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# Predictive value of echocardiography in Type 2 diabetes

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**Aims** Echocardiography is suggested in the diagnostic work-up of patients with Type 2 diabetes (T2D). We investigated which echocardiographic parameters that best predicted cardiovascular disease (CVD) and whether this was persistent in both genders in a large cohort of outpatients with T2D.

**Methods and results** We performed comprehensive echocardiography in 933 patients with T2D followed at specialized out-patients clinics in Copenhagen, Denmark. Follow-up was performed using national registries and included admission with future CVD events and non-CVD death as competing risk. Median follow-up was 4.8 years and 138 CVD events occurred. In univariable and multivariable analyses, a wide range of structural, diastolic, and systolic measurements predicted CVD including mean *E*/*e*′ [hazard ratio (HR) 1.06, 95% confidence interval: (1.03–1.10), $P < 0.001$, C-statistics 0.74 (0.70–0.78)] and global longitudinal strain (GLS) [1.10 (1.01–1.20), $P = 0.03$, C-statistics 0.73 (0.69–0.77)]. However, this was modified by gender. In men, mean *E*/*e*′ remained the strongest predictor in multivariable analyses and performed best measured by highest C-statistics [HR 1.15, 95% confidence interval: (1.08–1.21), $P < 0.001$, C-statistics 0.75 (0.71–0.80)] whereas in women this was GLS [1.39 (1.14–1.70), $P = 0.001$, C-statistics 0.79 (0.70–0.87)]. These findings persisted when excluding patients with known heart disease and when regarding all-cause mortality as a competing risk.

**Conclusion** A range of echocardiographic parameters predicted CVD in patients with Type 2 diabetes, however, in multivariable analyses, mean *E*/*e*′ was the strongest predictor and had the highest model performance. Importantly, this study identifies a hitherto undescribed gender interaction as mean *E*/*e*′ performed best in men, whereas in women this was GLS.

**Keywords** echocardiography • type 2 diabetes • prospective study • cardiovascular disease

## Introduction

In patients with Type 2 diabetes, cardiovascular disease (CVD) is the most common cause of death despite declines in diabetes-related complications over the past decades.[1–3] Identification of patients at risk of developing CVD is a major clinical challenge. Guidelines recommend echocardiography—a fast, non-invasive, reliable, and reproducible examination—in the diagnostic work-up of Type 2 diabetes patients with suspected heart disease.[4] Diabetes is thought to affect the myocardium both through its association with coronary artery disease and through a direct effect on the myocardium often termed the 'diabetic cardiomyopathy'.[5,6]

A number of structural and functional alterations detected by echocardiography have been described in patients with Type 2 diabetes including left ventricular hypertrophy[7–9] and decreased diastolic and systolic function.[10–13] However, while diastolic dysfunction is common, systolic dysfunction as defined by reduced left ventricular ejection fraction is a relatively rare finding. Accordingly, diastolic dysfunction has been described in 25–75% of patients with Type 2 diabetes,[13–15] while reduced ejection fraction has been found in approximately 1% of the patients.[12] However, with the advent of 2D speckle tracking that can measure subtle changes in longitudinal, myocardial deformation, the distinction between systolic and diastolic dysfunction has been diminished.[16]

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Previous studies have identified, myocardial deformation by 2D speckle tracking as a predictor of adverse events in a wide range of populations including in patients with Type 2 diabetes.[17] In addition, both diastolic dysfunction and left atrial end-systolic volume index have been identified as strong predictors of adverse events in this patient population.[17–19] However, recent studies have indicated that important gender differences exist between the prognostic significance of these measures[20,21] and also gender differences in the echocardiographic phenotypes of patients with Type 2 diabetes have recently been described.[22,23]

To enable accurate risk stratification of patients with Type 2 diabetes with the use of echocardiography as described in the guidelines, knowledge on the prognostic significance of echocardiographic measures as well as identification of any gender specific differences are warranted. Hence, we aimed to describe prognostic significance of structural as well as functional alterations associated with Type 2 diabetes with respect to gender to aid the clinician to accurately risk stratify patients with Type 2 diabetes with the use of echocardiography.

