycemic status should be considered when interpreting biomarker concentrations.

11. PERSPECTIVES

Cardiovascular risk assessment in the primary preventive setting remains challenging and may be both affected and complicated by glycemic status. Numerous potential strategies have not been properly studied or validated, and most attempts to enhance risk stratification have yielded insignificant to modest effects. Given the results of this thesis, the following may be considered for future observational and interventional research:

1. The adverse myocardial alterations in diabetes might stem from extended exposure to hyperglycemia and obesity, and the presence of IFG may provide a window of opportunity to prevent or reduce LVH and diastolic dysfunction by halting progression into manifest diabetes.

2. Targeting both systemic and cardiovascular comorbidities at an early stage, including blood pressure lowering, regression of LVH, glucose-lowering, weight reduction, lipid-lowering, and anti-inflammatory therapy, may delay the progression of subclinical diastolic dysfunction to overt heart failure.

3. Subclinical echocardiographic abnormalities may be particularly deleterious in subjects with hyperglycemia, represent a key mechanistic link between diabetes and overall cardiovascular risk, and may thus be used to enrich study populations in future clinical trials of such individuals.

4. Different prognostic roles of traditional risk factors and biomarkers according to a priori risk should be considered. Multimarker strategies may have a prognostic role among low risk subjects, but there is a need for validation of specific biomarker combinations in different populations and across different risk categories.

5. Biomarkers may be used to enrich study populations in future clinical trials of primary preventive strategies, regardless of baseline glycemic status, but more data regarding the potential benefit of biomarker-based intervention, including initiation or intensification of diagnostic, therapeutic, and monitoring strategies, is needed, particularly among low risk subjects.

6. Biomarkers may be more representative of subclinical echocardiographic abnormalities among subjects with hyperglycemia, but should be considered complimentary, rather than as replacements to, echocardiography, regardless of glycemic status.

12. SUMMARY

12.1. Background

Traditional cardiovascular risk stratification tools that employ clinical risk factors are limited by their modest discriminative abilities. As such, robust cardiovascular risk assessment, including our understanding of the complex interplay between risk factors, in the primary preventive setting, remains incomplete. Phenotypical heterogeneity may be even greater among subjects with hyperglycemic conditions, i.e., prediabetes and diabetes, which is worrisome, given the dramatic global rise in mean fasting glucose levels, and the strong association with adverse cardiovascular outcomes. The unmet need for refinement or restratification of risk based on these conventional prediction models is only emphasized by our entrance into the era of precision medicine. Potential tools for closing these gaps and increasing our understanding of the pathways from risk factors through subclinical changes to manifest disease include echocardiography and circulating biomarkers.

12.2. Objectives

1) To examine whether greater fasting plasma glucose (FPG) levels were associated with left ventricular mass (LVM), geometric pattern, diastolic function, and concentrations of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-TnT) in apparently healthy, elderly subjects with a preserved LV ejection fraction $\geq$ 50%; 2) To examine whether FPG levels modified the prognostic role of abnormal LVM, geometric pattern, diastolic dysfunction, NT-proBNP, and hs-TnT, in predicting cardiovascular morbidity and mortality; 3) To define the incremental prognostic value of NT-proBNP and hs-TnT for predicting incident cardiovascular outcomes, beyond traditional risk factors, glycemic status, and subclinical echocardiographic abnormalities; 4) To explore the associations of NT-proBNP and hs-TnT with key echocardiographic measures of LV structure and function, including the effects of FPG levels.

12.3. Methods

The thesis was based on a series of cross-sectional and prospective observational studies. The study population was derived from the echocardiography subsample (n=1,792) of the Malmö Preventive Project Re-Examination Study (MPP-RES) (2002-2006, n=18,238), a population-based screening program that included inhabitants from Malmö, Sweden, who belonged to prespecified birth cohorts between 1921-1949. Subjects, who underwent echocardiography, were randomly chosen from the three categories defined by baseline FPG, i.e., normal fasting glucose, impaired fasting glucose, and diabetes, including use of anti-diabetic medication. Blood samples for cardiovascular biomarker assessments were drawn at the time of echocardiography and kept frozen until analysis. Outcome data were obtained through national and local registries. The original echocardiography subsample was stratified into patients and apparently healthy subjects, the latter being the focus of this thesis.

12.4. Results

1) Subjects with diabetes had a greater prevalence of concentric LV hypertrophy (LVH), grade 2 or 3 diastolic dysfunction, and higher hs-TnT concentrations. Subjects with impaired fasting glucose had the lowest NT-proBNP concentrations. LVMI was primarily associated with diastolic function in subjects with hyperglycemia; 2) LV diastolic dysfunction was associated with an increased risk of incident cardiovascular events, but did not provide discriminative improvement. Concentric LVH and diastolic dysfunction were more strongly associated with adverse prognosis in subjects with hyperglycemia. High concentrations of NT-proBNP and hs-TnT predicted incident cardiovascular events, with no effect modification by FPG; 3) NT-proBNP, but not hs-TnT, provided discriminative improvement beyond traditional risk factors, FPG, and LVH and/or diastolic dysfunction; 4) NT-proBNP and hs-TnT were associated with several echocardiographic parameters, but effect sizes were generally modest. Associations between biomarkers and echocardiographic measures were affected by hyperglycemia.

12.5. Conclusions

FPG influenced the interplay between subclinical echocardiographic abnormalities, circulating biomarkers, and cardiovascular outcomes at multiple stages, in this cohort of apparently healthy, elderly subjects. Newly diagnosed diabetes, but not impaired fasting glucose, was associated with adverse subclinical changes. The associations between structural echocardiographic abnormalities and biomarker concentrations were stronger in subjects with hyperglycemia. NT-proBNP, but not echocardiographic measures or hs-TnT, provided discriminative improvement on top of traditional cardiovascular risk factors. FPG further modified the prognosis related to echocardiographic alterations, but not that predicted by biomarkers. Therefore, FPG should be considered when assessing markers of subclinical cardiovascular alterations.

13. REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1459-1544.
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.
3. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987-1003.
4. Goff DC,Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB S, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC,Jr, Sorlie P, Stone NJ, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935-2959.
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies

and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;
6. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-234.
7. Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation* 2004;109:855-860.
8. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005;28:2901-2907.
9. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 2007;30:1292-1293.
10. van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. *Diabetes Care* 2009;32:2094-2098.
11. Mukamal KJ, Kizer JR, Djousse L, Ix JH, Zieman S, Siscovick DS, Sibley CT, Tracy RP, Arnold AM. Prediction and classification of cardiovascular disease risk in older adults with diabetes. *Diabetologia* 2013;56:275-283.
12. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1659-1724.
13. Jameson JL, Longo DL. Precision medicine--personalized, problematic, and promising. *N Engl J Med* 2015;372:2229-2234.
14. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfil the promise of personalised medicine. *Lancet* 2015;385:2118-2119.
15. Ashley EA. The precision medicine initiative: a new national effort. *JAMA* 2015;313:2119-2120.
16. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;355:2631-2639.
17. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlov J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358:2107-2116.
18. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788-795.
19. Lindekleiv H, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T, Schirmer H. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. *JAMA Intern Med* 2013;173:1592-1598.
20. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jockel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol* 2015;66:1643-1653.
21. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation. 2006. http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf?ua=1 (Oct 6, 2016)
22. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. WHO 2011 http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/ (Oct 4, 2016)
23. American Diabetes Association. Standards of medical care in diabetes - 2016. *Diabetes care* 2016;39:S1-S112.
24. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002;19:708-723.
25. Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, Imperatore G, Williams DE, Albright AL. A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 2010;33:1665-1673.
26. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513-1530.
27. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1545-1602.
28. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1603-1658.
29. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM, South Tees Diabetes Mortality Study. Cause-specific mortality in a population with diabetes: South Tees Diabetes Mortality Study. *Diabetes Care* 2002;25:43-48.
30. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001;161:397-405.
31. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med* 2004;164:2147-2155.

32. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med* 2004;141:413-420.
33. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800-811.
34. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829-841.
35. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC,Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134-1146.
36. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
37. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-952.
38. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993;88:1444-1455.
39. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, O'Leary DH, Savage PJ, Tell GS, Tracy R. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation* 1995;92:720-726.
40. Psaty BM, Furberg CD, Kuller LH, Bild DE, Rautaharju PM, Polak JF, Bovill E, Gottdiener JS. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: the Cardiovascular Health Study. *Arch Intern Med* 1999;159:1339-1347.
41. Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, Burke GL, Manolio TA, Chaves PH. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch Intern Med* 2006;166:71-78.
42. Pearte CA, Furberg CD, O'Meara ES, Psaty BM, Kuller L, Powe NR, Manolio T. Characteristics and baseline clinical predictors of future fatal versus nonfatal coronary heart disease events in older adults: the Cardiovascular Health Study. *Circulation* 2006;113:2177-2185.
43. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000;102:470-479.
44. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165-193.
45. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol* 2014;63:407-416.
46. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-270.
47. Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J,3rd, Feinleib M, Castelli WP. The spectrum of left ventricular hypertrophy in a general population sample: the Framingham Study. *Circulation* 1987;75:I26-33.
48. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988;108:7-13.
49. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol* 1998;32:1454-1459.
50. Redfield MM, Jacobsen SJ, Burnett JC,Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.
51. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006;92:1259-1264.
52. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation* 2011;124:24-30.
53. Mureddu GF, Agabiti N, Rizzello V, Forastiere F, Latini R, Cesaroni G, Masson S, Cacciatore G, Colivicchi F, Uguccioni M, Perucci CA, Boccanelli A, PREDICTOR Study Group. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. *Eur J Heart Fail* 2012;14:718-729.
54. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. *Ann Intern Med* 1992;117:831-836.
55. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010;55:300-305.
56. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC,Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856-863.

