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

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2 **Left atrial diameter, left ventricle filling indices and association with all-cause mortality. Results**

3 **from the population-based Tromsø Study**

4 **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

73   mortality (10, 13). In the latest guidelines septal and lateral e' peaks, average E/e' ratio, LA volume

74   index and peak tricuspid regurgitation velocity are recommended for use as indices for identification

75   of diastolic dysfunction (10). However, no current population-based cohort has yet the power to

76   examine the predictive value of these newest indices, but several including the Tromsø Study have the

77   possibility to validate the older guidelines, but so far this has not been done. Redfield et al. validated a

78   tissue Doppler, mitral and pulmonary vein flow derived definition of diastolic dysfunction against

79   total mortality in a general population, but only tissue Doppler indices is still part of guideline defined

80   diastolic dysfunction (14). The latest guideline have been validated against left ventricular end-

81   diastolic pressure with a high negative predictive value 93% and area under the curve (AUC) of 0.78

82   (15), but only the individual components of the 2009 and 2016 guidelines have been validated against

83   mortality and morbidity (16).

84   Our aim was to study the long-term risk of all-cause mortality according to diastolic dysfunction

85   measured as LA diameter and the mitral flow Doppler markers such as DT and E/A ratio using a

86   population-based cohort. In addition, we tested the hypothesis that outcome derived cut-off values of

87   diastolic dysfunction indices are more accurate for predicting fatal outcomes than normal cut-off

88   values derived from a general population.

89   **Methods**

90   **Study population**

91   The Tromsø Study was initiated in 1974 as a prospective cohort study with the primary aim of

92   assessing the role of modifiable risk factors for cardiovascular diseases. The study design has been

93   described in detail previously (17). At present, seven consecutive surveys have been conducted. Both

94   total birth cohorts and random samples from the general population of the Tromsø municipality were

95   invited to participate, and many of the participants attended several surveys. Echocardiography was

96   performed on a random selection of participants in the Tromsø 4 (1994-1995), Tromsø 5 (2001) and

97   Tromsø 6 (2007-2008) surveys.

98   A total of 3272 participants of the Tromsø 4 survey underwent echocardiographic examination. Of

99   these, 1946 and 1462 had another echocardiographic examination in the Tromsø 5 and/or Tromsø 6

100   surveys, respectively (Fig. 1). The reason that some participants at Tromsø 4 did not have further

101   echocardiography examinations at Tromsø 5 and Tromsø 6 are various. They include moving away

102   from the Tromsø municipality (n=155, out of them n=21 died afterwards), emigration from Norway

103   (n=18), non-attendance despite being invited (n=368) and death (n=457) between Tromsø 4 and

104   Tromsø 6 survey dates.

105   For the purposes of this analysis we excluded those aged 50 years or younger (n=470), those with

106   atrial fibrillation (n=39) during echocardiographic examination to prevent potential inaccuracy of DT

107   measurements and those who had LVEF<50% (n=37) in the Tromsø 4 survey. Following these

108   exclusions, 2734 participants were included in the analyses, each having had echocardiography at

109   Tromsø 4 and possibly at later sweeps. The numbers included in analyses of specific endpoints were

110   slightly smaller due to missing data on these parameters: 2616 participants for LA diameter analysis,

111   2691 participants for DT analysis, and 2699 participants for E/A ratio analysis. We included 1875

112   participants from the Tromsø 6 survey in additional analysis of the ratio of mitral peak velocity of

113   early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio).

114   **Data collection**

115   Information on risk factors and comorbidities was obtained from self-administered questionnaires.

116   Participants provided information on their date of birth, sex, current smoking (yes/no), leisure time

117   physical activity and current use of antihypertensive treatment (yes/no), history of angina (yes/no),

118   myocardial infarction (yes/no), stroke (yes/no) (17). Body mass index was defined as weight

119   (kg)/height (m^2). Blood pressure was measured using an automated device Dinamap Pro care 300

120   Monitor (GE Medical Systems Information Technologies, Tampa, FL, USA). Three readings were

121   made after 2 minutes' rest and separated by 1-minute intervals. The mean of the last two readings was

122   used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic

123   blood pressure ≥ 90 mm Hg or self-reported use of antihypertensive medication. Non-fasting serum

124   levels of total cholesterol and glycated haemoglobin (HbA1c) were measured according to the

125   previously described procedure (17, 18).

126   **Echocardiography imaging**

127   The echocardiography in the Tromsø 4 survey was performed by two expert cardiologists using a

128   Vingmed CFM 750 ultrasound scanner (Vingmed Sound A/S, Horten, Norway), and details have been

129   described previously (7). In the Tromsø 5 and 6 surveys, Acuson Seqoia C258 or C512 scanner

130   (Acuson, Mountain view, California, USA) were used (19). Coefficients of variation for intra- and

131   interobserver variability in the Tromsø 4-6 surveys were less than 10% for chamber dimensions and

132   Doppler-derived values (19, 20).

133   Echocardiographic assessment was performed with the use of standard imaging planes in the left

134   lateral decubitus position according to ASE and EACVI recommendations (12). All of the

135   echocardiographic measurements were performed online once per examination, but remeasured online

136   if deviating from eye-balled estimates. M-mode echocardiography was used for LA diameter

137   measurement. LA was measured from the posterior aortic wall to the posterior LA wall using both the

138   parasternal long-axis and short axis view perpendicular to the aortic root long axis at the level of the

139   aortic sinuses by using the leading-edge to leading-edge convention. LA diameter measurement was

140   performed during end ventricular systole. Body surface area indexed LA diameter (LA BSA) as 1.5-

141   2.3 cm/m^2 was considered as normal cut-off value range both for men and women. BSA was

142   calculated by the Du Bois formula (BSA = [weight {kg} 0.425 × height {cm} 0.725] × 0.007184)

143   (21).

144   Doppler examination was performed using the apical 4-chamber view with placing of the 2-mm

145   Doppler sample volume between the mitral leaflet tips. For Doppler measurements the insonation

146   angle was kept as perpendicular as possible toward the mitral inflow to obtain maximal velocity flow

147   in early diastole. Spectral gain was adjusted until the flow curve became clear relatively to the

148   background (22). Normal values of DT were considered as 140-220 ms. E/A ratio between 0.8-1.5

149   characterize a normal filling pattern (10). Values of E/e' ratio used in analysis were within 4-25.