# Methods

## Study population

The Thousand&2 study is a prospective cohort study, that was initiated in 2011 and recruited patients with Type 2 diabetes from two large, secondary care centres in the Copenhagen area: The Steno Diabetes Center and Center for Diabetes Research, Gentofte University Hospital. The study details have been published previously.[23,24] In brief, a total of 2158 patients were invited and 1030 participated in the study. All patients filled out a questionnaire with information on current medication, prior heart disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, congestive heart failure, and atrial fibrillation), prior stroke and peripheral artery disease, family history of coronary heart disease, smoking habits, height, and weight. Blood pressure was measured in the supine position after at least 15 min of rest. Body mass index (BMI) was calculated (weight (kg)/height (m)$^2$) based on self-reported measurements. Lipid levels, haemoglobin $A_{1c}$, albuminuria status, and creatinine were obtained from routine blood tests performed at either Steno Diabetes Center or Center for Diabetes Research, Herlev and Gentofte Hospital. For the present study, patients with atrial fibrillation at the time of the echocardiographic examination and patients with more than moderate valve disease and/or previous heart valve surgery were excluded ($n = 96$). One patient with incorrectly collected social security number was also excluded yielding a study population of 933 patients with Type 2 diabetes.

The study was conducted in accordance with the Helsinki Declaration, approved by The Danish National Committee on Biomedical Research Ethics, amendment to protocol no. H-3-2009-139.[25] All participants gave written, informed consent.

## Echocardiography

Details on the echocardiographic examination has been published previously.[23,24,26,27] In brief, echocardiography was performed using GE General Electrics, Vivid 7 and Vivid E9 (GE Vingmed Ultrasound, Horten, Norway). The offline analyses were performed using GE EchoPAC software, BT13. Chamber quantification was performed in accordance with the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.[28] Left ventricular (LV) mass was indexed according to height,[27] which was chosen in line with our previous studies. Mid-myocardial global strain provided by the software algorithm was used, and global longitudinal strain (GLS) was the mean value of the GLS provided by the software from all three standard projections. Global circumferential strain (GCS) was measured at the level of the papillary muscle. The mean frame rate for the GLS analyses was 67.1/s (standard deviation: 9.9).

## Follow-up

Follow-up was performed using 'The Danish National Board of Health's National Patient Registry and Registry of Cause of Death', that has previously been found to have high accuracy when comparing to medical journals.[29] The endpoint was CVD event that was the composite of admission with CVD [including coronary revascularization, myocardial infarction [international classification of diseases (ICD)-10 codes I21–I25], heart failure (ICD-10 codes I11, I13, I42, I43, and I50), cardiac arrest (I46), cerebrovascular disease (I60–I69), and peripheral artery disease (I70–I79)] and CVD death. Because all death certificates are reviewed before entering the registers, follow-up for CVD death ended in 2015 and deaths after this period were considered as non-CVD deaths. Non-CVD death obtained from the same registry was considered as competing risk. Follow-up was 100%.

## Statistics

Continuous variables were compared using the Welsh's *t*-test or Mann–Whitney *U* test in case of non-Gaussian distribution. Categorical variables were compared using the $\chi^2$ test. Cox proportionate hazard regression was used to determine the univariable and multivariable association of echocardiographic parameters and the risk of CVD event. Competing risk regression with the Fine–Gray method was performed with non-CVD death as a competing risk. Model discrimination was tested with the C-statistic and the net reclassification index. Statistics were performed using R for Mac, version 3.4.3 (R Project for Statistical Computing, Vienna University of Economics and Business Administration, Wien, Austria).

# Results

The median follow-up time was 4.8 years (interquartile range: 4.0–5.3) for the composite endpoint CVD event. The event rate was 14.8% for the entire population (17.7% for men and 9.4% for women). A total of 62 (6.6%) died a non-CVD death [46 (7.6%) men and 16 (4.8%) women]. There was significant interaction between gender and the following: left ventricular mass index ($P = 0.03$), left ventricular posterior wall thickness ($P = 0.009$), septal ratio of early mitral inflow and early myocardial velocity ($E/e'$) ($P = 0.003$), mean $E/e'$ (0.007), left ventricular ejection fraction ($P = 0.01$), GLS ($P = 0.003$), and GLS rate (0.02). Because gender modified the effect of the echocardiographic parameters, we stratified the population according to gender.

