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1 **Cardiovascular event rates and mortality according to achieved systolic and diastolic blood**

2 **pressure in patients with stable coronary artery disease: an international cohort study**

3

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29 **Word count (main body):** 3494

30   **SUMMARY 289 words**

31   **Background.** The optimal blood pressure (BP) target in hypertension remains debated, especially in

32   coronary artery disease (CAD), given concerns for reduced myocardial perfusion if diastolic BP is too

33   low. We studied the relationship between achieved BP and cardiovascular outcomes in CAD patients

34   with hypertension.

35   **Methods.** We analysed data from 22,672 patients with stable CAD enrolled (November 2009–June

36   2010) in the CLARIFY registry (45 countries) and treated for hypertension. Systolic and diastolic BPs

37   before each event were averaged and categorised into 10-mmHg increments. The primary outcome

38   was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary outcomes

39   were each component of the primary outcome, all-cause death, and hospitalisation for heart failure.

40   Hazard ratios (HRs) were estimated with multivariable adjusted Cox proportional hazards models,

41   using the 120–129 systolic BP and 70–79 mmHg diastolic BP subgroups as reference.

42   **Findings.** After a median follow-up of 5.0 years, elevated systolic BP ≥140 mm Hg and diastolic BP

43   ≥80 mmHg were each associated with increased risk of cardiovascular events. Systolic BP <120

44   mmHg was also associated with increased risk for the primary outcome (adjusted HR 1·56 [95% CI

45   1·36–1·81]) and all secondary outcomes except stroke. Likewise, diastolic BP <70 mmHg was

46   associated with an increase in the primary outcome (adjusted HR 1·41 [1·24–1·61] for diastolic BP

47   60–69 mmHg and 2·01 [1·50–2·70] for <60 mmHg) and in all secondary outcomes except stroke.

48   **Interpretation.** In hypertensive patients with CAD from routine clinical practice, systolic BP <120

49   mmHg and diastolic BP <70 mmHg were each associated with adverse cardiovascular outcomes,

50   including mortality, supporting the existence of a J-curve phenomenon. This finding suggests caution

51   in the use of BP-lowering treatment in CAD patients

52   **Funding.** The CLARIFY registry was supported by Servier.

53

54

Introduction

Lowering blood pressure (BP) in patients with hypertension reduces the risk of cardiovascular events and death,[1,2] but the optimal target BP remains unresolved.[3-6] Randomised trials failed to demonstrate a benefit of targets <140/90 mmHg,[7,8] and post-hoc analyses have suggested that the benefit of BP-lowering treatment might even be reversed below a certain threshold,[5,9-16] the so-called "J-curve phenomenon".[9] Conversely, a large meta-analysis of trials that randomly assigned participants to intensive versus less-intensive BP-lowering treatment showed that intensive BP lowering was associated with decreased cardiovascular events, and the recent SPRINT trial[18] demonstrated that targeting a systolic BP <120 mmHg in high-risk patients was associated with a reduction in BP-related adverse outcomes, rather favouring a "lower is better" approach.

These contradictory results leave clinicians with uncertainty as to the optimal BP target in patients treated for hypertension. The concern for a J-curve phenomenon is particularly relevant for cardiac events,[10] as the heart is perfused during diastole, and its perfusion may be compromised at low diastolic BP values, especially in patients with coronary artery disease (CAD), both because a coronary stenosis will lower perfusion pressure in the downstream territory and because autoregulation is altered in these patients.[19] Our aim was to study the association between achieved BP levels and cardiovascular outcomes in a large cohort of patients with stable CAD treated for hypertension from the CLARIFY registry.

Methods

CLARIFY (ISRCTN43070564; www.clarify-registry.com) was a prospective longitudinal registry of 32,706 outpatients with stable CAD receiving standard care. The registry was observational, did not interfere with clinical management or mandate any test, procedure, or treatment.[20] Patients were enrolled in 45 countries (excluding the United States). Eligible patients had stable CAD, defined as at least one of the following: documented myocardial infarction >3 months before enrolment; angiographic demonstration of coronary stenosis >50%; chest pain with evidence of myocardial ischaemia (at least a stress electrocardiogram or preferably imaging); or coronary artery bypass graft or percutaneous coronary intervention >3 months before enrolment. These criteria were not mutually exclusive. Exclusion criteria were hospital admission for cardiovascular reasons (including revascularisation) in the past 3 months, planned revascularisation, or conditions compromising the

3

85 participation or 5-year follow-up (including severe other cardiovascular disease, e.g. advanced heart

86 failure, severe valve disease, history of valve repair/replacement).[20] In each practice, enrolment was

87 restricted over a brief period to achieve near-consecutive patient recruitment. The first patient was

88 included on 26 November 2009; recruitment was completed on 30 June 2010. This analysis was

89 restricted to patients treated for hypertension (see Figure S1 in the Supplementary Appendix).

90 Hypertension (with the usual 140/90 mmHg threshold) was defined as the combination of "treated

91 hypertension", which was a required item on the baseline form, and the use of at least one

92 antihypertensive agent at baseline. The study was conducted in accordance with the Declaration of

93 Helsinki and local ethical approval was obtained in all countries. All patients gave written informed

94 consent.

95

96 **Data collection**

97 The investigators completed standardised electronic case report forms at baseline and at a patient

98 visit every year±3 months for up to 5 years. For patients missing the yearly visit, telephone contact

99 with the patient, a designated relative or contact, or his/her physician was attempted. Where

100 applicable, registries could be used to retrieve the vital status. Several measures were implemented to

101 ensure data quality, including onsite monitoring visits of 100% of the data in 5% of centres selected at

102 random; regular telephone contact with investigators to limit missing data and loss to follow-up; and

103 centralised verification of the electronic case report forms for completeness, consistency, and

104 accuracy. At each yearly visit, symptoms, clinical examination, results of the main clinical and

105 biological tests, treatment and clinical outcomes were recorded. The registry was observational, with

106 no recommendation regarding BP management, and therefore reflects routine practice.

107

108 **BP analysis**

109 Office BP was measured yearly in patients, after a rest of 5 minutes in the sitting position. The main

110 analysis was performed using the arithmetic mean of all BP values measured throughout follow-up,

111 from the baseline visit to the visit before an event or, in patients without an event, up to the last visit.

112 Outcomes were also analysed according to the baseline BP value (BP at enrolment) and to the last

113 measured BP before an event during follow-up. All analyses were performed for systolic BP and

114 diastolic BP separately. Patients were categorised into 5 groups: systolic BP <120, 120–129

115   (reference), 130–139, 140–149, and ≥150 mmHg; diastolic BP <60, 60–69, 70–79 (reference), 80–89,

116   and ≥90 mmHg.

117

118   **Outcomes**

119   The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke.

120   Secondary outcomes were each component of the primary endpoint, all-cause death, and

121   hospitalisation for heart failure. For all composite outcomes, we analysed the number of patients with

122   at least one event from the composite outcome. Patients experiencing more than one contributing

123   event were counted only once. Events were accepted as reported by physicians and were not

124   adjudicated. However, all events were source-verified during audits.

125

126   **Statistical analysis**

127   A Cox proportional hazards model was used to evaluate the relationship between BP and

128   cardiovascular outcomes. In addition to crude HRs, adjusted HRs were estimated after adjustment for

129   potential confounding factors, selected using stepwise methods in the Cox proportional hazards

130   models, namely age, geographic region, smoking status, myocardial infarction, percutaneous coronary

131   intervention, diabetes, body mass index, glomerular filtration rate estimated with the chronic kidney

132   disease Epidemiology Collaboration (CKD-EPI) equation, peripheral artery disease, hospitalisation for

133   or symptoms of heart failure, left ventricular ejection fraction, stroke, transient ischaemic attack,

134   angiotensin-receptor blockers, diuretics, and aspirin (model 1). In a separate model, we also adjusted

135   for sex, coronary artery bypass grafting, low- and high-density lipoprotein cholesterol levels, ethnicity,

136   statins, angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and other

137   antihypertensive medications (model 2). Unless specified, all results are given for the fully adjusted

138   model. Data were analysed as recorded without any imputation for missing data. Adjustment variables

139   with a large amount of missing data were categorised including a category for missing data to

140   minimise the loss of data in the analysis.

141   A restricted cubic spline smoothing technique was used to interpolate the overall trend of risks

142   through the range of BP values. A sensitivity analysis excluding all patients with heart failure, defined

143   as previous hospitalisation for or symptoms of heart failure or a left ventricular ejection fraction <45%,

144   was also performed to ensure that results were not due to reverse causality.

145   Interactions between average systolic or diastolic BP and the covariates age (>75 *vs* ≤75

146   years), diabetes, history of stroke or transient ischaemic attack, heart failure, previous coronary

147   revascularisation, and chronic kidney disease (defined by an estimated glomerular filtration rate

148   [eGFR] <60 mL/min/1·73 m^2) at baseline were tested. Subgroup analyses were performed when

149   interactions were significant even after adjustment on the same variables as for the Cox proportional

150   hazards model (model 2).

151   The statistical analysis was performed using SAS (version 9.2, Cary, NC, USA), and the

152   restricted cubic splines were obtained using a SAS macro.[21]

153

154   **Role of the funding source**

155   The CLARIFY registry is supported by Servier. The sponsor had no role in the study design or in data

156   analysis, and interpretation; or in the decision to submit the manuscript for publication, but assisted

157   with the set-up, data collection and management of the study in each country. The corresponding

158   author had full access to all the data in the study and had final responsibility for the decision to submit

159   for publication.

