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ARTICLE

Echocardiography improves prediction of major adverse cardiovascular events in a population with type 1 diabetes and without known heart disease: the Thousand & 1 Study

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Abstract

Aims/hypothesis Cardiovascular disease is the most common comorbidity in type 1 diabetes. However, current guidelines do not include routine assessment of myocardial function. We investigated whether echocardiography provides incremental prognostic information in individuals with type 1 diabetes without known heart disease.

Methods A prospective cohort of individuals with type 1 diabetes without known heart disease was recruited from the outpatient clinic. Follow-up was performed through Danish national registers. The association of echocardiography with major adverse cardiovascular events (MACE) and the incremental prognostic value when added to the clinical Steno T1D Risk Engine were examined.

Results A total of 1093 individuals were included: median (interquartile range) age 50.2 (39.2–60.3) years and HbA_{1c} 65 (56–74) mmol/mol; 53% men; and mean (SD) BMI 25.5 (3.9) kg/m^2 and diabetes duration 25.8 (14.6) years. During 7.5 years of follow-up, 145 (13.3%) experienced MACE. Echocardiography significantly and independently predicted MACE: left ventricular ejection fraction (LVEF) <45% ($n = 18$) vs ≥45% ($n = 1075$), HR (95% CI) 3.93 (1.91, 8.08), $p < 0.001$; impaired global longitudinal strain (GLS), 1.65 (1.17, 2.34) ($n = 263$), $p = 0.005$; diastolic mitral early velocity (E)/early diastolic tissue Doppler velocity (e′) <8 ($n = 723$) vs E/e′ 8–12 ($n = 285$), 1.59 (1.04, 2.42), $p = 0.031$; and E/e′ <8 vs E/e′ ≥12 ($n = 85$), 2.30 (1.33, 3.97), $p = 0.003$. In individuals with preserved LVEF ($n = 1075$), estimates for impaired GLS were 1.49 (1.04, 2.15), $p = 0.032$; E/e′ <8 vs E/e′ 8–12, 1.61 (1.04, 2.49), $p = 0.033$; and E/e′ <8 vs E/e′ ≥12, 2.49 (1.41, 4.37), $p = 0.001$. Adding echocardiographic variables to the Steno T1D Risk Engine significantly improved risk prediction: Harrell's C statistic, 0.791 (0.757, 0.824) vs 0.780 (0.746, 0.815), $p = 0.027$; and net reclassification index, 52%, $p < 0.001$.

Conclusions/interpretation In individuals with type 1 diabetes without known heart disease, echocardiography significantly improves risk prediction over and above guideline-recommended clinical risk factors alone and could have a role in clinical care.

Keywords Cardiovascular · Diabetes · Echocardiography · Heart disease · Prognosis · Type 1 diabetes

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Research in context

What is already known about this subject?

- Cardiovascular disease is the most common complication and cause of death among people with type 1 diabetes
- Early identification of individuals with type 1 diabetes who are at particular risk of developing heart disease is of pivotal importance
- There are currently no recommendations to assess myocardial function in routine clinical care for type 1 diabetes

What is the key question?

- Can echocardiography improve the prediction of prognosis in individuals with type 1 diabetes, and without known heart disease, receiving care from an outpatient clinic?

What are the new findings?

- The addition of echocardiography to clinical risk factors significantly improved the prediction of prognosis vs clinical risk factors alone in individuals with type 1 diabetes and without known heart disease, followed up for 7.5 years for major adverse cardiovascular events (MACE)
- Echocardiography also significantly predicted MACE in individuals with type 1 diabetes and preserved ejection fraction

How might this impact on clinical practice in the foreseeable future?

- Echocardiography could have a place in clinical follow-up in type 1 diabetes. Further studies are needed to address the effectiveness and cost-benefit of adding echocardiography to routine clinical care for people with type 1 diabetes

Abbreviations

CABG	Coronary artery bypass graft
CVD	Cardiovascular disease
e′	Early diastolic tissue Doppler velocity
E	Early mitral peak diastolic velocity
GLS	Global longitudinal strain
IDI	Integrated discrimination improvement
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
NRI	Net reclassification index
PCI	Percutaneous coronary intervention
UAER	Urinary AER

Introduction

Cardiovascular disease (CVD) is the most common complication and cause of death [1] in individuals with type 1 diabetes [1]. Overall, CVD mortality is increased between 6- and 12-fold compared with the general population [2] and, in individuals under the age of 40 years, the risk is increased up to 40-fold [3]. There is an increased incidence and prevalence of type 1 diabetes. In Europe and most other parts of the world, the incidence of type 1 diabetes is increasing by approximately 3% per year [4]; in the USA, it has been estimated that 0.5% of the population have type 1 diabetes [5], corresponding to 10% of all US individuals with diabetes. For these reasons, there has been a call to action from European and American health organisations in diabetes and cardiology to increase the focus on prevention of CVD in type 1 diabetes [1, 6].