57. Cioffi G, Rossi A, Zoppini G, Targher G, de Simone G, Devereux RB, Vassanelli C, Bonora E. Inappropriate left ventricular mass independently predicts cardiovascular mortality in patients with type 2 diabetes. *Int J Cardiol* 2013;168:4953-4956.
58. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561-1566.
59. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;52:2148-2155.
60. Eguchi K, Ishikawa J, Hoshide S, Ishikawa S, Pickering TG, Schwartz JE, Homma S, Shimada K, Kario K. Differential impact of left ventricular mass and relative wall thickness on cardiovascular prognosis in diabetic and nondiabetic hypertensive subjects. *Am Heart J* 2007;154:79.e9-79.15.
61. Gerdts E, Cramariuc D, de Simone G, Wachtell K, Dahlof B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). *Eur J Echocardiogr* 2008;9:809-815.
62. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;115:3213-3223.
63. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol* 2008;51:93-102.
64. Battiprolu PK, Gillette TG, Wang ZV, Lavandero S, Hill JA. Diabetic Cardiomyopathy: Mechanisms and Therapeutic Targets. *Drug Discov Today Dis Mech* 2010;7:e135-e143.
65. Teupe C, Rosak C. Diabetic cardiomyopathy and diastolic heart failure -- difficulties with relaxation. *Diabetes Res Clin Pract* 2012;97:185-194.
66. Huynh K, Bernardo BC, McMullen JR, Ritchie RH. Diabetic cardiomyopathy: mechanisms and new treatment strategies targeting antioxidant signaling pathways. *Pharmacol Ther* 2014;142:375-415.
67. Lee M, Gardin JM, Lynch JC, Smith VE, Tracy RP, Savage PJ, Szklo M, Ward BJ. Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: The Cardiovascular Health Study. *Am Heart J* 1997;133:36-43.
68. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 2000;101:2271-2276.
69. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. *Circulation* 2001;103:102-107.
70. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003;41:611-617.
71. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol* 2004;93:870-875.
72. Eguchi K, Boden-Albala B, Jin Z, Rundek T, Sacco RL, Homma S, Di Tullio MR. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. *Am J Cardiol* 2008;101:1787-1791.
73. From AM, Scott CG, Chen HH. Changes in diastolic dysfunction in diabetes mellitus over time. *Am J Cardiol* 2009;103:1463-1466.
74. Jorgensen PG, Jensen MT, Mogelvang R, von Scholten BJ, Bech J, Fritz-Hansen T, Galatius S, Biering-Sorensen T, Andersen HU, Vilsboll T, Rossing P, Jensen JS. Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. *Diab Vasc Dis Res* 2016;13:321-330.
75. Jorgensen PG, Jensen MT, Mogelvang R, Fritz-Hansen T, Galatius S, Biering-Sorensen T, Storgaard H, Vilsboll T, Rossing P, Jensen JS. Impact of type 2 diabetes and duration of type 2 diabetes on cardiac structure and function. *Int J Cardiol* 2016;221:114-121.
76. Kuller LH, Velentgas P, Barzilay J, Beauchamp NJ, O'Leary DH, Savage PJ. Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality. *Arterioscler Thromb Vasc Biol* 2000;20:823-829.
77. Ingelsson E, Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, Meigs JB, Keyes MJ, O'Donnell CJ, Wang TJ, D'Agostino RB S, Wolf PA, Vasan RS. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes* 2007;56:1718-1726.
78. Xanthakis V, Sung JH, Samdarshi TE, Hill AN, Musani SK, Sims M, Ghraibeh KA, Liebson PR, Taylor HA, Vasan RS, Fox ER. Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care* 2015;38:1082-1088.
79. Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function: The Strong Heart Study. *Am Heart J* 2001;141:992-998.
80. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003;107:448-454.
81. Rerkpattanapipat P, D'Agostino RB,Jr, Link KM, Shahar E, Lima JA, Bluemke DA, Sinha S, Herrington DM, Hundley WG. Location of arterial stiffening differs in those with impaired fasting glucose versus diabetes: implications for left ventricular hypertrophy from the Multi-Ethnic Study of Atherosclerosis. *Diabetes* 2009;58:946-953.
82. Leosdottir M, Willenheimer R, Plehn J, Borgquist R, Gudmundsson P, Harris TB, Launer LJ, Bjornsdottir H, Nilsson PM, Gudnason V. Myocardial structure and function by echocardiography in relation to glucometabolic status in elderly subjects from 2 population-based cohorts:

a cross-sectional study. *Am Heart J* 2010;159:414-420.e4.
83. Stahrenberg R, Edelmann F, Mende M, Kockskamper A, Dungen HD, Scherer M, Kochen MM, Binder L, Herrmann-Lingen C, Schonbrunn L, Gelbrich G, Hasenfuss G, Pieske B, Wachter R. Association of glucose metabolism with diastolic function along the diabetic continuum. *Diabetologia* 2010;53:1331-1340.
84. De Marco M, de Simone G, Roman MJ, Chinali M, Lee ET, Calhoun D, Howard BV, Devereux RB. Cardiac geometry and function in diabetic or prediabetic adolescents and young adults: the Strong Heart Study. *Diabetes Care* 2011;34:2300-2305.
85. Capaldo B, Di Bonito P, Iaccarino M, Roman MJ, Lee ET, Devereux RB, Riccardi G, Howard BV, de Simone G. Cardiovascular characteristics in subjects with increasing levels of abnormal glucose regulation: the Strong Heart Study. *Diabetes Care* 2013;36:992-997.
86. Skali H, Shah A, Gupta DK, Cheng S, Claggett B, Liu J, Bello N, Aguilar D, Vardeny O, Matsushita K, Selvin E, Solomon S. Cardiac structure and function across the glycemic spectrum in elderly men and women free of prevalent heart disease: the Atherosclerosis Risk In the Community study. *Circ Heart Fail* 2015;8:448-454.
87. Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR, BEST Investigators. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;42:914-922.
88. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ, CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377-1385.
89. Cavender MA, Steg PG, Smith SC,Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL, REACH Registry Investigators. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;132:923-931.
90. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M, PARADIGM-HF Investigators and Committees. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;9:10.1161/CIRCHEARTFAILURE.115.002560.
91. Authors/Task Force Members, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document Reviewers, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035-3087.
1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1459-1544.
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.
3. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM, SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987-1003.
4. Goff DC,Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB S, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC,Jr, Sorlie P, Stone NJ, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935-2959.
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM, Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;
6. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and

without prior myocardial infarction. *N Engl J Med* 1998;339:229-234.
7. Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation* 2004;109:855-860.
8. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care* 2005;28:2901-2907.
9. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. *Diabetes Care* 2007;30:1292-1293.
10. van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. *Diabetes Care* 2009;32:2094-2098.
11. Mukamal KJ, Kizer JR, Djousse L, Ix JH, Zieman S, Siscovick DS, Sibley CT, Tracy RP, Arnold AM. Prediction and classification of cardiovascular disease risk in older adults with diabetes. *Diabetologia* 2013;56:275-283.
12. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1659-1724.
13. Jameson JL, Longo DL. Precision medicine--personalized, problematic, and promising. *N Engl J Med* 2015;372:2229-2234.
14. Dzau VJ, Ginsburg GS, Van Nuys K, Agus D, Goldman D. Aligning incentives to fulfil the promise of personalised medicine. *Lancet* 2015;385:2118-2119.
15. Ashley EA. The precision medicine initiative: a new national effort. *JAMA* 2015;313:2119-2120.
16. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;355:2631-2639.
17. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlov J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 2008;358:2107-2116.
18. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788-795.
19. Lindekleiv H, Lochen ML, Mathiesen EB, Njolstad I, Wilsgaard T, Schirmer H. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. *JAMA Intern Med* 2013;173:1592-1598.
20. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jockel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol* 2015;66:1643-1653.
21. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation. 2006. http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf?ua=1 (Oct 6, 2016)
22. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. WHO 2011 http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/ (Oct 4, 2016)
23. American Diabetes Association. Standards of medical care in diabetes - 2016. *Diabetes care* 2016;39:S1-S112.
24. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002;19:708-723.
25. Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, Imperatore G, Williams DE, Albright AL. A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 2010;33:1665-1673.
26. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513-1530.
27. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1545-1602.
28. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1603-1658.
29. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM, South Tees Diabetes Mortality Study. Cause-specific mortality in a population with diabetes: South Tees Diabetes Mortality Study. *Diabetes Care* 2002;25:43-48.
30. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001;161:397-405.
31. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med* 2004;164:2147-2155.
32. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med* 2004;141:413-420.
33. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800-811.

34. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829-841.
35. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC,Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134-1146.
36. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-3421.
37. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-952.
38. Devereux RB, Alderman MH. Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events. *Circulation* 1993;88:1444-1455.
39. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, O'Leary DH, Savage PJ, Tell GS, Tracy R. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation* 1995;92:720-726.
40. Psaty BM, Furberg CD, Kuller LH, Bild DE, Rautaharju PM, Polak JF, Bovill E, Gottdiener JS. Traditional risk factors and subclinical disease measures as predictors of first myocardial infarction in older adults: the Cardiovascular Health Study. *Arch Intern Med* 1999;159:1339-1347.
41. Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, Burke GL, Manolio TA, Chaves PH. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch Intern Med* 2006;166:71-78.
42. Pearte CA, Furberg CD, O'Meara ES, Psaty BM, Kuller L, Powe NR, Manolio T. Characteristics and baseline clinical predictors of future fatal versus nonfatal coronary heart disease events in older adults: the Cardiovascular Health Study. *Circulation* 2006;113:2177-2185.
43. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000;102:470-479.
44. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165-193.
45. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol* 2014;63:407-416.
46. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-270.
47. Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J,3rd, Feinleib M, Castelli WP. The spectrum of left ventricular hypertrophy in a general population sample: the Framingham Study. *Circulation* 1987;75:I26-33.
48. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Intern Med* 1988;108:7-13.
49. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol* 1998;32:1454-1459.
50. Redfield MM, Jacobsen SJ, Burnett JC,Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.
51. Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006;92:1259-1264.
52. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. *Circulation* 2011;124:24-30.
53. Mureddu GF, Agabiti N, Rizzello V, Forastiere F, Latini R, Cesaroni G, Masson S, Cacciatore G, Colivicchi F, Uguccioni M, Perucci CA, Boccanelli A, PREDICTOR Study Group. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. *Eur J Heart Fail* 2012;14:718-729.
54. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. *Ann Intern Med* 1992;117:831-836.
55. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010;55:300-305.
56. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC,Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856-863.
57. Cioffi G, Rossi A, Zoppini G, Targher G, de Simone G, Devereux RB, Vassanelli C, Bonora E. Inappropriate left ventricular mass independently predicts cardiovascular mortality in patients with type 2 diabetes. *Int J Cardiol* 2013;168:4953-4956.
58. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561-1566.

59. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;52:2148-2155.
60. Eguchi K, Ishikawa J, Hoshide S, Ishikawa S, Pickering TG, Schwartz JE, Homma S, Shimada K, Kario K. Differential impact of left ventricular mass and relative wall thickness on cardiovascular prognosis in diabetic and nondiabetic hypertensive subjects. *Am Heart J* 2007;154:79.e9-79.15.
61. Gerdts E, Cramariuc D, de Simone G, Wachtell K, Dahlof B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the LIFE study). *Eur J Echocardiogr* 2008;9:809-815.
62. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;115:3213-3223.
63. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol* 2008;51:93-102.
64. Battiprolu PK, Gillette TG, Wang ZV, Lavandero S, Hill JA. Diabetic Cardiomyopathy: Mechanisms and Therapeutic Targets. *Drug Discov Today Dis Mech* 2010;7:e135-e143.
65. Teupe C, Rosak C. Diabetic cardiomyopathy and diastolic heart failure -- difficulties with relaxation. *Diabetes Res Clin Pract* 2012;97:185-194.
66. Huynh K, Bernardo BC, McMullen JR, Ritchie RH. Diabetic cardiomyopathy: mechanisms and new treatment strategies targeting antioxidant signaling pathways. *Pharmacol Ther* 2014;142:375-415.
67. Lee M, Gardin JM, Lynch JC, Smith VE, Tracy RP, Savage PJ, Szklo M, Ward BJ. Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: The Cardiovascular Health Study. *Am Heart J* 1997;133:36-43.
68. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 2000;101:2271-2276.
69. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. *Circulation* 2001;103:102-107.
70. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003;41:611-617.
71. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol* 2004;93:870-875.
72. Eguchi K, Boden-Albala B, Jin Z, Rundek T, Sacco RL, Homma S, Di Tullio MR. Association between diabetes mellitus and left ventricular hypertrophy in a multiethnic population. *Am J Cardiol* 2008;101:1787-1791.
73. From AM, Scott CG, Chen HH. Changes in diastolic dysfunction in diabetes mellitus over time. *Am J Cardiol* 2009;103:1463-1466.
74. Jorgensen PG, Jensen MT, Mogelvang R, von Scholten BJ, Bech J, Fritz-Hansen T, Galatius S, Biering-Sorensen T, Andersen HU, Vilsboll T, Rossing P, Jensen JS. Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. *Diab Vasc Dis Res* 2016;13:321-330.
75. Jorgensen PG, Jensen MT, Mogelvang R, Fritz-Hansen T, Galatius S, Biering-Sorensen T, Storgaard H, Vilsboll T, Rossing P, Jensen JS. Impact of type 2 diabetes and duration of type 2 diabetes on cardiac structure and function. *Int J Cardiol* 2016;221:114-121.
76. Kuller LH, Velentgas P, Barzilay J, Beauchamp NJ, O'Leary DH, Savage PJ. Diabetes mellitus: subclinical cardiovascular disease and risk of incident cardiovascular disease and all-cause mortality. *Arterioscler Thromb Vasc Biol* 2000;20:823-829.
77. Ingelsson E, Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, Meigs JB, Keyes MJ, O'Donnell CJ, Wang TJ, D'Agostino RB S, Wolf PA, Vasan RS. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes* 2007;56:1718-1726.
78. Xanthakis V, Sung JH, Samdarshi TE, Hill AN, Musani SK, Sims M, Ghraibeh KA, Liebson PR, Taylor HA, Vasan RS, Fox ER. Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care* 2015;38:1082-1088.
79. Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function: The Strong Heart Study. *Am Heart J* 2001;141:992-998.
80. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003;107:448-454.
81. Rerkpattanapipat P, D'Agostino RB,Jr, Link KM, Shahar E, Lima JA, Bluemke DA, Sinha S, Herrington DM, Hundley WG. Location of arterial stiffening differs in those with impaired fasting glucose versus diabetes: implications for left ventricular hypertrophy from the Multi-Ethnic Study of Atherosclerosis. *Diabetes* 2009;58:946-953.
82. Leosdottir M, Willenheimer R, Plehn J, Borgquist R, Gudmundsson P, Harris TB, Launer LJ, Bjornsdottir H, Nilsson PM, Gudnason V. Myocardial structure and function by echocardiography in relation to glucometabolic status in elderly subjects from 2 population-based cohorts: a cross-sectional study. *Am Heart J* 2010;159:414-420.e4.
83. Stahrenberg R, Edelmann F, Mende M, Kockskamper A, Dungen HD, Scherer M, Kochen MM, Binder L, Herrmann-Lingen C, Schonbrunn L, Gelbrich G, Hasenfuss G, Pieske B, Wachter R. Association of glucose metabolism with diastolic function along the diabetic continuum. *Diabetologia* 2010;53:1331-1340.
84. De Marco M, de Simone G, Roman MJ, Chinali M, Lee ET, Calhoun D, Howard BV, Devereux RB. Cardiac geometry and function in diabetic or prediabetic adolescents