160

161   **Results**

162   A total of 22,672 adult patients with CAD and hypertension were included in the analysis.

163   Demographic data and baseline characteristics of the patients, overall and for each 10-mmHg-

164   increment BP subgroup, are given in Tables 1 and 2; baseline medications are indicated in Table S1

165   of the supplementary appendix. Mean age at baseline was 65·2 years (SD 10·0), 17,019 (75%)

166   patients were men, and 15,190 (67%) were white. Compared to patients with high systolic BP, those

167   with a lower systolic BP tended to be younger, leaner, more likely to be men, without diabetes, and

168   current smokers, with a higher baseline incidence of myocardial infarction and percutaneous coronary

169   intervention, a lower prevalence of stroke, and lower baseline high-density and low-density lipoprotein

170   cholesterol levels. Patients with lower diastolic BP tended to be older, leaner, more likely to be women,

171   diabetic, and non-smokers, with lower baseline levels of low-density lipoprotein cholesterol. Mean

172   average systolic and diastolic BPs were 133·7 (SD 16·7) and 78·2 mmHg (SD 10·1), respectively.

173   Changes from baseline BP during follow-up were <2 mmHg, as expected from the non-interventional

174   nature of the study (Figure S2 of the supplementary appendix).

175   After a median follow-up of 5·0 years (interquartile range 4·5–5·1), 2101 patients (9·3%) met

176   the primary composite outcome. Cardiovascular death, all-cause death, myocardial infarction (fatal or

177   not), stroke (fatal or not), and hospitalisation for heart failure occurred in 1209 (5·3%), 1890 (8·3%),

178   827 (3·6%), 526 (2·3%), and 1306 (5·8%) patients, respectively.

179   Crude and adjusted HRs for average systolic and diastolic BP subgroups are given in Table 3.

180   Even after multiple adjustments for baseline cardiovascular disease, risk factors, and medication, a

181   steep J-shaped curve was evidenced for the occurrence of the primary outcome, with increased risk at

182   low and high BP values, both for systolic and diastolic BP (Figures 1 and 2). Compared with the

183   reference group (systolic BP 120–129), the adjusted HR for the primary outcome was 1·51 (95% CI

184   1·32–1·73) for systolic BP 140–149 mmHg, and 2·48 (95% CI 2·14–2·87) for systolic BP ≥150 mmHg.

185   Systolic BP <120 mmHg was also associated with an increased risk for the primary outcome (adjusted

186   HR 1·56 [95% CI 1·36–1·81]). Likewise, in comparison with a reference group of patients with diastolic

187   BP 70–79 mmHg, diastolic BP ≥80 mmHg was associated with an increased risk for the primary

188   outcome, with adjusted HRs 1·41 (1·27–1·57) for diastolic BP 80–89 mmHg and 3·72 (3·15–4·38) for

189   diastolic BP ≥90 mmHg; diastolic BP <70 mmHg was associated with an increase in the primary

190   outcome (adjusted HR 1·41 [1·24–1·61] and 2·01 [1·50–2·70] for diastolic BP 60–69 and <60 mmHg

191   respectively). A similar steep J-curve, for both systolic and diastolic BP, was seen for cardiovascular

192   death, all-cause death, myocardial infarction, and hospitalisation for heart failure, but not for stroke

193   (Figure 1 and Figure S3 in the Supplementary Appendix). Elevated systolic and diastolic BPs were

194   associated with a marked increase in the risk of stroke. Adjusted HRs were 1·51 (95% CI 1·16–1·97)

195   and 2·57 (1·94–3·41) for systolic BP 140–149 and ≥150 mmHg, respectively. Adjusted HRs were 1·46

196   (1·18–1·79) and 4·33 (3·15–5·94) for diastolic BP 80–89 and ≥90 mmHg, respectively. In contrast,

197   there was no increased risk of stroke after the same adjustments for the lowest systolic and diastolic

198   BP subgroups (adjusted HRs 1·06 [0·77–1·46] for systolic BP <120 mmHg and 1·23 [0·94–1·61] and

199   1·31 [0·64-2·69] for diastolic BP 60–69 and <60 mmHg, respectively). The results were similar

200   regardless of whether the fully adjusted model included baseline medications (data not shown). Similar

201   results were observed in a sensitivity analysis excluding patients with heart failure at baseline (Table

202   3), and similar trends were obtained when using baseline BP and last BP before an event or during

203   follow-up (Table S2 in the Supplementary Appendix). Evaluation of the assumption of non-

204   proportionality of the hazards in the Cox models suggested evidence that the strength of the

205 differences among the BP groups in their association with outcome was slightly attenuated with

206 increasing time. However this does not change the overall interpretation of the results.

207   Interaction analyses are presented in Table S3 in the Supplementary Appendix. No significant

208 effect-modification of diabetes, previous stroke or transient ischaemic attack, heart failure, previous

209 revascularisation, or chronic kidney disease at baseline was detected on the relationship between

210 systolic or diastolic BP and the primary outcome. However, a significant interaction with age was seen

211 for both systolic (p=0·0176) and diastolic BP (p=0·0180). Patients >75 years had an increased risk of

212 the primary outcome for systolic BP ≥150 mmHg (adjusted HR, 1·84 [1·40–2·43]) and systolic BP

213 <120 mmHg (adjusted HR 1·47 [1·12–1·94]), but not for systolic BP 140–149 mmHg (adjusted HR

214 1·19 [0·92–1·56]), whereas patients ≤75 years had an increased risk for the primary outcome in these

215 three BP subgroups in comparison with the 120–129-mmHg systolic BP subgroup. For diastolic BP,

216 the increased risk at low BP was only significant for diastolic BP <60 mmHg in patients >75 years,

217 whereas it was significant as early as 70 mmHg in the younger patients (Table 3 and Figure S4 in the

218 Supplementary Appendix).

219

220 **Discussion**

221 This observational study, conducted in "real-life" stable CAD patients treated for hypertension, shows

222 that low systolic (<120 mmHg) and low diastolic (<70 mmHg) BPs are associated with an increased

223 risk of cardiovascular events, with a steep J-curve not only for the composite of cardiovascular death,

224 myocardial infarction, or stroke, but also separately for cardiovascular death, all-cause death,

225 myocardial infarction, or hospitalisation for heart failure.

226   Our results are consistent with previous post-hoc analyses from randomised trials in patients

227 with hypertension and CAD.[10,12,19] Likewise, a J-curve (i.e. an increase in risk of cardiovascular events

228 below a certain BP level) has also been described in other high-risk populations, such as patients with

229 a previous cardiovascular event, or diabetes with target organ damage.[14,15] However, our study was

230 based on a large cohort from routine practice with no predefined BP intervention, which may confound

231 the analysis: any retrospective analysis of a BP-intervention trial will carry the bias of baseline BP,

232 which will differ between the groups defined by BP achieved during the trial. Additionally, the J-curve

233 phenomenon was robust and persisted after multiple adjustment procedures for potential confounders.

234   Previous observational studies have yielded conflicting results regarding the risk of stroke,

235   which was J-shaped with systolic BP in the post-hoc analysis of patients with previous stroke from the

236   PRoFESS trial[22] and was unaffected by the large decrease in systolic BP in the SPRINT trial,[18] but

237   decreased with decreasing diastolic or systolic BP with no evidence of a J-curve inflection in other

238   trials.[10-12,15] In our study, neither a low diastolic nor a low systolic BP was associated with increased

239   risk of stroke, in contrast with high systolic or diastolic BP, and no interaction between BP and

240   previous stroke was evidenced. The number of patients with a stroke was, however, smaller than that

241   for other endpoints.

242   In the debate about the J-curve concept, there is a concern for "reverse causality" (i.e. a low

243   systolic or diastolic BP may only be a marker of poor health rather than the cause of worse clinical

244   outcomes).[5,6,23] For instance, in patients with baseline systolic BP <130 mmHg from the ONTARGET

245   trial, Redon et al demonstrated that patients who had a cardiovascular event during follow-up had a

246   higher baseline risk but similar on-treatment BP reduction compared with those who did not have an

247   event, suggesting that the occurrence of cardiovascular events may be related to baseline vascular

248   disease rather than to an excessive BP reduction.[15] However, several lines of evidence argue against

249   this explanation for our findings. First, serious non-cardiovascular disease, conditions interfering with

250   life expectancy (e.g. cancer, drug abuse) and other severe cardiovascular disease (e.g. advanced

251   heart failure, severe valve disease, or history of valve repair/replacement) were exclusion criteria in

252   CLARIFY. Second, the association between low systolic and diastolic BP and increased risk was

253   robust and persisted throughout multiple adjustments, including adjusting for peripheral artery disease,

254   heart failure, left ventricular ejection fraction, and baseline medications, and also in a sensitivity

255   analysis excluding patients with heart failure. Finally, there was no association between low BP and

256   stroke. Altogether, these points strongly argue against reverse causality, but rather are in favour of a

257   direct deleterious effect of low BP on cardiovascular events.

