Left atrial diameter, left ventricle filling indices and association with all-cause mortality. Results from the population-based Tromsø Study

Running head (Left atrial size, diastolic dysfunction and mortality)

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Abstract

Aims: To examine the associations between diastolic dysfunction indices and long-term risk of all-cause mortality in adults over 23 year follow-up.

Methods and results: Participants (n=2734) of the population-based Tromsø Study of Norway had echocardiography in 1994-1995. Of these 67% were repeated in 2001 and/or 2007-2008. Mortality between 1994 and 2016 was determined by linkage to the national death registry. Cox regression was used to model the hazard of all-cause mortality in relation to left atrial parameters (treated as time-dependent using repeated measurements) adjusted for traditional risk factors and cardiovascular disease.

During the follow-up 1399 participants died. Indexed left atrial diameter, mitral peak E deceleration time and mitral peak E to peak A ratio showed an U-shaped association with all-cause mortality. Combining left atrial diameter with mitral peak E deceleration time increased the prognostic accuracy for all-cause mortality whereas adding mitral peak E to peak A ratio did not increase prognostic value. We estimated new optimal cut-off values of left atrial diameter, mitral peak E deceleration time and mitral peak E to peak A ratio for all-cause mortality outcome. E/e' had a cubic relation to mortality.

Conclusion: Both enlarged and small left atrial diameter were associated with increased all-cause mortality risk. A combination of Doppler-based left ventricle filling parameters had an incremental effect on all-cause mortality risk. The cut-off values of diastolic dysfunction indices we determined had similar all-cause mortality prediction ability as those recommended by American Association of Echocardiography and European Association of Cardiovascular Imaging.

Key words: Left atrial diameter, prognosis, all-cause mortality, diastolic dysfunction, epidemiology, echocardiography.

Introduction

Heart failure (HF) is associated with reduced quality of life and premature mortality (1). It is defined as a clinical syndrome associated with a wide range of left ventricular (LV) structural and functional abnormalities of different underlying aetiologies (2). Recent data suggest that the incidence of HF with reduced LV ejection fraction (HFrEF) and HF with mid-range LV ejection fraction (HFmrEF) is decreasing while incidence of HF with preserved LV ejection fraction (HFpEF) is increasing (1).

Detection of asymptomatic diastolic dysfunction is a strong risk factor for developing HFpEF (3). Left atrial (LA) diameter measured in M-mode and mitral flow measurements such as the ratio of the maximal E wave to the maximal A wave (E/A ratio) and the deceleration time of the E wave (DT) has been commonly used as indices of diastolic dysfunction. Enlarged LA diameter is a significant predictor of adverse cardiovascular events (4). Additionally, LA enlargement has been found to be an independent predictor of HF development, atrial fibrillation, coronary heart disease, stroke and all-cause mortality (5-8).

A short as well as long DT are associated with poor cardiovascular outcomes (9). E/A ratio is used for evaluating filling pressure and degree of diastolic dysfunction and also provides prognostic information (10).

The number of studies on the diagnostic impact of LA size and function through the last decades indicates its importance for cardiovascular health (11). However, there is a lack of data on associations between lower ranges of LA size and all-cause mortality rates. The American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) has put forward a series of LA diameter cut-offs that are defined purely in terms of percentiles of the distribution. Their ability to predict mortality has not so far been ascertained (12).

The recent ASE and EACVI guidelines define diastolic dysfunction in terms of a combination of statistically “normal” values of mitral flow indices derived from a small sample of healthy individuals and predictions of mortality by LA diameter from a surveys of the general population (13). These guidelines have not validated the combination of these indices as predictors of disease development or mortality (10, 13). In the latest guidelines septal and lateral e’ peaks, average E/e’ ratio, LA volume index and peak tricuspid regurgitation velocity are recommended for use as indices for identification of diastolic dysfunction (10). However, no current population-based cohort has yet the power to examine the predictive value of these newest indices, but several including the Tromsø Study have the possibility to validate the older guidelines, but so far this has not been done. Redfield et al. validated a tissue Doppler, mitral and pulmonary vein flow derived definition of diastolic dysfunction against total mortality in a general population, but only tissue Doppler indices is still part of guideline defined diastolic dysfunction (14). The latest guideline have been

validated against left ventricular end-diastolic pressure with a high negative predictive value 93% and area under the curve (AUC) of 0.78 (15), but only the individual components of the 2009 and 2016 guidelines have been validated against mortality and morbidity (16).

Our aim was to study the long-term risk of all-cause mortality according to diastolic dysfunction measured as LA diameter and the mitral flow Doppler markers such as DT and E/A ratio using a population-based cohort. In addition, we tested the hypothesis that outcome derived cut-off values of diastolic dysfunction indices are more accurate for predicting fatal outcomes than normal cut-off values derived from a general population.

Methods

Study population

The Tromsø Study was initiated in 1974 as a prospective cohort study with the primary aim of assessing the role of modifiable risk factors for cardiovascular diseases. The study design has been described in detail previously (17). At present, seven consecutive surveys have been conducted. Both total birth cohorts and random samples from the general population of the Tromsø municipality were invited to participate, and many of the participants attended several surveys. Echocardiography was performed on a random selection of participants in the Tromsø 4 (1994-1995), Tromsø 5 (2001) and Tromsø 6 (2007-2008) surveys.

A total of 3272 participants of the Tromsø 4 survey underwent echocardiographic examination. Of these, 1946 and 1462 had another echocardiographic examination in the Tromsø 5 and/or Tromsø 6 surveys, respectively (Fig. 1). The reason that some participants at Tromsø 4 did not have further echocardiography examinations at Tromsø 5 and Tromsø 6 are various. They include moving away from the Tromsø municipality (n=155, out of them n=21 died afterwards), emigration from Norway (n=18), non-attendance despite being invited (n=368) and death (n=457) between Tromsø 4 and Tromsø 6 survey dates.

For the purposes of this analysis we excluded those aged 50 years or younger (n=470), those with atrial fibrillation (n=39) during echocardiographic examination to prevent potential inaccuracy of DT measurements and those who had LVEF<50% (n=37) in the Tromsø 4 survey. Following these exclusions, 2734 participants were included in the analyses, each having had echocardiography at Tromsø 4 and possibly at later sweeps. The numbers included in analyses of specific endpoints were slightly smaller due to missing data on these parameters: 2616 participants for LA diameter analysis, 2691 participants for DT analysis, and 2699 participants for E/A ratio analysis. We included 1875 participants from the Tromsø 6 survey in additional analysis of the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio).

Data collection

Information on risk factors and comorbidities was obtained from self-administered questionnaires. Participants provided information on their date of birth, sex, current smoking (yes/no), leisure time physical activity and current use of antihypertensive treatment (yes/no), history of angina (yes/no), myocardial infarction (yes/no), stroke (yes/no) (17). Body mass index was defined as weight (kg)/height (m^2). Blood pressure was measured using an automated device Dinamap Pro care 300 Monitor (GE Medical Systems Information Technologies, Tampa, FL, USA). Three readings were made after 2 minutes' rest and separated by 1-minute intervals. The mean of the last two readings was

used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or self-reported use of antihypertensive medication. Non-fasting serum levels of total cholesterol and glycated haemoglobin (HbA1c) were measured according to the previously described procedure (17, 18).