Despite the increased risk of CVD in type 1 diabetes, risk assessment consists predominantly of evaluation of conventional risk factors [7]. As such, there is currently no routine assessment of myocardial function in standard outpatient care in stable type 1 diabetes [8]. Imaging by echocardiography, a key examination in the assessment of myocardial function, may add important information for identifying individuals at risk. Echocardiography can be performed in an outpatient setting and, unlike other cardiac imaging modalities, irrespective of the presence of insulin pumps, prostheses or other devices, without concerns for claustrophobia and with no exposure to radiation.

The purpose of this study was to evaluate the prognostic importance of performing echocardiography in a type 1 diabetes population without known heart disease using the Thousand & 1 Study cohort, recruited through the outpatient clinic of Steno Diabetes Center Copenhagen. We hypothesised that common echocardiographic variables of myocardial function would, first, be associated with an increased risk of adverse events and, second, that echocardiography would improve prediction of adverse events beyond conventional clinical risk factors alone.

Methods

Study population

The Thousand & 1 Study started as a cross-sectional planned longitudinal observation cohort study of individuals with type 1 diabetes without known heart disease. Individuals were included from the Steno Diabetes Center Copenhagen and examined at the Department of Cardiology, Copenhagen University Hospital Herlev-Gentofte.

Invitation, screening and inclusion of individuals started on 1 April 2010 and was completed on 1 April 2012. Individuals were eligible if they were: 18 years or older; attending the outpatient clinic at Steno Diabetes Center Copenhagen; diagnosed with type 1 diabetes; without known heart disease; and willing to participate. Known heart disease was defined as: heart failure; coronary artery disease, including previous myocardial infarction, stable angina, previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG); atrial fibrillation or atrial flutter; left bundle branch block; congenital heart disease; or pacemaker or implantable cardioverter-defibrillator implantation. No financial compensation was offered to individuals for their participation. The study population and study visit schedule have been described in detail elsewhere [9–12]. The study was performed in accordance with the second Declaration of Helsinki and approved by the regional ethics committee (H-3-2009-139) and the Danish Data Protection Agency (00934-Geh-2010-003). All participants completed a study questionnaire and gave written informed consent.

Echocardiography

Echocardiography was performed with a General Electric Vivid 7 Dimension imaging system device (GE Vingmed Ultrasound, Horten, Norway) with a 3.5 MHz transducer, in accordance with recommendations from the European Association of Echocardiography/American Society of Echocardiography [13]. Echocardiographic examinations were read and analysed using General Electric EchoPAC software (BT11).

Three consecutive heart cycles were recorded. Left ventricular ejection fraction (LVEF) was determined by Simpson's biplane method. Pulsed-wave Doppler was performed in the apical four-chamber view with the sample volume placed between the mitral leaflet tips to obtain diastolic mitral early velocity (E) wave. Pulsed-wave early diastolic tissue Doppler velocity (e′) values were determined from the apical four-chamber view at the lateral region of the mitral annulus [14]. Left ventricular global longitudinal strain (GLS) was measured using two-dimensional speckle-tracking. The method, including inter- and intra-observer variability, has been described in detail elsewhere [10, 15, 16]. For the present analysis, GLS was determined as the average of the three apical views, which were available for analysis in 1065 individuals, thus excluding 28 individuals (2.6%).

In the present study, common echocardiographic variables were defined to assess gross systolic dysfunction (LVEF), discrete systolic dysfunction (GLS) and discrete and gross diastolic dysfunction (E/e′). Gross systolic dysfunction was defined as LVEF <45% and preserved ejection fraction as LVEF ≥45% [9, 17]. GLS was stratified into sex-specific quartiles and the highest GLS quartile defined as impaired. The cut-offs were GLS >−16.0% in men and GLS >−17.4% in women, similar to cut-offs used in other echo labs [18]. Estimated left ventricular filling pressure, as a measure of diastolic dysfunction, was categorised into three groups: no/low, E/e′ <8; discrete/moderate, E/e′ 8–12; and gross/high, E/e′ ≥12 [14].

Biochemistry

Information about biochemistry such as HbA_{1c}, p-creatinine and albuminuria status was collected from electronic patient records at Steno Diabetes Center Copenhagen. Urinary AER (UAER) was measured from sterile urine samples collected over 24 h by enzyme immunoassay. Participants were categorised as normoalbuminuric if UAER was <30 mg/24 h in two out of three consecutive measurements, microalbuminuric if UAER was 30–299 mg/24 h and macroalbuminuric if UAER ≥300 mg/24 h. HbA_{1c} was measured by HPLC (normal range 21–46 mmol/mol [4.1–6.4%]; Variant, Bio-Rad Laboratories, Munich, Germany) and serum creatinine concentration by an enzymatic method (Hitachi 912, Roche Diagnostics, Mannheim, Germany). Estimated GFR was calculated by the Modification of Diet in Renal Disease (MDRD) method [19].