258   A particular strength of our study is that it includes a large international cohort of patients,

259   treated in "real-life" conditions. Results from this broad representative cohort may have greater

260   external validity than the highly selected populations from randomised trials.[24] There is a concern that

261   low BP goals from randomised trials, when translated into routine practice, may be associated with

262   higher adverse effects or worse outcomes, especially in older patients.[3,25]

263   In light of discrepant results of tight BP control trials in patients with diabetes[7] or stroke[8] versus

264   neither of these conditions,[18] we examined interactions between BP lowering and these conditions and

265   found none, which is consistent with previous observations.[10,12,15] However, we found an interaction

266   between both systolic and diastolic BP and age. Interestingly, the J-curve for systolic BP was shifted to

267   the right in patients >75 years, which is in agreement with international guidelines, which advocate for

268   a higher target systolic BP of 150 mmHg in older patients.[26]

269   The SPRINT trial and a recent meta-analysis appeared to argue against a J-curve

270   phenomenon.[17,18] However, our observations are not inconsistent with their findings. In the recent

271   meta-analysis of more versus less intensive BP treatment, which included relatively old studies,[17] the

272   BP level reached in the more intensive BP-lowering treatment group was 133/76 mmHg *vs* 140/81

273   mmHg in the less intensive treatment group, so that the "strict control" BP arm remains clearly above

274   the potentially harmful thresholds we observed. Our results are also consistent with the SPRINT trial,

275   even though the BP reached in the intensive treatment group was fairly low (121·4/68·7 vs 136·2/76·3

276   mmHg in the standard treatment group), as unlike other BP intervention trials, the BP values in

277   SPRINT were measured under unattended conditions to minimise any white coat effect,[18] but may

278   underestimate casual BP values by at least 5–10 mmHg,[25] or up to 16 mmHg.[27] This actually led

279   hypertension experts to warn that the SPRINT target translated into community practice may have

280   deleterious effects[3,25] because the same targets obtained in routine practice would potentially lie within

281   the left part of the J-curve. Our results, which demonstrate a J-curve in patients with casual BP

282   measurements with harmful thresholds very close to the achieved BP obtained in the intensive arm of

283   SPRINT, indeed support this word of caution.

284   Our observations are in agreement with the fact that after decades of hypertension trials,[1,2] the

285   benefit of lowering BP <140 mmHg remains unquestionable, whereas the benefit of lowering BP to

286   <130 mmHg is uncertain.[7,8,13] These findings are in keeping with the HOPE-3 trial results in which

287   lowering BP was only beneficial when baseline BP was >140/90,[28] and with a meta-analysis of

288   randomised trials showing benefit of BP lowering only when systolic BP was >140 mmHg.[29] For

289   diastolic BP, a target <90 mmHg is undoubtedly beneficial,[1,30] but there is more uncertainty below this

290   threshold. Our study shows that a diastolic BP of 70–79 mmHg is associated with a better outcome

291   than a diastolic BP ≥80 mmHg, consistent with the SPRINT trial results,[18] but also strongly argues

292   against further lowering BP <70 mmHg.

293   Our results only apply to hypertensive patients with CAD and should not be extrapolated to

294   hypertensive patients with other conditions. Compared with post-hoc analyses of BP-lowering trials,

295   there are some disadvantages to using data from an observational registry, such as the open nature of

296   the information (including events), the possible lower accuracy of outcome identification, and the

297   greater heterogeneity of the treatment employed. In addition, the casual BP values from our study are

298   less accurate and standardised than in randomised trials or than BP values obtained from ambulatory

299   measurements; on the other hand, they are also more readily applicable to community practice. Also,

300   these observations derive from an observational study and are prone to confounding. Only dedicated

301   randomised controlled trials comparing BP targets can provide definitive evidence of the risk

302   associated with each BP threshold. In particular, our results call for specific trials to address whether

303   patients with a SBP >140 mmHg and a high pulse pressure should be treated with the goal of a

304   systolic BP <140 mmHg, even at the cost of a diastolic BP <70 mmHg, and whether the answer to that

305   question is different depending on the presence of CAD, a history of stroke, diabetes, or advanced

306   age.

307   In conclusion, this large observational international study shows that high but also low systolic

308   BP and diastolic BP levels are associated with an increased risk of cardiovascular events in CAD

309   patients with hypertension. The increased risk appears under a threshold of 120 mmHg for systolic BP

310   and 70 mmHg for diastolic BP. However, these observations should not slow down the constant effort

311   that is still necessary to improve patient care, as even with the conventional BP goal of <140/90

312   mmHg, only about half of the hypertensive population is controlled.[31]

313

314   **Contributors**

315   EVP designed the study, interpreted the data, designed tables and figures, and wrote the first draft

316   and subsequent iterations of the manuscript. IF and NG did the statistical analysis, designed tables

317   and figures, and reviewed and provided critical comments on drafts. RF, KMF, JCT, MT and LT

318   conceived and initiated the CLARIFY registry, coordinated the study and collected data in their

319   respective countries, and reviewed and provided critical comments on the manuscript. DLB provided

320   the initial idea for the study, interpreted the data, and provided critical comments on the manuscript.

321   PGS initiated and coordinated the CLARIFY registry, designed the study, interpreted the data, and

322   provided critical comments on the manuscript.

356 **References**

357 1.   Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure

358 lowering in hypertension: a critical reappraisal. *Circ Res* 2015; **116**(6): 1058-73.

359 2.   Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular

360 disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387**(10022): 957-67.

361 3.   Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended Blood Pressure

362 Measurements in the Systolic Blood Pressure Intervention Trial: Implications for Entry and Achieved

363 Blood Pressure Values Compared With Other Trials. *Hypertension* 2016; **67**(5): 808-12.

364 4.   Jones DW, Weatherly L, Hall JE. SPRINT: What Remains Unanswered and Where Do We Go

365 From Here? *Hypertension* 2016; **67**(2): 261-2.

366 5.   Mancia G, Grassi G. Aggressive blood pressure lowering is dangerous: the J-curve: pro side

367 of the arguement. *Hypertension* 2014; **63**(1): 29-36.

368 6.   Verdecchia P, Angeli F, Mazzotta G, Garofoli M, Reboldi G. Aggressive blood pressure

369 lowering is dangerous: the J-curve: con side of the arguement. *Hypertension* 2014; **63**(1): 37-40.

370 7.   Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in

371 type 2 diabetes mellitus. *N Engl J Med* 2010; **362**(17): 1575-85.

372 8.   Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent

373 lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; **382**(9891): 507-15.

374 9.   Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood

375 pressure. *Lancet* 1987; **1**(8533): 581-4.

376 10.   Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood

377 pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;

378 **144**(12): 884-93.

379 11.   Sleight P, Redon J, Verdecchia P, et al. Prognostic value of blood pressure in patients with

380 high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint

381 Trial study. *J Hypertens* 2009; **27**(7): 1360-9.

382 12. Bangalore S, Messerli FH, Wun CC, et al. J-curve revisited: An analysis of blood pressure and

383 cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010; **31**(23): 2897-908.

384 13. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and

385 cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease.

386 *JAMA* 2010; **304**(1): 61-8.

387 14. Mancia G, Schumacher H, Redon J, et al. Blood pressure targets recommended by guidelines

388 and incidence of cardiovascular and renal events in the Ongoing Telmisartan Alone and in

389 Combination With Ramipril Global Endpoint Trial (ONTARGET). *Circulation* 2011; **124**(16): 1727-36.

390 15. Redon J, Mancia G, Sleight P, et al, Safety and efficacy of low blood pressures among

391 patients with diabetes: subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in

392 combination with Ramipril Global Endpoint Trial). *J Am Coll Cardiol* 2012; **59**(1):74-83.

393 16. Sim JJ, Shi J, Kovesdy CP, Kalantar-Zadeh K, Jacobsen SJ. Impact of achieved blood

394 pressures on mortality risk and end-stage renal disease among a large, diverse hypertension

395 population. *J Am Coll Cardiol* 2014; **64**(6): 588-97.

396 17. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and

397 renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016; **387**(10017): 435-43.

398 18. Wright JT, Jr., Williamson JD, Whelton PK, et al. A randomized trial of intensive versus

399 standard blood-pressure control. *N Engl J Med* 2016; **373**(22): 2103-16.

400 19. Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease

401 or essential hypertension: exactly how essential? *J Am Coll Cardiol* 2009; **54**(20): 1827-34.

402 20. Steg PG, Greenlaw N, Tendera M, Tardif JC, Ferrari R, Al-Zaibag M, Dorian P, Hu D,

403 Shalnova S, Sokn FJ, Ford I, Fox KM; Prospective Observational Longitudinal Registry of Patients

404 With Stable Coronary Artery Disease (CLARIFY) Investigators. Prevalence of anginal symptoms and

405 myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery

406 disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med.*

407 2014;**174**:1651-9.

408 21. Heinzl H, Kaider A. SAS Technical Report KB-1-96: manual for the SAS macro RCS (version

409 2.0).

410 22. Ovbiagele B, Diener HC, Yusuf S, et al. Level of systolic blood pressure within the normal

411 range and risk of recurrent stroke. *JAMA* 2011; **306**(19): 2137-44.

412 23. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP, INDANA Project Steering Committee.

413 INdividual Data ANalysis of Antihypertensive intervention. J-shaped relationship between blood

414 pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient

415 data. *Ann Intern Med* 2002; **136**(6): 438-48.

416 24. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this

417 trial apply?". *Lancet* 2005; **365**(9453): 82-93.

418 25. Schiffrin EL, Calhoun DA, Flack JM. SPRINT Proves that Lower Is Better for Nondiabetic

419 High-Risk Patients, but at a Price. *Am J Hypertens* 2016; **29**(1): 2-4.

420 26. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of

421 arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European

422 Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;

423 **34**(28): 2159-219.

424 27. Filipovsky J, Seidlerova J, Kratochvil Z, Karnosova P, Hronova M, Mayer O, Jr. Automated

425 compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood*

426 *Press* 2016; **25**(4): 228-34.

427 28. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk

428 Persons without Cardiovascular Disease. *N Engl J Med* 2016; **374**(21): 2009-20.

429 29. Sundstrom J, Arima H, Woodward M, et al. Blood pressure-lowering treatment based on

430 cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014; **384**(9943): 591-8.

431 30. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and

432 low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment

433 (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351**(9118): 1755-62.

434 31. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of

435 hypertension, 1988-2008. *JAMA* 2010; **303**(20): 2043-50.

