Tissue Doppler E/E’ ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy

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Received 5 March 2009; revised 17 July 2009; accepted 21 September 2009

Aims
Patients with controlled hypertension are at risk of future cardiac events, but predicting first events remains difficult. We hypothesized that modern echocardiographic measures of left ventricular diastolic function may be more sensitive than traditional echocardiographic methods of risk prediction and set out to test this in a cohort of patients with well-controlled hypertension.

Methods and results
Conventional and tissue Doppler echocardiography was performed on 980 participants in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). All subjects had hypertension, but no known cardiac disease. Cardiac events were defined as fatal and non-fatal myocardial infarction (including silent myocardial infarction), coronary revascularization procedures, new-onset angina (stable or unstable), fatal and non-fatal heart failure, and life-threatening arrhythmias. Analysis was performed by a single, blinded observer. There were 56 primary cardiac events during 4.2 ± 0.7 years follow-up. The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E’) was the strongest predictor of first cardiac events in Cox-proportional hazards models. Following adjustment for covariates, a unit rise in the E/E’ ratio was associated with a 17% increment in risk of a cardiac event (HR 1.17, CI 1.05–1.29; P = 0.003).

Conclusion
Tissue Doppler E/E’, a non-invasive estimate of left atrial filling pressure, independently predicts primary cardiac events in a hypertensive population and out-performed traditional echocardiographic measures in this moderately sized, well-treated hypertensive population. E/E’ represents a simple, effective tool for assessing cardiac risk in a hypertensive population.

Keywords
Diastole • Left ventricle • Tissue Doppler • Hypertension • Outcome

Introduction
Reliable methods for predicting primary cardiac events in individuals with well-controlled hypertension remain limited. Inclusion of cardiac measures of hypertensive structural and functional change, such as left ventricular hypertrophy, raised left atrial size, and transmitral Doppler assessment of diastolic blood flow, have improved risk prediction, but it is unclear which measure best predicts outcome and provides the most appropriate tool for risk stratification.

By combining the early filling velocity on transmitral Doppler (E) with the early relaxation velocity on tissue Doppler (E’), the E/E’ ratio of diastolic function has been shown to have good prognostic value in established and advanced cardiac disease, but this...
measure has not been shown to predict risk of primary cardiac events.

We set out to test whether this measure is able to predict first events in a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and to compare performance against traditional echocardiographic measures of risk.

Methods

A full description of ASCOT can be found elsewhere. ASCOT was a clinical trial of antihypertensive therapy (amlodipine + perindopril vs. atenolol + bendroflumethiazide) in 19,257 men and women aged 40–79 years with hypertension. Detailed cardiovascular phenotypic data were purposefully collected on a subset of 1,006 participants recruited from two centres (579 subjects from St Mary’s Hospital, London and 427 subjects from the Adapt Centre, Beaumont Hospital, Dublin) as part of the Hypertension Associated Cardiovascular Disease (HACVD) substudy. A detailed description of the protocols for this substudy, including quality control measures used for acquisition of data, can be found in detail elsewhere. Briefly, brachial BP was measured as the mean of three readings made in a seated position using an Omron HEM 705-CP semiautomatic oscillometric recorder. Participants rested for 5 min before testing. The measures mentioned here are those taken at the time of echocardiography.

Height and weight were measured in light clothing by a trained observer. Body mass index (BMI) was calculated as weight (kg)/height (m²). Plasma glucose and serum total cholesterol were measured using standard enzymatic methods on a Roche/Hitachi 921 (Roche Diagnostics, Basel, Switzerland) automated analyzer. The values given here for lipids and glucose are those taken at the time of echocardiography. eGFR was calculated using the MDRD formula.

Inclusion and exclusion criteria

The criteria for inclusion were hypertension (either untreated hypertension: systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg at both screening and randomization; or treated hypertension: systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg at randomization) with any three of the following cardiovascular risk factors: type 2 diabetes, peripheral vascular disease, previous TIA/stroke, male sex, age > 55, microalbuminuria/proteinuria, current smoker; plasma total cholesterol/HDL ratio > 6, family history of ischaemic heart disease (IHD) in a first degree relative. The final inclusion criterion was ‘previously identified echo or ECG LVH’. This was required to have been identified within normal clinical practice prior to any assessment of the study and was not influenced by any subsequent investigation performed as part of ASCOT.

Exclusion criteria included those with a diagnosis of, or symptoms consistent with, IHD or heart failure. Patients demonstrated through the study to have severe valvular heart disease were excluded from the analysis.