Independent variables

The Steno T1D Risk Engine [7] is a validated risk model to predict risk of first CVD event in type 1 diabetes; it has been demonstrated to be superior to other CVD risk-prediction models in type 1 diabetes [7]. The Steno T1D Risk Engine includes ten clinical conventional risk factors including age, sex, duration of diabetes, systolic BP, LDL-cholesterol, HbA_{1c}, albuminuria (normo-, micro and macroalbuminuria), eGFR, smoking (ever smoker) and physical activity (light, moderate, high) (Table 1). In the present study, these ten clinical characteristics were included in the multivariable models. Furthermore, the Steno T1D Risk Engine variables were used as the baseline model when testing the incremental prognostic performance of adding the echocardiographic variables.

Endpoints and follow-up

A major cardiovascular adverse event (MACE) was defined as the composite endpoint of the first occurring incident of death

Table 1 Demographics of study participants

Characteristic	All	No MACE	MACE	*p* value
Clinical and medication				
n	1093	948	145	
Age, years, median (IQR)	50.2 (39.2–60.3)	48.6 (38.1–58.4)	60.4 (52.0–68.7)	<0.001
Sex, male (%)	575 (52.6)	486 (51.3)	89 (61.4)	0.023
Diabetes duration, years, mean (SD)	25.8 (14.6)	24.5 (14.2)	34.2 (14.6)	<0.001
BMI, kg/m^2, mean (SD)	25.5 (3.9)	25.6 (3.9)	25.3 (4.2)	0.46
HbA_{1c}, mmol/mol, median (IQR)	65 (56–74)	64 (56–73)	66 (58–77)	0.032
HbA_{1c}, %, median (IQR)	8.1 (7.3–8.9)	8.0 (7.3–8.8)	8.2 (7.5–9.2)	0.032
Ever smoker (%)	614 (56.2)	511 (53.9)	103 (71.0)	<0.001
Systolic BP, mmHg, mean (SD)	133.3 (16.4)	132.3 (15.6)	140.3 (19.7)	<0.001
Physical activity 0–3 h/week (%)	363 (33.2)	303 (32.0)	60 (41.4)	0.070
Physical activity 3–7 h/week (%)	531 (48.6)	467 (49.3)	64 (44.1)	
Physical activity >7 h/week (%)	199 (18.2)	178 (18.8)	21 (14.5)	
LDL-cholesterol, mmol/l, mean (SD)	2.6 (0.8)	2.6 (0.8)	2.5 (0.8)	0.085
eGFR, ml min^{-1} [1.73 m]$^{-2}$, mean (SD)	87.4 (22.3)	88.9 (21.6)	77.8 (24.6)	<0.001
eGFR <60 ml min^{-1} [1.73 m]$^{-2}$ (%)[a]	112 (10.3)	81 (8.6)	31 (21.5)	<0.001
Normoalbuminuria (%)	760 (69.5)	692 (73.0)	68 (46.9)	<0.001
Microalbuminuria (%)	227 (20.8)	178 (18.8)	49 (33.8)	
Macroalbuminuria (%)	106 (9.7)	78 (8.2)	28 (19.3)	
Statin (%)	475 (43.5)	373 (39.3)	102 (70.3)	<0.001
Beta blockers (%)	50 (4.6)	25 (2.6)	25 (17.2)	<0.001
ACE or ATII inhibitors (%)	503 (46.0)	397 (41.9)	106 (73.1)	<0.001
Diuretics (%)	285 (26.1)	213 (22.5)	72 (49.7)	<0.001
Echocardiography				
LVEF <45% (%)	18 (1.6)	9 (0.9)	9 (6.2)	<0.001
LVEF, %, mean (SD)	57.6 (5.4)	57.7 (5.2)	56.9 (6.8)	0.096
E/e′ <8 (%)	723 (66.1)	673 (71.0)	50 (34.5)	<0.001
E/e′ 8–12 (%)	285 (26.1)	225 (23.7)	60 (41.4)	
E/e′ >12 (%)	85 (7.8)	50 (5.3)	35 (24.1)	
GLS, %, mean (SD)	−18.3 (2.6)	−18.4 (2.5)	−17.3 (2.8)	<0.001
Impaired GLS (highest quartile) (%)[b]	263 (24.7)	206 (22.3)	57 (40.4)	<0.001
Endpoints				
MACE, composite (%)	145 (13.3)	NA	145 (100.0)	NA
Death (%)	65 (5.9)	NA	65 (44.8)	NA
ACS (%)	23 (2.1)	NA	23 (15.9)	NA
PCI or CABG (%)	37 (3.4)	NA	37 (25.5)	NA
Heart failure, admission (%)	9 (0.8)	NA	9 (6.2)	NA
Stroke (%)	52 (4.8)	NA	52 (35.9)	NA

[a] Three individuals without eGFR data

[b] 28 individuals without GLS data

ACS, acute coronary syndrome; ATII, angiotensin II; IQR, interquartile range; NA, not applicable

from all causes ($n = 65$), hospital admission for acute coronary syndromes (ICD-10 [http://apps.who.int/classifications/icd10/browse/2016/en]: DI20–22) ($n = 23$), cardiac revascularisation (PCI or CABG) (ICD-10: KFN) ($n = 37$), hospital admission for heart failure (ICD-10: DI50–51; DI42; DI11) ($n = 9$) or stroke (ICD-10: DI60–68; DG45) ($n = 52$). The first event to occur was death in 45 participants, acute coronary syndrome in 18 participants, heart failure in six participants, revascularisation in 28 participants and stroke in 50 participants. Follow-up was 100% complete.