436

Research in context

Evidence before this study

We systematically searched PubMed without date or language restriction with the terms "J-curve",

"blood pressure OR hypertension", "Blood pressure target", "tight blood pressure control", "SPRINT",

"coronary artery disease" and synonyms or various combinations of those words to identify systematic

reviews, observational studies, randomised controlled trials, and meta-analysis describing the

relationship between achieved blood pressure (BP) and cardiovascular events and/or mortality, with a

last update in July 2016. We screened papers by title and abstract and title and full text in editorials to

identify articles relevant for the study aim. We also screened cited papers from the full-texts of these

articles for other relevant research. When restricting the search to original studies including only

patients with coronary artery disease (CAD), with a minimum of 500 patients, we identified post-hoc

analyses of three trials (INVEST, n=22,576; TNT, n=10,001; and ACTION, n=7,665), and no

observational study or randomised controlled trial devoted prospectively to explore the J-curve. Other

studies were based on BP trials that included subgroups of patients with CAD (ONTARGET, n=19,102

of 25,620 patients; VALUE, n=6981 of 15,244 patients; Syst-Eur, n=681 of 4695 patients; and HOT,

n=3080 of 18,790 patients). The papers cited in this article were selected to be representative of the

existing evidence both in patients with CAD and other populations, and reviews from before and after

the publication of the SPRINT trial are referenced.

Overall, although the benefits of BP-lowering treatment for the prevention of cardiovascular

disease and death in hypertensive patients were well established, the results of the studies derived

from these trials were conflicting regarding the existence of a "J-curve" or a threshold of achieved

systolic and diastolic BP within the physiological range under which antihypertensive treatment may be

harmful.

Added value of the study

In this contemporary international observational study in 22,672 hypertensive patients with CAD using

casual BP measurements, and in which there was no pre-specified intervention on BP, there was a

clear J-curve phenomenon. Achieved systolic BP <120 mmHg and achieved diastolic BP <70 mmHg

were both associated with an increased risk of cardiovascular events and mortality, independently of

potential confounding factors.

Implications of all the available evidence

467   Together with previous literature, our study suggests caution when treating CAD patients with

468   antihypertensive drugs. Future randomised controlled trials will be necessary to confirm the cut-off BP

469   value below which harm outweighs benefit in this population.

Figure legends

Figure 1: Forest plots of adjusted hazard ratio (95% CI) of the primary outcome (cardiovascular

death, myocardial infarction, or stroke), A), cardiovascular death (B), all-cause death (C),

myocardial infarction (D), or stroke (E), and hospitalisation for heart failure (F) by systolic

blood pressure (SBP) and diastolic blood pressure (DBP) increments

The analysis were adjusted for all the variables in the fully adjusted model (model 2), including age,

sex, geographic region, smoking status, myocardial infarction, percutaneous coronary intervention,

coronary artery bypass grafting, diabetes, low and high density lipoprotein cholesterol levels, body

mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of

heart failure, left ventricular ejection fraction, ethnicity, stroke, transient ischaemic attack, and baseline

medications (aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers,

beta-blockers, calcium channel blockers, diuretics and other antihypertensive medications).

Figure 2: Restricted cubic splines of the primary outcome versus average systolic (upper

panel) and diastolic (lower panel) blood pressure (BP)

Restricted cubic splines are represented for the association between average BP level and primary

composite outcome of cardiovascular death, myocardial infarction, or stroke. The analyses were

adjusted for a variables selected using stepwise methods in the Cox proportional hazards models,

namely age, geographic region, smoking status, myocardial infarction, percutaneous coronary

Intervention, diabetes, body mass index, glomerular filtration rate, peripheral artery disease,

hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, stroke, transient

ischaemic attack, angiotensin-receptor blockers, diuretics, and aspirin.

Table 1: Demographic and baseline characteristics of the patients, for the total population and each average on-treatment systolic blood-pressure subgroup

Parameter	Number of patients	Mean systolic BP categories						p value
		Total population (n=22,672)	<120 mmHg (n=2693)	120–129 mmHg (n=6946)	130–139 mmHg (n=7586)	140–149 mmHg (n=3584)	≥150 mmHg (n=1863)	
Age (years)	22,666	65·2 (10·0)	63·9 (10·4)	64·3 (10·2)	65·4 (9·8)	66·2 (9·6)	67·21 (9·8)	<0·0001
Men	22,672	17,019 (75%)	2104 (78%)	5399 (78%)	5677 (75%)	2578 (72%)	1261 (68%)	<0·0001
Body mass index (kg/m²)	22,654	27·7 (25·2–30·9)	26·7 (24·2–29·7)	27·5 (25·1–30·5)	27·9 (25·3–31·1)	28·4 (25·6–31·5)	28·4 (25·5–31·9)	<0·0001
Diabetes	22,670	7591 (33%)	835 (31%)	2160 (31%)	2545 (34%)	1306 (36%)	745 (40%)	<0·0001
Smoking status	22,672							
Current		2569 (11%)	352 (13%)	780 (11%)	861 (11%)	383 (11%)	193 (10%)	<0·0001
Former		10,158 (45%)	1254 (47%)	3222 (46%)	3325 (44%)	1553 (43%)	804 (43%)	
Never		9945 (44%)	1087 (40%)	2944 (42%)	3400 (45%)	1648 (46%)	866 (46%)	
Systolic BP (mmHg)	22,659	133·7 (16·7)	114·3 (10·7)	125·9 (10·3)	135·8 (11·3)	145·5 (13·4)	159·3 (16·4)	–
Diastolic BP (mmHg)	22,659	78·2 (10·1)	71·0 (8·8)	76·0 (8·4)	79·2 (9·2)	82·2 (10·3)	85·5 (11·7)	–
Heart rate (beats/minute)	22,660	68·5 (10·6)	67·4 (10·2)	67·9 (10·2)	68·7 (10·6)	69·4 (11·1)	69·6 (11·7)	<0·0001
Myocardial Infarction	22,670	13,258 (58%)	1789 (66%)	4165 (60%)	4298 (57%)	2017 (56%)	989 (53%)	<0·0001
Percutaneous coronary intervention	22,670	12,962 (57%)	1632 (61%)	4106 (59%)	4282 (56%)	1962 (55%)	980 (53%)	<0·0001
Coronary artery bypass graft surgery	22,670	5691 (25%)	676 (25%)	1658 (24%)	1894 (25%)	939 (26%)	524 (28%)	0·0019
Transient ischaemic attack	22,670	801 (4%)	74 (3%)	235 (3%)	277 (4%)	137 (4%)	78 (4%)	0·0652
Stroke	22,670	1089 (5%)	125 (5%)	327 (5%)	341 (4%)	181 (5%)	115 (6%)	0·0407
Hospitalisation for heart failure	22,670	1211 (5%)	219 (8%)	317 (5%)	364 (5%)	193 (5%)	118 (6%)	<0·0001
Symptoms of heart failure								
None	22,671	18,787 (83%)	2201 (82%)	5813 (84%)	6318 (83%)	2923 (82%)	1532 (82%)	0·0033
NYHA Class II		3229 (14%)	396 (15%)	976 (14%)	1044 (14%)	545 (15%)	268 (14%)	
NYHA Class III		655 (3%)	96 (4%)	157 (2%)	223 (3%)	116 (3%)	63 (3%)	
Left ventricular ejection fraction (%)	15,969	56·1 (11·0)	52·7 (13·2)	56·2 (10·9)	56·6 (10·3)	56·7 (10·5)	57·0 (10·7)	<0·0001

| Parameter | Number of patients | Mean systolic BP categories | | | | | | p value |
		Total population (n=22,672)	<120 mmHg (n=2693)	120–129 mmHg (n=6946)	130–139 mmHg (n=7586)	140–149 mmHg (n=3584)	≥150 mmHg (n=1863)	
HbA$_{1C}$ (%)	6173	6·9 (1·8)	6·8 (1·4)	6·8 (1·8)	6·9 (1·4)	7·1 (2·8)	7·1 (1·5)	<0·0001
Creatinine (mmol/L)	17,165	0·088 (0·076–0·104)	0·088 (0·078–0·106)	0·088 (0·076–0·102)	0·088 (0·076–0·103)	0·088 (0·075–0·103)	0·088 (0·076–0·106)	0·0005
Total cholesterol (mmol/L)	18,265	4·3 (3·7–5·1)	4·1 (3·5–4·8)	4·2 (3·6–5·0)	4·4 (3·7–5·1)	4·5 (3·8–5·3)	4·6 (3·9–5·4)	<0·0001
HDL-cholesterol (mmol/L)	16,054	1·14 (0·96–1·36)	1·10 (0·94–1·32)	1·12 (0·96–1·35)	1·14 (0·99–1·38)	1·16 (0·97–1·40)	1·14 (0·99–1·39)	<0·0001
LDL-cholesterol (mmol/L)	15,257	2·37 (1·89–2·96)	2·26 (1·80–2·73)	2·30 (1·84–2·86)	2·39 (1·90–3·00)	2·42 (1·92–3·09)	2·55 (1·98–3·20)	<0·0001
Fasting triglycerides (mmol/L)	16,806	1·4 (1·0–2·0)	1·3 (1·0–1·9)	1·4 (1·0–1·9)	1·4 (1·0–2·0)	1·5 (1·1–2·1)	1·5 (1·1–2·0)	<0·0001

Data are n (%) for categorical data and mean (SD) or median (IQR) for continuous data, depending on the distribution of the data.

Some percentages do not add up to 100 because of rounding·

BP=blood pressure. NYHA=New York Heart Association Functional Classification. HDL-cholesterol=high-density lipoprotein cholesterol. LDL-cholesterol=

low-density lipoprotein cholesterol.