and young adults: the Strong Heart Study. *Diabetes Care* 2011;34:2300-2305.
85. Capaldo B, Di Bonito P, Iaccarino M, Roman MJ, Lee ET, Devereux RB, Riccardi G, Howard BV, de Simone G. Cardiovascular characteristics in subjects with increasing levels of abnormal glucose regulation: the Strong Heart Study. *Diabetes Care* 2013;36:992-997.
86. Skali H, Shah A, Gupta DK, Cheng S, Claggett B, Liu J, Bello N, Aguilar D, Vardeny O, Matsushita K, Selvin E, Solomon S. Cardiac structure and function across the glycemic spectrum in elderly men and women free of prevalent heart disease: the Atherosclerosis Risk In the Community study. *Circ Heart Fail* 2015;8:448-454.
87. Domanski M, Krause-Steinrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR, BEST Investigators. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol* 2003;42:914-922.
88. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ, CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377-1385.
89. Cavender MA, Steg PG, Smith SC,Jr, Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL, REACH Registry Investigators. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015;132:923-931.
90. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M, PARADIGM-HF Investigators and Committees. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;9:10.1161/CIRCHEARTFAILURE.115.002560.
91. Authors/Task Force Members, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document Reviewers, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schachinger V, Scheen A, Schirmer H, Stromberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035-3087.
92. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, Deedwania P, Eckel RH, Ershow AG, Fradkin J, Inzucchi SE, Kosiborod M, Nelson RG, Patel MJ, Pignone M, Quinn L, Schauer PR, Selvin E, Vafiadis DK, American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. *Circulation* 2015;132:691-718.
93. Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S, Edelman S, Henry R, Maisel A. Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. *Diabetes Care* 2003;26:2081-2087.
94. Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH. Screening for heart disease in diabetic subjects. *Am Heart J* 2005;149:349-354.
95. Abhayaratna WP, Marwick TH, Becker NG, Jeffery IM, McGill DA, Smith WT. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide. *Am Heart J* 2006;152:941-948.
96. Goetze JP, Mogelvang R, Maage L, Scharling H, Schnohr P, Sogaard P, Rehfeld JF, Jensen JS. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. *Eur Heart J* 2006;27:3004-3010.
97. de Lemos JA, McGuire DK, Khera A, Das SR, Murphy SA, Omland T, Drazner MH. Screening the population for left ventricular hypertrophy and left ventricular systolic dysfunction using natriuretic peptides: results from the Dallas Heart Study. *Am Heart J* 2009;157:746-53.e2.
98. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;304:2503-2512.
99. Choi EY, Bahrami H, Wu CO, Greenland P, Cushman M, Daniels LB, Almeida AL, Yoneyama K, Opdahl A, Jain A, Criqui MH, Siscovick D, Darwin C, Maisel A, Bluemke DA, Lima JA. N-terminal pro-B-type natriuretic peptide, left ventricular mass, and incident heart failure: Multi-Ethnic Study of Atherosclerosis. *Circ Heart Fail* 2012;5:727-734.
100. Neeland IJ, Drazner MH, Berry JD, Ayers CR, deFilippi C, Seliger SL, Nambi V, McGuire DK, Omland T, de Lemos

