ORIGINAL ARTICLE

Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode in the general population

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ABSTRACT
Objective Tissue Doppler imaging (TDI) M-mode through the mitral leafllet is an easy and precise method to estimate the cardiac time intervals. The aim was to evaluate the usability of the cardiac time intervals in predicting major cardiovascular events (MACE) in the general population.

Methods In a large prospective community-based study, cardiac function was evaluated in 1915 participants by both conventional echocardiography and TDI. The cardiac time intervals, including the isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT) and ejection time (ET), were obtained by TDI M-mode through the mitral leafllet. IVCT/ET, IVRT/ET and the myocardial performance index (MPI=IVRT+IVCT/ET) were calculated.

Results During follow-up (median 10.8 years), 383 (20%) participants reached the combined endpoint MACE (ischaemic heart disease, heart failure or cardiac death). After multivariable adjustment for clinical predictors and conventional echocardiography, only the combined indexes, including information on both systolic and diastolic performance (IVRT/ET and MPI), remained significant prognosticators (p<0.05 for both). Adding IVRT/ET or MPI to a model already including all other echocardiographic parameters resulted in a significant increase in the c-statistics (0.76 vs 0.75 p<0.01 for both). IVRT/ET or MPI improved reclassification significantly when added to the clinical predictors (p<0.05 for both).

Conclusions In the general population, the combined cardiac time intervals that include information on both systolic and diastolic function in one index (IVRT/ET and MPI) are not only powerful and independent predictors of future MACE, but provide additional prognostic information to clinical and conventional echocardiographic measures of systolic and diastolic function.

INTRODUCTION
Preservation of normal cardiac time intervals is intimately related to normal cardiac physiology. In the ailing myocardium, the cardiac time intervals will change during disease progression. As LV systolic function deteriorates, the time it takes for myocardial myocytes to achieve an LV pressure equal to that of aorta increases, resulting in a prolongation of isovolumic contraction time (IVCT). Furthermore, the ability of myocardial myocytes to maintain the LV pressure decreases, resulting in reduction in the ejection time (ET). As LV diastolic function declines further, early diastolic relaxation proceeds more slowly, explaining the prolongation of isovolumic relaxation time (IVRT). Consequently, the IVRT/ET and the myocardial performance index (MPI), defined as (IVRT+IVCT)/ET, will detect cardiac dysfunction with an increase, irrespective of whether the LV is suffering from impaired systolic or diastolic function. The MPI increases even in patients with severe diastolic dysfunction with a restrictive filling pattern, which is seen as a short IVRT time. This is attributable to the increase in IVCT or decrease in ET, illustrating the subtle impaired systolic function identified by novel echocardiographic parameters that is found in patients with severe diastolic dysfunction, even though they display a preserved LV ejection fraction. Therefore, cardiac time intervals, especially combined indexes containing information on both systolic and diastolic performance (IVRT/ET and MPI), may be useful to identify subtle impairments in cardiac function (both systolic and diastolic) in the general population, which are unnoticed by conventional echocardiography. These echocardiographic parameters may thus identify patients in high risk of future fulminant cardiovascular disease.

The novel method of obtaining the global cardiac time intervals, by using tissue Doppler imaging (TDI) M-mode through the mitral leafllet, is easy, has a high reproducibility and obtains all of the time intervals from the same cardiac cycle.

We hypothesised that the cardiac time intervals, especially the combined indexes containing information on both systolic and diastolic function (IVRT/ET and MPI), are strong predictors of future cardiovascular morbidity and mortality in the general population. Furthermore, we hypothesised that the combined indexes provide prognostic information incremental to clinical predictors and conventional echocardiographic measures of systolic and diastolic function.

METHODS
Study population
The Copenhagen City Heart Study is a longitudinal cohort study of cardiovascular disease and its risk factors. Information about the study population, the health examination, the echocardiographic examination and what has previously been published on cardiac time intervals in this cohort is described in detail in the online supplementary material.