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Table 2: Demographic and baseline characteristics of the patients, for each average on-treatment diastolic blood-pressure subgroup

Parameter	Number of patients	Mean diastolic BP categories					p value
		<60 mmHg (n=214)	60–69 mmHg (n=2838)	70–79 mmHg (n=10,816)	80–89mmHg (n=7681)	≥90 mmHg (n=1123)	
Age (years)	22,666	71·9 (8·9)	69·2 (9·3)	65·9 (9·8)	63·1 (9·9)	60·3 (9·9)	<0·0001
Men	22,672	144 (67%)	2009 (71%)	8154 (75%)	5850 (76%)	862 (77%)	<0·0001
Body mass index (kg/m²)	22,654	25·6 (23·4–29·0)	26·8 (24·2–30·0)	27·5 (25·0–30·5)	28·4 (25·7–31·4)	29·1 (26·2–32·4)	<0·0001
Diabetes	22,670	91 (43%)	1144 (40%)	3634 (34%)	2373 (31%)	349 (31%)	<0·0001
Smoking status	22,672						<0·0001
Current		11 (5%)	257 (9%)	1094 (10%)	1033 (13%)	174 (15%)	
Former		103 (48%)	1252 (44%)	4994 (46%)	3333 (43%)	476 (42%)	
Never		100 (47%)	1329 (47%)	4728 (44%)	3315 (43%)	473 (42%)	
Systolic BP (mmHg)	22,659	120·5 (18·3)	125·9 (16·3)	130·7 (15·0)	138·4 (15·6)	152·6 (17·8)	-
Diastolic BP (mmHg)	22,659	57·7 (7·1)	66·9 (7·5)	75·8 (7·2)	84·0 (7·4)	94·7 (8·0)	-
Heart rate (beats/minute)	22,660	64·9 (10·4)	66·6 (10·6)	67·7 (10·3)	69·7 (10·6)	72·8 (11·9)	<0·0001
Myocardial infarction	22,670	123 (57%)	1582 (56%)	6241 (58%)	4560 (59%)	752 (67%)	<0·0001
Percutaneous coronary intervention	22,670	101 (47%)	1645 (58%)	6402 (59%)	4260 (55%)	554 (49%)	<0·0001
Coronary artery bypass graft surgery	22,670	80 (37%)	823 (29%)	2772 (26%)	1780 (23%)	236 (21%)	<0·0001
Transient ischaemic attack	22,670	9 (4%)	116 (4%)	361 (3%)	272 (4%)	43 (4%)	0·3604
Stroke	22,670	22 (10%)	138 (5%)	523 (5%)	344 (4%)	62 (6%)	0·0018
Hospitalisation for heart failure	22,670	27 (13%)	170 (6%)	546 (5%)	400 (5%)	68 (6%)	<0·0001
Symptoms of heart failure							
None	22,671	187 (87%)	2515 (89%)	9321 (86%)	5991 (78%)	773 (69%)	<0·0001
NYHA Class II		22 (10%)	260 (9%)	1264 (12%)	1400 (18%)	283 (25%)	
NYHA Class III		5 (2%)	63 (2%)	231 (2%)	289 (4%)	67 (6%)	
Left ventricular ejection fraction (%)	15,969	51·4 (15·1)	54·5 (12·8)	56·4 (10·9)	56·4 (10·4)	55·1 (10·5)	<0·0001
HbA$_{1C}$ (%)	6173	8·0 (8·4)	7·0 (1·6)	6·8 (1·6)	6·8 (1·3)	7·1 (1·7)	<0·0001

Parameter	Number of patients	Mean diastolic BP categories					p value
		<60 mmHg (n=214)	60–69 mmHg (n=2838)	70–79 mmHg (n=10,816)	80–89mmHg (n=7681)	≥90 mmHg (n=1123)	
Creatinine (mmol/L)	17,165	0·103 (0·085–0·124)	0·088 (0·076–0·107)	0·088 (0·076–0·103)	0·088 (0·076–0·101)	0·088 (0·078–0·102)	<0·0001
Total cholesterol (mmol/L)	18,265	3·8 (3·4–4·6)	4·0 (3·5–4·7)	4·2 (3·6–4·9)	4·5 (3·8–5·3)	4·9 (4·1–5·8)	<0·0001
HDL-cholesterol (mmol/L)	16,054	1·11 (0·92–1·35)	1·14 (0·96–1·35)	1·14 (0·96–1·38)	1·13 (0·96–1·36)	1·10 (0·95–1·35)	0·2758
LDL-cholesterol (mmol/L)	15,257	2·09 (1·66–2·62)	2·16 (1·73–2·68)	2·31 (1·87–2·86)	2·50 (1·98–3·12)	2·83 (2·20–3·60)	<0·0001
Fasting triglycerides (mmol/L)	16,806	1·2 (0·9–1·7)	1·3 (1·0–1·9)	1·4 (1·0–1·9)	1·5 (1·1–2·1)	1·7 (1·2–2·3)	<0·0001

Data are n (%) for categorical data and mean (SD) or median (IQR) for continuous data, depending on the distribution of the data.

Some percentages do not add up to 100 because of rounding·

BP=blood pressure. NYHA=New York Heart Association Functional Classification. HDL-cholesterol=high-density lipoprotein cholesterol. LDL-cholesterol=

low-density lipoprotein cholesterol.

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Table 3: Crude and adjusted hazard ratios for average systolic (A) and diastolic (B) blood pressure subgroups

Table 3A		HR (95% CI) for average systolic BP subgroups					
Outcome	Model	<120 mmHg	120–129 mmHg	130–139 mmHg	140–149 mmHg	≥150 mmHg	p value
Cardiovascular death, myocardial infarction, or stroke	Unadjusted	1·80 (1·57–2·07)	1·00 (–)	1·11 (0·99–1·25)	1·62 (1·42–1·85)	2·86 (2·48–3·29)	<0·0001
	Model 1	1·56 (1·35–1·80)	1·00 (–)	1·08 (0·96–1·22)	1·51 (1·32–1·73)	2·51 (2·17–2·89)	<0·0001
	Model 2	1·56 (1·36–1·81)	1·00 (–)	1·08 (0·95–1·21)	1·51 (1·32–1·73)	2·48 (2·14–2·87)	<0·0001
	Excluding heart failure	1·54 (1·27–1·87)	1·00 (–)	1·05 (0·90–1·22)	1·49 (1·25–1·76)	2·40 (2·00–2·88)	<0·0001
	≤75 years	1·56 (1·32–1·85)	1·00 (–)	1·07 (0·93–1·24)	1·66 (1·41–1·94)	2·80 (2·36–3·33)	<0·0001
	>75 years	1·47 (1·12–1·94)	1·00 (–)	1·12 (0·89–1·41)	1·19 (0·92–1·56)	1·84 (1·40–2·43)	0·0001
All-cause death	Unadjusted	1·89 (1·65–2·18)	1·00 (–)	1·02 (0·90–1·16)	1·34 (1·16–1·55)	2·25 (1·93–2·63)	<0·0001
	Model 1	1·61 (1·39–1·85)	1·00 (–)	0·98 (0·87–1·11)	1·22 (1·05–1·40)	1·88 (1·61–2·20)	<0·0001
	Model 2	1·60 (1·38–1·84)	1·00 (–)	0·98 (0·87–1·11)	1·22 (1·05–1·40)	1·86 (1·59–2·18)	<0·0001
	Excluding heart failure	1·51 (1·24–1·84)	1·00 (–)	0·97 (0·83–1·14)	1·22 (1·01–1·46)	1·75 (1·43–2·14)	<0·0001
Cardiovascular death	Unadjusted	2·30 (1·93–2·75)	1·00 (–)	1·11 (0·94–1·30)	1·65 (1·38–1·97)	2·84 (2·35–3·44)	<0·0001
	Model 1	1·83 (1·53–2·19)	1·00 (–)	1·07 (0·91–1·25)	1·50 (1·26–1·80)	2·39 (1·97–2·90)	<0·0001
	Model 2	1·83 (1·53–2·19)	1·00 (–)	1·07 (0·91–1·25)	1·50 (1·25–1·80)	2·35 (1·93–2·86)	<0·0001
	Excluding heart failure	1·71 (1·32–2·22)	1·00 (–)	1·04 (0·84–1·28)	1·62 (1·29–2·05)	2·19 (1·69–2·84)	<0·0001
Myocardial infarction	Unadjusted	1·65 (1·31–2·08)	1·00 (–)	1·17 (0·97–1·41)	1·60 (1·29–1·98)	3·01 (2·41–3·76)	<0·0001
	Model 1	1·48 (1·17–1·86)	1·00 (–)	1·17 (0·97–1·42)	1·57 (1·26–1·95)	2·85 (2·28–3·57)	<0·0001
	Model 2	1·48 (1·17–1·87)	1·00 (–)	1·18 (0·97–1·43)	1·60 (1·29–1·99)	2·92 (2·32–3·67)	<0·0001
	Excluding heart failure	1·46 (1·09–1·96)	1·00 (–)	1·15 (0·91–1·45)	1·53 (1·17–1·99)	2·88 (2·19–3·80)	<0·0001
Stroke	Unadjusted	1·11 (0·81–1·53)	1·00 (–)	1·12 (0·89–1·41)	1·63 (1·26–2·12)	2·90 (2·21–3·82)	<0·0001
	Model 1	1·05 (0·76–1·45)	1·00 (–)	1·08 (0·85–1·36)	1·54 (1·19–2·00)	2·64 (2·00–3·49)	<0·0001
	Model 2	1·06 (0·77–1·46)	1·00 (–)	1·06 (0·84–1·34)	1·51 (1·16–1·97)	2·57 (1·94–3·41)	<0·0001
	Excluding heart failure	1·25 (0·85–1·84)	1·00 (–)	1·04 (0·79–1·38)	1·32 (0·95–1·83)	2·09 (1·46–2·97)	0·0004
Hospitalisation for heart failure	Unadjusted	1·59 (1·33–1·90)	1·00 (–)	0·94 (0·81–1·10)	1·62 (1·37–1·91)	2·83 (2·38–3·37)	<0·0001
	Model 1	1·38 (1·15–1·66)	1·00 (–)	0·89 (0·76–1·04)	1·45 (1·23–1·70)	2·40 (2·01–2·86)	<0·0001
	Model 2	1·39 (1·16–1·67)	1·00 (–)	0·88 (0·75–1·03)	1·42 (1·20–1·68)	2·36 (1·98–2·83)	<0·0001
	Excluding heart failure	1·15 (0·83–1·60)	1·00 (–)	0·75 (0·58–0·95)	1·12 (0·85–1·48)	1·49 (1·09–2·04)	0·0003