JA. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. *J Am Coll Cardiol* 2013;61:187-195.
101. Xanthakis V, Larson MG, Wollert KC, Aragam J, Cheng S, Ho J, Coglianese E, Levy D, Colucci WS, Michael Felker G, Benjamin EJ, Januzzi JL, Wang TJ, Vasan RS. Association of novel biomarkers of cardiovascular stress with left ventricular hypertrophy and dysfunction: implications for screening. *J Am Heart Assoc* 2013;2:e000399.
102. McGrady M, Reid CM, Shiel L, Wolfe R, Boffa U, Liew D, Campbell DJ, Prior D, Krum H. N-terminal B-type natriuretic peptide and the association with left ventricular diastolic function in a population at high risk of incident heart failure: results of the SCReening Evaluationof the Evolution of New-Heart Failure Study (SCREEN-HF). *Eur J Heart Fail* 2013;15:573-580.
103. Masson S, Latini R, Mureddu GF, Agabiti N, Miceli M, Cesaroni G, Forastiere F, Wienhues-Thelen UH, Block D, Zaugg C, Vago T, Boccanelli A, PREDICTOR study. High-sensitivity cardiac troponin T for detection of subtle abnormalities of cardiac phenotype in a general population of elderly individuals. *J Intern Med* 2013;273:306-317.
104. McGrady M, Reid CM, Shiel L, Wolfe R, Boffa U, Liew D, Campbell DJ, Prior D, Stewart S, Krum H. NT-proB natriuretic peptide, risk factors and asymptomatic left ventricular dysfunction: results of the SCReening Evaluation of the Evolution of New Heart Failure study (SCREEN-HF). *Int J Cardiol* 2013;169:133-138.
105. Seliger SL, de Lemos J, Neeland IJ, Christenson R, Gottdiener J, Drazner MH, Berry J, Sorkin J, deFilippi C. Older Adults, "Malignant" Left Ventricular Hypertrophy, and Associated Cardiac-Specific Biomarker Phenotypes to Identify the Differential Risk of New-Onset Reduced Versus Preserved Ejection Fraction Heart Failure: CHS (Cardiovascular Health Study). *JACC Heart Fail* 2015;3:445-455.
106. Ravassa S, Kuznetsova T, Varo N, Thijs L, Delles C, Dominiczak A, Diez J, Staessen JA. Biomarkers of cardiomyocyte injury and stress identify left atrial and left ventricular remodelling and dysfunction: A population-based study. *Int J Cardiol* 2015;185:177-185.
107. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994;90:195-203.
108. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005;352:666-675.
109. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146-150.
110. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD, Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581-1598.
111. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J* 2012;33:579-586.
112. Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. *J Am Coll Cardiol* 2013;61:1753-1758.
113. Olsen MH, Hansen TW, Christensen MK, Gustafsson F, Rasmussen S, Wachtell K, Ibsen H, Torp-Pedersen C, Hildebrandt PR. N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population. *Eur Heart J* 2007;28:1374-1381.
114. Huelsmann M, Neuhold S, Strunk G, Moertl D, Berger R, Prager R, Abrahamian H, Riedl M, Pacher R, Luger A, Clodi M. NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. *Eur Heart J* 2008;29:2259-2264.
115. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engstrom G, Persson M, Smith JG, Magnusson M, Christensson A, Struck J, Morgenthaler NG, Bergmann A, Pencina MJ, Wang TJ. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA* 2009;302:49-57.
116. Everett BM, Cook NR, Magnone MC, Bobadilla M, Kim E, Rifai N, Ridker PM, Pradhan AD. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: the Women's Health Study. *Circulation* 2011;123:2811-2818.
117. Bruno G, Landi A, Barutta F, Ghezzo G, Baldin C, Spadafora L, Schimmenti A, Prinzis T, Cavallo Perin P, Gruden G. N-terminal probrain natriuretic peptide is a stronger predictor of cardiovascular mortality than C-re-