The baseline characteristics and echocardiographic measures according to no event vs. event and according to gender are shown in *Table 1* and Supplementary data online, *Table S1*. In general, patients experiencing an event had a worse cardiovascular risk profile. They were older, more often men, had longer duration of T2D, prior CVD, albuminuria, lower high density lipoprotein-cholesterol and had higher creatinine levels. In addition, they were less often on metformin and more often on insulin and beta-blockers.

**Table 1 Baseline characteristics according to patients having no event vs. patients with CVD event during follow-up and according to gender**

| | No event (*n* = 795) | CVD event (*n* = 138) | *P*-value | Men (*n* = 603) | Women (*n* = 330) | *P*-value |
|---|---|---|---|---|---|---|
| Clinical characteristics | | | | | | |
| Age (years) | 64 (57–70) | 68 (62–74) | <0.001 | 65 (58–70) | 65 (57–72) | 0.73 |
| Female gender, *n* (%) | 299 (37.6) | 31 (22.5) | 0.001 | | | |
| Diabetes duration (years) | 10 (5–17) | 15 (8–20) | <0.001 | 12 (6–17) | 10 (5–17) | 0.28 |
| Body mass index (kg/m$^2$) | 29 (26–33) | 30 (27–34) | 0.38 | 29 (27–33) | 30 (26–34) | 0.26 |
| Systolic blood pressure (mmHg) | 136 (16) | 137 (21) | 0.60 | 135 (17) | 138 (17) | 0.004 |
| Diastolic blood pressure (mmHg) | 80 (11) | 79 (12) | 0.38 | 80 (11) | 80 (11) | 0.76 |
| Prior known heart disease, n (%) | 108 (13.6) | 56 (40.6) | <0.001 | 138 (22.9) | 26 (7.9) | <0.001 |
| Prior CVD, *n* (%) | 145 (18.2) | 67 (48.6) | <0.001 | 168 (27.9) | 44 (13.3) | <0.001 |
| Biochemistry | | | | | | |
| Albuminuria, *n* (%) | 145 (18.2) | 67 (48.6) | <0.001 | 161 (27.1) | 51 (15.9) | <0.001 |
| Total cholesterol (mmol/L) | 4.1 (3.6–4.8) | 4.2 (3.4–4.9) | 0.73 | 4.0 (3.4–4.7) | 4.3 (3.8–5.1) | <0.001 |
| Low density lipoprotein cholesterol (mmol/L) | 2.0 (1.5–2.6) | 2.0 (1.6–2.5) | 0.91 | 1.9 (1.5–2.5) | 2.1 (1.6–2.8) | 0.005 |
| Creatinine (μmol/L) | 76 (64–93) | 92 (75–123) | <0.001 | 83 (72–101) | 67 (56–81) | <0.001 |
| Haemoglobin $A_{1c}$ (mmol/mol) | 7.4 (1.4) | 7.8 (1.8) | 0.01 | 7.5 (1.4) | 7.5 (1.5) | 0.74 |
| Glucose lowering medication, *n* (%) | | | | | | |
| Metformin | 592 (74.5) | 83 (60.1) | 0.001 | 438 (72.6) | 237 (71.8) | 0.85 |
| Dipeptidyl peptidase-4 inhibitors | 78 (9.8) | 10 (7.2) | 0.427 | 58 (9.6) | 30 (9.1) | 0.88 |
| Sulfonylurea | 125 (15.7) | 19 (13.8) | 0.646 | 101 (16.7) | 43 (13.0) | 0.16 |
| Glucagon-like peptide-1 receptor agonists | 198 (24.9) | 30 (21.7) | 0.489 | 132 (21.9) | 96 (29.1) | 0.02 |
| Insulin | 351 (44.2) | 80 (58.0) | 0.004 | 284 (47.1) | 147 (44.5) | 0.50 |
| Other medication, *n* (%) | | | | | | |
| Beta-blockers | 165 (20.8) | 59 (42.8) | <0.001 | 165 (27.4) | 59 (17.9) | 0.002 |
| Angiotensin-converting enzyme inhibitors | 292 (36.7) | 63 (45.7) | 0.058 | 248 (41.1) | 107 (32.4) | 0.01 |
| Angiotensin II receptor blockers | 317 (39.9) | 47 (34.1) | 0.231 | 237 (39.3) | 127 (38.5) | 0.86 |
| Calcium antagonists | 251 (31.6) | 47 (34.1) | 0.632 | 208 (34.5) | 90 (27.3) | 0.03 |
| Diuretics | 379 (47.7) | 77 (55.8) | 0.095 | 301 (49.9) | 155 (47.0) | 0.43 |
| Statins | 633 (79.6) | 103 (74.6) | 0.226 | 491 (81.4) | 245 (74.2) | 0.01 |
| Antiplatelets | 511 (64.3) | 103 (74.6) | 0.023 | 425 (70.5) | 189 (57.3) | <0.001 |

