



Vidal-Petiot, E., Ford, I., Greenlaw, N., Ferrari, R., Fox, K. M., Tardif, J.-C., Tendera, M., Tavazzi, L., Bhatt, D. L., and Steg, P. G. (2016) Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet*, 388(10056), pp. 2142-2152. (doi:[10.1016/S0140-6736\(16\)31326-5](https://doi.org/10.1016/S0140-6736(16)31326-5))

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Appendix

Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study

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Study oversight

The study was designed and conducted by the investigators. All data were collected and analysed by NG and IF at the independent academic statistics centre (Robertson Centre for Biostatistics, University of Glasgow, UK), and were interpreted by the investigators. Sophie Rushton-Smith, PhD, provided editorial assistance, limited to editing, checking content and language, formatting, referencing, and preparing tables and figures, and was compensated by the sponsor. The CLARIFY registry enforces a no ghost-writing policy. This manuscript was written by the authors, who take full responsibility for its content.

Table S1: Baseline medications of the patients, for the total population and each average on-treatment systolic blood-pressure subgroup (S1a) and each average on-treatment diastolic subgroup (S2b)

| Table S1a | Parameter | Number of patients | Mean systolic blood pressure 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) |
| | Beta-blockers | 22,671 | 17,825 (79%) | 2162 (80%) | 5501 (79%) | 5896 (78%) | 2806 (78%) | 1460 (78%) | 0.0440 |
| | Calcium channel blockers | 22,670 | 7608 (34%) | 656 (24%) | 2086 (30%) | 2637 (35%) | 1447 (40%) | 782 (42%) | <0.0001 |
| | Angiotensin-converting enzyme inhibitors | 22,670 | 12,415 (55%) | 1450 (54%) | 3817 (55%) | 4151 (55%) | 1978 (55%) | 1019 (55%) | 0.8597 |
| | Angiotensin-receptor blockers | 22,667 | 7300 (32%) | 819 (30%) | 2121 (31%) | 2481 (33%) | 1226 (34%) | 653 (35%) | <0.0001 |
| | Diuretics | 22,670 | 8132 (36%) | 999 (37%) | 2197 (32%) | 2655 (35) | 1448 (40%) | 833 (45%) | <0.0001 |
| | Other antihypertensive agents | 22,669 | 2025 (9%) | 204 (8%) | 454 (7%) | 666 (9%) | 404 (11%) | 297 (16%) | <0.0001 |
| | Number of antihypertensive drugs | 22,672 | 2 (2-3) | 2 (2-3) | 2 (2-3) | 2 (2-3) | 3 (2-3) | 3 (2-3) | <0.0001 |
| | Aspirin | 22,670 | 19,849 (88%) | 2363 (88%) | 6131 (88%) | 6632 (87%) | 3131 (87%) | 1592 (86%) | 0.0277 |
| | Lipid-lowering drugs | 22,672 | 21,008 (93%) | 2516 (93%) | 6458 (93%) | 7047 (93%) | 3307 (92%) | 1680 (90%) | 0.0002 |

Data are number (%) for categorical data or median (IQR) for continuous data. Some percentages do not add up to 100 because of rounding.

| Table S1b | Parameter | Number of patients | Mean diastolic blood pressure 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) | |
| | Beta-blockers | 22,671 | 167 (78%) | 2187 (77%) | 8417 (78%) | 6134 (80%) | 920 (82%) | 0.0001 |
| | Calcium channel blockers | 22,670 | 76 (36%) | 1024 (36%) | 3579 (34%) | 2512 (33%) | 417 (37%) | 0.0010 |
| | Angiotensin-converting enzyme inhibitors | 22,670 | 86 (40%) | 1365 (48%) | 5818 (54%) | 4436 (58%) | 710 (63%) | <0.0001 |
| | Angiotensin-receptor blockers | 22,667 | 89 (42%) | 1020 (36%) | 3554 (33%) | 2315 (30%) | 322 (29%) | <0.0001 |
| | Diuretics | 22,670 | 95 (44%) | 1103 (39%) | 3756 (35%) | 2719 (35%) | 459 (41%) | <0.0001 |
| | Other antihypertensive agents | 22,669 | 41 (19%) | 313 (11%) | 885 (8%) | 639 (8%) | 147 (13%) | <0.0001 |
| | Number of antihypertensive drugs | 22,672 | 2 (2-3) | 2 (2-3) | 2 (2-3) | 2 (2-3) | 3 (2-3) | <0.0001 |
| | Aspirin | 22,670 | 177 (83%) | 2449 (86%) | 9422 (87%) | 6791 (88%) | 1010 (90%) | 0.0002 |
| | Lipid-lowering drugs | 22,672 | 202 (94%) | 2662 (94%) | 10,079 (93%) | 7056 (92%) | 1009 (90%) | <0.0001 |