TDI M-mode
The cardiac time intervals were obtained by placing a 2–4 cm straight M-mode line through the septal half of the mitral leafllet in the colour TDI four...
chamber view, and the time intervals were measured directly from the colour diagram (figure 1). We have previously described the method,\(^1\)\(^3\) and it is described in detail in the online supplementary material. The method has previously been validated,\(^1\)\(^3\)\(^12\) and we have previously demonstrated high reproducibility of the measure in this population.\(^1\) Both isovolumic time intervals were divided with ET creating IVRT/ET and IVCT/ET, respectively, and MPI was calculated as the sum of the two ((IVRT+IVCT)/ET).

Follow-up and end outcome
The primary endpoint of major cardiovascular events (MACE) was the combined endpoint of being admitted with ischaemic heart disease (IHD), admitted due to heart failure (congestive heart failure (CHF)) or cardiovascular mortality. Follow-up was 100%. Follow-up data on admission with IHD and CHF were obtained from the Danish National Board of Health’s National Patient Registry, using International Classification of Diseases (ICD)-10 codes (DI20-DI259 for IHD and DI500-DI509 and DJ818 for CHF). Follow-up data on cardiovascular mortality was collected from the national Danish Causes of Death Registry. Cardiovascular death was defined as ICD-10 codes I00–I99.

Statistics
The statistical methods are described in detail in the online supplementary material.

RESULTS
During follow-up (median 10.8 years, IQR 8.6–11.5 years), 267 (13.9%) were admitted with IHD, 137 (7.2%) were admitted to hospital due to CHF and 134 (7.0%) participants died due to cardiovascular causes. The combined endpoint was reached by 383 (20.0%) participants.

Baseline characteristics are displayed in tables 1 and 2.

The cardiac time intervals and prognosis
The risk of future IHD, being admitted with CHF or dying due to cardiovascular causes, increased with increasing tertile of the IVRT (see online supplementary figure S1a) and the IVCT (see online supplementary figure S1b), being approximately two times as high in the third tertile compared with the first tertile (IVRT: subdistribution HRs (SHR) (95% CI) 2.4 (1.9 to 3.1); p<0.001; IVCT: SHR 1.6 (1.2 to 2.0); p<0.001). For the ET, the risk of future MACE increased with decreasing tertile of the ET (see online supplementary figure S1c), being approximately two times as high in the first tertile compared with the third tertile (ET: SHR 1.5 (1.2 to 2.0); p<0.001). After multivariable adjustment for all other clinical predictors of MACE in our population, declining cardiac function, determined by prolongation of the IVRT and the IVCT, remained independent predictors of MACE (table 3). However, when adding the conventional echocardiographic parameters to the model, none of the cardiac time intervals remained independent predictors of MACE (table 3).

The combined indexes obtained by combining the cardiac time interval and prognosis
The risk of MACE increased incrementally with increasing tertile of IVRT/ET, IVCT/ET and MPI (see online supplementary figure S2), being approximately two times as high for the IVCT/ET and approximately three times as high for the IVRT/ET and MPI in the third tertile compared with the first tertile.
Cardiac risk factors and prevention

| Table 1  Baseline clinical characteristics for the participants stratified according to major adverse cardiovascular (MACE) outcome |
|---------------------------------|----------------|----------------|---------------|--------|
|                                | All (n=1915) | No MACE (n=1532) | MACE (n=383) | p Value |
| Age (years)*                   | 58±16        | 55±16          | 71±11        | <0.001  |
| Male gender                    | 42%          | 41%            | 49%          | 0.006   |
| Systolic blood pressure (mm Hg)*| 136±23       | 133±22         | 148±21       | <0.001  |
| Diastolic blood pressure (mm Hg)* | 78±12        | 78±12          | 81±13        | <0.001  |
| Heart rate (bpm)*              | 67±12        | 66±11          | 70±12        | <0.001  |
| Hypertension                   | 43%          | 36%            | 73%          | <0.001  |
| Diabetes                       | 10%          | 8%             | 19%          | <0.001  |
| Smoking status                 |              |                |              |         |
| Never                          | 33%          | 36%            | 25%          |         |
| Previous                       | 33%          | 31%            | 42%          | <0.001  |
| Current                        | 33%          | 33%            | 34%          | <0.001  |
| Cholesterol*                   | 5.5±1.2      | 5.5±1.2        | 5.6±1.1      | 0.247   |
| Previous ischaemic heart disease| 6%           | 2%             | 23%          | <0.001  |
| Previous ischaemic stroke      | 2%           | 1%             | 5%           | <0.001  |
| BMI (kg/m²)*                   | 25.4±3.9     | 25.1±3.8       | 26.9±4.1     | <0.001  |
| eGFR (mL/min/1.73 m²)*         | 76.3±16.2    | 77.2±15.5      | 72.4±18.0    | <0.001  |
| Atrial fibrillation/flutter     | 2%           | 1%             | 6%           | <0.001  |