Echocardiography imaging

The echocardiography in the Tromsø 4 survey was performed by two expert cardiologists using a Vingmed CFM 750 ultrasound scanner (Vingmed Sound A/S, Horten, Norway), and details have been described previously (7). In the Tromsø 5 and 6 surveys, Acuson Seqoia C258 or C512 scanner (Acuson, Mountain view, California, USA) were used (19). Coefficients of variation for intra- and interobserver variability in the Tromsø 4-6 surveys were less than 10% for chamber dimensions and Doppler-derived values (19, 20).

Echocardiographic assessment was performed with the use of standard imaging planes in the left lateral decubitus position according to ASE and EACVI recommendations (12). All of the echocardiographic measurements were performed online once per examination, but remeasured online if deviating from eye-balled estimates. M-mode echocardiography was used for LA diameter measurement. LA was measured from the posterior aortic wall to the posterior LA wall using both the parasternal long-axis and short axis view perpendicular to the aortic root long axis at the level of the aortic sinuses by using the leading-edge to leading-edge convention. LA diameter measurement was performed during end ventricular systole. Body surface area indexed LA diameter (LA BSA) as 1.5-2.3 cm/m^2 was considered as normal cut-off value range both for men and women. BSA was calculated by the Du Bois formula (BSA = [weight {kg} 0.425 × height {cm} 0.725] × 0.007184) (21).

Doppler examination was performed using the apical 4-chamber view with placing of the 2-mm Doppler sample volume between the mitral leaflet tips. For Doppler measurements the insonation angle was kept as perpendicular as possible toward the mitral inflow to obtain maximal velocity flow in early diastole. Spectral gain was adjusted until the flow curve became clear relatively to the background (22). Normal values of DT were considered as 140-220 ms. E/A ratio between 0.8-1.5 characterize a normal filling pattern (10). Values of E/e' ratio used in analysis were within 4-25.

Follow-up and outcome data

Subjects included in the analysis contributed to risk from the date of attendance of the Tromsø 4 survey until date of death, date of emigration from Norway or the end of follow-up on 31st December 2016, whichever came first. Of the 2734 aged > 50 years who had echocardiography at the Tromsø 4 survey, 1399 died during the follow-up period. Table I shows the numbers of participants and deaths according to which sweeps they were examined in. In the Cox

model we treated the indices of diastolic dysfunction as time varying covariates. Those participants who had repeat echocardiography examinations in T5 or T6, were still free of atrial fibrillation, and had LVEF≥50%, had their indices of diastolic dysfunction and values for other covariates updated. E/e' ratio was measured only in the Tromsø 6 survey, giving a follow-up of only 10 years for this parameter.

The all-cause mortality endpoint was identified by linkage of the participants to the National Causes of Death Registry at the Norwegian Institute of Public Health using personal identification number. Information on the participants who had emigrated from Tromsø was obtained through the Population Register of Norway.

Statistical methods

Means with standard deviations and proportions were used to describe baseline characteristics of the study participants according to the three categories of LA diameter (<1.5 cm/m^2; 1.5-2.3 cm/m^2; >2.3 cm/m^2), DT (<140 ms; 140-220 ms; >220 ms), and E/A ratio (<0.8; 0.8-1.5; >1.5). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively.

Associations of the three echocardiographic variables with all-cause mortality were assessed using time dependent Cox proportional hazards regression models with fractional polynomials of LA diameter, DT and E/A ratio as the main predictors. Baseline information for the participants can change during a follow-up period of 23 years. To take into account these changes we updated baseline information for those participants who also attended following surveys using time-dependent Cox regression. Models were tested for possible interactions between sex and LA diameter, DT, E/A ratio and E/e' ratio. We found no interaction between sex and LA diameter, sex and DT, sex and E/A ratio, or sex and E/e' ratio (p=0.489, p=0.696, p=0.199 and 0.730 respectively), and therefore results were presented for men and women combined. We chose the best-fitting fractional polynomials of LA diameter, DT, E/A ratio and E/e' ratio while adjusting for sex and fractional polynomials of age using the Akaike information criterion (23). Hazard ratios (HRs) were estimated for a range of LA diameter values from 1.1 to 4.0 cm/m^2, using 1.8 cm/m^2 as the reference value, for a range of DT levels from 80 to 300 ms with 155 ms as the reference value, for a range of E/A ratio levels from 0.3 to 4.0 with 1.1 as the reference value and for a range of E/e' ratio from 4 to 25 with 4 as the reference value. HRs with 95% confidence intervals (CIs) were adjusted for sex and fractional polynomials of age because we expected non-linear associations between age and endpoint. In order to estimate the independent effect of left ventricular filling indices on all-cause mortality we adjusted the model for systolic blood pressure, total cholesterol, body mass index, smoking, antihypertensive treatment, history of stroke, angina and myocardial infarction. Likelihood ratio test between a model with and model without fractional polynomial terms of LA diameter,

DT, E/A ratio or E/e' ratio were used to test the associations. The proportional hazard assumption was met in all models.

The best cut-off values for LA diameter, DT and E/A ratio were estimated using receiver operating characteristic (ROC) curves and AUCs. We used the maximum value of Youden's index as a criterion for selecting the optimal cut-off points for LA diameter, DT and E/A ratio (24). For the two latter with an U-shaped relation to risk, ROC curves were estimated for the upper and lower part of values separately.

A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were performed using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

Ethical considerations

The study conformed to the principles outlined in the Declaration of Helsinki, and the Tromsø Study protocol was approved by the Regional Committee for Medical and Health Research Ethics, North Norway (2009/2536/REK North). Informed consent was obtained from all individual participants included in the study.

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the study participants are presented according to the three ASE and EACVI categories of LA diameter (Table II), DT (Table III), and E/A ratio (Table IV).

LA diameter, DT, E/A and E/e' ratio's and all-cause mortality

We found that models with LA diameter, DT and E/A ratio adjusted for age and sex showed the very similar pattern of HRs compared to the fully adjusted models. We identified a U-shaped association between LA diameter and all-cause death (Fig. 2). When adjusted for sex and age, participants with LA diameter of 1.1 cm/m^2 had a higher risk of death compared with those with LA diameter of 1.8 cm/m^2 (HR=4.35; 95% CI 1.84 to 10.30). For values above the reference significant increase in the risk of death was observed starting from 2.1 cm/m^2 (HR=1.09; 95% CI 1.01 to 1.18). In the fully adjusted model, risk of death was 4.60 and 5.72 times higher for those with LA diameter of 1.1 cm/m^2 and 4.0 cm/m^2, respectively when compared to LA diameter of 1.8 cm/m^2.