At the inclusion phase of the Thousand & 1 Study, participants with gross myocardial dysfunction assessed with the echocardiography were referred for further cardiac evaluation in the outpatient clinic with a tentative diagnosis. To decrease the risk of

bias in the assessment of endpoints, only hospital admissions and not outpatient diagnoses were included. Information about vital status and incident events were collected up to 1 October 2017 from the Danish National Health and Mortality registers. Vital status was collected from the Central Person Register and admission and procedure codes were collected from the National Patient Register. Data on cause of death were incomplete because of delay in the national registers and were not used in the present study. Investigators were blinded to endpoints and biochemistry during echocardiographic image analysis as the analysis was performed prior to the collection of outcome data.

Statistical analysis

All analyses were performed with STATA 15.1 (StataCorp, TX, USA). Categorical variables were analysed with the χ^2 test and continuous variables with ANOVA or Student's *t* test.

The associations between common echocardiographic measures (LVEF, GLS and E/e′) and MACE were analysed in Cox proportional hazards models. The proportional hazards assumption was tested using log–log Kaplan–Meier and Cox survival rate estimates plotted against time and was found to be met. Both crude and multivariable analyses including variables from the Steno T1D Risk Engine were performed. In some analyses, the number of variables included were relatively large compared with the number of endpoints; however, potential overfitting would draw the findings toward the null hypothesis and this was therefore accepted [20]. As a sensitivity analysis, a reduced model was performed that included only the variable of interest, age, sex and degree of albuminuria. As shown in the electronic supplementary material (ESM; ESM Tables 1–4), the estimates were in the same magnitude as the full models. Furthermore, to assess the prognostic accuracy of the echocardiographic variables, Harrell's C statistic was calculated for the Steno T1D Risk Engine alone and following addition of echocardiographic variables. Also, the continuous net reclassification index (NRI) and relative integrated discrimination improvement (IDI), which are developed to assess the improvement in prediction when adding information to prediction models, were calculated [21, 22]. The full models are shown in ESM Tables 5–9. To study population subgroups of particular risk of MACE, a separate reduced logistic regression model was performed that included only significant conventional predictors of MACE. HbA_{1c} values were stratified by age group to allow clinical interpretability. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 1093 individuals with type 1 diabetes were included, 575 of whom were men (53%). The median (IQR) age was 50.2 (39.2–60.3) years, median HbA_{1c} was 65 mmol/mol (8.1%) and mean diabetes duration was 25.8 years. During 7.5 years (median 6.5 years) of follow-up, 145 individuals experienced MACE. Individuals experiencing MACE were more likely to be older, smokers, have higher BP and worse kidney function, including greater degree of albuminuria, and were more likely to be receiving reno- or cardioprotective medication (see Table 1). In terms of echocardiographic characteristics, individuals experiencing an event had overall slightly, non-significantly, lower LVEF, though the mean was well within the normal limits, with higher E/e′, indicating higher prevalence of diastolic dysfunction, and worse GLS.

Echocardiography and association with prognosis

Type 1 diabetes population without known heart disease

Figures 1, 2 and 3 and Table 2 show the associations between echocardiographic variables and the risk of MACE during follow-up in the whole study population. As shown, in both univariable and multivariable models, echocardiographic characteristics were highly significantly associated with adverse events. Thus, impaired LVEF was, after multivariable adjustment, associated with an almost fourfold increased risk of MACE (Table 2). E/e′ was associated with increased risk in a dose–response relationship, in which moderately elevated E/e′ was associated with a 59% increased risk and high E/e′ was associated with more than twofold increased risk. Impaired GLS was associated with a 65% increased risk of a MACE.