Data are number (%) for categorical data or median (IQR) for continuous data. Some percentages do not add up to 100 because of rounding.

Table S2: Crude and adjusted hazard ratios for baseline and last measured systolic and diastolic blood pressure subgroups

| | | | Hazard ratios for systolic BP | | | | | | Hazard ratios for diastolic BP | | | | | |
|-----------------------------------|-------------|------------|-------------------------------|-------------|-------------------|-------------------|-------------------|---------|--------------------------------|-------------------|-----------|-------------------|-------------------|---------|
| | | | 10-mmHg BP groups | | | | | | 10-mmHg BP groups | | | | | |
| BP variable | Model | | 1 (<120) | 2 (120-129) | 3 (130-139) | 4 (140-149) | 5 (>150) | p value | 1 (<60) | 2 (60-69) | 3 (70-79) | 4 (80-89) | 5 (>=90) | p value |
| Composite outcome* | Baseline BP | unadjusted | 1.26 (1.09, 1.46) | 1.00 (-) | 1.08 (0.95, 1.23) | 1.10 (0.96, 1.27) | 1.38 (1.21, 1.58) | <0.0001 | 1.48 (1.13, 1.95) | 1.37 (1.20, 1.58) | 1.00 (-) | 0.88 (0.79, 0.98) | 1.04 (0.91, 1.18) | <0.0001 |
| | | model 2 | 1.17 (1.01, 1.36) | 1.00 (-) | 1.06 (0.93, 1.20) | 1.06 (0.92, 1.22) | 1.28 (1.12, 1.47) | 0.0024 | 1.10 (0.83, 1.45) | 1.19 (1.03, 1.36) | 1.00 (-) | 0.94 (0.85, 1.05) | 1.14 (1.00, 1.31) | 0.0031 |
| | Last BP | unadjusted | 1.54 (1.34, 1.77) | 1.00 (-) | 1.04 (0.91, 1.18) | 1.30 (1.13, 1.49) | 1.75 (1.53, 2.01) | <0.0001 | 1.72 (1.36, 2.16) | 1.25 (1.09, 1.43) | 1.00 (-) | 0.96 (0.86, 1.06) | 1.26 (1.09, 1.45) | <0.0001 |
| | | model 2 | 1.41 (1.23, 1.63) | 1.00 (-) | 1.04 (0.91, 1.18) | 1.27 (1.11, 1.46) | 1.63 (1.42, 1.88) | <0.0001 | 1.16 (0.91, 1.46) | 1.12 (0.97, 1.28) | 1.00 (-) | 1.00 (0.90, 1.11) | 1.36 (1.18, 1.58) | <0.0001 |
| All-cause death | Baseline BP | unadjusted | 1.26 (1.08, 1.46) | 1.00 (-) | 1.06 (0.92, 1.21) | 0.97 (0.84, 1.13) | 1.22 (1.06, 1.40) | 0.0011 | 1.98 (1.54, 2.54) | 1.45 (1.26, 1.67) | 1.00 (-) | 0.87 (0.78, 0.97) | 0.87 (0.76, 1.01) | <0.0001 |
| | | model 2 | 1.15 (0.98, 1.34) | 1.00 (-) | 1.03 (0.90, 1.18) | 0.94 (0.81, 1.09) | 1.13 (0.98, 1.31) | 0.0513 | 1.34 (1.04, 1.74) | 1.19 (1.03, 1.37) | 1.00 (-) | 0.97 (0.87, 1.09) | 1.09 (0.94, 1.26) | 0.0114 |