150   **Follow-up and outcome data**

151   Subjects included in the analysis contributed to risk from the date of attendance of the Tromsø 4

152   survey until date of death, date of emigration from Norway or the end of follow-up on 31st December

153   2016, whichever came first. Of the 2734 aged > 50 years who had echocardiography at the Tromsø 4

154   survey, 1399 died during the follow-up period. Table I shows the numbers of participants and deaths

155   according to which sweeps they were examined in. In the Cox model we treated the indices of

156   diastolic dysfunction as time varying covariates. Those participants who had repeat echocardiography

157   examinations in T5 or T6, were still free of atrial fibrillation, and had LVEF≥50%, had their indices of

158   diastolic dysfunction and values for other covariates updated. E/e' ratio was measured only in the

159   Tromsø 6 survey, giving a follow-up of only 10 years for this parameter.

160   The all-cause mortality endpoint was identified by linkage of the participants to the National Causes of

161   Death Registry at the Norwegian Institute of Public Health using personal identification number.

162   Information on the participants who had emigrated from Tromsø was obtained through the Population

163   Register of Norway.

164   **Statistical methods**

165   Means with standard deviations and proportions were used to describe baseline characteristics of the

166   study participants according to the three categories of LA diameter (<1.5 cm/m^2; 1.5-2.3 cm/m^2; >2.3

167 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

168 age) and proportions were adjusted for age using linear or logistic regression, respectively.

169 Associations of the three echocardiographic variables with all-cause mortality were assessed using

170 time dependent Cox proportional hazards regression models with fractional polynomials of LA

171 diameter, DT and E/A ratio as the main predictors. Baseline information for the participants can

172 change during a follow-up period of 23 years. To take into account these changes we updated baseline

173 information for those participants who also attended following surveys using time-dependent Cox

174 regression. Models were tested for possible interactions between sex and LA diameter, DT, E/A ratio

175 and E/e' ratio. We found no interaction between sex and LA diameter, sex and DT, sex and E/A ratio,

176 or sex and E/e' ratio (p=0.489, p=0.696, p=0.199 and 0.730 respectively), and therefore results were

177 presented for men and women combined. We chose the best-fitting fractional polynomials of LA

178 diameter, DT, E/A ratio and E/e' ratio while adjusting for sex and fractional polynomials of age using

179 the Akaike information criterion (23). Hazard ratios (HRs) were estimated for a range of LA diameter

180 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

181 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

182 as the reference value and for a range of E/e' ratio from 4 to 25 with 4 as the reference value. HRs

183 with 95% confidence intervals (CIs) were adjusted for sex and fractional polynomials of age because

184 we expected non-linear associations between age and endpoint. In order to estimate the independent

185 effect of left ventricular filling indices on all-cause mortality we adjusted the model for systolic blood

186 pressure, total cholesterol, body mass index, smoking, antihypertensive treatment, history of stroke,

187 angina and myocardial infarction. Likelihood ratio test between a model with and model without

188 fractional polynomial terms of LA diameter, DT, E/A ratio or E/e' ratio were used to test the

189 associations. The proportional hazard assumption was met in all models.

190 The best cut-off values for LA diameter, DT and E/A ratio were estimated using receiver operating

191 characteristic (ROC) curves and AUCs. We used the maximum value of Youden's index as a criterion

192 for selecting the optimal cut-off points for LA diameter, DT and E/A ratio (24). For the two latter with

193   an U-shaped relation to risk, ROC curves were estimated for the upper and lower part of values

194   separately.

195   A two-sided p<0.05 was considered statistically significant. All statistical analyses were performed

196   using SAS statistical package, version 9.4 (SAS Institute, Cary, NC).

197   **Ethical considerations**

198   The study conformed to the principles outlined in the Declaration of Helsinki, and the Tromsø Study

199   protocol was approved by the Regional Committee for Medical and Health Research Ethics, North

200   Norway (2009/2536/REK North). Informed consent was obtained from all individual participants

201   included in the study.

202 **Results**

203 **Baseline characteristics**

204 The baseline clinical and echocardiographic characteristics of the study participants are presented

205 according to the three ASE and EACVI categories of LA diameter (Table II), DT (Table III), and E/A

206 ratio (Table IV).

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

208 We found that models with LA diameter, DT and E/A ratio adjusted for age and sex showed the very

209 similar pattern of HRs compared to the fully adjusted models. We identified a U-shaped association

210 between LA diameter and all-cause death (Fig. 2). When adjusted for sex and age, participants with

211 LA diameter of 1.1 cm/m^2 had a higher risk of death compared with those with LA diameter of 1.8

212 cm/m^2 (HR=4.35; 95% CI 1.84 to 10.30). For values above the reference significant increase in the

213 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

214 adjusted model, risk of death was 4.60 and 5.72 times higher for those with LA diameter of 1.1 cm/m^2

215 and 4.0 cm/m^2, respectively when compared to LA diameter of 1.8 cm/m^2.

216 LA diameter of 1.8 cm/m^2 corresponded to the lowest HR in both age- and sex-adjusted and fully

217 adjusted models (Fig. 2) and accordingly we estimated the optimal cut-off points based on ROC curve

218 analysis above and below this value. The AUC for LA diameter values ≤ 1.8 cm/m^2 was 0.56

219 (p=0.117). The optimal lower cut-off value for LA diameter was estimated as 1.7 cm/m^2. For those

220 with LA diameter > 1.8 cm/m^2 the AUC value was 0.60 (p<0.001) with an optimal upper cut-off point

221 for LA diameter of 2.3 cm/m^2 (Table V).

222

223 Association between mitral peak E DT and risk of all-cause death was U-shaped (Fig. 3). In the sex-

224 and age-adjusted model, those with DT of 80 ms had approximately four times higher risk of death

225 compared with the reference value of 155 ms (HR=4.65; 95% CI 2.37 to 9.12). Those with DT of 300

226 ms had a 55% increased risk of death compared with the reference value. In the fully adjusted model,

227 when compared to the reference DT of 155 ms, HRs for DT of 80 ms and DT of 300 ms were 5.37

228 (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

229 ms was associated with increased risk of death starting from DT of 130 ms (HR=1.09; 95% CI 1.02 to

230 1.17) (Fig. 3).

231 The DT value of 155 ms conferred the lowest risk and the population was accordingly divided at this

232 value. For those with DT levels ≤155 ms (AUC=0.56, p=0,030) an optimal cut-off point was 150 ms.