Table 3B		HR (95% CI) for average diastolic BP subgroups					
Outcome	Model	<60 mmHg	60–69 mmHg	70–79 mmHg	80–89 mmHg	≥90 mmHg	p value
Cardiovascular death, myocardial infarction, or stroke	Unadjusted	3·47 (2·61–4·62)	1·74 (1·53–1·97)	1·00 (–)	1·24 (1·12–1·37)	2·98 (2·55–3·48)	<0·0001
	Model 1	1·99 (1·49–2·67)	1·41 (1·24–1·60)	1·00 (–)	1·41 (1·27–1·57)	3·74 (3·18–4·39)	<0·0001
	Model 2	2·01 (1·50–2·70)	1·41 (1·24–1·61)	1·00 (–)	1·41 (1·27–1·57)	3·72 (3·15–4·38)	<0·0001
	Excluding heart failure	1·67 (1·09–2·55)	1·30 (1·11–1·53)	1·00 (–)	1·46 (1·28–1·67)	4·11 (3·30–5·12)	<0·0001
	≤75 years	2·36 (1·57–3·56)	1·70 (1·45–2·00)	1·00 (–)	1·37 (1·22–1·55)	3·15 (2·64–3·77)	<0·0001
	>75 years	1·64 (1·07–2·53)	1·10 (0·88–1·37)	1·00 (–)	1·37 (1·11–1·70)	4·66 (3·08–7·05)	<0·0001
All-cause death	Unadjusted	3·96 (2·99–5·22)	1·93 (1·70–2·19)	1·00 (–)	1·11 (1·00–1·24)	2·21 (1·84–2·66)	<0·0001
	Model 1	2·13 (1·60–2·83)	1·47 (1·30–1·68)	1·00 (–)	1·37 (1·23–1·53)	3·19 (2·64–3·86)	<0·0001
	Model 2	2·13 (1·60–2·83)	1·48 (1·30–1·68)	1·00 (–)	1·37 (1·22–1·53)	3·19 (2·63–3·87)	<0·0001
	Excluding heart failure	1·89 (1·23–2·89)	1·51 (1·28–1·78)	1·00 (–)	1·55 (1·34–1·79)	3·19 (2·42–4·21)	<0·0001
Cardiovascular death	Unadjusted	4·05 (2·86–5·74)	1·88 (1·60–2·20)	1·00 (–)	1·16 (1·01–1·33)	2·69 (2·17–3·33)	<0·0001
	Model 1	2·05 (1·43–2·93)	1·43 (1·21–1·68)	1·00 (–)	1·42 (1·24–1·64)	3·81 (3·05–4·77)	<0·0001
	Model 2	2·06 (1·44–2·96)	1·44 (1·22–1·70)	1·00 (–)	1·42 (1·24–1·63)	3·81 (3·04–4·77)	<0·0001
	Excluding heart failure	1·68 (0·95–2·96)	1·30 (1·04–1·63)	1·00 (–)	1·57 (1·31–1·88)	3·97 (2·88–5·49)	<0·0001
Myocardial infarction	Unadjusted	3·42 (2·16–5·44)	1·66 (1·35–2·04)	1·00 (–)	1·32 (1·12–1·55)	3·35 (2·64–4·24)	<0·0001
	Model 1	2·31 (1·44–3·71)	1·42 (1·15–1·75)	1·00 (–)	1·43 (1·21–1·69)	3·61 (2·81–4·63)	<0·0001
	Model 2	2·38 (1·48–3·83)	1·43 (1·16–1·76)	1·00 (–)	1·44 (1·22–1·70)	3·68 (2·86–4·73)	<0·0001
	Excluding heart failure	1·49 (0·73–3·05)	1·23 (0·95–1·59)	1·00 (–)	1·43 (1·17–1·75)	3·77 (2·71–5·25)	<0·0001
Stroke	Unadjusted	2·18 (1·08–4·42)	1·49 (1·15–1·94)	1·00 (–)	1·27 (1·04–1·56)	3·28 (2·44–4·42)	<0·0001
	Model 1	1·34 (0·65–2·73)	1·22 (0·94–1·60)	1·00 (–)	1·44 (1·17–1·77)	4·29 (3·14–5·87)	<0·0001
	Model 2	1·31 (0·64–2·69)	1·23 (0·94–1·61)	1·00 (–)	1·46 (1·18–1·79)	4·33 (3·15–5·94)	<0·0001
	Excluding heart failure	1·46 (0·64–3·34)	1·17 (0·85–1·60)	1·00 (–)	1·42 (1·10–1·83)	4·88 (3·26–7·31)	<0·0001
Hospitalisation for heart failure	Unadjusted	3·32 (2·22–4·97)	1·56 (1·31–1·87)	1·00 (–)	1·61 (1·41–1·83)	6·32 (5·37–7·44)	<0·0001
	Model 1	2·22 (1·47–3·36)	1·53 (1·28–1·84)	1·00 (–)	1·38 (1·21–1·58)	4·60 (3·86–5·48)	<0·0001
	Model 2	2·36 (1·55–3·58)	1·55 (1·29–1·86)	1·00 (–)	1·38 (1·21–1·59)	4·58 (3·83–5·48)	<0·0001
	Excluding heart failure	2·32 (1·12–4·78)	1·67 (1·26–2·22)	1·00 (–)	1·53 (1·22–1·91)	4·58 (3·21–6·54)	<0·0001

Data are indicated for the whole population and for the sensitivity analysis excluding patients with heart failure for all outcomes. Data are also given by age subgroup (≤75 years or >75 years) for the primary outcome. BP=blood pressure. The p-value reported represents the heterogeneity of the association of BP with each outcome across the BP categories.

Model 1: adjusted for age, geographical region, smoking status, myocardial infarction, percutaneous coronary Intervention, diabetes, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, stroke, transient ischaemic attack, angiotensin-receptor blockers, diuretics and aspirin.

Model 2: adjusted for age, sex, geographical region, smoking status, myocardial infarction, percutaneous coronary Intervention, coronary artery bypass graft, diabetes, low- and high-density lipoprotein cholesterol levels, body mass index, glomerular filtration rate, peripheral artery disease, hospitalisation for or symptoms of heart failure, left ventricular ejection fraction, ethnicity, stroke, transient ischaemic attack and baseline medications, namely aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers, diuretics and other antihypertensive medications.

Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

Cardiovascular death, myocardial infarction, or stroke

SBP < 120 mmHg	323 / 2687	(12.0)	1.56 (1.36 – 1.81); < 0.0001
SBP 120 - 129 mmHg	490 / 6938	(7.1)	1.00 (-)
SBP 130 - 139 mmHg	584 / 7578	(7.7)	1.08 (0.95 – 1.21); 0.2368
SBP 140 - 149 mmHg	386 / 3577	(10.8)	1.51 (1.32 – 1.73); < 0.0001
SBP ≥ 150 mmHg	316 / 1859	(17.0)	2.48 (2.14 – 2.87); < 0.0001
DBP < 60 mmHg	50 / 214	(23.4)	2.01 (1.50 – 2.70); < 0.0001
DBP 60 - 69 mmHg	351 / 2833	(12.4)	1.41 (1.24 – 1.61); < 0.0001
DBP 70 - 79 mmHg	813 / 10802	(7.5)	1.00 (-)
DBP 80 - 89 mmHg	684 / 7667	(8.9)	1.41 (1.27 – 1.57); < 0.0001
DBP ≥ 90 mmHg	201 / 1123	(17.9)	3.72 (3.15 – 4.38); < 0.0001

0.5 1 2 4

Hazard ratio (95% CI)

← Lower risk   Higher risk →
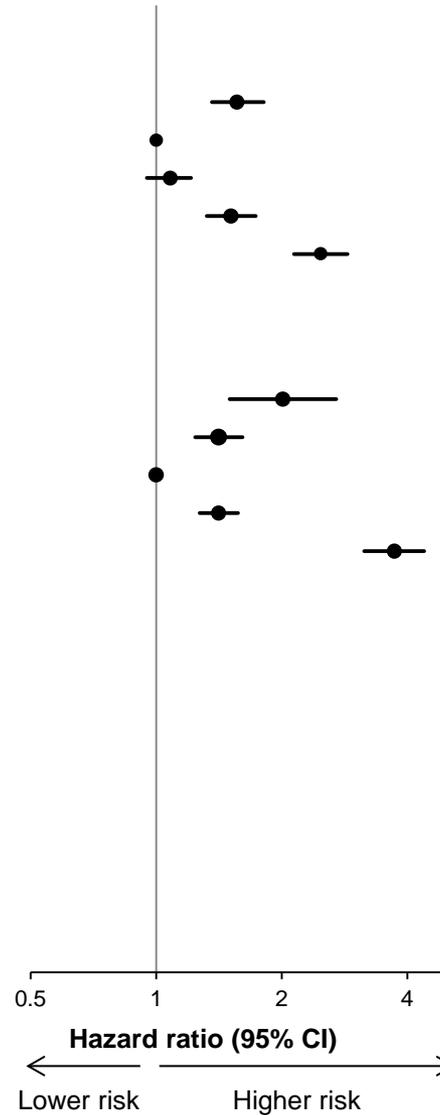
Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