LA diameter of 1.8 cm/m^2 corresponded to the lowest HR in both age- and sex-adjusted and fully adjusted models (Fig. 2) and accordingly we estimated the optimal cut-off points based on ROC curve analysis above and below this value. The AUC for LA diameter values ≤ 1.8 cm/m^2 was 0.56 (p=0.117). The optimal lower cut-off value for LA diameter was estimated as 1.7 cm/m^2. For those with LA diameter > 1.8 cm/m^2 the AUC value was 0.60 (p<0.001) with an optimal upper cut-off point for LA diameter of 2.3 cm/m^2 (Table V).

Association between mitral peak E DT and risk of all-cause death was U-shaped (Fig. 3). In the sex- and age-adjusted model, those with DT of 80 ms had approximately four times higher risk of death compared with the reference value of 155 ms (HR=4.65; 95% CI 2.37 to 9.12). Those with DT of 300 ms had a 55% increased risk of death compared with the reference value. In the fully adjusted model, when compared to the reference DT of 155 ms, HRs for DT of 80 ms and DT of 300 ms were 5.37 (95% CI 2.64 to 10.94) and 1.44 (95% CI 1.23 to 1.68), respectively. DT less than the reference of 155 ms was associated with increased risk of death starting from DT of 130 ms (HR=1.09; 95% CI 1.02 to 1.17) (Fig. 3).

The DT value of 155 ms conferred the lowest risk and the population was accordingly divided at this value. For those with DT levels ≤155 ms (AUC=0.56, p=0,030) an optimal cut-off point was 150 ms. AUC for those with DT >155 ms was 0.60, p<0.001. Here a value of 200 ms was the best cut-off point with 67% sensitivity and 50% specificity (Table V).

Similarly to LA and DT, the association between mitral valve E/A ratio and risk of death was U-shaped. Sex- and age-adjusted HRs of death for E/A ratio of 0.3 and for E/A ratio of 4.0 compared with E/A ratio of 1.1 was 4.63 and 5.00, respectively. In the fully adjusted model HRs for E/A ratio of 0.3 and of 4.0 in comparison with the reference value were 4.12 (95% CI 2.66 to 6.40) and 4.50 (95% CI 2.64 to 7.67), respectively (Fig. 4).

Results of the analysis of E/A ratio's and HR's showed that a value of 1.1 had the lowest HR and at this value the population was divided in two groups. Lower part of values with E/A ratio ≤ 1.1 had an AUC of 0.54, $p<0.001$. An optimal cut-off was considered as 0.6. Results of ROC curve analysis for those with E/A ratio > 1.1 showed that AUC was 0.58, $p<0.001$. The best cut-off value for E/A ratio >1.1 equals 1.2 with levels of sensitivity of 67% and specificity of 46% (Table V).

Optimal cut-off values for all-cause mortality derived from time-dependent Cox regression models adjusted for age and sex were 1.4-2.1 cm/m^2 for LA diameter, 120-185 ms for DT and 0.8-1.4 for E/A ratio (Table V).

Comparison between ROC curves and AUC's of models with new outcome derived, maximal Youden index based reference values with different variables showed that the largest AUC of 0.63 was estimated when LA diameter cut-off was combined with similarly derived cut-offs for DT and E/A ratio. Combination of LA diameter with DT gave similar AUC. Other combinations of LA diameter with left ventricular filling indices did not result in increase of AUC. HR derived cutoffs produced identical AUC's and were not presented.
ROC analysis using ASE and EACVI recommended cut-offs revealed the highest AUCs when LA diameter was combined with DT and with DT+E/A ratio. These combinations gave AUCs of 0.63.

We revealed a cubic association between E/e' ratio and all-cause mortality (Fig. 5). In the age- and sex-adjusted model those with E/e' of 25 had 3.48-fold increase of overall mortality risk in comparison with reference value of 4. In the fully-adjusted model the risk of all-cause mortality in those with the extreme E/e' value compared with E/e' of 4 was 4.54 (95% CI 1.80 to 11.44).
The AUC for models with E/e' ratio, LA diameter, DT, or E/A ratio as predictor of all-cause mortality from 2007 and onwards were 0.59 (95% CI 0.54-0.63), 0.60 (95% CI 0.55-0.64), 0.62 (95% CI 0.58-0.66), 0.60 (95% CI 0.56-0.64) respectively. No significant difference was found between the models with echocardiographic determinants of diastolic dysfunction and all-cause mortality.

Discussion

Results overview

Our study reveals that echocardiographic markers of diastolic dysfunction such as LA diameter, DT and E/A ratio can be used for prediction of all-cause mortality risk. We were able to estimate HRs for all of the described parameters, assess new outcome derived cut-off points for them and describe the best combinations of echocardiographic markers for all-cause mortality outcome prediction. The association remained U-shaped after additional adjustment for systolic blood pressure, body mass index, total cholesterol, smoking, antihypertensive treatment, history of stroke, angina and myocardial infarction. It shows that LA diameter, DT and E/A ratio each have independent effects on all-cause mortality also after adjustment for sex, age and cardiovascular risk factors. We also used all-cause mortality risk estimation models for assessing optimal cut-offs of the left ventricular filling indices. These cut-offs were slightly different from those obtained with maximal Youden index but gave identical prediction ability for all-cause mortality outcome.

Comparison with other studies

Left atrial diameter

LA diameter has been shown to be an important prognostic parameter of mortality in several but not all studies conducted in general population samples (5, 25). Pritchett et al. reported that BSA-indexed LA volume was not associated with all-cause mortality when adjusted for age, gender, ejection fraction and diastolic dysfunction grade (26). Diversity in results may be explained by differences in the study populations, methods of LA diameter measurement and indexation.

In our study, the HRs for LA diameter above the reference of 1.8 cm/m^2 increased from 1.12 (1.01-1.23) to 5.72 (3.65-8.95) in the fully adjusted model corresponding to previous publications (25). The underlying mechanisms linking an enlarged LA diameter with increased all-cause mortality have been described previously (27). Elevated LA filling pressures, decreased flow velocities in LA appendages, atrial fibrillation as well as structural heart disease and hypertension are among those mechanisms which result in all-cause mortality risk increase.

A novel finding of our study is that LA diameter below 1.5 cm/m^2 independently increases risk of all-cause death. This finding is supported by a few recent studies, however with several limitations. Aviram et al. found that decreased LA volume was associated with increased mortality risk in patients with acute pulmonary embolism (28). Rozenbaum et al. also reported that patients with very small LA volume index <24 ml/m^2 had HR of 3.6 (95% CI: 1.46-8.87) for all-cause mortality (29). Limitations of these studies were small sample sizes and short follow-up periods. Acquisition

of images in these studies were based on computed tomography. To our knowledge, there is no literature data on the association of small atrial diameters and all-cause mortality rates based on two-dimensional echocardiography.

One of the possible explanation of association between small LA size and mortality could be a decrease of LA emptying fraction, a functional parameter, which is independently associated with LA remodeling and mortality prediction (30).