Continuous traits are reported as mean (standard deviation) or median (interquartile range) in case of non-normal distribution.
CVD, cardiovascular disease.

Stratifying according to gender, women had higher blood pressure and cholesterol levels, but in general had a more favourable cardiovascular risk profile with lower prevalence of prior coronary heart disease, albuminuria and lower creatinine levels. Regarding medication, they were more likely to be treated with glucagon-like peptide-1 receptor agonists and less likely to be treated with beta blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, statins and antiplatelets but were just as likely as men treated with diuretics. Again, there was no difference in glucose control between men and women expressed as similar haemoglobin $A_{1c}$ levels.

Regarding echocardiographic measurements, patient experiencing an event had higher LV mass index, thicker septal and posterior walls, increased LV internal diameter and slightly larger left atrial volume indexes. The diastolic measures were more affected at baseline with lower septal and mean e′, higher septal and mean *E*/e′ and a higher fraction of patients with diastolic dysfunction. In addition, all systolic measures were affected at baseline. Stratifying by gender revealed that in women, all structural measures were lower than in men. The mitral inflow velocities, septal and mean *E*/e′ were higher and *E*/*A* ratio, septal and mean e′ were lower in women compared to men. The systolic measures were also more affected in men expressed as lower left ventricular ejection fraction (LVEF), GLS, and GCS rate and a higher proportion of patients with reduced ejection fraction.

The univariable associations with echocardiographic parameters for the entire population and stratified by gender is shown in *Figure 1*. For the entire population, structural measures including LV mass index, LV wall thicknesses, and left atrial volume index were associated with CVD event. Additionally, the diastolic myocardial velocities, their derived measures and all systolic measures were significantly associated with CVD event. Stratifying by gender revealed that of the structural measures, only LV mass index was significantly associated with CVD event for both genders. The diastolic myocardial velocities, their derived measures and the systolic measures LV ejection fraction, GLS and GLS rate were significantly associated with CVD event