All cause death

SBP < 120 mmHg	330 / 2693	(12.3)	1.60 (1.38 – 1.84); < 0.0001
SBP 120 - 129 mmHg	479 / 6987	(6.9)	1.00 (-)
SBP 130 - 139 mmHg	526 / 7611	(6.9)	0.98 (0.87 – 1.11); 0.7701
SBP 140 - 149 mmHg	312 / 3555	(8.8)	1.22 (1.05 – 1.40); 0.0081
SBP ≥ 150 mmHg	239 / 1793	(13.3)	1.86 (1.59 – 2.18); < 0.0001

DBP < 60 mmHg	53 / 210	(25.2)	2.13 (1.60 – 2.83); < 0.0001
DBP 60 - 69 mmHg	365 / 2842	(12.8)	1.48 (1.30 – 1.68); < 0.0001
DBP 70 - 79 mmHg	759 / 10891	(7.0)	1.00 (-)
DBP 80 - 89 mmHg	574 / 7633	(7.5)	1.37 (1.22 – 1.53); < 0.0001
DBP ≥ 90 mmHg	135 / 1063	(12.7)	3.19 (2.63 – 3.87); < 0.0001
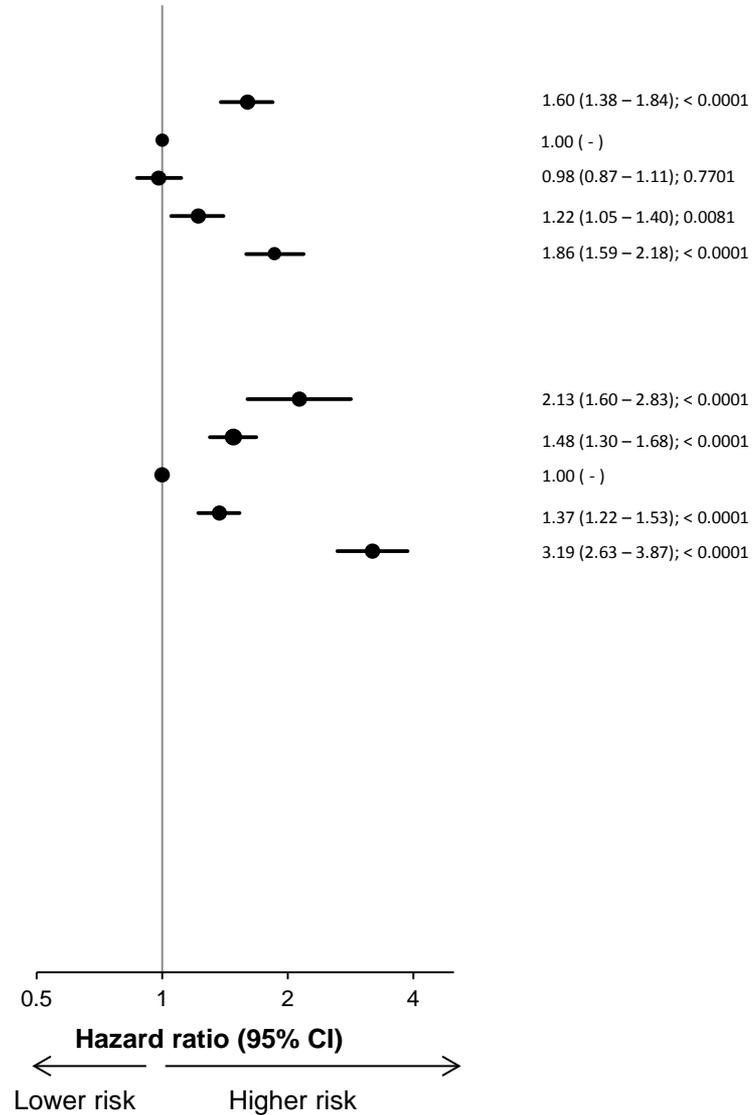
0.5 1 2 4

Hazard ratio (95% CI)

← Lower risk   Higher risk →

Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

Cardiovascular death

Outcome by BP Group	No. events / No. in group (%)	Hazard Ratio (95% CI); P Value
SBP < 120 mmHg	227 / 2693 (8.4)	1.83 (1.53 – 2.19); < 0.0001
SBP 120 - 129 mmHg	271 / 6992 (3.9)	1.00 (-)
SBP 130 - 139 mmHg	322 / 7606 (4.2)	1.07 (0.91 – 1.25); 0.4463
SBP 140 - 149 mmHg	217 / 3555 (6.1)	1.50 (1.25 – 1.80); < 0.0001
SBP ≥ 150 mmHg	171 / 1793 (9.5)	2.35 (1.93 – 2.86); < 0.0001
DBP < 60 mmHg	34 / 210 (16.2)	2.06 (1.44 – 2.96); < 0.0001
DBP 60 - 69 mmHg	223 / 2842 (7.8)	1.44 (1.22 – 1.70); < 0.0001
DBP 70 - 79 mmHg	475 / 10895 (4.4)	1.00 (-)
DBP 80 - 89 mmHg	373 / 7630 (4.9)	1.42 (1.24 – 1.63); < 0.0001
DBP ≥ 90 mmHg	103 / 1062 (9.7)	3.81 (3.04 – 4.77); < 0.0001

0.5   1   2   4

Hazard ratio (95% CI)

← Lower risk   Higher risk →
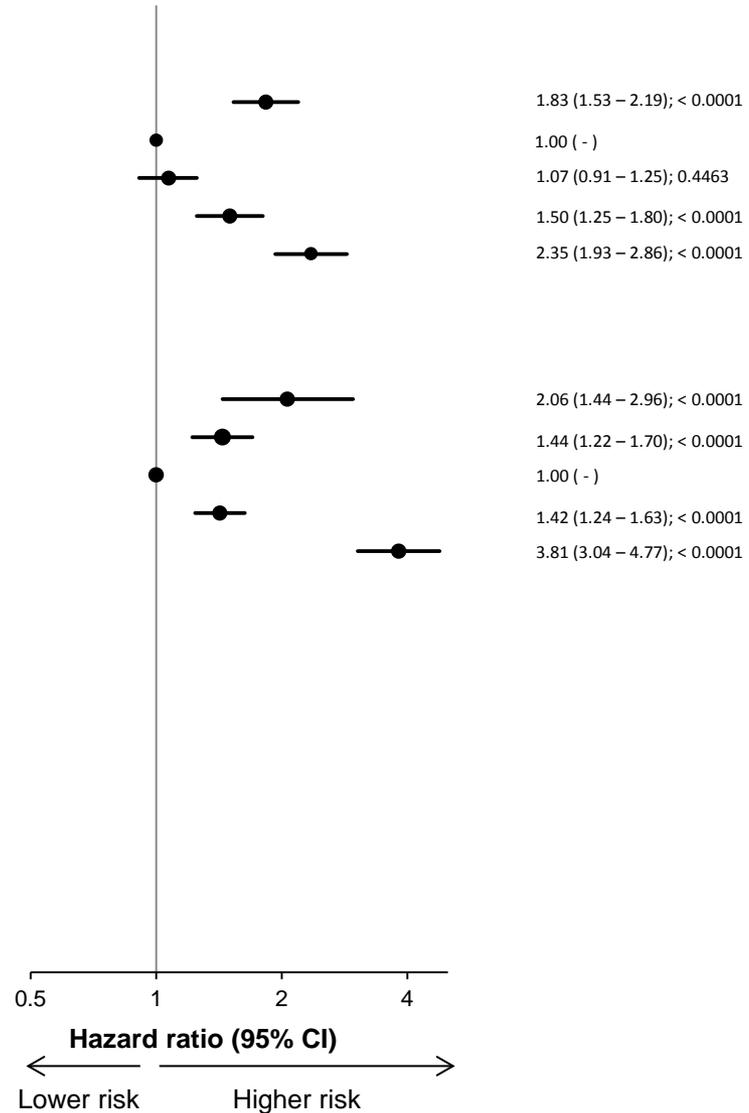
Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

Myocardial infarction (fatal or non-fatal)

SBP < 120 mmHg	115 / 2688	(4.3)	1.48 (1.17 – 1.87); 0.0010
SBP 120 - 129 mmHg	191 / 6956	(2.7)	1.00 (-)
SBP 130 - 139 mmHg	240 / 7600	(3.2)	1.18 (0.97 – 1.43); 0.0925
SBP 140 - 149 mmHg	149 / 3559	(4.2)	1.60 (1.29 – 1.99); < 0.0001
SBP ≥ 150 mmHg	131 / 1836	(7.1)	2.92 (2.32 – 3.67); < 0.0001
DBP < 60 mmHg	19 / 211	(9.0)	2.38 (1.48 – 3.83); 0.0003
DBP 60 - 69 mmHg	129 / 2835	(4.6)	1.43 (1.16 – 1.76); 0.0009
DBP 70 - 79 mmHg	311 / 10836	(2.9)	1.00 (-)
DBP 80 - 89 mmHg	280 / 7654	(3.7)	1.44 (1.22 – 1.70); < 0.0001
DBP ≥ 90 mmHg	87 / 1103	(7.9)	3.68 (2.86 – 4.73); < 0.0001

0.5   1   2   4

Hazard ratio (95% CI)