Echocardiography

Following a 1 year period of blood pressure control according to the ASCOT protocol, 980 patients underwent echocardiography. Those with poor echocardiographic windows or incomplete data sets were excluded and adequate on-axis images and tissue Doppler tracings from all three left ventricular territories were available in 828 subjects (84%). Of these, 12 suffered first cardiac events between randomization and the time of echocardiography, and so were also excluded from the analysis, leaving a total of 816 subjects.

Scanning was performed by one experienced echocardiographer at the Dublin site, and two experienced echocardiographers at the St Mary’s site using ATL HDI 5000 ultrasound machines. Each patient underwent standard two-dimensional echocardiography in the left lateral position using a standard multi-frequency probe, with detailed LV measurements made from M-mode in the parasternal long-axis according to the American Society of Echocardiography guidelines.

If the technical quality of the M-mode was suboptimal, measurements were required to be made from the two-dimensional images.

LV mass was calculated according to the formula:

\[
\text{LV mass (g)} = 0.8 [(\text{IVSd + LVIDd + PWTd}) - (\text{LVIDd})^3] + 0.6
\]

where IVSd is intraventricular septal thickness in diastole (cm), LVIDd the LV diameter in diastole (cm), and PWTd the posterior wall thickness in diastole.

This was then divided by body surface area to give LV mass index (LVMI), Relative wall thickness was calculated according to the formula:

\[
\text{Relative wall thickness} = \frac{\text{IVSd + PWTd}}{\text{LVIDd}}
\]

Pulsed spectral Doppler echocardiography was performed using a 5 mm sample volume placed at the tips of the mitral leaflets parallel to inflow during diastole at end-expiration, with a sweep speed of 100 mm/s. Tissue Doppler measurements were sampled at the level of the mitral annulus over the septal, lateral, and inferior walls with filters adjusted to obtain the lowest wall filter settings and the minimal optimal gain; Nyquist limits of 15–20 cm/s and a frame rate of 200 Hz were used. Each spectral trace was downloaded for offline analysis using the HDILab software program by a single researcher (A.S.), who was masked to all patient outcome data until the final cleaned data set was presented for outcome analysis.

Values for each component of the TDE waveform (S’, E’ and A’) were measured and averaged over three consecutive cardiac cycles. A composite mean for each of these parameters was then formed by taking the average of the values from the septal, lateral, and inferior wall. The ratio of the transmitral Doppler E wave velocity and the composite mean of E’ was then used to calculate the E/E’ ratio. This therefore means that the mean tissue Doppler variable E’ incorporates data from nine cardiac cycles, minimizing the effect of beat to beat variation or respiratory artefact.

Reproducibility of data

Between centre and between echocardiographer variability of echocardiographic measurements were assessed before commencement of the study and subsequently at regular intervals during the study. Using the Bland–Altman method, the standard deviation of difference of individual variables (e.g. E/E’) was found to be between 3.5 and 7.5% of the mean value, demonstrating that our reproducibility measurements were in keeping with other studies. We also confirmed within a separate multivariate model that the centre of origin of the subject had no effect on outcome, further eliminating the possibility of bias from differences in acquisition of data between echocardiographers.

Endpoints

The cardiac endpoints used for this substudy were pre-specified in the ASCOT protocol as non-fatal myocardial infarction (including silent myocardial infarction), fatal myocardial infarction, coronary revascularization procedures, new-onset angina (stable or unstable), fatal and non-fatal heart failure, and life-threatening arrhythmias. All endpoint
events were confirmed by the ASCOT endpoints committee, by procedures detailed elsewhere. Where a patient suffered more than one cardiac event during the course of the study, only the first cardiac event for that patient was incorporated into the analysis.

### Statistical methods
Statistical analysis was performed using SPSS v14.0 for Windows (SPSS Inc., 2005, Chicago, IL, USA). Two groups were established for the purposes of analysis—those who were event-free, and those who had suffered a first cardiac event during the course of the study. For those subjects who suffered multiple events, only the first event was used for the analysis.

All continuous variables were tested for normality and logarithm transformed where skewed distributions were demonstrated. These are presented as mean ± standard deviation. Demographic and echocardiographic factors were analysed between groups using ANOVA for continuous variables and chi-square for categorical variables.

### Multivariate analysis
Multivariate analysis was performed using tiered Cox proportional hazards models incorporating factors with predictive significance on univariate analysis and hypothesized important factors.