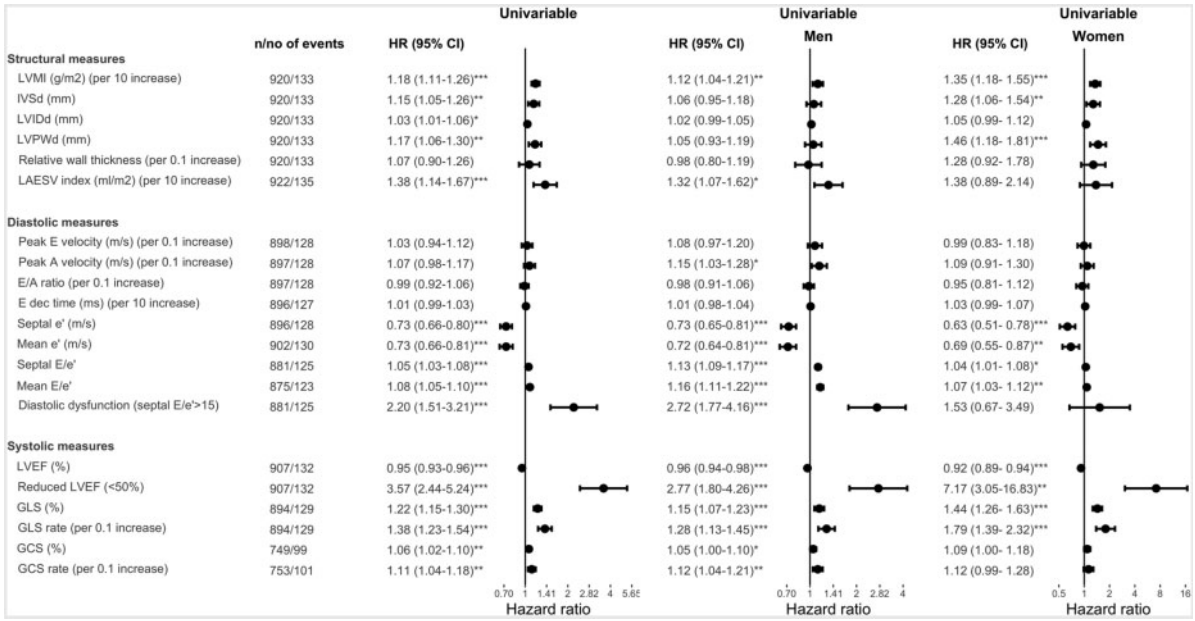


**Figure 1** Univariable associations of echocardiographic parameters and risk of CVD event. Significance levels: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. E, early diastolic inflow velocity; e′, early diastolic myocardial velocity at the level of the mitral annulus; GCS, global circumferential strain; GLS, global longitudinal strain; IVSd, interventricular septum thickness, end-diastolic; LAESV, left atrial end-systolic volume; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter, end-diastolic; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness, end-diastolic; *n*, number of available echocardiographic measurements.

for both genders. Also, excluding patients with known heart disease showed similar results except GLS was not associated with CVD event in men, Supplementary data online, *Figure S1*.

The multivariable analyses are shown in *Table 2*. The results were quite similar to univariable associations for the entire population for Model 1 (adjusted for age, BMI, diabetes duration, systolic blood pressure, and prior CVD), but when stratifying by gender a different pattern emerged: LV mass index was associated with CVD event only in women and GLS and GLS rate only in women. Also, diastolic velocities and their derived measures were stronger associated with the endpoint in men that in women. Further, when adjusting for echocardiographic measures significant in Model 1 (omitting collinear measures), we found that the mean *E*/e′ was the only parameter significantly associated with the endpoint in men and GLS was the only in women. These results were in general repeated when excluding patients with known heart disease however GLS was not associated with CVD event in men, Supplementary data online, *Table S2*. Also, results were similar when excluding patients with prior CVD (data not shown).

When performing competing risk analyses with the Fine-Gray method with non-CVD death as a competing risk, Supplementary data online, *Table S3*, we found similar results. The diastolic measure mean *E*/e′ in men and the systolic measure GLS in women were highly significantly associated with CVD event when considering non-CVD death as a competing risk.

Examining model performances using C-statistics and net reclassification index (*Table 3*), we found that in both univariable and multivariable analyses mean *E*/e′ and GLS had the highest C-statistics and correctly reclassified the highest proportion of the population. Again, in men mean *E*/e′ had the highest C-statistics and correctly reclassified the highest proportion of the patients. In women, on the other hand, we confirmed that GLS was the best predictor with the highest both univariable and multivariable C-statistics. However, LVEF correctly reclassified the highest proportion of patients but with large confidence intervals.

## Discussion

In this paper, we have examined the association of echocardiographic parameters and development of CVD events in a large population of outpatients with Type 2 diabetes. We found that a wide range of parameters including structural, diastolic, and systolic measures were strongly associated with risk of developing CVD. These associations were independent of other established cardiovascular risk factors. The association was strongest for the functional measures of both diastolic and systolic function but also present for structural measures especially left ventricular mass index. The best overall parameter—estimated by highest C-statistic and net reclassification index was mean *E*/e′—a diastolic measure. Importantly, the predictive value of the echocardiographic measurements was modified by gender: In men, the diastolic measures were more strongly associated with CVD events and mean *E*/e′ emerged as the only significant predictor in fully adjusted models including other echocardiographic parameters. In women, however, GLS emerged as the strongest predictor of CVD event and was also the only significant predictor in fully adjusted modes including other echocardiographic parameters.