233 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

234 with 67% sensitivity and 50% specificity (Table V).

235 Similarly to LA and DT, the association between mitral valve E/A ratio and risk of death was U-

236 shaped. Sex- and age-adjusted HRs of death for E/A ratio of 0.3 and for E/A ratio of 4.0 compared

237 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

238 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%

239 CI 2.64 to 7.67), respectively (Fig. 4).

240 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

241 this value the population was divided in two groups. Lower part of values with E/A ratio ≤ 1.1 had an

242 AUC of 0.54, p<0.001. An optimal cut-off was considered as 0.6. Results of ROC curve analysis for

243 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

244 >1.1 equals 1.2 with levels of sensitivity of 67% and specificity of 46% (Table V).

245

246 Optimal cut-off values for all-cause mortality derived from time-dependent Cox regression models

247 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

248 ratio (Table V).

249

250 Comparison between ROC curves and AUC's of models with new outcome derived, maximal Youden

251 index based reference values with different variables showed that the largest AUC of 0.63 was

252 estimated when LA diameter cut-off was combined with similarly derived cut-offs for DT and E/A

253 ratio. Combination of LA diameter with DT gave similar AUC. Other combinations of LA diameter

254   with left ventricular filling indices did not result in increase of AUC. HR derived cutoffs produced

255   identical AUC's and were not presented.

256   ROC analysis using ASE and EACVI recommended cut-offs revealed the highest AUCs when LA

257   diameter was combined with DT and with DT+E/A ratio. These combinations gave AUCs of 0.63.

258

259   We revealed a cubic association between E/e' ratio and all-cause mortality (Fig. 5). In the age- and

260   sex-adjusted model those with E/e' of 25 had 3.48-fold increase of overall mortality risk in

261   comparison with reference value of 4. In the fully-adjusted model the risk of all-cause mortality in

262   those with the extreme E/e' value compared with E/e' of 4 was 4.54 (95% CI 1.80 to 11.44).

263   The AUC for models with E/e' ratio, LA diameter, DT, or E/A ratio as predictor of all-cause mortality

264   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-

265   0.66), 0.60 (95% CI 0.56-0.64) respectively. No significant difference was found between the models

266   with echocardiographic determinants of diastolic dysfunction and all-cause mortality.

267 **Discussion**

268 **Results overview**

269 Our study reveals that echocardiographic markers of diastolic dysfunction such as LA diameter, DT

270 and E/A ratio can be used for prediction of all-cause mortality risk. We were able to estimate HRs for

271 all of the described parameters, assess new outcome derived cut-off points for them and describe the

272 best combinations of echocardiographic markers for all-cause mortality outcome prediction. The

273 association remained U-shaped after additional adjustment for systolic blood pressure, body mass

274 index, total cholesterol, smoking, antihypertensive treatment, history of stroke, angina and myocardial

275 infarction. It shows that LA diameter, DT and E/A ratio each have independent effects on all-cause

276 mortality also after adjustment for sex, age and cardiovascular risk factors. We also used all-cause

277 mortality risk estimation models for assessing optimal cut-offs of the left ventricular filling indices.

278 These cut-offs were slightly different from those obtained with maximal Youden index but gave

279 identical prediction ability for all-cause mortality outcome.

280 **Comparison with other studies**

281 **Left atrial diameter**

282 LA diameter has been shown to be an important prognostic parameter of mortality in several but not

283 all studies conducted in general population samples (5, 25). Pritchett et al. reported that BSA-indexed

284 LA volume was not associated with all-cause mortality when adjusted for age, gender, ejection

285 fraction and diastolic dysfunction grade (26). Diversity in results may be explained by differences in

286 the study populations, methods of LA diameter measurement and indexation.

287 In our study, the HRs for LA diameter above the reference of 1.8 cm/m^2 increased from 1.12 (1.01-

288 1.23) to 5.72 (3.65-8.95) in the fully adjusted model corresponding to previous publications (25). The

289 underlying mechanisms linking an enlarged LA diameter with increased all-cause mortality have been

290 described previously (27). Elevated LA filling pressures, decreased flow velocities in LA appendages,

291 atrial fibrillation as well as structural heart disease and hypertension are among those mechanisms

292 which result in all-cause mortality risk increase.

293   A novel finding of our study is that LA diameter below 1.5 cm/m^2 independently increases risk of all-

294   cause death. This finding is supported by a few recent studies, however with several limitations.

295   Aviram et al. found that decreased LA volume was associated with increased mortality risk in patients

296   with acute pulmonary embolism (28). Rozenbaum et al. also reported that patients with very small LA

297   volume index <24 ml/m^2 had HR of 3.6 (95% CI: 1.46-8.87) for all-cause mortality (29). Limitations

298   of these studies were small sample sizes and short follow-up periods. Acquisition of images in these

299   studies were based on computed tomography. To our knowledge, there is no literature data on the

300   association of small atrial diameters and all-cause mortality rates based on two-dimensional

301   echocardiography.

302   One of the possible explanation of association between small LA size and mortality could be a

303   decrease of LA emptying fraction, a functional parameter, which is independently associated with LA

304   remodeling and mortality prediction (30).

305   According to our findings 11 individuals with LA diameter <1.5 cm/m^2 died during the follow-up.

306   Cause of death of two individuals was not established. Only one person had myocardial infarction as

307   cause of death indicating a maximal possible proportion of cardiovascular death to 30%. In patients

308   with LA diameter >2.3 cm/m^2, most of the mortality were due to myocardial infarction 191 (40.1%)

309   and ischemic heart disease 78 (16.4%). Other causes of death in this group were; stroke 48 (10.1%),

310   sudden death 10 (2.1%) and subarachnoid haemorrhage 1 (0.2%) indicating less than half the risk of

311   CVD death for small atria compared to enlarged.

312   We defined lower and upper cut-offs with optimal sensitivity and specificity levels using the Youden

313   index. Thus, lower reference cut-off value for LA diameter was 1.7 cm/m^2 (ROC curve p-

314   value=0.117) which is higher than the ASE and EACVI recommended value of 1.5 cm/m^2. According

315   to our findings the value of 1.5 cm/m^2 has a higher sensitivity level of 81% which corresponds to the

316   higher negative predictive value. The upper cut-off point was 2.3 cm/m^2 with a 46% sensitivity and

317   71% specificity and had significantly higher risk than 2.1 cm/m^2, which conforms to recent

318   recommendations (12).