According to our findings 11 individuals with LA diameter <1.5 cm/m^2 died during the follow-up. Cause of death of two individuals was not established. Only one person had myocardial infarction as cause of death indicating a maximal possible proportion of cardiovascular death to 30%. In patients with LA diameter >2.3 cm/m^2, most of the mortality were due to myocardial infarction 191 (40.1%) and ischemic heart disease 78 (16.4%). Other causes of death in this group were; stroke 48 (10.1%), sudden death 10 (2.1%) and subarachnoid haemorrhage 1 (0.2%) indicating less than half the risk of CVD death for small atria compared to enlarged.

We defined lower and upper cut-offs with optimal sensitivity and specificity levels using the Youden index. Thus, lower reference cut-off value for LA diameter was 1.7 cm/m^2 (ROC curve p-value=0.117) which is higher than the ASE and EACVI recommended value of 1.5 cm/m^2. According to our findings the value of 1.5 cm/m^2 has a higher sensitivity level of 81% which corresponds to the higher negative predictive value. The upper cut-off point was 2.3 cm/m^2 with a 46% sensitivity and 71% specificity and had significantly higher risk than 2.1 cm/m^2, which conforms to recent recommendations (12).

Mitral peak E deceleration time

In our study the optimal cut-off level for lower DT reference value was defined as 150 ms which is higher than the current normality-based cut-off of 140 ms (10). It was a key parameter in Redfield definition (14) and has shown strong independent predictive ability in patient population with myocardial infarction (31). Our results demonstrate that risk of all-cause mortality increased gradually with decreasing DT starting from 130 ms when compared with the reference value of 155 ms in the fully adjusted model. Our findings can be explained by the inverse relation of DT to the left ventricle filling pressure and association of a short DT with restrictive filling pattern, which increases the risk of left ventricular dilatation.

We found an optimal upper cut-off value of 200 ms with 67% sensitivity and 50% specificity for identification of a fatal outcome. Prolonged DT is associated with low left ventricular filling pressures and impaired ventricular relaxation, which lead to progression of diastolic dysfunction and heart failure. Although the prognostic value of

elevated DT has been documented before (32), this is the first estimation of the diagnostic accuracy of different DT values for prediction of all-cause mortality in a general population.

Unlike the U-shaped relationships between all-cause mortality and LA size or E/A ratio with a narrow normal range, DT effect is linked to extreme values at each end of a wide normal range in concordance with ASE and EACVI normality cut-offs. However, our approach of using outcome-derived values allowed narrowing the fraction of DT middle values and improves risk assessment non-significantly.

E/A ratio

Results from the second wave in the Strong Heart Study indicated that in middle-aged and elderly participants, an E/A ratio level above 1.5 was independently associated with a 2-fold increase in all-cause mortality risk (33). E/A levels below 0.6 were similarly associated with increased mortality risk. In our study the risk of all-cause mortality increased gradually for E/A values above 1.3. Risk of all-cause mortality increased also with decreasing E/A ratios starting from 0.8.

Analysis of the predictive ability of E/A ratio showed that optimal cut-offs differed from those recommended by ASE and EACVI. Thus, the lower optimal cut-off was found as 0.6 with a corresponding 17% sensitivity and 89% specificity. Upper cut-off value of 1.2 had a specificity level of 46% which is lower than ASE and EACVI guideline based E/A ratio value of 1.5 (specificity 59%) with all-cause mortality as outcome.

E/e' ratio

Our findings suggest that an elevated E/e' ratio is independently associated with increased risk of all-cause mortality in a general population. This is in contrast to Mogelvang et al. in the Copenhagen City Heart Study who found no association of E/e' with overall mortality (34). Kuznetsova et al. reported borderline association of E/e'ratio and risk of cardiac events (16). These studies had 90 and 59 cases respectively and half the follow up time of our study where 240 cases and 10 years follow up increases power in support of our finding. Interestingly E/e' did not have a superior predictive ability for overall mortality when compared with other diastolic dysfunction markers.

Comparison of prognostic values of LA diameter, DT and E/A

We aimed to explore the hypothesis that reference values based on outcome data would predict all-cause mortality better than those recommended by ASE and EACVI. The outcome-derived model, which combines LA diameter, DT and E/A ratio showed the best prediction on all-cause mortality, but not significantly different from the model with only LA diameter and DT included.

Using the cut-off values from current ASE and EACVI classification of diastolic dysfunction gave the same AUCs for LA diameter as Youden index based outcome derived cut-offs. For models with the three variables combined the largest AUC was detected in LA diameter+DT+E/A ratio model (AUC=0.63, $p<0.001$) which was the same as in a model with ASE and EACVI cut-off values. When assessing the incremental value of each parameter both DT and E/A ratio added prognostic value to LA diameter, but E/A ratio did not add to the prognostic accuracy of LA diameter in combination with DT.

Study strengths and limitations

This was a large prospective population-based study with a long follow-up period. The prospective design of the Tromsø study and a random sample of a large age span from the general population with a high attendance rate increases generalizability to other Caucasian populations. Another strength was the updating of baseline values as the participants attended following surveys. Although biplane or 3D echocardiography are now regarded as the most accurate methods of LA volume estimation, M-mode anteroposterior LA diameter has higher intra- and interobserver reproducibility especially while assessing minimal atrial dimensions (35).

A main limitation of the study is that we used M-mode based linear measurements of LA which is less accurate than those based on LA volumes performed by biplane method. Unfortunately, LA echocardiographic data from the Tromsø 4-6 surveys contain only M-mode measurements. Our findings need validation using LA volumes which will be explored in future studies. The raw images from Tromsø 4-6 surveys are available as well as measurements of volumes from the latest Tromsø 7 survey (2015-2016) which when enough endpoints have occurred, will give us the possibility to perform further analysis of LA volumes and diastolic dysfunction patterns according to the recent recommendations. Tricuspid regurgitation was not measured in the Tromsø 4-6 surveys. E/A ratio pseudonormal filling pattern was not considered in our study. However, individuals with severe left ventricular dysfunction were excluded from the study, and we suppose that influence of pseudonormalisation was relatively small. Information on smoking, current use of antihypertensive treatment, and history of angina, myocardial infarction and stroke was self-reported. It could potentially result in the presence of information bias. Models were not adjusted for laboratory markers such as N-terminal pro brain natriuretic peptide due to inconsistent presence of these parameters in all studied waves of the Tromsø Study. The maximal Youden index as classic data-driven approach for optimal cut-off estimation has its own disadvantages. The main is that Youden index is not sensitive for differences in the sensitivity and specificity of the test. To avoid the limitation we presented optimal cut-off points based on HR's along with cut-off values based on maximal Youdex index. The study only assesses the ability to predict mortality. As presence of

diastolic dysfunction is associated with an increased risk of developing heart failure as well as death, estimation of cut-off values based on a composite endpoint of death and heart failure could have yielded different results and potentially a higher predictive accuracy.