← Lower risk   Higher risk →
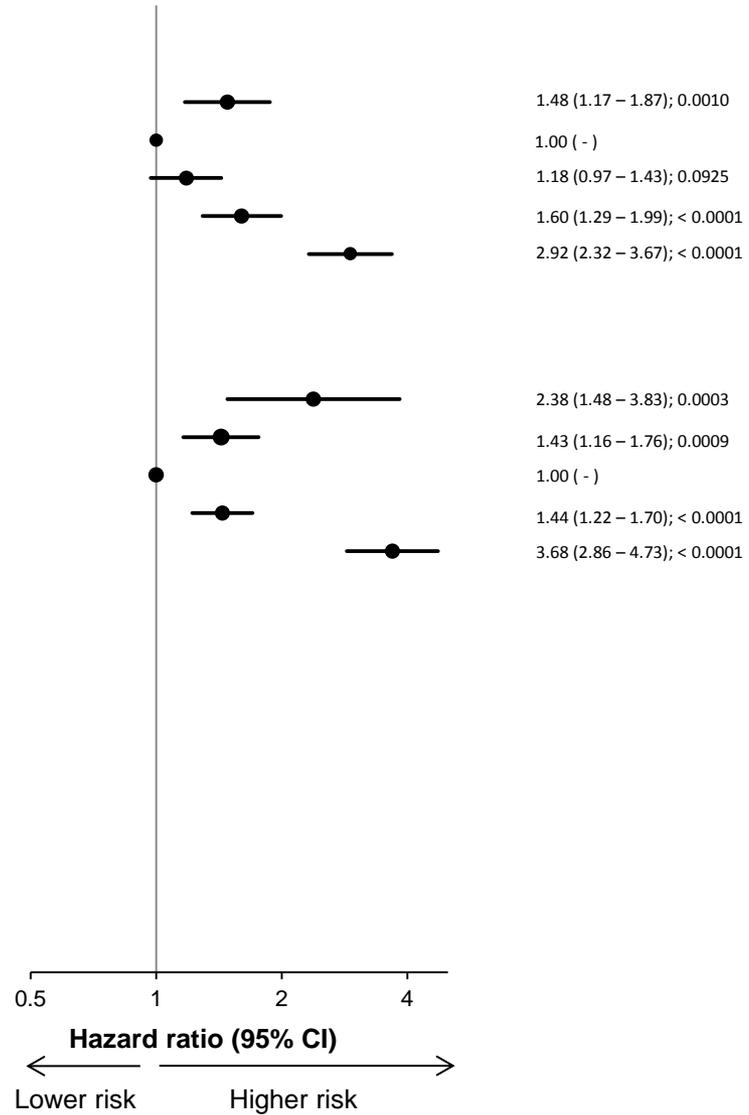
Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

Stroke (fatal or non-fatal)

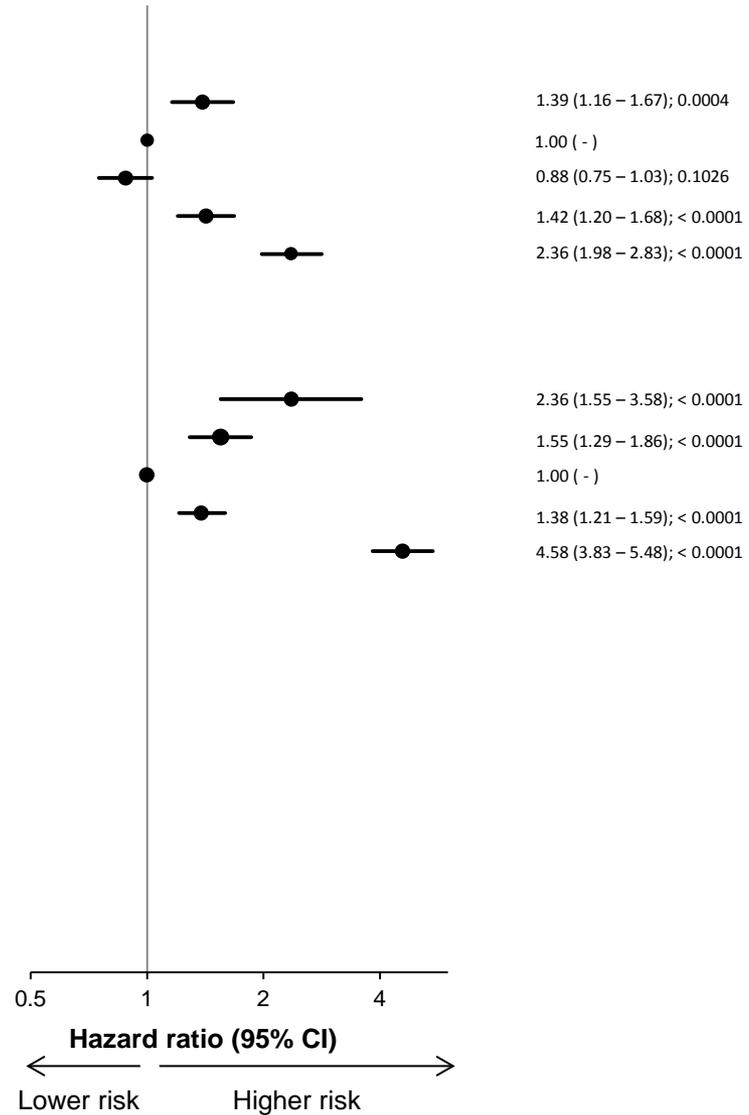|			
SBP < 120 mmHg	53 / 2692	(2.0)	1.06 (0.77 – 1.46); 0.7257
SBP 120 - 129 mmHg	130 / 6978	(1.9)	1.00 (-)
SBP 130 - 139 mmHg	155 / 7589	(2.0)	1.06 (0.84 – 1.34); 0.6134
SBP 140 - 149 mmHg	103 / 3564	(2.9)	1.51 (1.16 – 1.97); 0.0020
SBP ≥ 150 mmHg	84 / 1816	(4.6)	2.57 (1.94 – 3.41); < 0.0001
DBP < 60 mmHg	8 / 213	(3.8)	1.31 (0.64 – 2.69); 0.4614
DBP 60 - 69 mmHg	77 / 2842	(2.7)	1.23 (0.94 – 1.61); 0.1244
DBP 70 - 79 mmHg	207 / 10857	(1.9)	1.00 (-)
DBP 80 - 89 mmHg	178 / 7646	(2.3)	1.46 (1.18 – 1.79); 0.0004
DBP ≥ 90 mmHg	55 / 1081	(5.1)	4.33 (3.15 – 5.94); < 0.0001

0.5　1　2　4

Hazard ratio (95% CI)

← Lower risk　　Higher risk →
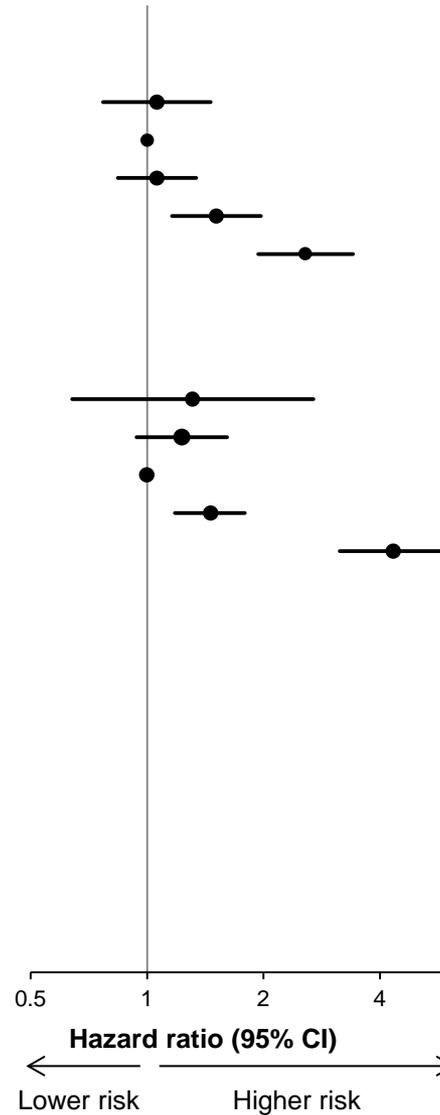
Outcome by BP Group	No. events / No. in group (%)		Hazard Ratio (95% CI); P Value

Heart failure hospitalisation

SBP < 120 mmHg	187 / 2559	(7.3)	1.39 (1.16 – 1.67); 0.0004
SBP 120 - 129 mmHg	325 / 6784	(4.8)	1.00 (-)
SBP 130 - 139 mmHg	328 / 7339	(4.5)	0.88 (0.75 – 1.03); 0.1026
SBP 140 - 149 mmHg	257 / 3473	(7.4)	1.42 (1.20 – 1.68); < 0.0001
SBP ≥ 150 mmHg	208 / 1756	(11.8)	2.36 (1.98 – 2.83); < 0.0001
DBP < 60 mmHg	25 / 206	(12.1)	2.36 (1.55 – 3.58); < 0.0001
DBP 60 - 69 mmHg	167 / 2721	(6.1)	1.55 (1.29 – 1.86); < 0.0001
DBP 70 - 79 mmHg	430 / 10559	(4.1)	1.00 (-)
DBP 80 - 89 mmHg	463 / 7347	(6.3)	1.38 (1.21 – 1.59); < 0.0001
DBP ≥ 90 mmHg	220 / 1078	(20.4)	4.58 (3.83 – 5.48); < 0.0001

0.5   1   2   4

Hazard ratio (95% CI)

← Lower risk   Higher risk →

Cardiovascular death, myocardial infarction or stroke

Cardiovascular death, myocardial infarction or stroke