319 **Mitral peak E deceleration time**

320 In our study the optimal cut-off level for lower DT reference value was defined as 150 ms which is

321 higher than the current normality-based cut-off of 140 ms (10). It was a key parameter in Redfield

322 definition (14) and has shown strong independent predictive ability in patient population with

323 myocardial infarction (31). Our results demonstrate that risk of all-cause mortality increased gradually

324 with decreasing DT starting from 130 ms when compared with the reference value of 155 ms in the

325 fully adjusted model. Our findings can be explained by the inverse relation of DT to the left ventricle

326 filling pressure and association of a short DT with restrictive filling pattern, which increases the risk of

327 left ventricular dilatation.

328 We found an optimal upper cut-off value of 200 ms with 67% sensitivity and 50% specificity for

329 identification of a fatal outcome. Prolonged DT is associated with low left ventricular filling pressures

330 and impaired ventricular relaxation, which lead to progression of diastolic dysfunction and heart

331 failure. Although the prognostic value of elevated DT has been documented before (32), this is the

332 first estimation of the diagnostic accuracy of different DT values for prediction of all-cause mortality

333 in a general population.

334 Unlike the U-shaped relationships between all-cause mortality and LA size or E/A ratio with a narrow

335 normal range, DT effect is linked to extreme values at each end of a wide normal range in

336 concordance with ASE and EACVI normality cut-offs. However, our approach of using outcome-

337 derived values allowed narrowing the fraction of DT middle values and improves risk assessment non-

338 significantly.

339 **E/A ratio**

340 Results from the second wave in the Strong Heart Study indicated that in middle-aged and elderly

341 participants, an E/A ratio level above 1.5 was independently associated with a 2-fold increase in all-

342 cause mortality risk (33). E/A levels below 0.6 were similarly associated with increased mortality risk.

343 In our study the risk of all-cause mortality increased gradually for E/A values above 1.3. Risk of all-

344 cause mortality increased also with decreasing E/A ratios starting from 0.8.

345 Analysis of the predictive ability of E/A ratio showed that optimal cut-offs differed from those

346 recommended by ASE and EACVI. Thus, the lower optimal cut-off was found as 0.6 with a

347 corresponding 17% sensitivity and 89% specificity. Upper cut-off value of 1.2 had a specificity level

348 of 46% which is lower than ASE and EACVI guideline based E/A ratio value of 1.5 (specificity 59%)

349 with all-cause mortality as outcome.

350 **E/e' ratio**

351 Our findings suggest that an elevated E/e' ratio is independently associated with increased risk of all-

352 cause mortality in a general population. This is in contrast to Mogelvang et al. in the Copenhagen City

353 Heart Study who found no association of E/e' with overall mortality (34). Kuznetsova et al. reported

354 borderline association of E/e'ratio and risk of cardiac events (16). These studies had 90 and 59 cases

355 respectively and half the follow up time of our study where 240 cases and 10 years follow up increases

356 power in support of our finding. Interestingly E/e' did not have a superior predictive ability for overall

357 mortality when compared with other diastolic dysfunction markers.

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

359 We aimed to explore the hypothesis that reference values based on outcome data would predict all-

360 cause mortality better than those recommended by ASE and EACVI. The outcome-derived model,

361 which combines LA diameter, DT and E/A ratio showed the best prediction on all-cause mortality, but

362 not significantly different from the model with only LA diameter and DT included.

363 Using the cut-off values from current ASE and EACVI classification of diastolic dysfunction gave the

364 same AUCs for LA diameter as Youden index based outcome derived cut-offs. For models with the

365 three variables combined the largest AUC was detected in LA diameter+DT+E/A ratio model

366 (AUC=0.63, p<0.001) which was the same as in a model with ASE and EACVI cut-off values. When

367 assessing the incremental value of each parameter both DT and E/A ratio added prognostic value to

368 LA diameter, but E/A ratio did not add to the prognostic accuracy of LA diameter in combination with

369 DT.

370 **Study strengths and limitations**

371   This was a large prospective population-based study with a long follow-up period. The prospective

372   design of the Tromsø study and a random sample of a large age span from the general population with

373   a high attendance rate increases generalizability to other Caucasian populations. Another strength was

374   the updating of baseline values as the participants attended following surveys. Although biplane or 3D

375   echocardiography are now regarded as the most accurate methods of LA volume estimation, M-mode

376   anteroposterior LA diameter has higher intra- and interobserver reproducibility especially while

377   assessing minimal atrial dimensions (35).

378   A main limitation of the study is that we used M-mode based linear measurements of LA which is less

379   accurate than those based on LA volumes performed by biplane method. Unfortunately, LA

380   echocardiographic data from the Tromsø 4-6 surveys contain only M-mode measurements. Our

381   findings need validation using LA volumes which will be explored in future studies. The raw images

382   from Tromsø 4-6 surveys are available as well as measurements of volumes from the latest Tromsø 7

383   survey (2015-2016) which when enough endpoints have occurred, will give us the possibility to

384   perform further analysis of LA volumes and diastolic dysfunction patterns according to the recent

385   recommendations. Tricuspid regurgitation was not measured in the Tromsø 4-6 surveys. E/A ratio

386   pseudonormal filling pattern was not considered in our study. However, individuals with severe left

387   ventricular dysfunction were excluded from the study, and we suppose that influence of

388   pseudonormalisation was relatively small. Information on smoking, current use of antihypertensive

389   treatment, and history of angina, myocardial infarction and stroke was self-reported. It could

390   potentially result in the presence of information bias. Models were not adjusted for laboratory markers

391   such as N-terminal pro brain natriuretic peptide due to inconsistent presence of these parameters in all

392   studied waves of the Tromsø Study. The maximal Youden index as classic data-driven approach for

393   optimal cut-off estimation has its own disadvantages. The main is that Youden index is not sensitive

394   for differences in the sensitivity and specificity of the test. To avoid the limitation we presented

395   optimal cut-off points based on HR's along with cut-off values based on maximal Youdex index. The

396   study only assesses the ability to predict mortality. As presence of diastolic dysfunction is associated

397   with an increased risk of developing heart failure as well as death, estimation of cut-off values based

398 on a composite endpoint of death and heart failure could have yielded different results and potentially

399 a higher predictive accuracy.