Conclusions

Our study concludes that not only enlarged but also small LA diameter is associated with increased all-cause mortality risk. Using our new outcome derived cut-offs of LA diameter, DT and E/A ratio did not result in a better predictive ability for all-cause mortality in comparison with current ASE and EACVI recommended cut-off points. A combination of the Doppler based LV filling parameter DT with LA diameter is preferable while assessing risk of all-cause mortality, while E/A ratio did not add incremental value.

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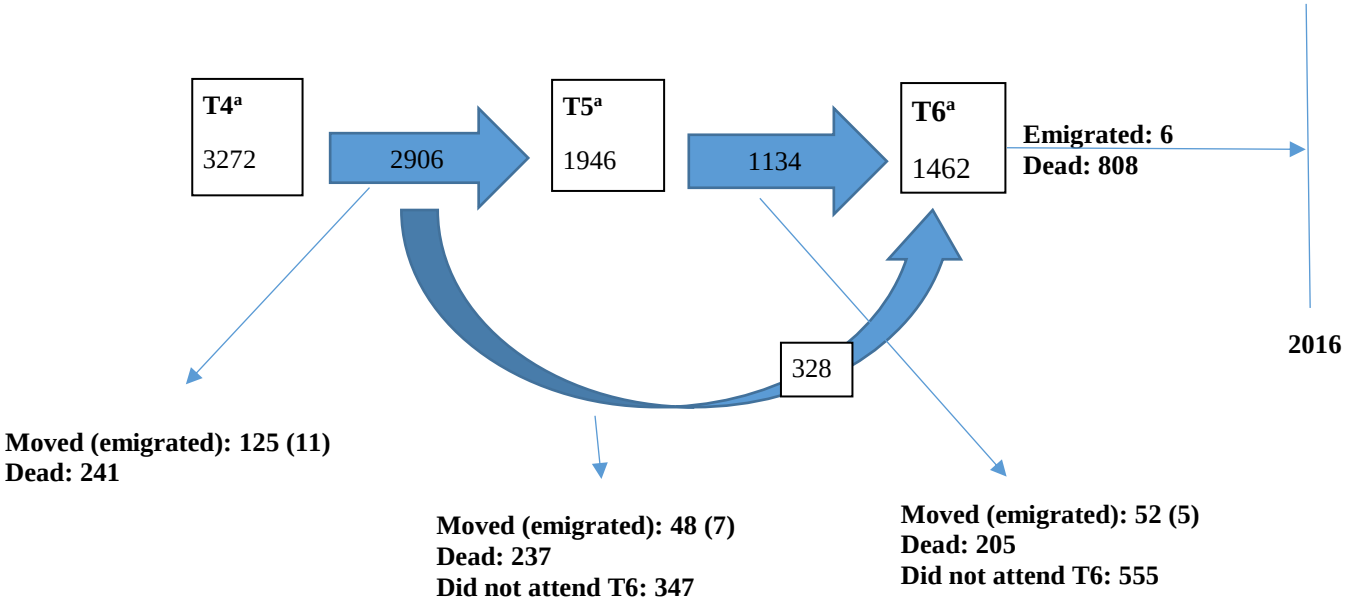
Conflict of Interest

The authors declare that they have no conflict of interest.

Author contributions

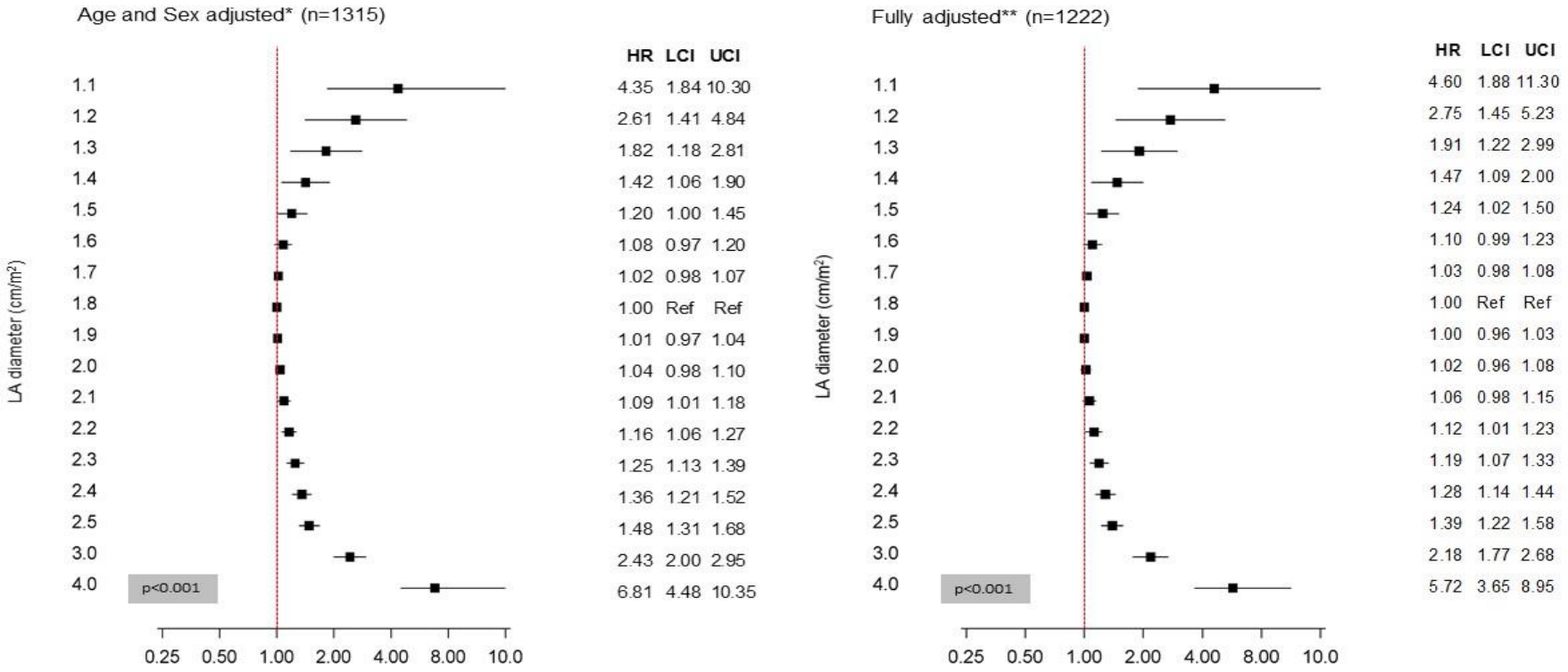
Michael Stylidis – Conceptualization, Study design, Statistical analysis, Methodology, Writing – original draft preparation; Ekaterina Sharashova – Methodology, Study design, Statistical analysis, Investigation, Writing – review and editing; Tom Wilsgaard – Methodology, Study design, Statistical Analysis, Validation, Writing – review and editing; David A. Leon – Formal analysis, Methodology, Validation, Supervision, Project administration, Writing – review and editing; Geir Heggelund – Data curation, Methodology, Writing – review and editing; Assami Rösner - Formal analysis, Methodology, Validation, Writing – review and editing; Inger Njølstad – Methodology, Data curation, Validation, Writing – review and editing; Maja-Lisa Løchen - Methodology, Data curation, Validation, Investigation, Writing – review and editing; Henrik Schirmer – Conceptualization, Study design, Data curation, Formal analysis, Methodology, Supervision, Project administration, Validation, Writing – review and editing.