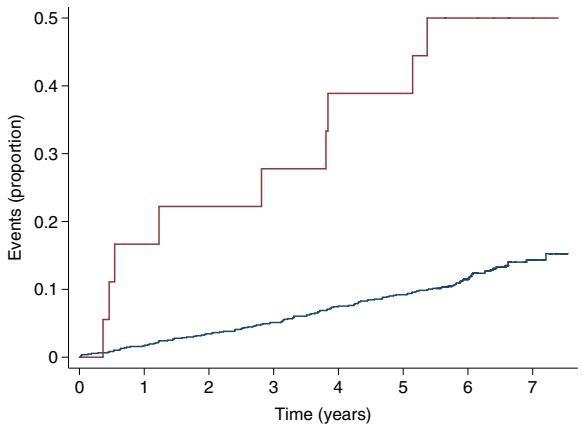

Fig. 1 The association between LVEF below or above 45% and MACE in individuals with type 1 diabetes and without known heart disease followed at the outpatient clinic of Steno Diabetes Center Copenhagen ($n = 1093$). In these individuals, LVEF <45% was not a common finding (1.6%) but was associated with a highly increased risk of MACE. Logrank $p < 0.001$. Blue, LVEF ≥45% ($n = 1075$); red, LVEF <45% ($n = 18$)

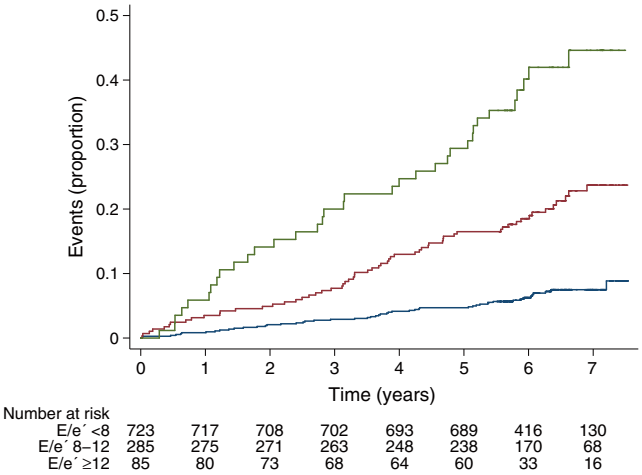

Fig. 2 The association between E/e′, an estimate of left ventricular filling pressure and diastolic dysfunction, and MACE in individuals with type 1 diabetes and without known heart disease followed at the outpatient clinic of Steno Diabetes Center Copenhagen ($n = 1093$). E/e′ was highly significantly associated with increased risk of MACE in a dose-dependent relationship. Logrank $p < 0.001$. Blue, E/e′ <8 ($n = 723$); red, E/e′ 8–12 ($n = 285$); green, E/e′ ≥12 ($n = 85$)

Type 1 diabetes population with preserved ejection fraction

To examine the relationship between echocardiographic characteristics and prognosis in individuals with preserved LVEF, we performed the analyses restricting the population to participants with LVEF ≥45% ($n = 1075$). ESM Figs 1 and 2 show the relationship between E/e′, GLS and prognosis in these individuals with type 1 diabetes without known heart disease and with preserved ejection fraction. ESM Fig. 3 shows all four quartiles of GLS and their association with prognosis. As shown in Table 2, both E/e′ and GLS were highly significantly associated with increased risk, with estimates essentially unchanged compared with the analyses including the whole population. As shown in Table 1, the risk of MACE was increased by 61% with moderate E/e′ and 2.5-fold increased for high E/e′. For GLS, an impaired GLS was associated with a 49% increased risk of MACE in individuals with preserved LVEF after multivariable adjustment.

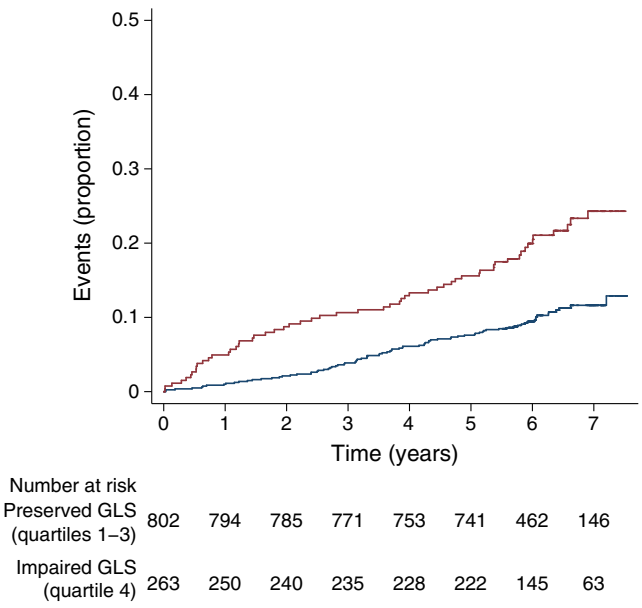

Fig. 3 The association between impaired GLS, estimated as the worst sex-specific quartile (men GLS >−16%; women GLS >−17.4%), and MACE in individuals with type 1 diabetes and without known heart disease followed at the outpatient clinic of Steno Diabetes Center Copenhagen ($n = 1065$). Impaired GLS was highly significantly associated with increased risk of MACE. Logrank $p < 0.001$. Blue, preserved GLS (quartiles 1–3), ($n = 802$); red, impaired GLS (quartile 4), ($n = 263$)

Incremental value of echocardiography in prediction of prognosis The addition of echocardiography to the validated Steno T1D Risk Engine significantly improved the prediction of prognosis in individuals with type 1 diabetes and without known heart disease.