400 **Conclusions**

401 Our study concludes that not only enlarged but also small LA diameter is associated with increased

402 all-cause mortality risk. Using our new outcome derived cut-offs of LA diameter, DT and E/A ratio

403 did not result in a better predictive ability for all-cause mortality in comparison with current ASE and

404 EACVI recommended cut-off points. A combination of the Doppler based LV filling parameter DT

405 with LA diameter is preferable while assessing risk of all-cause mortality, while E/A ratio did not add

406 incremental value.

407 **Acknowledgements**

413 **Conflict of Interest**

414 The authors declare that they have no conflict of interest.

415 **Author contributions**

416 Michael Stylidis – Conceptualization, Study design, Statistical analysis, Methodology, Writing –

417 original draft preparation; Ekaterina Sharashova – Methodology, Study design, Statistical analysis,

418 Investigation, Writing – review and editing; Tom Wilsgaard – Methodology, Study design, Statistical

419 Analysis, Validation, Writing – review and editing; David A. Leon – Formal analysis, Methodology,

420 Validation, Supervision, Project administration, Writing – review and editing; Geir Heggelund – Data

421 curation, Methodology, Writing – review and editing; Assami Rösner - Formal analysis, Methodology,

422 Validation, Writing – review and editing; Inger Njølstad – Methodology, Data curation, Validation,

423 Writing – review and editing; Maja-Lisa Løchen - Methodology, Data curation, Validation,

424 Investigation, Writing – review and editing; Henrik Schirmer – Conceptualization, Study design, Data

425   curation, Formal analysis, Methodology, Supervision, Project administration, Validation, Writing –

426   review and editing.

427

References

1.   Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.

2.   Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.

3.   Wan SH, Vogel MW, Chen HH. Pre-Clinical Diastolic Dysfunction. J Am Coll Cardiol. 2014;63(5):407-16.

4.   Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. The Ochsner journal. 2009;9(4):191-6.

5.   Gardin JM, McClelland R, Kitzman D, Lima JA, Bommer W, Klopfenstein HS, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). The American journal of cardiology. 2001;87(9):1051-7.

6.   Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc. 2001;76(5):467-75.

7.   Tiwari S, Schirmer H, Jacobsen BK, Hopstock LA, Nyrnes A, Heggelund G, et al. Association between diastolic dysfunction and future atrial fibrillation in the Tromso Study from 1994 to 2010. Heart (British Cardiac Society). 2015;101(16):1302-8.

8.   Bouzas-Mosquera A, Broullon FJ, Alvarez-Garcia N, Mendez E, Peteiro J, Gandara-Sambade T, et al. Left atrial size and risk for all-cause mortality and ischemic stroke. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2011;183(10):E657-64.

9.   Zacharoulis A, Kotseroglou V, Lerakis S, Karavidas A, Arapi S, Zacharoulis A. Predictive value of C-reactive protein and left ventricular diastolic filling pattern after a non-ST elevation myocardial infarction. Am J Med Sci. 2006;331(3):113-8.

10.   Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

11.   Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014;63(6):493-505.

12.   Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.

13.   Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10(2):165-93.

14.   Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194-202.

476   15.   Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, et al. Echo-
477   Doppler estimation of left ventricular filling pressure: results of themulticentre EACVI Euro-
478   Filling study. European Heart Journal-Cardiovascular Imaging. 2017;18(9):961-8.
479   16.   Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of
480   left ventricular diastolic dysfunction in a general population. J Am Heart Assoc.
481   2014;3(3):e000789.
482   17.   Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I. Cohort profile: the
483   Tromso Study. Int J Epidemiol. 2012;41(4):961-7.
484   18.   Eggen AE, Mathiesen EB, Wilsgaard T, Jacobsen BK, Njolstad I. The sixth survey of
485   the Tromso Study (Tromso 6) in 2007-08: collaborative research in the interface between
486   clinical medicine and epidemiology: study objectives, design, data collection procedures, and
487   attendance in a multipurpose population-based health survey. Scand J Public Health.
488   2013;41(1):65-80.
489   19.   Eveborn GW, Schirmer H, Heggelund G, Rasmussen K. Incidence of aortic stenosis in
490   subjects with normal and slightly elevated aortic gradients and flow. Heart.
491   2015;101(23):1895-900.
492   20.   Schirmer H, Lunde P, Rasmussen K. Mitral flow derived Doppler indices of left
493   ventricular diastolic function in a general population; the Tromso study. Eur Heart J.
494   2000;21(16):1376-86.
495   21.   Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height
496   and weight be known. 1916. Nutrition. 1989;5(5):303-11; discussion 12-3.
497   22.   Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right
498   ventricular diastolic function: a technical guide for obtaining optimal flow velocity
499   recordings. J Am Soc Echocardiogr. 1997;10(3):271-92.
500   23.   Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous
501   Covariates - Parsimonious Parametric Modeling. Journal of the Royal Statistical Society
502   Series C-Applied Statistics. 1994;43(3):429-67.
503   24.   Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3(1):32-5.
504   25.   Nagarajarao HS, Penman AD, Taylor HA, Mosley TH, Butler K, Skelton TN, et al.
505   The predictive value of left atrial size for incident ischemic stroke and all-cause mortality in
506   African Americans: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke.
507   2008;39(10):2701-6.
508   26.   Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM.
509   Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol.
510   2005;45(1):87-92.
511   27.   Benjamin EJ, Dagostino RB, Belanger AJ, Wolf PA, Levy D. Left Atrial Size and the
512   Risk of Stroke and Death - the Framingham Heart-Study. Circulation. 1995;92(4):835-41.
513   28.   Aviram G, Soikher E, Bendet A, Shmueli H, Ziv-Baran T, Amitai Y, et al. Prediction
514   of Mortality in Pulmonary Embolism Based on Left Atrial Volume Measured on CT
515   Pulmonary Angiography. Chest. 2016;149(3):667-75.
516   29.   Rozenbaum Z, Granot Y, Turkeltaub P, Cohen D, Ziv-Baran T, Topilsky Y, et al.
517   Very Small Left Atrial Volume as a Marker for Mortality in Patients Undergoing Nongated
518   Computed Tomography Pulmonary Angiography. Cardiology. 2018;139(1):62-9.
519   30.   Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, et al. Left
520   atrial structure and function and clinical outcomes in the general population. Eur Heart J.
521   2013;34(4):278-85.
522   31.   Temporelli PL, Giannuzzi P, Nicolosi GL, Latini R, Franzosi MG, Gentile F, et al.
523   Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular
524   remodeling and survival after acute myocardial infarction - Results of the GISSI-3 echo
525   substudy. J Am Coll Cardiol. 2004;43(9):1646-53.