Fig. 1 Flowchart of the participants with performed echocardiographic examination. The Tromsø Study



[a]Numbers in boxes represent numbers of subjects examined with echocardiography in each wave of the Tromsø Study

Fig. 2 Left atrial (LA) diameter and all-cause mortality. The Tromsø Study



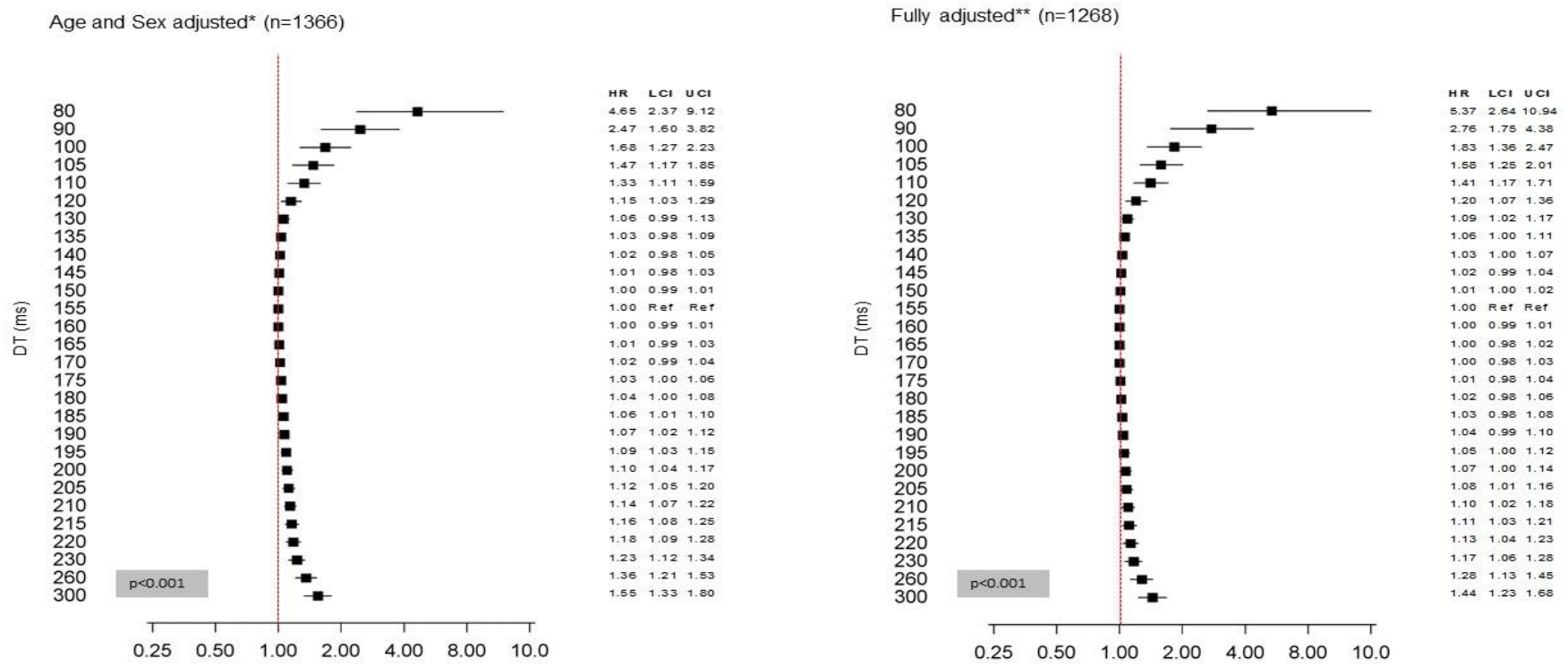
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of LA diameter

*Adjusted for sex and fractional polynomials of age

**Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

HR hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

Fig. 3 Mitral peak E deceleration time (DT) and all-cause mortality. The Tromsø Study



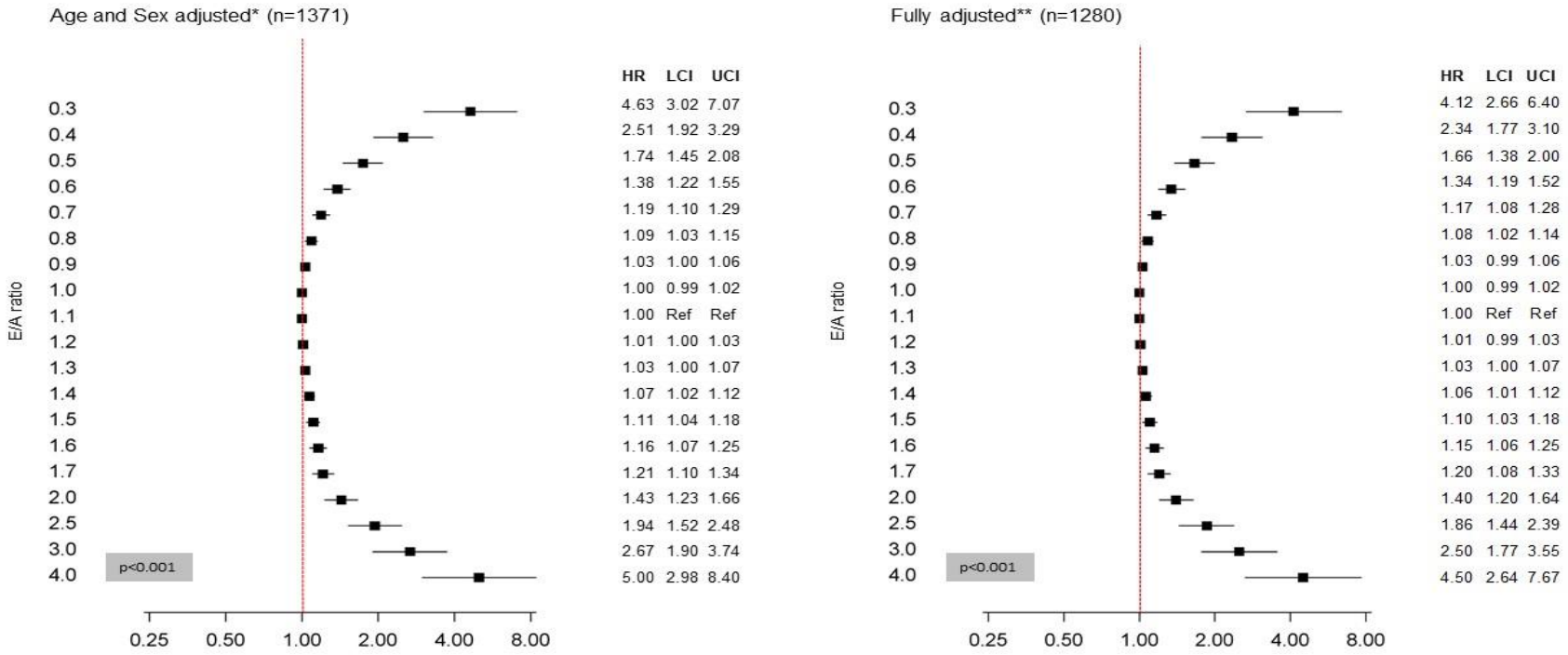
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of DT