active protein and albumin excretion rate in elderly patients with type 2 diabetes: the Casale Monferrato population-based study. *Diabetes Care* 2013;36:2677-2682.
118. Tang WH, Wu Y, Britt EB,Jr, Iqbal N, Hazen SL. Detectable subclinical myocardial necrosis is associated with cardiovascular risk in stable patients with diabetes. *Diabetes Care* 2013;36:1126-1131.
119. Eggers KM, Al-Shakarchi J, Berglund L, Lindahl B, Siegbahn A, Wallentin L, Zethelius B. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *Am Heart J* 2013;166:541-548.
120. Hillis GS, Welsh P, Chalmers J, Perkovic V, Chow CK, Li Q, Jun M, Neal B, Zoungas S, Poulter N, Mancia G, Williams B, Sattar N, Woodward M. The relative and combined ability of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide to predict cardiovascular events and death in patients with type 2 diabetes. *Diabetes Care* 2014;37:295-303.
121. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, Hoogeveen RC, Sharrett AR, Ballantyne CM, Coresh J. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation* 2014;130:1374-1382.
122. Everett BM, Berger JS, Manson JE, Ridker PM, Cook NR. B-type natriuretic peptides improve cardiovascular disease risk prediction in a cohort of women. *J Am Coll Cardiol* 2014;64:1789-1797.
123. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL, BARI 2D Study Group. Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes. *N Engl J Med* 2015;373:610-620.
124. Everett BM, Ridker PM, Cook NR, Pradhan AD. Usefulness of B-type Natriuretic Peptides to Predict Cardiovascular Events in Women (from the Women's Health Study). *Am J Cardiol* 2015;116:532-537.
125. Gori M, Gupta DK, Claggett B, Selvin E, Folsom AR, Matsushita K, Bello NA, Cheng S, Shah A, Skali H, Vardeny O, Ni H, Ballantyne CM, Astor BC, Klein BE, Aguilar D, Solomon SD. Natriuretic Peptide and High-Sensitivity Troponin for Cardiovascular Risk Prediction in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 2016;39:677-685.
126. Hendriks SH, van Dijk PR, van Hateren KJ, van Pelt JL, Groenier KH, Bilo HJ, Bakker SJ, Landman GW, Kleefstra N. High-sensitive troponin T is associated with all-cause and cardiovascular mortality in stable outpatients with type 2 diabetes (ZODIAC-37). *Am Heart J* 2016;174:43-50.
127. Blankenberg S, Salomaa V, Makarova N, Ojeda F, Wild P, Lackner KJ, Jorgensen T, Thorand B, Peters A, Nauck M, Petersmann A, Vartiainen E, Veronesi G, Brambilla P, Costanzo S, Iacoviello L, Linden G, Yarnell J, Patterson CC, Everett BM, Ridker PM, Kontto J, Schnabel RB, Koenig W, Kee F, Zeller T, Kuulasmaa K, BiomarCaRE Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016;37:2428-2437.
128. Scirica BM, Bhatt DL, Braunwald E, Raz I, Cavender MA, Im K, Mosenzon O, Udell JA, Hirshberg B, Pollack PS, Steg PG, Jarolim P, Morrow DA. Prognostic Implications of Biomarker Assessments in Patients With Type 2 Diabetes at High Cardiovascular Risk: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol* 2016;
129. Resl M, Clodi M, Vila G, Luger A, Neuhold S, Wurm R, Adlbrecht C, Strunk G, Fritzer-Szekeres M, Prager R, Pacher R, Hulsmann M. Targeted multiple biomarker approach in predicting cardiovascular events in patients with diabetes. *Heart* 2016;
130. Natriuretic Peptides Studies C. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *Lancet Diabetes Endocrinol* 2016;4:840-849.
131. McEvoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA Cardiol* 2016;1:519-528.
132. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 2002;25:1129-1134.
133. Davis TM, Coleman RL, Holman RR, UKPDS Group. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. *Circulation* 2013;127:980-987.
134. van den Hurk K, Alssema M, Kamp O, Henry RM, Stehouwer CD, Diamant M, Boomsma F, Heine RJ, Nijpels G, Paulus WJ, Dekker JM. Slightly elevated B-type natriuretic peptide levels in a non-heart failure range indicate a worse left ventricular diastolic function in individuals with, as compared with individuals without, type 2 diabetes: the Hoorn Study. *Eur J Heart Fail* 2010;12:958-965.
135. Kroon MH, van den Hurk K, Alssema M, Kamp O, Stehouwer CD, Henry RM, Diamant M, Boomsma F, Nijpels G, Paulus WJ, Dekker JM. Prospective associations of B-type natriuretic peptide with markers of left ventricular function in individuals with and without type 2 diabetes: an 8-year follow-up of the Hoorn Study. *Diabetes Care* 2012;35:2510-2514.
136. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S. Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care* 2004;27:1929-1935.
137. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA* 2010;304:2494-2502.
138. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367-1376.
139. Zhu WH, Chen LY, Dai HL, Chen JH, Chen Y, Fang LZ. Correlation between B type natriuretic peptide and metabolic risk factors. *Arch Med Sci* 2016;12:334-340.

140. Bao Y, Shang X, Zhou L, Hu R, Li Y, Ding W. Relationship between N-terminal pro-B-type natriuretic peptide levels and metabolic syndrome. *Arch Med Sci* 2011;7:247-256.
141. Leosdottir M, Willenheimer R, Hall C, Tjora S, Malm J, Melander O, Nilsson PM. Age and gender differences in the association between Nt-proBNP and glucometabolic disturbances. *Scand Cardiovasc J* 2011;45:294-300.
142. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. *J Am Coll Cardiol* 2012;59:484-489.
143. Zheng J, Ye P, Luo L, Xiao W, Xu R, Wu H. Association between blood glucose levels and high-sensitivity cardiac troponin T in an overt cardiovascular disease-free community-based study. *Diabetes Res Clin Pract* 2012;97:139-145.
144. Nilsson P, Berglund G. Prevention of cardiovascular disease and diabetes: lessons from the Malmo Preventive Project. *J Intern Med* 2000;248:455-462.
145. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450-2458-11-450.
146. Harrell FE,Jr, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;247:2543-2546.
147. Pencina MJ, D'Agostino RB S, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30:11-21.
148. Okin PM, Devereux RB, Gerdts E, Snapinn SM, Harris KE, Jern S, Kjeldsen SE, Julius S, Edelman JM, Lindholm LH, Dahlof B, LIFE Study Investigators. Impact of diabetes mellitus on regression of electrocardiographic left ventricular hypertrophy and the prediction of outcome during antihypertensive therapy: the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study. *Circulation* 2006;113:1588-1596.
149. Gerdts E, Okin PM, Omvik P, Wachtell K, Dahlof B, Hildebrandt P, Nieminen MS, Devereux RB. Impact of diabetes on treatment-induced changes in left ventricular structure and function in hypertensive patients with left ventricular hypertrophy. The LIFE study. *Nutr Metab Cardiovasc Dis* 2009;19:306-312.
150. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC,Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH,Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-2559.
151. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-2572.
152. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129-139.
153. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC,Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH,Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818-828.
154. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, Arima H, Monaghan H, Joshi R, Colagiuri S, Cooper ME, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Lisheng L, Mancia G, Marre M, Matthews DR, Mogensen CE, Perkovic V, Poulter N, Rodgers A, Williams B, MacMahon S, Patel A, Woodward M, ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392-1406.
155. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, McCarren M, Duckworth WC, Emanuele NV, VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;372:2197-2206.
156. Liu J, Masurekar MR, Vatner DE, Jyothirmayi GN, Regan TJ, Vatner SF, Meggs LG, Malhotra A. Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. *Am J Physiol Heart Circ Physiol* 2003;285:H2587-91.
157. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 2006;48:1548-1551.
158. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Effect of diabetes and hypertension on left ventricular diastolic function in a high-risk population without evidence of heart disease. *Eur J Heart Fail* 2010;12:454-461.
159. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation* 2006;114:2850-2870.
160. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part II: Clinical trial evidence (acute coronary syndromes through renal disease) and future directions. *Circulation* 2006;114:2871-2891.
161. O'Rourke MF, Safar ME, Dzau V. The Cardiovascular Continuum extended: aging effects on the aorta and microvasculature. *Vasc Med* 2010;15:461-468.
162. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263-271.
163. Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J, Multiple Risk Factor Intervention Trial Research Group. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. *Arch Intern Med* 2004;164:1438-1443.

164. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol* 2003;41:1387-1393.
165. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40:1286-1292.
166. Asbun J, Villarreal FJ. The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. *J Am Coll Cardiol* 2006;47:693-700.
167. Rivera JJ, Nasir K, Choi EK, Yoon YE, Chun EJ, Choi SI, Choi DJ, Brancati FL, Blumenthal RS, Chang HJ. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. *Atherosclerosis* 2009;203:442-448.
168. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109:594-600.
169. Olsen MH, Hansen TW, Christensen MK, Gustafsson F, Rasmussen S, Wachtell K, Borch-Johnsen K, Ibsen H, Jorgensen T, Hildebrandt P. N-terminal pro brain natriuretic peptide is inversely related to metabolic cardiovascular risk factors and the metabolic syndrome. *Hypertension* 2005;46:660-666.
170. Das SR, Drazner MH, Dries DL, Vega GL, Stanek HG, Abdullah SM, Canham RM, Chung AK, Leonard D, Wians FH,Jr, de Lemos JA. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation* 2005;112:2163-2168.
171. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. *Circulation* 2007;115:1345-1353.
172. Abdulle AM, Nagelkerke NJ, Adem A, Abouchacra S, Pathan JY, Al-Rukhaimi M, Suleiman MN, Mathew MC, Nicholls MG, Obineche EN. Plasma N terminal pro-brain natriuretic peptide levels and its determinants in a multi-ethnic population. *J Hum Hypertens* 2007;21:647-653.
173. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail* 2004;6:261-268.
174. Minami J, Nishikimi T, Matsuoka H. Plasma brain natriuretic peptide and N-terminal proatrial natriuretic peptide levels in obese patients: a cause or result of hypertension? *Circulation* 2004;110:e76; author reply e76.
175. Valle R, Bagolin E, Canali C, Giovinazzo P, Barro S, Aspromonte N, Carbonieri E, Milani L. The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients. *Eur J Echocardiogr* 2006;7:40-44.
176. Grant AD, Negishi K, Negishi T, Collier P, Kapadia SR, Thomas JD, Marwick TH, Griffin BP, Popovic ZB. Grading diastolic function by echocardiography: hemodynamic validation of existing guidelines. *Cardiovasc Ultrasound* 2015;13:28-015-0023-6.
177. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, Kangawa K, Matsuo H, Omae T, Matsuoka H. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996;28:22-30.
178. Rivera Otero JM, Talens-Visconti R, Salvador A, Bertomeu V, Miro V, Jordan A, Sogorb F, Cortes R, Paya R, Diago JL, Grau G, Grupo de Disfuncion VI, Comunidad Valenciana. Ventricular hypertrophy increases NT-proBNP in subjects with and without hypertension. *Int J Cardiol* 2004;96:265-271.
179. Lukowicz TV, Fischer M, Hense HW, Doring A, Stritzke J, Riegger G, Schunkert H, Luchner A, MONICA Investigators. BNP as a marker of diastolic dysfunction in the general population: Importance of left ventricular hypertrophy. *Eur J Heart Fail* 2005;7:525-531.
180. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. *Eur Heart J* 2005;26:2277-2284.
181. Suzuki M, Yamamoto K, Watanabe S, Iwata T, Hamada M, Hiwada K. Association between elevated brain natriuretic peptide levels and the development of left ventricular hypertrophy in patients with hypertension. *Am J Med* 2000;108:627-633.
182. Schafer S, Kelm M, Mingers S, Strauer BE. Left ventricular remodeling impairs coronary flow reserve in hypertensive patients. *J Hypertens* 2002;20:1431-1437.
183. O'Donoghue ML, Morrow DA, Cannon CP, Jarolim P, Desai NR, Sherwood MW, Murphy SA, Gerszten RE, Sabatine MS. Multimarker Risk Stratification in Patients With Acute Myocardial Infarction. *J Am Heart Assoc* 2016;5:10.1161/JAHA.115.002586.
184. Ruff CT, Giugliano RP, Braunwald E, Murphy SA, Brown K, Jarolim P, Mercuri M, Antman EM, Morrow DA. Cardiovascular Biomarker Score and Clinical Outcomes in Patients With Atrial Fibrillation: A Subanalysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. *JAMA Cardiol* 2016;
185. Blankenberg S, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, Kuulasmaa K, Yarnell J, Schnabel RB, Wild PS, Munzel TF, Lackner KJ, Tiret L, Evans A, Salomaa V, MORGAM Project. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. *Circulation* 2010;121:2388-2397.
186. Tzoulaki I, Siontis KC, Evangelou E, Ioannidis JP. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med* 2013;173:664-671.
187. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A, Platonov PG, Hedblad B, Engstrom G, Wang TJ, Melander O. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol* 2010;56:1712-1719.
188. Diaz T, Pencina MJ, Benjamin EJ, Aragam J, Fuller DL, Pencina KM, Levy D, Vasan RS. Prevalence, clinical correlates, and prognosis of discrete upper septal thickening on echocardiography: the Framingham Heart Study. *Echocardiography* 2009;26:247-253.
189. Firstenberg MS, Levine BD, Garcia MJ, Greenberg NL, Cardon L, Morehead AJ, Zuckerman J, Thomas JD. Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. *J Am Coll Cardiol* 2000;36:1664-1669.

190. Kugler KG, Hackl WO, Mueller LA, Fiegl H, Graber A, Pfeiffer RM. The Impact of Sample Storage Time on Estimates of Association in Biomarker Discovery Studies. *J Clin Bioinforma* 2011;1:9.