526   32.   Nielsen OW, Sajedieh A, Petersen F, Fischer Hansen J. Value of left ventricular filling
527   parameters to predict mortality and functional class in patients with heart disease from the
528   community. Eur J Echocardiogr. 2005;6(2):85-91.
529   33.   Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, et al. Mitral ratio of
530   peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and
531   elderly adults: the Strong Heart Study. Circulation. 2002;105(16):1928-33.
532   34.   Mogelvang R, Sogaard P, Pedersen SA, Olsen NT, Marott JL, Schnohr P, et al.
533   Cardiac dysfunction assessed by echocardiographic tissue Doppler imaging is an independent
534   predictor of mortality in the general population. Circulation. 2009;119(20):2679-85.
535   35.   Aune E, Baekkevar M, Roislien J, Rodevand O, Otterstad JE. Normal reference ranges
536   for left and right atrial volume indexes and ejection fractions obtained with real-time three-
537   dimensional echocardiography. Eur J Echocardiogr. 2009;10(6):738-44.
538

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)	M-895 (53.1)	M-392 (43.2)	<0.001
	F-12 (50.0)	F-790 (46.9)	F-515 (56.8)	
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)	M-902 (47.2)	M-404 (57.0)	<0.001
	W-44 (62.0)	W-1010 (52.8)	W-304 (43.0)	
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)	M-899 (49.9)	M-68 (60.2)	0.021
	W-419 (53.3)	W-901 (50.1)	W-45 (39.8)	
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

Figure legends

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

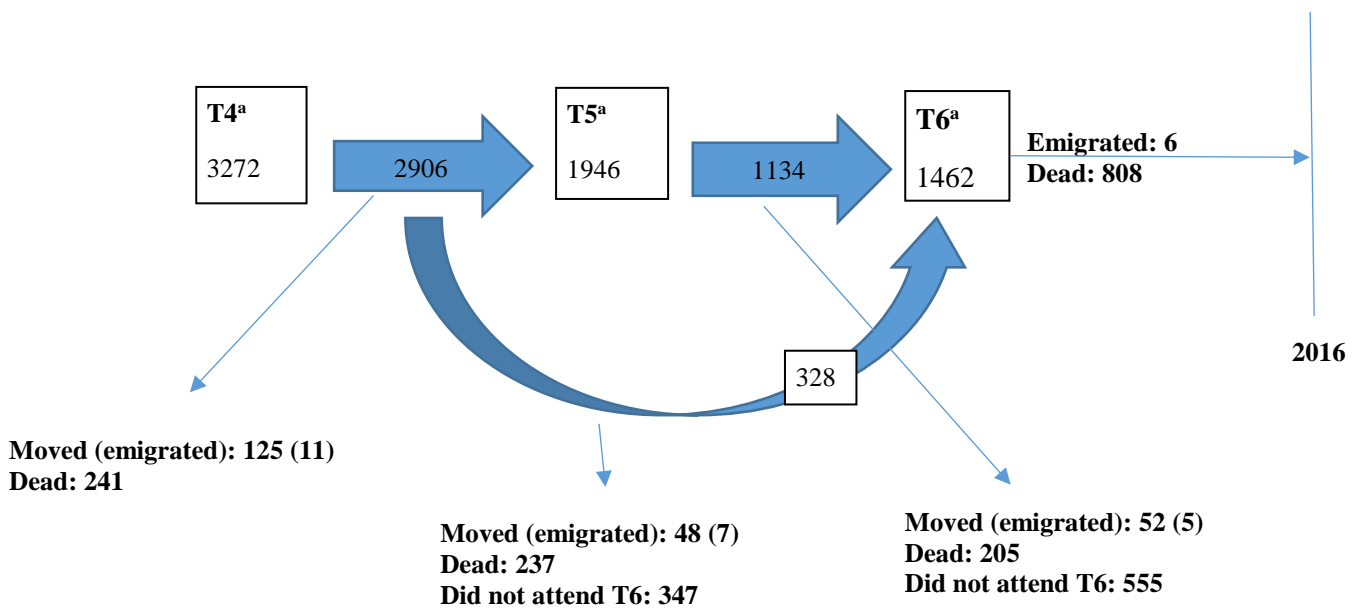**Fig. 4** Mitral peak E to peak A ratio and all-cause mortality. The Tromsø Study