*Mean±SD. BMI, body mass index; eGFR, estimated glomerular filtration rate.

(IVRT/ET: SHR 2.7 (2.1 to 3.5), p<0.001; IVCT/ET: SHR 1.8 (1.4 to 2.3), p<0.001; MPI: SHR 2.8 (2.2 to 3.7), p<0.001). After multivariable adjustment for significant univariable predictors (both clinical and conventional echocardiographic measures), only the combined indexes, including information on both systolic and diastolic performance (IVRT/ET and MPI) remained independent predictors of future MACE (table 3). The SHR, 95% CI and the p values for all the variables included in the final multivariable models are displayed in the online supplementary table S1.

As a sensitivity analysis, we stratified participants into two groups according to their history of previous IHD and/or CHF or not (see online supplementary tables S2 and S3).

Added value of IVRT/ET and MPI in relation to predicting future MACE

Adding the combined indexes, including information on both systolic and diastolic performance, the IVRT/ET or the MPI, to a Cox model already including all other echocardiographic parameters (LVEF <50%, E/e', diastolic dysfunction defined by E/A ratio and deceleration time of early diastolic inflow (DT), left atrium volume index (LAVI), IV mass index (LVMI)) resulted in a significant but small increase in the Harrell's c-statistics (figure 2). Furthermore, reclassification analysis when adding the combined indexes (IVRT/ET or MPI), to our clinical predictors (age, gender, body mass index (BMI), estimated glomerular filtration rate, heart rate, hypertension, diabetes, smoking status and atrial fibrillation), yielded better predicting models with a significant increase in the continuous net reclassification improvement (NRI) (95% CI) of 18.2% (2.0% to 32.2%) for the IVRT/ET and of 17.6% (3.2% to 32.3%) for the MPI, respectively. In comparison, none of the conventional echocardiographic parameters (LVEF <50%, E/e', LAVI, diastolic dysfunction defined by E/A ratio and DT or LVMI) yielded better predicting models when added to our clinical predictors (LVEF <50%: NRI 0.7% (−45.3% to 25.3%); E/e': NRI −5.0% (−23.2% to 11.8%); LAVI: NRI 8.3% (−3.3% to 24.6%); diastolic dysfunction by E/A ratio and DT: NRI −33.3% (−59.7% to 11.0%); LVMI: NRI 15.4% (−2.0% to 32.5%).

Additionally, when adding MPI to the variables from the Systematic Coronary Risk Evaluation (SCORE) risk chart (age, gender, cholesterol, smoking status and systolic blood pressure), a better predicting model for predicting future cardiovascular mortality was obtained with a significant increase in the categorical NRI of 7.0% (1.9% to 11.6%, p=0.006). Adding IVRT/ET to the SCORE risk chart did not improve the predicting model (p=0.101).

DISCUSSION

In the largest (n=1915) prospective study to date, of a random sample of participants from the general population undergoing comprehensive echocardiography including an assessment of the cardiac time intervals by TDI M-mode, we demonstrate: impaired cardiac time intervals are predictors of future IHD, CHF or cardiovascular mortality in the general population. The combined indexes containing information on both systolic and diastolic function (IVRT/ET and MPI) are independent predictors of future MACE, even after adjustment for all other echocardiographic predictors. The IVRT/ET and the MPI provides prognostic information in the general population, not only independently, but also over and above all significant clinical and conventional echocardiographic predictors of future MACE.