*Adjusted for sex and fractional polynomials of age

**Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

HR hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

Fig. 4 Mitral peak E to peak A ratio and all-cause mortality. The Tromsø Study



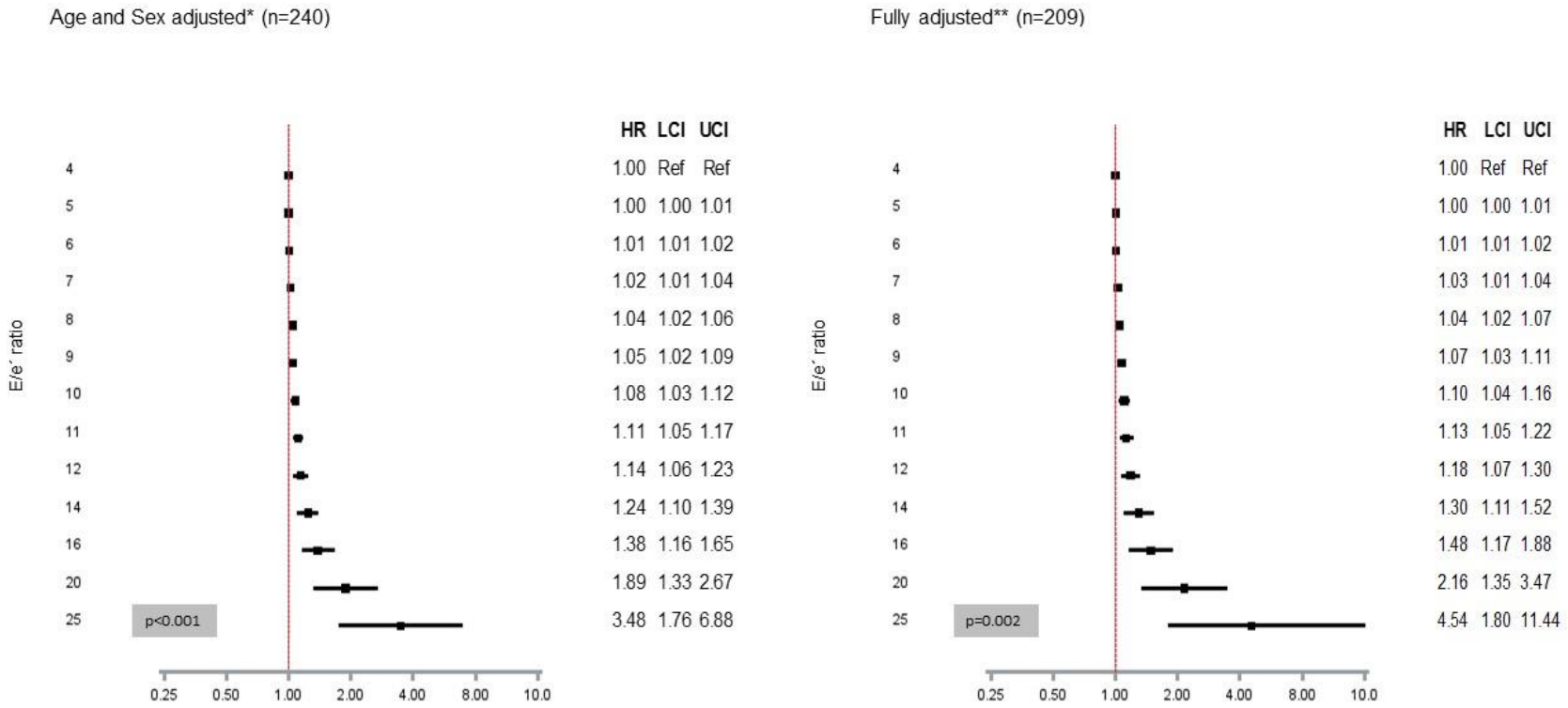
p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/A ratio

*Adjusted for sex and fractional polynomials of age

**Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

HR hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval

Fig. 5 Mitral peak E to peak e' ratio and all-cause mortality. The Tromsø Study



p-value: Likelihood ratio test between a model with and a model without fractional polynomial terms of E/e' ratio

*Adjusted for sex and fractional polynomials of age

**Adjusted for sex, fractional polynomials of age, mean systolic blood pressure, body mass index, total cholesterol, stroke, angina, myocardial infarction, smoking, antihypertensive treatment

HR hazard ratio, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interva

Tables

Table I Numbers of participants and deaths included in analyses according to the sweeps of the Tromsø Study in which they had echocardiographic examinations

	Number of participants	Number of deaths
Tromsø 4 only	914	710
Tromsø 4 + Tromsø 5	694	459
Tromsø 5 + Tromsø 6	252	61
Tromsø 4 + Tromsø 5 + Tromsø 6	874	169
Total	2734	1399

Table II Baseline characteristics of study participants by left atrial diameter (n=2616); the Tromsø Study 1994-1995

Characteristics	Left atrial diameter, cm/m^2			P value
	< 1.5 (n=24)	1.5 – 2.3 (n=1685)	> 2.3 (n=907)	
Death	11 (45.8)	780 (46.3)	524 (57.8)	<0.001
Sex (M-male, F-female)	M-12 (50.0) F-12 (50.0)	M-895 (53.1) F-790 (46.9)	M-392 (43.2) F-515 (56.8)	<0.001
Age, years	62.3 (7.1)	62.2 (6.1)	64.7 (6.3)	<0.001
BMI, kg/m^2	25.5 (3.4)	26.2 (3.9)	26.1 (4.0)	0.630
DBP, mm Hg	85.4 (9.6)	84.2 (12.1)	84.5 (13.1)	0.428
SBP, mm Hg	148.7 (21.0)	145.9 (21.4)	149.4 (23.0)	<0.001
Total cholesterol, mmol/L	6.40 (1.12)	6.84 (1.25)	6.81 (1.19)	0.215
HbA1c, %	5.27 (0.36)	5.49 (0.68)	5.49 (0.81)	0.199
History of stroke	1 (3.7)	34 (1.9)	30 (2.5)	0.486
History of angina	2 (7.7)	125 (7.1)	133 (11.8)	<0.001
History of myocardial infarction	0 (0.0)	91 (5.4)	79 (7.6)	0.076
Smoking	9 (36.7)	551 (31.9)	250 (28.6)	0.195
Physical activity				0.742
Low	3 (13.8)	196 (11.9)	122 (12.3)	