- Model 1 adjusted for age and gender.
- Model 2 adjusted for age, gender, diabetes and systolic blood pressure.
- Model 3 corrected for the traditional Framingham risk factors of age, diabetes, total cholesterol, HDL, smoking, gender, and systolic blood pressure.

We then compared the ability of E/E’ to predict risk against other traditional measures quoted in the literature (LVMI, RWT, left atrial size, ejection fraction, transmitral E/A ratio, transmitral E wave velocity, mean tissue Doppler E’ wave velocity, and mean tissue Doppler S’ wave velocity). This was done by substituting E/E’ for each value in turn in the models listed above.

During the analysis, we also incorporated several measures of blood pressure into the modelling process to ensure adequate representation of the distribution of hypertension within our cohort. These included baseline systolic and diastolic blood pressure, systolic and diastolic blood pressure taken at the time of echocardiography, and the average blood pressure measured over time (between study enrolment and time of echocardiography [Baseline systolic BP + Echocardiography systolic BP)/2]). Using each of these measures within the modelling process in place of systolic blood pressure did not change our findings and therefore data are not shown.

### Results
Demographic data for the population are shown in Table 1. Only diastolic blood pressure differed between those who were event-free and those who suffered a cardiac event at follow-up (P = 0.047); however, after adjustment for age and sex, this difference was no longer significant. Mean follow-up period was 4.2 ± 0.7 years. During this time, there were 101 cardiac events in total, of which 56 were first cardiac events (Table 2). The cardiac event rates reported in this substudy proved to be similar to those in the parent ASCOT-BPLA study.[16]

On univariate analysis of echocardiographic parameters, tissue Doppler E/E’ was the only parameter to predict first cardiac events (Table 3).

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Continuous variables, Mean ± SD</th>
<th>Event free (n = 760)</th>
<th>Cardiac event (n = 56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.2 ± 7.9</td>
<td>64.1 ± 7.1</td>
<td>0.079</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>143.5 ± 16.1</td>
<td>142.6 ± 14.6</td>
<td>0.685</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.9 ± 9.0</td>
<td>79.4 ± 8.4</td>
<td>0.047</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>64.4 ± 13.0</td>
<td>64.1 ± 11.7</td>
<td>0.863</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9 ± 4.6</td>
<td>28.1 ± 3.7</td>
<td>0.220</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.2 ± 1.1</td>
<td>5.1 ± 1.0</td>
<td>0.783</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>0.610</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>99.2 ± 17.2</td>
<td>103.0 ± 15.6</td>
<td>0.116</td>
</tr>
<tr>
<td>Calculated GFR (mL/min/1.73 m²)</td>
<td>69.5 ± 12.4</td>
<td>66.7 ± 13.6</td>
<td>0.102</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.9 ± 2.0</td>
<td>6.1 ± 1.9</td>
<td>0.449</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables (%)</th>
<th>Event free (n = 760)</th>
<th>Cardiac event (n = 56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n</td>
<td>79.1</td>
<td>87.5</td>
<td>0.086</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20.4</td>
<td>25.0</td>
<td>0.253</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8.7</td>
<td>8.9</td>
<td>0.549</td>
</tr>
<tr>
<td>Smoker</td>
<td>24.5</td>
<td>33.9</td>
<td>0.081</td>
</tr>
<tr>
<td>Amlodipine-based treatment</td>
<td>49.9</td>
<td>51.8</td>
<td>0.445</td>
</tr>
</tbody>
</table>

### Table 2 Cardiac events

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal coronary heart disease</td>
<td>11</td>
<td>18.3</td>
</tr>
<tr>
<td>Non-fatal and fatal MI (including silent)</td>
<td>23</td>
<td>38.3</td>
</tr>
<tr>
<td>New onset angina</td>
<td>24</td>
<td>40.0</td>
</tr>
<tr>
<td>Coronary revascularization procedures</td>
<td>35</td>
<td>58.3</td>
</tr>
<tr>
<td>Fatal and non-fatal heart failure</td>
<td>3</td>
<td>5.0</td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
<td>5</td>
<td>8.3</td>
</tr>
<tr>
<td>Total events</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

### Multivariate analysis
After adjustment for age and gender, E/E’ remained the only significant predictor of first cardiac events (HR 1.17, CI 1.05–1.29; P = 0.003; Table 4). Additional adjustment for diabetes and systolic blood pressure had little effect (HR 1.17, CI 1.05–1.30; P = 0.003). Model 3 adjusted for traditional Framingham risk factors (age, gender, diabetes, systolic BP, smoker, total cholesterol, and HDL) and E/E’ remained a highly significant predictor of events (HR 1.17, CI 1.05–1.29; P = 0.003). When E/E’ was adjusted for the 10 year coronary heart disease Framingham risk score itself, it remained a powerful predictor of events (HR 1.14; P = 0.006).
The Framingham score did not significantly predict outcomes in this model.