The novel method of obtaining the global cardiac time intervals

Cardiac intervals have been suggested and investigated as potential markers of cardiac dysfunction for several decades.14–17 However, the main concern has always been how to obtain these cardiac time intervals in a fast, easy, non-invasive and reproducible manner. Tei and colleagues16 17 proposed in 1995 to overcome this problem by obtaining the cardiac time intervals from the velocity curves obtained from pulsed-Doppler echocardiography of the LVMV inflow and outflow tract and hereby calculating the index of combined systolic and diastolic performance, the MPI. The method suggested by Tei and colleagues16 17 has several limitations. Most importantly, the time intervals are obtained from two projections and at least two cardiac cycles, and may therefore be prone to changes in the cardiac time intervals caused by heart rate variations in-between obtaining the two projections. Using TDI and the velocity curves from the myocardium is an alternative non-invasive approach to obtain the cardiac time intervals.2 18–20 With this method the time intervals can be obtained from one projection and one cardiac cycle. But the time intervals obtained from the TDI velocity curves are prone to regional differences in myocardial activation, mechanics and physiology.21–23 However, we can overcome this problem by analysing the global time intervals through evaluating the MV movement by a simple colour TDI M-mode analysis,24 instead of the regional velocity curves. Thus, using colour TDI M-mode through the mitral leafllet to estimate the cardiac time intervals is an improved method reflecting global cardiac time intervals and eliminating beat-to-beat variation and regional differences. We have previously demonstrated that the MPI obtained by TDI M-mode is less influenced by physical parameters (including heart rate) compared with the conventional method described by Tei and colleagues.5 Furthermore, the precision and reproducibility of the cardiac time intervals and MPI are improved when they are obtained by the TDI M-mode method compared with the conventional method.1 12 The mean difference±SD for the MPI
TDI velocity curve method.\textsuperscript{18,19} This is due to the absence of variability and 0.010±0.038 for the interobserver variability, 0.082±0.114 for the interobserver variability and 8%.

In contrast, all cardiac time intervals can be obtained by the conventional method\textsuperscript{16,17} or the newer regional TDI velocity curve method\textsuperscript{18,19} regardless of the presence of atrial fibrillation.\textsuperscript{5}

Also, the time intervals obtained by clear colour shifts marking minimal changes in direction in the MV by the colour TDI M-mode method are very easy to identify (Figure 1). In contrast, the time intervals obtained by the conventional method\textsuperscript{16,17} or the newer regional TDI velocity curve method\textsuperscript{18,19} are assessed from velocity curves where the signals obtained by the TDI M-mode method was reported to be between −0.004 to 0.016±0.020 to 0.038 for the intraobserver variability and 0.010±0.038 for the interobserver variability, compared with between −0.01 to 0.013±0.030 to 0.057 for the intraobserver variability and 0.082±0.114 for the interobserver variability when obtained by the conventional method.\textsuperscript{11,12} Additionally, it is not possible to obtain the cardiac time intervals from velocity curves in patients with atrial fibrillation regardless if they are obtained by the conventional method as described by Tei and colleagues\textsuperscript{16,17} or by the newer regional TDI velocity curve method.\textsuperscript{18,19} This is due to the absence of the A and a’ velocity curves in patients with atrial fibrillation, which are needed to obtain the time intervals by both methods.