**Table 2 Multivariable associations of echocardiographic parameters and risk of CVD**

| | All HR (95% CI) | Men HR (95% CI) | Women HR (95% CI) |
|---|---|---|---|
| Model 1 | | | |
| Structural measures | | | |
| LVMI (g/m$^2$) (per 10 increase) | 1.11 (1.04–1.19)** | 1.05 (0.96–1.14) | 1.28 (1.10–1.49)** |
| IVSd (mm) | 1.06 (0.96–1.17) | 0.98 (0.87–1.11) | 1.13 (0.92–1.38) |
| LVIDd (mm) | 1.04 (1.01–1.06)* | 1.02 (0.98–1.05) | 1.06 (0.99–1.13) |
| LVPWd (mm) | 1.08 (0.96–1.21) | 0.96 (0.84–1.10) | 1.35 (1.07–1.71)* |
| LAESV index (mL/m$^2$) (per 10 increase) | 1.16 (0.95–1.43) | 1.08 (0.85–1.37) | 1.25 (0.79–1.97) |
| Diastolic measures | | | |
| Septal e' (m/s) | 0.76 (0.68–0.85)*** | 0.78 (0.69–0.89)*** | 0.61 (0.47–0.79)*** |
| Mean e' (m/s) | 0.79 (0.70–0.89)*** | 0.81 (0.70–0.92)** | 0.71 (0.54–0.94)* |
| Septal *E*/e′ | 1.05 (1.02–1.08)*** | 1.09 (1.05–1.14)*** | 1.03 (0.99–1.08) |
| Mean *E*/e′ | 1.07 (1.04–1.11)*** | 1.14 (1.08–1.21)*** | 1.05 (1.00–1.11)* |
| Diastolic dysfunction (septal *E*/e′ >15) | 1.71 (1.13–2.58)* | 1.89 (1.19–3.01)** | 1.12 (0.44–2.82) |
| Systolic measures | | | |
| LVEF (%) | 0.96 (0.95–0.98)*** | 0.98 (0.96–1.00) | 0.92 (0.89–0.96)*** |
| Reduced LVEF (<50%) | 2.76 (1.85–4.12)*** | 2.09 (1.34–3.27)** | 5.75 (2.12–15.62)*** |
| GLS (%) | 1.16 (1.09–1.24)*** | 1.09 (1.01–1.17)* | 1.39 (1.21–1.60)*** |
| GLS rate (/s) (per 0.1 increase) | 1.22 (1.09–1.37)*** | 1.12 (0.99–1.27) | 1.64 (1.24–2.16)*** |
| GCS (%) | 1.04 (1.01–1.09)* | 1.03 (0.99–1.07) | 1.09 (1.00–1.19) |
| GCS rate (/s) (per 0.1 increase) | 1.07 (1.01–1.14)* | 1.06 (0.98–1.14) | 1.15 (1.00–1.33) |
| Model 2 | | | |
| LVMI (g/m$^2$) (per 10 increase) | 1.02 (0.98–1.07) | 1.01 (0.96–1.06) | 1.02 (0.92–1.12) |
| LVIDd (mm) | 1.02 (0.91–1.13) | 0.99 (0.87–1.12) | 1.15 (0.91–1.46) |
| Mean *E*/e′ | 1.06 (1.03–1.10)*** | 1.15 (1.08–1.21)*** | 1.01 (0.93–1.09) |
| LVEF (%) | 0.99 (0.97–1.02) | 0.99 (0.97–1.02) | 1.01 (0.95–1.08) |
| GLS (%) | 1.10 (1.01–1.20)* | 1.01 (0.92–1.12) | 1.39 (1.14–1.70)** |

Model 1: adjusted for age, body mass index, diabetes duration, systolic blood pressure, and prior ischaemic heart disease. Model 2: as Model 1 and LVMI, LVIDd, Mean *E*/e′, LVEF, and GLS.