Each of these models were then re-run, sequentially replacing E/E' with: LVMI, RWT, LA size, ejection fraction, transmiltal E wave velocity, transmiltal E/A ratio, tissue Doppler E’ wave velocity, and tissue Doppler S’ wave velocity. None of these measures significantly predicted primary cardiac events, with or without adjustment for covariates. We then forced E/E’ in the same model with age, gender, diabetes, and systolic BP, in order to demonstrate the additional value of E/E’ over existing echocardiographic variables. The only significant echocardiographic predictor of risk within this model remained E/E’ (P = 0.02). Finally, incorporating centre of origin of the subject into model 3 did not significantly alter our data (data not shown).

Quartile analysis
E/E’ values were next divided into four equal groups for the purposes of Kaplan–Meier survival analysis (E/E’ < 6.43, 6.44–7.52, 7.53–9.18, and > 9.18). Using the log-rank test, increasing risk was demonstrated with each rise in quartile (P = 0.03).

The highest quartile (E/E’ > 9.19) had more than twice the risk of events (Figure 1) as the lowest (E/E’ < 6.43), with a hazard ratio of 2.42 (CI 1.15–5.10, log-rank = 0.048).

Discussion
We demonstrate that in a cohort of patients with well-controlled hypertension and three cardiac risk factors, the E/E’ ratio of transmiltal flow to mitral annular velocity is a strong, independent predictor of cardiac outcomes. For each unit rise in the E/E’ ratio, there was a 15% increase in first cardiac events, which rose to 17% when adjusted for Framingham risk factors. Those with an E/E’ in the uppermost quartile of this population (>9.18) had a hazard ratio of 2.4 times that of patients in the lowest quartile (<6.43).

Traditional echocardiographic measures of cardiac target organ damage such as LVMI and left atrial size, only trended towards predicting cardiac events in this population. This likely reflects the size of this cohort, rather than the validity of these proven methods. The power of tissue Doppler measures to predict events is all the more impressive in this context.

E/E’ and risk prediction
The current study is the first to prospectively demonstrate the ability of the E/E’ ratio to predict primary cardiac events in a hypertensive population without established cardiac disease. Our findings therefore significantly extend previous observations showing that the E/E’ ratio predicts outcomes in individuals with established, symptomatic heart disease. These data also, for the first time, emphasize that values previously thought to be within the normal range can be associated with an increased risk of cardiac events.

Elevated E/E’ has been shown to be a strong predictor of death following myocardial infarction and to be superior in this regard to other clinical or echocardiographic features. More recently, it was also demonstrated to predict cardiac events in subjects following coronary angioplasty and survival in those with established cardiac arrhythmias, but has not been looked at prospectively in the field of primary prevention until now.

Table 3 Echocardiographic results

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
<th>Event free (n = 760)</th>
<th>Cardiac event (n = 56)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean E/E’ ratio</td>
<td>7.87 ± 2.15</td>
<td>8.77 ± 2.94</td>
<td>0.003</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>120.4 ± 30.9</td>
<td>125.3 ± 34.4</td>
<td>0.282</td>
</tr>
<tr>
<td>RWT</td>
<td>0.51 ± 0.10</td>
<td>0.53 ± 0.12</td>
<td>0.097</td>
</tr>
<tr>
<td>Left atrial size (cm)</td>
<td>4.19 ± 0.62</td>
<td>4.29 ± 0.62</td>
<td>0.273</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>69.4 ± 11.8</td>
<td>69.2 ± 10.8</td>
<td>0.899</td>
</tr>
<tr>
<td>Mean tissue Doppler E’ velocity (cm/s)</td>
<td>8.36 ± 1.96</td>
<td>8.02 ± 2.41</td>
<td>0.215</td>
</tr>
<tr>
<td>Mean tissue Doppler A’ velocity (cm/s)</td>
<td>11.57 ± 2.34</td>
<td>11.35 ± 2.25</td>
<td>0.501</td>
</tr>
<tr>
<td>Mean tissue Doppler S’ velocity (cm/s)</td>
<td>8.86 ± 2.10</td>
<td>8.77 ± 2.18</td>
<td>0.766</td>
</tr>
<tr>
<td>Transmiltal E wave velocity (cm/s)</td>
<td>61.49 ± 14.98</td>
<td>64.00 ± 15.67</td>
<td>0.228</td>
</tr>
<tr>
<td>Transmiltal E/A wave ratio</td>
<td>0.88 ± 0.24</td>
<td>0.85 ± 0.23</td>
<td>0.320</td>
</tr>
</tbody>
</table>