### Cardiac risk factors and prevention

#### Table 2  Baseline echocardiographic characteristics for the participants stratified according to major adverse cardiovascular outcome (MACE) (n=1915)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=1915)</th>
<th>No MACE (n=1463)</th>
<th>MACE (n=383)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF&lt;50%</td>
<td>1%</td>
<td>0%</td>
<td>4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVIDd (cm)*</td>
<td>4.8±0.6</td>
<td>4.8±0.5</td>
<td>4.8±0.7</td>
<td>0.913</td>
</tr>
<tr>
<td>LAVI (mL/m\textsuperscript{2})*</td>
<td>18.4 (15.0–22.6)</td>
<td>18.0 (14.8–21.8)</td>
<td>20.6 (16.2–26.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>80%</td>
<td>82%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>Mildly increased</td>
<td>5%</td>
<td>4%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Moderately increased</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severely increased</td>
<td>12%</td>
<td>12%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>E (m/s)*</td>
<td>0.72±0.17</td>
<td>0.73±0.16</td>
<td>0.69±0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A (m/s)*</td>
<td>0.68±0.19</td>
<td>0.67±0.18</td>
<td>0.76±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio\textsuperscript{+}</td>
<td>1.04 (0.82–1.37)</td>
<td>1.10 (0.87–1.42)</td>
<td>0.86 (0.73–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DT (ms)\textsuperscript{+}</td>
<td>166±40</td>
<td>165±37</td>
<td>174±49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic dysfunction by E/A ratio and DT</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e\textsuperscript{†}</td>
<td>10.1 (8.2–12.7)</td>
<td>9.5 (7.9–11.8)</td>
<td>12.6 (10.2–16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVI (g/m\textsuperscript{2})\textsuperscript{†}</td>
<td>83.0 (71.3–98.3)</td>
<td>80.9 (70.1–95.1)</td>
<td>94.7 (79.2–113.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiac time intervals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVRT (ms)*</td>
<td>101±24</td>
<td>98±22</td>
<td>111±29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVCT (ms)*</td>
<td>37±14</td>
<td>36±13</td>
<td>40±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ET (ms)*</td>
<td>284±27</td>
<td>286±25</td>
<td>277±31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT/ET\textsuperscript{*}</td>
<td>0.36±0.10</td>
<td>0.35±0.08</td>
<td>0.41±0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVCT/ET\textsuperscript{*}</td>
<td>0.13±0.06</td>
<td>0.13±0.05</td>
<td>0.15±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPI\textsuperscript{*}</td>
<td>0.49±0.13</td>
<td>0.47±0.11</td>
<td>0.56±0.18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean±SD.
+Median (IQR).
†Mean±SD.

A, peak transmitral late diastolic inflow velocity; diastolic dysfunction by E/A ratio and DT, DT<140 ms and E/A\textsuperscript{0–10 years}<2.5, E/A\textsuperscript{>70 years}>1.5; DT, deceleration time of early diastolic inflow; e\textsuperscript{†}, average peak early diastolic longitudinal mitral annular velocity determined by colour TDI; E, peak transmitral early diastolic inflow velocity; ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LAVI, left atrium volume index; LVIDd, LV dimensions in end-diastole; LVMI, LV mass index; MPI, myocardial performance index; TDI, tissue Doppler imaging.

### Table 3  Unadjusted and adjusted competing risk Cox proportional hazards regression models depicting the cardiac time intervals as predictors of future major adverse cardiovascular outcome (MACE) (n=1915)