Moderate	5 (21.9)	645 (38.1)	336 (38.8)	
Active	13 (59.4)	749 (45.3)	394 (43.5)	
Highly active	1 (4.4)	73 (4.3)	42 (4.9)	
Antihypertensive treatment	4 (16.4)	173 (10.2)	200 (19.7)	<0.001
DT, ms	226.6 (64.5)	204.6 (43.2)	201.1 (46.7)	0.067
E/A ratio	0.85 (0.23)	0.96 (0.27)	1.02 (0.36)	0.086

Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

Table III Baseline characteristics of study participants by deceleration time (n=2691); the Tromsø Study 1994-1995

Characteristics	Deceleration time, ms			P value
	< 140 (n=71)	140 - 220 (n=1912)	> 220 (n=708)	
Death	39 (54.9)	863 (45.1)	464 (65.5)	<0.001
Sex (M-male, F-female)	M-27 (38.0) W-44 (62.0)	M-902 (47.2) W-1010 (52.8)	M-404 (57.0) W-304 (43.0)	<0.001
Age, years	62.8 (6.6)	62.4 (6.1)	65.1 (6.2)	<0.001
BMI, kg/m^2	26.7 (3.4)	26.1 (4.0)	26.3 (3.9)	0.307
DBP, mm Hg	86.2 (13.5)	83.7 (12.1)	86.0 (13.1)	<0.001
SBP, mm Hg	151.7 (23.0)	146.8 (21.7)	148.2 (22.9)	<0.001
Total cholesterol, mmol/L	7.00 (1.36)	6.88 (1.23)	6.68 (1.23)	0.006
HbA1c, %	5.52 (0.60)	5.48 (0.69)	5.52 (0.84)	0.073
History of stroke	2 (2.5)	41 (2.0)	26 (2.7)	0.441
History of angina	10 (12.5)	198 (9.6)	65 (6.7)	0.024
History of myocardial infarction	11 (14.8)	117 (6.0)	48 (5.6)	0.010
Smoking	17 (23.5)	588 (30.0)	243 (36.1)	0.006
Physical activity				0.225
Low	13 (18.0)	217 (11.5)	102 (13.3)	

Moderate	28 (39.3)	754 (39.5)	232 (34.7)	
Active	28 (39.5)	834 (44.2)	325 (46.7)	
Highly active	2 (2.8)	85 (4.4)	32 (4.8)	
Antihypertensive treatment	19 (26.5)	254 (13.0)	124 (14.6)	0.006
LA diameter, cm/m^2	2.29 (0.30)	2.21 (0.32)	2.17 (0.33)	0.070
E/A ratio	1.16 (0.49)	1.01 (0.29)	0.87 (0.24)	<0.001

Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

Table IV Baseline characteristics of study participants by mitral peak E to peak A ratio (n=2699); the Tromsø Study 1994-1995

Characteristics	E/A ratio			P value
	< 0.8 (n=786)	0.8 – 1.5 (n=1800)	> 1.5 (n=113)	
Death	510 (64.9)	811 (45.1)	50 (44.3)	<0.001
Sex (M-male, F-female)	M-367 (46.7) W-419 (53.3)	M-899 (49.9) W-901 (50.1)	M-68 (60.2) W-45 (39.8)	0.021
Age, years	65.9 (6.0)	62.1 (6.0)	62 (6.3)	<0.001
BMI, kg/m^2	26.8 (4.1)	25.9 (3.9)	24.9 (3.6)	<0.001
DBP, mm Hg	88.3 (13.3)	82.9 (11.8)	80.2 (11.5)	<0.001
SBP, mm Hg	152.3 (22.9)	145.4 (21.0)	143.1 (21.4)	<0.001
Total cholesterol, mmol/L	6.86 (1.25)	6.83 (1.23)	6.59 (1.13)	0.039
HbA1c, %	5.54 (0.87)	5.47 (0.67)	5.39 (0.50)	<0.001
History of stroke	31 (2.8)	35 (1.9)	3 (3.0)	0.209
History of angina	94 (8.4)	157(8.3)	19 (19.1)	0.002
History of myocardial infarction	63 (6.3)	94 (5.2)	18 (18.0)	<0.001
Smoking	238 (32.5)	581(31.3)	31 (25.1)	0.288
Physical activity				0.242
Low	122 (13.9)	208 (11.9)	7 (6.8)	

Moderate	280 (37.9)	687 (38.1)	46 (39.2)	
Active	348 (44.3)	790 (44.7)	53 (47.9)	
Highly active	24 (3.2)	89 (4.9)	6 (5.1)	
Blood pressure treatment	153 (15.9)	228 (12.7)	16 (15.8)	0.077
DT, ms	221.5 (52.1)	197.8 (38.6)	179.3 (35.5)	<0.001
LA diameter, cm/m^2	2.16 (0.32)	2.21 (0.31)	2.36 (0.41)	<0.001

Values in the table are mean (standard deviation) or number (%). Means (except for age) and proportions were adjusted for age using linear or logistic regression, respectively

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HbA1c* glycated haemoglobin, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *LA* left atrium

Table V Optimal cut-off values of left ventricular filling indices associated with all-cause mortality outcome; the Tromsø Study

		Optimal cut-off values[a]	Sensitivity/ Specificity, %	Youden index	AUC[*] (95% CI)	ROC curve p-value	Optimal cut-off values[b]
LA diameter, cm/m^2	Upper cut-off	2.3	46/71	0.17	0.60 (0.58-0.62)	<0.001	2.1
	Lower cut-off	1.7	71/46	0.16	0.56 (0.49-0.63)	0.117	1.4
DT, ms	Upper cut-off	200	67/50	0.17	0.60 (0.58-0.63)	<0.001	185
	Lower cut-off	150	98/18	0.16	0.56 (0.51-0.62)	0.030	120
E/A ratio	Upper cut-off	1.2	67/46	0.14	0.58 (0.53-0.63)	<0.001	1.4
	Lower cut-off	0.6	17/89	0.06	0.54 (0.52-0.57)	<0.001	0.8

[a]Optimal cut-off values for all-cause mortality outcome estimated according to the highest Youden index

[b]Optimal cut-off values for all-cause mortality outcome derived from time-dependent Cox regression models adjusted for age and sex

[*]AUCs for ranges which include optimal (maximal Youden index based) upper and lower cut-off values. Ranges are estimated above and below the values with lowest HRs for LA diameter: 1.8 cm/m^2; for DT: 155 ms; for E/A ratio: 1.1

LA left atrium, *DT* mitral peak E deceleration time, *E/A* mitral peak E to peak A ratio, *AUC* area under the curve, *ROC* receiver operating characteristic

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