Table 4 Multivariate analysis: hazard ratios for E/E’

<table>
<thead>
<tr>
<th>Model</th>
<th>Adjusted</th>
<th>Hazard ratio</th>
<th>CI1</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td>1.15</td>
<td>1.05–1.26</td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>Age, gender</td>
<td>1.17</td>
<td>1.05–1.29</td>
<td>0.003</td>
</tr>
<tr>
<td>2</td>
<td>Age, gender, diabetes, systolic BP</td>
<td>1.17</td>
<td>1.05–1.30</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>Age, gender, systolic BP, total Chol, HDL, diabetes, smoker</td>
<td>1.17</td>
<td>1.05–1.29</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Comparison with other echocardiographic identifiers of risk

Left ventricular mass index is known to predict events in high-risk hypertensive populations, but was not able to predict events in this population, though mean values in each group did trend towards prediction. Similarly, left atrial size did not predict outcomes nor did other methods for the indirect assessment of diastolic function such as transmitral E/A ratio or each component of the E/E′ ratio when considered individually.

The explanation for why recognized risk markers proved less effective may lie in the size of the cohort and in the overall likelihood of this cohort developing cardiovascular disease. This was a group of hypertensive patients who were at only moderate risk, selected on the basis of an estimated 5 year cardiovascular risk of 5%, which makes the power of any outcome prediction measure all the more impressive. Mean LVMI (125.3 g/m²) and LA size (4.29 cm) were only marginally above the normal in those patients with events, suggesting that in well-treated populations such as these, additional methods are likely be required to further stratify cardiovascular risk.

**Why would E/E′ predict cardiac outcomes?**

All of these patients were asymptomatic and most of the values for E/E′ were within what is thought to be the ‘normal range’. Why, therefore, would this measure predict future myocardial infarctions or new onset angina?

One possible explanation is that we are detecting occult coronary artery disease. When coronary disease causes regional hibernation of the myocardium, the E′ velocity drops. This velocity has been shown to rise again after percutaneous coronary intervention. Those who went on to have coronary events may, therefore, have had a higher E/E′ ratio due to regional changes in myocardium, caused by subclinical coronary disease.

An alternative hypothesis is that the cumulative burden of hypertension per patient is proportionate to the degree of diastolic ‘dysfunction’. This measure may therefore be acting as a surrogate for the overall effect hypertension has had on the myocardium to date, which in turn may predict outcomes.

**Study limitations**

The ASCOT study took hypertensive subjects with three cardiovascular risk factors and then aggressively treated them to a strict blood pressure target. Such aggressive treatment is not uniform across the worldwide hypertensive population, and therefore we cannot say with certainty that E/E′ would predict risk in a less well-treated hypertensive population, though it seems likely.

**Conclusion**

Tissue Doppler E/E′ independently predicts primary cardiac events in a hypertensive population and out-performed traditional
echocardiographic measures in this moderately sized, well-treated hypertensive population. E/E' represents a simple, effective tool for assessing cardiac risk in a hypertensive population and provides additional information over and above that of clinical risk factor assessment.

Supplementary material

Further descriptive echocardiographic data from this cohort are contained in Supplementary Table 1, which is available at European Heart Journal online.

Acknowledgements

We thank all trial participants, physicians, nurses, and practices in the participating countries for their important contribution to the study.

Funding

This substudy was supported by an investigational grant by Pfizer International, New York, NY, USA. The principal funding source for ASCOT was Pfizer, New York, NY, USA, additional funding was also provided by Servier Research Group, Paris, France, and Leo Laboratories, Copenhagen, Denmark. A.S.P.S. was funded through a research fellowship granted by the St Mary’s Hospital Special Trustees. R.J.T. is supported by a Sidney Sax fellowship from the National Health and Medical Research Council of Australia (grant no. 334173). D.P.F. is a supported by a Sidney Sax fellowship from the National Health and Medical Research Council of Australia. A.D.H., N.O., B.H., D.P.M., S.M.T. received support from the NIHR Biomedical Research Centre Funding Scheme.

Conflict of interest:

none declared.

References