CI: confidence interval; E, early diastolic inflow velocity; e′, early diastolic myocardial velocity at the level of the mitral annulus; GCS, global circumferential strain; GLS, global longitudinal strain; IVSd, interventricular septum thickness, end-diastolic; LAESV, left atrial end-systolic volume; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter, end-diastolic; LVMI, left ventricular mass index; LVPWd, left ventricular posterior wall thickness, end-diastolic.

Significance levels: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

## Echocardiography and prognosis in patients with Type 2 diabetes

In this study, we explored the predictive potential of a wide range of echocardiographic parameters and found that both systolic and diastolic measures as well as left ventricular mass index were significantly associated with future CVD events. Before the advent of strain echocardiography, the association of diastolic dysfunction assessed by septal *E*/e′ >15 was examined in a retrospective study of 1760 patients with diabetes by From *et al.*[18] who found that diastolic dysfunction was significantly associated with the risk of developing heart failure. Rather recently, a few studies have included speckle tracking analyses of GLS in their analyses of prognostic echocardiographic markers in patients with Type 2 diabetes and found somewhat conflicting results. Blomstrand *et al.*[19] found that septal *E*/e′ was the strongest predictor of major cardiac events in 512 patients, whereas Liu *et al.*[17] found that GLS had slightly incremental prognostic value in predicting CVD in 247 patients with Type 2 diabetes. In opposition to our and others results, left atrial volume index emerged as the only significant predictor of cardiovascular events after adjusting for clinical and echocardiographic parameters in 305 patients with Type 2 diabetes without known CVD.[30] Our data confirm and expand existing knowledge of predictive power of the echocardiographic parameters in the hitherto largest prospective cohort of patients with Type 2 diabetes. Our data supports the notion that diastolic function is overall the strongest predictor of CVD in outpatients with Type 2 diabetes but also confirms that GLS and left ventricular ejection fraction are strongly associated with future CVD events. On the other hand, our data was not able to confirm left atrial volume index as an independent marker in these patients.

## Gender differences in cardiac structure, function and prognosis in patients with Type 2 diabetes

An important finding in our study was that gender modified the association of echocardiographic parameters and CVD events with diastolic function, *E*/e′, being the strongest predictor in men and systolic function, GLS, the strongest in women. We have previously reported gender differences in the prevalence of echocardiographic

**Table 3 Performance of echocardiographic parameters in predicting the composite endpoint**

| | C-statistics | | Net reclassification index | |
|---|---|---|---|---|
| | Univariable (95% confidence interval) | Multivariable (95% confidence interval) | Model without vs. with echocardiographic measure | |
| All patients | | | Percent (95% confidence interval) | *P*-value |
| Model *without* echocardiographic measures | | 0.70 (0.66–0.75) | | |
| Model including | | | | |
| LVMI | 0.60 (0.55–0.66) | 0.72 (0.68–0.76) | 19.7% (1.1–38.2) | 0.04 |
| Mean *E*/*e*′ | 0.63 (0.58–0.68) | 0.74 (0.70–0.78) | 28.5% (9.4–47.5) | 0.003 |
| LVEF | 0.61 (0.55–0.65) | 0.73 (0.69–0.77) | 26.1% (7.4–44.8) | 0.006 |
| GLS | 0.64 (0.59–0.69) | 0.73 (0.69–0.77) | 29.7% (10.8–48.6) | 0.002 |
| Men | | | | |
| Model *without* echocardiographic measures | | 0.71 (0.66–0.76) | | |
| Model including | | | | |
| LVMI | 0.56 (0.50–0.62) | 0.72 (0.67–0.77) | 1.8% (-18.6 to 22.2) | 0.86 |
| Mean *E*/*e*′ | 0.65 (0.59–0.70) | 0.75 (0.71–0.80) | 26.1% (4.1–48.0) | 0.02 |
| LVEF | 0.58 (0.52–0.65) | 0.73 (0.68–0.77) | 16.5% (-5.0 to 38.1) | 0.13 |
| GLS | 0.59 (0.53–0.66) | 0.72 (0.68–0.77) | 20.7% (-1.1 to 42.6) | 0.06 |
| Women | | | | |
| Model *without* echocardiographic measures | | 0.66 (0.56–0.76) | | |
| Model including | | | | |
| LVMI | 0.69 (0.58–0.80) | 0.74 (0.65–0.84) | 35.8% (-1.4 to 73.0) | 0.06 |
| Mean *E*/*e*′ | 0.67 (0.57–0.78) | 0.72 (0.61–0.83) | 12.7% (-25.0 to 50.5) | 0.51 |
| LVEF | 0.65 (0.53–0.77) | 0.74 (0.65–0.84) | 68.6% (30.6–1.07) | <0.001 |
| GLS | 0.74 (0.64–0.84) | 0.79 (0.70–0.87) | 55.2% (16.6–93.9) | 0.005 |