As shown in Table 3, the addition of information about LVEF <45% increased Harrell's C statistic compared with the estimate from the Steno T1 Risk Engine, but not significantly; this could be explained by the low number of individuals with LVEF <45%. This is also reflected in the NRI estimate, which was insignificant, whereas the addition of IDI showed significant improvement in the discrimination slope. The addition of E/e′ significantly increased all measures of improvement of risk prediction. GLS did not significantly increase the AUC but significantly improved both NRI and IDI.

The inclusion of information on ejection fraction, E/e′ and GLS significantly improved risk prediction across all risk improvement variables. In this analysis, abnormal echocardiography was defined as LVEF <45% and/or E/e′ ≥8 and/or impaired GLS.

When examining individuals with preserved LVEF (Table 3), estimates were essentially similar, displaying improvements in risk prediction from inclusion of measures of subclinical diastolic and systolic dysfunction.

Populations at particular risk Table 4 shows the risk estimates for subgroups of the population in both crude and mutually adjusted multivariable models. As shown, risk of MACE increased greatly with increase in age, increasing up to tenfold in individuals over 60 years of age. Male sex, albuminuria and eGFR below 60 ml min^{-1} 1.73^{-2} increased risk of MACE, whereas HbA_{1c} was only modestly associated with risk.

Discussion

In the present study, individuals with type 1 diabetes without known heart disease were included from the outpatient clinic

Table 2 Association between echocardiography and MACE in type 1 diabetes without known heart disease

Variable	*n*	Events	Crude			Multivariable[a]		
			HR	95% CI	*p*	HR	(95% CI)	*p*
Whole population (*n* = 1093)								
LVEF <45% vs ≥45%	1093	145	5.21	2.66, 10.25	<0.001	3.93	1.91, 8.08	<0.001
E/e′ <8	723	50	1 (ref.)	NA	NA	1 (ref.)	NA	NA
E/e′ 8–12	285	60	3.20	2.20, 4.65	<0.001	1.59	1.04, 2.42	0.031
E/e′ ≥12	85	35	7.28	4.72, 11.21	<0.001	2.30	1.33, 3.97	0.003
Impaired GLS (*n* = 263) vs preserved GLS (*n* = 802)	1065	141	2.18	1.56, 3.06	<0.001	1.65	1.17, 2.34	0.005
Abnormal echo[b] (*n* = 518)	1093	145	3.46	2.38, 5.02	<0.001	1.70	1.12, 2.58	0.013
Population with preserved ejection fraction (LVEF ≥45%) (*n* = 1075)								
E/e′ <8	714	47	1 (ref.)	NA	NA	1 (ref.)	NA	NA
E/e′ 8–12	279	56	3.17	2.15, 4.67	<0.001	1.61	1.04, 2.49	0.033
E/e′ ≥12	82	33	7.47	4.78, 11.66	<0.001	2.49	1.41, 4.37	0.001
Impaired GLS (*n* = 246) vs preserved GLS (*n* = 802)	1048	133	1.98	1.39, 2.82	<0.001	1.49	1.04, 2.15	0.032
Abnormal echo[c] (*n* = 500)	1075	136	3.26	2.23, 4.75	<0.001	1.61	1.05, 2.45	0.028

[a] Adjusted for variables in the Steno T1 Risk Engine: age, sex, diabetes duration, systolic BP, LDL-cholesterol, HbA_{1c}, albuminuria (normo-, micro-, macroalbuminuria), eGFR, smoking, leisure-time physical activity (low, moderate, high)

[b] Abnormal echo defined as LVEF < 45% and/or E/e′ ≥ 8 and/or impaired GLS (> −16% for men; > −17.4% for women)

[c] Abnormal echo defined as E/e′ ≥ 8 and/or impaired GLS (> −16% for men; > −17.4% for women)

Echo, echocardiography; NA, not applicable; ref., reference

and followed for more than 7 years for MACE. To the best of our knowledge, this is the first study to prospectively assess the use of echocardiography in prediction of prognosis in type 1 diabetes without known heart disease. We find that common established echocardiographic measures of myocardial function are significantly associated with increased risk of MACE, and that these echocardiographic parameters improve the early identification of individuals at risk above and beyond

Table 3 Incremental prognostic value of echocardiography in addition to clinical risk factors in type 1 diabetes without known heart disease for MACE