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Harrell’s c-statistics</th>
<th>SHR (95% CI)</th>
<th>p Value</th>
<th>SHR (95% CI)</th>
<th>p Value</th>
<th>SHR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVRT per 10 ms increase</td>
<td>0.62</td>
<td>1.20 (1.16 to 1.25)</td>
<td>&lt;0.001</td>
<td>1.07 (1.02 to 1.11)</td>
<td>0.003</td>
<td>1.06 (1.00 to 1.13)</td>
<td>0.091</td>
</tr>
<tr>
<td>IVCT per 10 ms increase</td>
<td>0.57</td>
<td>1.19 (1.11 to 1.28)</td>
<td>&lt;0.001</td>
<td>1.09 (1.01 to 1.18)</td>
<td>0.018</td>
<td>1.07 (0.98 to 1.17)</td>
<td>0.135</td>
</tr>
<tr>
<td>ET per 10 ms decrease</td>
<td>0.57</td>
<td>1.13 (1.08 to 1.18)</td>
<td>&lt;0.001</td>
<td>1.06 (1.00 to 1.11)</td>
<td>0.043</td>
<td>1.03 (0.97 to 1.10)</td>
<td>0.326</td>
</tr>
<tr>
<td>IVRT/ET per 0.1 increase</td>
<td>0.64</td>
<td>1.44 (1.31 to 1.58)</td>
<td>&lt;0.001</td>
<td>1.16 (1.08 to 1.26)</td>
<td>&lt;0.001</td>
<td>1.16 (1.01 to 1.34)</td>
<td>0.035</td>
</tr>
<tr>
<td>IVCT/ET per 0.1 increase</td>
<td>0.59</td>
<td>1.71 (1.46 to 2.02)</td>
<td>&lt;0.001</td>
<td>1.31 (1.09 to 1.57)</td>
<td>0.004</td>
<td>1.21 (0.98 to 1.49)</td>
<td>0.074</td>
</tr>
<tr>
<td>MPI per 0.1 increase</td>
<td>0.64</td>
<td>1.41 (1.33 to 1.50)</td>
<td>&lt;0.001</td>
<td>1.16 (1.08 to 1.24)</td>
<td>&lt;0.001</td>
<td>1.13 (1.03 to 1.24)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Harrell’s c-statistics were calculated for the univariable models. Model 1 is adjusted for age, gender, BMI, eGFR, heart rate, hypertension, diabetes, smoking status, atrial fibrillation, ischemic heart disease, previous ischemic stroke and heart medication. Model 2 is adjusted for the same variables as model 1 and for systolic dysfunction determined by LVEF<50%, LAVI, LVMI, diastolic dysfunction defined by E/A ratio and DT (DT<140 ms and E/A\textsuperscript{0–10 years}>2.5, E/A\textsuperscript{>70 years}>2 or E/A\textsuperscript{>70 years}>1.5) and E/e. A, peak transmitral late diastolic inflow velocity; BMI, body mass index; DT, deceleration time of early diastolic inflow; e\textsuperscript{†}, average peak early diastolic longitudinal mitral annular velocity determined by colour TDI; E, peak transmitral early diastolic inflow velocity; eGFR, estimated glomerular filtration rate; ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LAVI, left atrium volume index; LVMI, LV mass index; MPI, myocardial performance index; SHR, subdistribution HR; TDI, tissue Doppler imaging.
may be scattered, making it hard to accurately define the cardiac time intervals, which is illustrated by the poorer reproducibility.12 Furthermore, when good imaging quality is difficult to obtain, it is often possible to visualise the MV in the apical view due to the perpendicular nature between the ultrasound beam and the MV, which is why assessing its longitudinal movement by colour TDI M-mode nearly always is manageable.

**The global cardiac time intervals and risk of future MACE**

Previous studies, which evaluated the prognostic value of the MPI either obtained by the conventional method as proposed by Tei and colleagues16 17 or by using the regional TDI velocity curves18 19 were all performed in selected populations, for example, patients after acute myocardial infarction,23 elderly men,24 patients with cardiac amyloidosis,25 with idiopathic-dilated cardiomyopathy,26 with isolated diastolic dysfunction9 and in patients with systolic heart failure.27 In a population-based study of American Indians,28 the authors found that the MPI obtained by the conventional method16 17 did not predict future cardiovascular events. In accordance with this, we have previously demonstrated that the MPI obtained by the conventional method16 17 did not predict all-cause mortality in the general population when adjusted for significant risk factors. However, the MPI obtained by the novel colour TDI M-mode method was an independent predictor of mortality after multivariable adjustment.1 This discrepancy in predictive capacity between the two methods of obtaining the cardiac time intervals is probably due to the difference in the physical mechanisms of the two methods. When using the conventional method, the time intervals are derived from blood flow velocity curves, whereas when using the M-mode method the time intervals are derived from analysing the MV moving passively depending on shifts in pressure and blood flow between the left atrium and LV. Therefore, the method by Tei and colleagues16 17 seems to be influenced by more physical parameters than the M-mode method.1 This makes the MPI obtained by TDI M-mode less complex to interpret in a clinical setting. These differences may also explain why the MPI obtained by the TDI M-mode method is more precise and has better reproducibility.1 12 In accordance with this, MPI obtained by using the regional TDI velocity curves18 19 has also demonstrated to be superior to the conventional method16 17 in predicting cardiac mortality and admission with heart failure in patients with isolated diastolic dysfunction or heart failure with preserved LVEF.9