Model: adjusted for age, body mass index, diabetes duration, systolic blood pressure, and prior cardiovascular disease.
E, early diastolic inflow velocity; *e*′, early diastolic myocardial velocity at the level of the mitral annulus; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

parameters with women tending to have more left ventricular hypertrophy and diastolic dysfunction and men more often had reduced left ventricular ejection fraction, reduced right ventricular function and left atrial enlargement.[23] So, according to our data, while systolic impairment is more prevalent in men, diastolic dysfunction is more predictive and *vice versa* in women. A recent, central study examined clusters of echocardiographic phenotypes in 842 patients with Type 2 diabetes. In this study, three clusters of clinical and echocardiographic phenotypes were identified: men with preserved systolic and diastolic function, women with obesity and diastolic dysfunction and men with LV hypertrophy and systolic dysfunction. The two latter clusters proved to identify persons with increased risk of developing CVD and the authors concluded that cardiac phenotypes identified by echocardiography would aid in risk assessment in these patients underlining the importance of echocardiography in this patient population.[22] Though this study had results somewhat conflicting with ours, as they found that systolic function was predictive in men and diastolic dysfunction was in women, this may not be so conspicuous as the design and performed analyses were quite dissimilar between these studies.

The gender pattern is quite surprising when comparing to other populations. We have previously published, that in the general population, GLS is an independent predictor of heart failure and CVD in general in men but not in women.[21] The same pattern was found in a population of patients with heart failure with reduced ejection fraction where GLS only borderline significantly predicted all-cause mortality in women.[20] Neither of these studies, however, compared up front with measures of diastolic function. These discrepancies might in part be explained by differences in baseline characteristics that persist despite attempts to adjust for the differences. In general, men had a worse cardiovascular risk profile than women and known CVD was more prevalent in this population. Yet, this could not explain why GLS was the strongest predictor in women and a gender specific, intrinsic effect of diabetes is thus suggested by these results. As outlined previously, systolic dysfunction was more prevalent, but diastolic dysfunction was most predictive for future CVD in men with T2D, whereas the opposite was the case in women. Thus, systolic dysfunction, expressed as decreased GLS, might be an early and more benign sign of myocardial involvement and diastolic dysfunction a more severe sign of cardiac involvement in men whereas the opposite might be the case for women. In addition, women with T2D have a relatively higher LV mass compared to men with T2D making 2D speckle tracking of the myocardium more feasible possibly explaining some of the differences between populations.

# Conclusion

In this study, we found that a range of echocardiographic measures independently predicted future CVD events in patients with Type 2 diabetes. These measures included both structural, in particular left ventricular mass index, diastolic, in particular *E*/*e*′, and systolic, left ventricular ejection fraction, and GLS. The best overall measure was mean *E*/*e*′. Importantly, this study identified a hitherto undescribed significant gender interaction with prognosis. While mean *E*/*e*′ was the strongest predictor in men, whereas GLS was the strongest predictor in women supporting a gender specific effect of Type 2 diabetes on the myocardium. These findings underline the usefulness of echocardiography in identifying patients with Type 2 diabetes at increased risk of future CVD.

# Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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