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
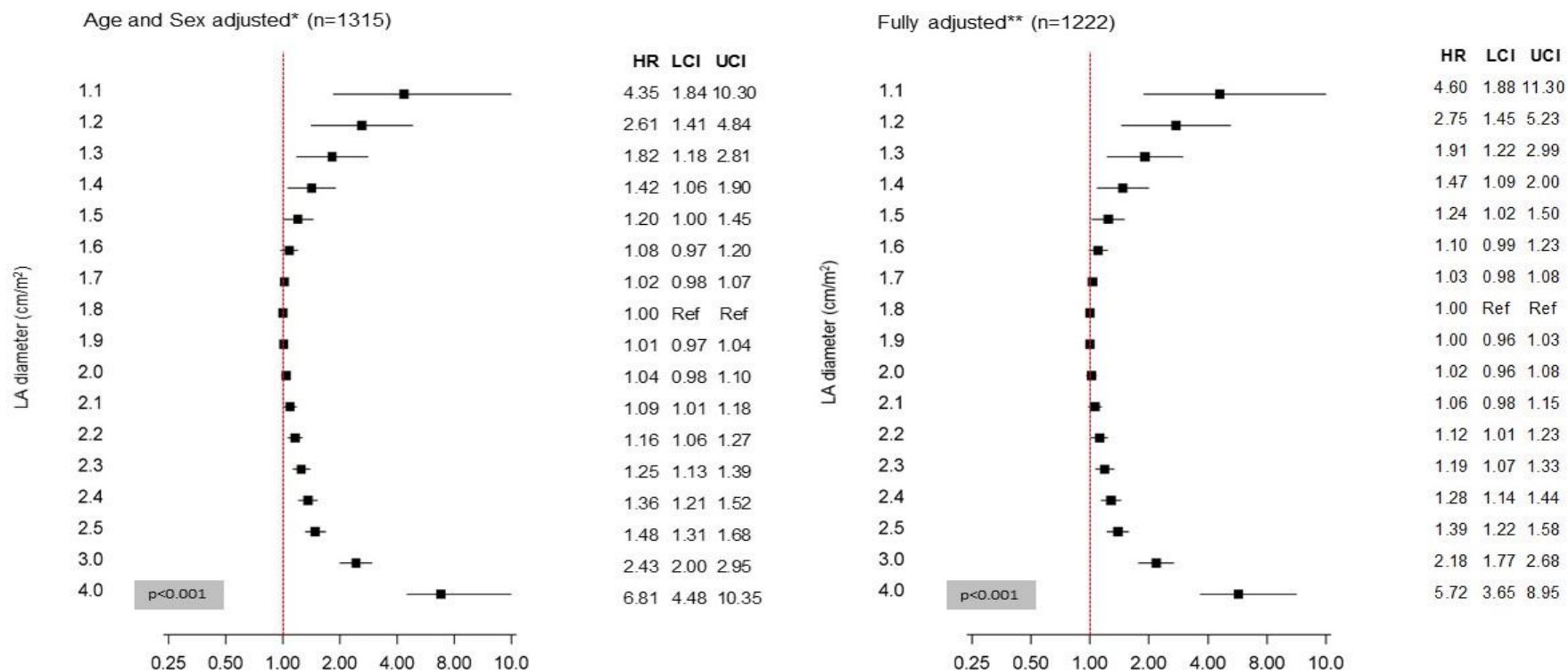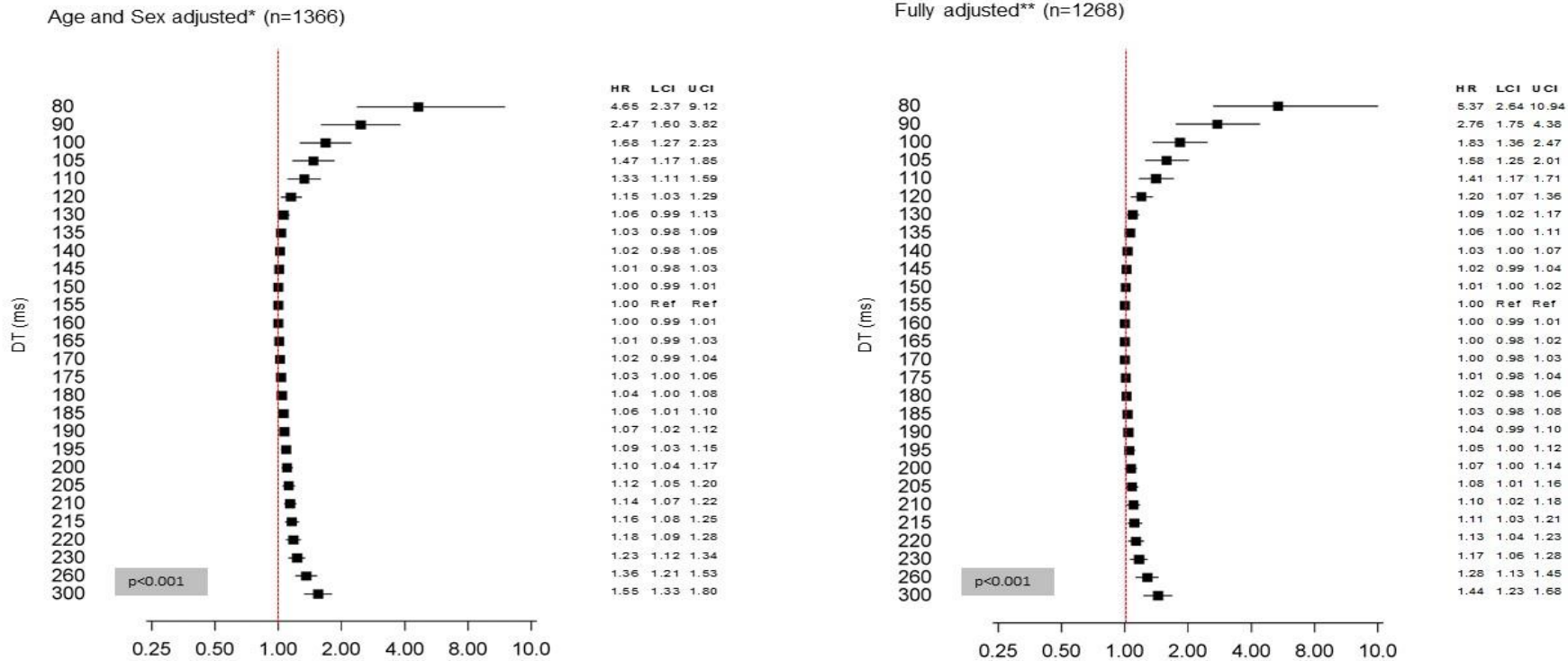
*Adjusted for sex and fractional polynomials of age