Our study is the first to evaluate the prognostic value of all the cardiac time intervals in a low-risk randomly selected general population, where subtle cardiac impairment often will go unrecognised if only using conventional echocardiographic parameters. We found that impairment in all the cardiac time intervals was individually associated with increased risk of MACE (see online supplementary figures S1, S2 and table 3). However, after multivariable adjustment for all other clinical and echocardiographic predictors, only the combined indexes containing information on both systolic and diastolic performance (IVRT/ET and MPI) remained independent predictors of future MACE (table 3). We have previously observed the same pattern in patients suffering a ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention.3 In this high-risk population of patients with STEMI, only the combined indexes containing information on both systolic and diastolic performance remained independent predictors of outcome after adjustment for all other clinical and echocardiographic predictors.3 The superiority of the IVRT/ET and the MPI compared with the remaining cardiac time intervals in predicting MACE may reflect that they detect myocardial dysfunction, irrespective of whether the myocardial suffers from an ailing systolic or diastolic function.3 In contrast, the remaining cardiac time intervals only detect isolated diastolic (IVRT) or systolic (IVCT, ET and IVCT/ET) dysfunction, respectively. Similar, when using TDI velocities in predicting outcome, studies have demonstrated that when combining the information on systolic (e’ and a’) and diastolic function (e and a) in one risk stratification strategy the prognostic information obtained improves.13 29

**Incremental prognostic value of adding IVRT/ET and MPI in relation to predicting future MACE**

We found that the combined indexes containing information on both systolic and diastolic performance (IVRT/ET and MPI) remained not only independent predictors of future MACE, but provided incremental prognostic value to all other echocardiographic predictors of MACE (figure 2). Adding the combined indexes (IVRT/ET or MPI) to all the conventional echocardiographic parameters may again reflect that they detect very miniscule impairment in the myocardial function, irrespective if the myocardium suffers from an ailing systolic or diastolic function.3 Therefore, the IVRT/ET and MPI identifies subtle impairments in the cardiac function (both systolic and diastolic), which may be unnoticed by conventional echocardiography,10 11 and can improve risk stratification strategies evaluating future risk of fulminant cardiovascular disease over and above the traditional predictors, in the low-risk general population. This is supported by the fact that MPI improved the prediction model for
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predicting future cardiovascular mortality when added to the variables included in SCORE risk chart.

LIMITATIONS
The inhabitants of Denmark and the study population are primarily Caucasian, which limits the generalisability of our findings to other general populations with other composition.

We did not perform consecutive echocardiographic examinations of the participants and are therefore unable to test the day-to-day physiological variability of the cardiac time intervals obtained by TDI M-mode. It has previously been demonstrated that the time intervals, like all other echocardiographic measures, are influenced by changes in loading conditions when obtained by the conventional method. 10 We would therefore also suspect the cardiac time intervals obtained by M-mode TDI to change with different loading conditions that will need to be investigated in future studies.

CONCLUSION
In the general population, the combined cardiac time intervals that include information on both systolic and diastolic function in one index (IVRT/TET and MPI) are powerful and independent predictors of future MACE. In addition, they provide prognostic information over and above clinical variables and conventional echocardiographic measures of systolic and diastolic function.

Key messages

What is already known on this subject?

- Cardiac time intervals are sensitive markers of cardiac dysfunction, even when the cardiac dysfunction goes unrecognised by conventional echocardiography.

What might this study add?

- A novel method has recently evolved where global cardiac time intervals are obtained through evaluation of the mitral valve movement through the cardiac cycle by using a simple colour tissue Doppler imaging M-mode analysis.

How might this impact on clinical practice?

- This new technique has the potential of being a new diagnostic and predictive echocardiographic parameter that can add to the information acquired from other echocardiographic parameters, which may often be ambiguous in a low-risk population.

Contributors Study design and concept: TB-S, RM and JSJ. All authors participated in analysing and interpretation of the data. All authors revised the paper. All authors have approved this paper in its final submitted form.

Funding Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was performed in accordance with the second Helsinki Declaration and approved by the Regional Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode in the general population
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Heart published online April 20, 2015

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