Population	C statistic			NRI – continuous		IDI – relative	
	Value	95% CI	*p* value	Reclassification, %	*p* value	Reclassification, %	*p* value
Whole (*n* = 1093)							
Steno T1D Risk Engine model[a]	0.780 (Ref.)	0.746, 0.815	Ref.	Ref.	NA	Ref.	NA
Steno T1D Risk Engine model + LVEF 45%	0.789	0.752, 0.822	0.107	−8	0.81	10.2	0.035
Steno T1D Risk Engine model + E/e′ ≥8	0.794	0.761, 0.827	0.008	34	<0.001	9.0	0.012
Steno T1D Risk Engine model + GLS (highest quartile)	0.786	0.752, 0.820	0.277	36	<0.001	6.6	0.025
Steno T1D Risk Engine model + abnormal echo[b]	0.791	0.757, 0.824	0.027	52	<0.001	4.5	0.036
With preserved LVEF (LVEF ≥45%) (*n* = 1075)							
Steno T1D Risk Engine model[a]	0.781 (ref.)	0.747, 0.815	NA	Ref.	NA	Ref.	NA
Steno T1D Risk Engine model + E/e′	0.794	0.761, 0.827	0.016	36.0	<0.001	10.1	0.008
Steno T1D Risk Engine model + GLS	0.786	0.752, 0.820	0.247	29.8	0.015	6.4	0.098
Steno T1D Risk Engine model + abnormal echo[c]	0.790	0.756, 0.823	0.031	49.0	<0.001	4.6	0.076

[a] Steno T1 Risk Engine: age, sex, diabetes duration, systolic BP, LDL-cholesterol, HbA_{1c}, albuminuria (normo-, micro-, macroalbuminuria), eGFR, smoking, leisure-time physical activity (low, moderate, high)

[b] Defined as LVEF < 45% and/or E/e′ ≥ 8 and/or impaired GLS

[c] Defined as E/e′ ≥ 8 and/or impaired GLS

Echo, echocardiography; NA, not applicable; ref., reference

Table 4 Clinical variables significantly associated with MACE (logistic regression)

Variable	Number of events/ subgroup ($n = 1093$)	Crude			Mutually adjusted		
		OR	95% CI	*p*	OR	(95% CI)	*p*
Age group, years							
<40	8/282	1 (ref.)	NA	NA	1 (ref)	NA	NA
40–49	26/231	3.85	1.71, 8.68	0.001	3.08	1.35, 7.04	0.008
50–59	47/224	7.19	3.33, 15.52	<0.001	6.03	2.75, 13.24	<0.001
>60	72/211	11.69	5.51, 24.80	<0.001	9.98	4.60, 21.63	<0.001
Male sex	95/480	1.57	1.11, 2.23	0.012	1.61	1.10, 2.35	0.014
HbA_{1c} quartile, mmol/mol (%)							
<57 (<7.3)	27/279	1 (ref.)	NA	NA	1 (ref.)	NA	NA
57–65 (7.3–8.1)	51/304	1.88	1.14, 3.10	0.013	1.90	1.12, 3.22	0.017
66–74 (8.2–8.9)	34/258	1.42	0.83, 2.42	0.203	1.18	0.67, 2.10	0.57
>75 (>9.0)	41/252	1.81	1.08, 3.05	0.025	2.05	1.17, 3.62	0.013
Albuminuria							
Normoalbuminuria	71/760	1 (ref.)	NA	NA	1 (ref.)	NA	NA
Microalbuminuria	50/227	2.74	1.84, 4.08	<0.001	1.92	1.25, 2.92	0.003
Macroalbuminuria	32/106	4.20	2.59, 7.79	<0.001	2.60	1.48, 4.66	0.001
eGFR <60 mL min^{-1} 1.73 m^{-2}	35/112	3.34	2.15, 5.21	<0.001	1.81	1.07, 3.06	0.028

NA, not applicable; ref., reference

conventional clinical risk factors alone. Together, our findings suggest that echocardiography added to the standard clinical follow-up in type 1 diabetes is a feasible method for detecting early myocardial dysfunction and identifying individuals at particular risk of adverse events.

Ischaemic heart disease and heart failure are both common in type 1 diabetes. Echocardiography cannot directly assess coronary pathology, but conventional echocardiography can detect gross myocardial function and Doppler echocardiography (e.g. E/e′) and speckle-tracking echocardiography (GLS) can detect subtle myocardial dysfunction. The most well-recognised heart disease in diabetes is the premature development of coronary atherosclerosis, which leads to ischaemic heart disease [23]. However, a subset of heart disease in diabetes has been proposed, diabetic cardiomyopathy, which can lead to diastolic and systolic heart failure [24–26]. Haemodynamic and biomechanical evidence of a diabetic cardiomyopathy comes primarily from Doppler echocardiography, indicating premature diastolic dysfunction [27–34], and, in the later stages, affected systolic function [35, 36]. Whereas late changes in systolic function can be detected by conventional echocardiography, early subclinical changes, whether from vascular or myocardial dysfunction, can only be detected by sensitive echocardiographic techniques such as E/e′ and GLS. In the present study, reduced ejection fraction, defined as LVEF <45%, was not a common finding (1.6%) but carried a fourfold increased risk of MACE compared with individuals with preserved LVEF. In individuals with preserved LVEF, elevated E/e′, an estimate of diastolic dysfunction, was common and carried a highly significantly increased risk of MACE. Most individual incident endpoints were all-cause mortality or atherosclerotic, whereas heart failure admissions were not common. It is possible that this pattern is explained by the relatively young study population and will change as follow-up time increases.