**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 interval

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

T4ᵃ 3272

2906

T5ᵃ 1946

1134

T6ᵃ 1462

Emigrated: 6
Dead: 808

328

2016

Moved (emigrated): 125 (11)
Dead: 241

Moved (emigrated): 48 (7)
Dead: 237
Did not attend T6: 347

Moved (emigrated): 52 (5)
Dead: 205
Did not attend T6: 555

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

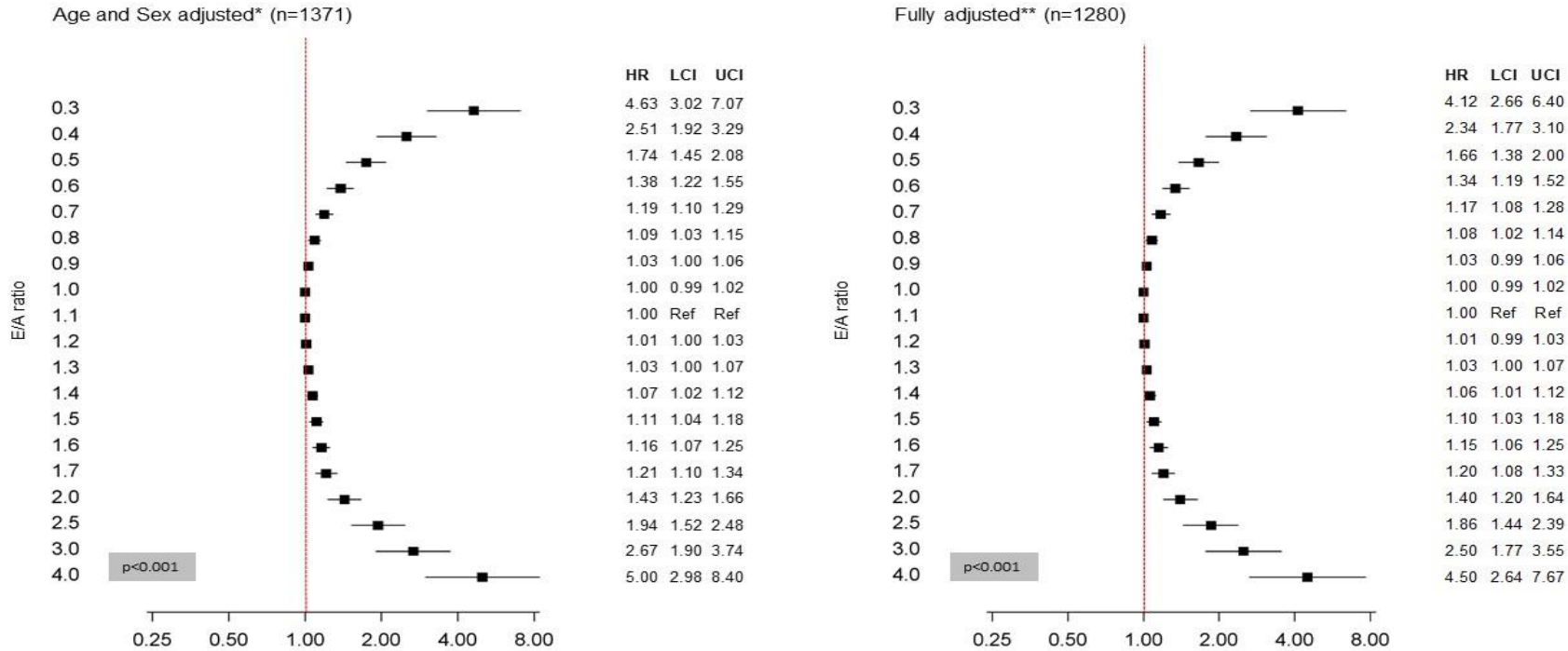**Fig. 3** Mitral peak E deceleration time (DT) and all-cause mortality. The Tromsø Study

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

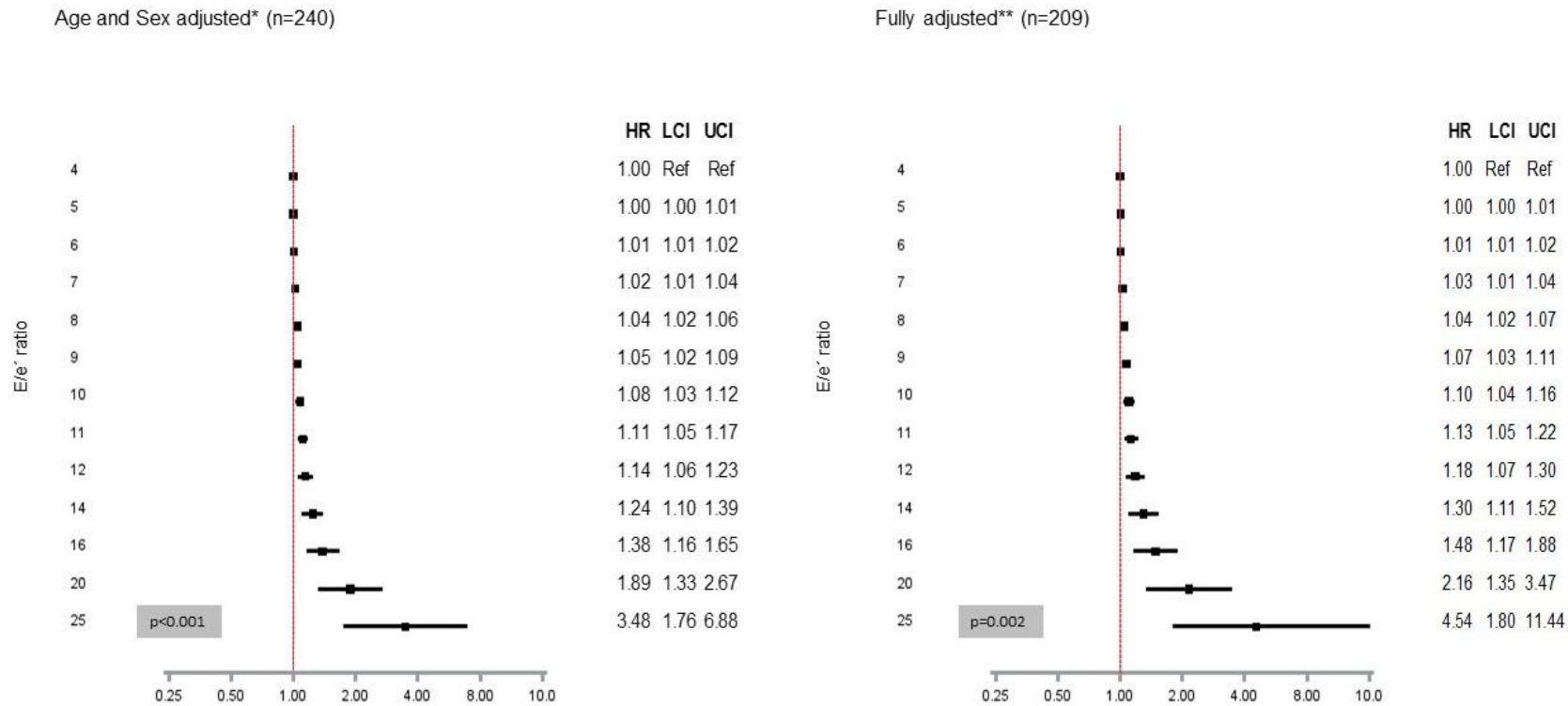**Fig. 4** Mitral peak E to peak A ratio and all-cause mortality. The Tromsø Study

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 interval