The Steno T1D Risk Engine has been demonstrated to be superior to other risk models in type 1 diabetes [7] and was used as the baseline model in the risk-prediction analyses. In situations where the baseline C-statistic is high, it can be difficult to improve the model when adding a new variable. NRI and IDI may therefore carry more information and were, in most cases, highly significant when echocardiography was added to traditional risk factors [22, 37]. Adding only LVEF to the model did not significantly improve prognosis, which may seem counterintuitive considering the highly increased risk estimate from the time-to-event data, but this is explained by the low prevalence of grossly reduced ejection fraction in the present cohort. In contrast, the addition of elevated E/e′, the hallmark of diabetic cardiomyopathy, improved risk prediction significantly. Subclinical impairment of systolic function, GLS, was highly significantly associated with increased risk and also improved risk prediction as measured using NRI and IDI but not Harrell's C statistic. Including LVEF, E/e′ and GLS with the Steno T1D Risk Engine significantly improved prediction.

While there are currently no guidelines for treating early impairment in myocardial dysfunction, the present findings suggest that it is feasible to use echocardiography for the early

detection of individuals at risk. In particular E/e′ >12 is robustly associated with future outcomes, even in individuals with preserved ejection fraction. This could therefore serve as a threshold for identifying high-risk individuals with relevant diastolic dysfunction. E/e′ 8–12 was also associated with increased risk and might identify individuals of intermediate risk. Furthermore, we identified subgroups of particular risk of MACE based from conventional risk factors in the clinical setting (Table 4). Risk increased in a dose–response dependent manner with age and other known risk factors, such as albuminuria, male sex and low eGFR. The timing of echocardiography in life-long clinical follow-up in type 1 diabetes may therefore be tailored to individual risk factors, such as age above a certain limit or presence of albuminuria. Future studies will have to address cost-benefit and other health policy implications of echocardiographic screening in risk populations.

Possible limitations should be considered. First, downstream testing from the initial echocardiography could have affected the treatment of individuals and thus affected the outcomes. However, only hospital admissions were included in the follow-up and referrals would only play a role in the initial months after the echocardiography. Moreover, the findings were unchanged by excluding individuals with reduced LVEF, thereby suggesting a minimal role of downstream testing. Second, the cause of death was not known because of delay in the administrative registration and participants could therefore have died of non-cardiovascular causes. Third, the echocardiographic definitions of myocardial dysfunction may differ between echocardiography laboratories. For instance, in the present study, impaired GLS was defined as the worst 25% of the population and was therefore population specific. Additionally, in the present study, LVEF <45% was defined as reduced [9]. Only four participants had LVEF <40% (0.4%) and excluding participants with LVEF <45% did not change the results, corroborating the robustness of the findings. Fourth, the majority of the population was also included in the derivation cohort of the Steno T1D Risk Engine. Findings should therefore be validated in other cohorts. Fifth, the type 1 diabetes population in the Thousand & 1 Study, who are being followed over their lifetimes at the Steno Diabetes Center Copenhagen, may have a better risk profile compared with other type 1 diabetes populations. This would, however, draw the findings toward the null hypothesis and therefore cannot explain the findings.

In summary, CVD is the most important complication in type 1 diabetes and the risk of a MACE is greatly increased compared with the background population. This observation has led to a call for action from leading cardiology and diabetes associations. However, so far, best practice guidelines for the monitoring of people with type 1 diabetes do not include echocardiography or any other regular examination of the heart. In the present study of 1093 individuals with type 1 diabetes without known heart disease, we found that echocardiography was a significant predictor of MACE during more than 7 years of follow-up. Gross myocardial systolic dysfunction with reduced LVEF was not common but was associated with a greatly increased risk of MACE. Subclinical myocardial dysfunction measured with E/e′ was prevalent and associated with highly increased risk of a MACE. Furthermore, the addition of LVEF, GLS and E/e′ to the validated Steno T1D Risk Engine, which includes common clinical variables, significantly and incrementally improved prediction of MACE.

To conclude, echocardiography is a non-invasive examination that significantly improves early detection of myocardial dysfunction and predicts prognosis in a population of individuals with type 1 diabetes without known heart disease.

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Contribution statement MTJ made substantial contributions to the conception and design of the work, the acquisition, analysis and interpretation of data and drafting the manuscript and revising it critically for important intellectual content. MTJ gave final approval of the version to be published. MTJ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. PS, HUA, TA and PR made substantial contributions to the conception and design of the work and interpretation of data; they revised the manuscript critically for important intellectual content and gave final approval of the version to be published. IG, JB, TFH, TA, ST, TB-S, PGJ and SG made substantial contributions to the acquisition and interpretation of data, revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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