| | Last BP | unadjusted | 1.77 (1.55, 2.04) | 1.00 (-) | 0.94 (0.83, 1.08) | 1.11 (0.96, 1.28) | 1.45 (1.25, 1.69) | <0.0001 | 2.16 (1.74, 2.67) | 1.43 (1.25, 1.63) | 1.00 (-) | 0.88 (0.79, 0.99) | 1.06 (0.91, 1.24) | <0.0001 |
| | | model 2 | 1.58 (1.38, 1.82) | 1.00 (-) | 0.95 (0.83, 1.08) | 1.09 (0.94, 1.27) | 1.30 (1.12, 1.52) | <0.0001 | 1.32 (1.06, 1.64) | 1.24 (1.08, 1.42) | 1.00 (-) | 0.94 (0.84, 1.05) | 1.23 (1.05, 1.45) | <0.0001 |
| Cardiovascular death | Baseline BP | unadjusted | 1.36 (1.13, 1.64) | 1.00 (-) | 1.01 (0.85, 1.19) | 1.01 (0.84, 1.21) | 1.33 (1.12, 1.59) | <0.0001 | 1.96 (1.44, 2.68) | 1.40 (1.17, 1.67) | 1.00 (-) | 0.82 (0.71, 0.94) | 0.92 (0.78, 1.10) | <0.0001 |
| | | model 2 | 1.20 (0.99, 1.45) | 1.00 (-) | 0.97 (0.82, 1.16) | 0.98 (0.81, 1.18) | 1.24 (1.03, 1.48) | 0.0105 | 1.34 (0.97, 1.84) | 1.15 (0.96, 1.37) | 1.00 (-) | 0.93 (0.80, 1.07) | 1.13 (0.95, 1.36) | 0.0232 |
| | Last BP | unadjusted | 1.85 (1.55, 2.21) | 1.00 (-) | 0.98 (0.83, 1.17) | 1.29 (1.07, 1.54) | 1.70 (1.41, 2.04) | <0.0001 | 2.10 (1.60, 2.76) | 1.32 (1.11, 1.56) | 1.00 (-) | 0.91 (0.79, 1.04) | 1.21 (1.00, 1.46) | <0.0001 |
| | | model 2 | 1.62 (1.35, 1.93) | 1.00 (-) | 1.00 (0.84, 1.19) | 1.28 (1.07, 1.54) | 1.54 (1.28, 1.86) | <0.0001 | 1.24 (0.93, 1.64) | 1.15 (0.96, 1.36) | 1.00 (-) | 0.96 (0.84, 1.11) | 1.38 (1.13, 1.67) | 0.0014 |
| Myocardial infarction | Baseline BP | unadjusted | 1.20 (0.94, 1.53) | 1.00 (-) | 1.16 (0.94, 1.42) | 1.26 (1.01, 1.56) | 1.38 (1.11, 1.72) | 0.0557 | 1.32 (0.82, 2.13) | 1.57 (1.26, 1.95) | 1.00 (-) | 1.00 (0.84, 1.19) | 1.17 (0.95, 1.44) | 0.0002 |
| | | model 2 | 1.11 (0.87, 1.42) | 1.00 (-) | 1.16 (0.94, 1.43) | 1.26 (1.01, 1.57) | 1.36 (1.09, 1.69) | 0.0762 | 1.13 (0.69, 1.83) | 1.40 (1.12, 1.75) | 1.00 (-) | 1.06 (0.89, 1.27) | 1.19 (0.96, 1.47) | 0.0369 |
| | Last BP | unadjusted | 1.42 (1.13, 1.77) | 1.00 (-) | 0.99 (0.81, 1.22) | 1.20 (0.96, 1.49) | 1.75 (1.41, 2.17) | <0.0001 | 1.37 (0.92, 2.03) | 1.07 (0.86, 1.34) | 1.00 (-) | 0.92 (0.78, 1.08) | 1.23 (0.99, 1.54) | 0.0402 |
| | | model 2 | 1.32 (1.05, 1.65) | 1.00 (-) | 1.00 (0.82, 1.23) | 1.22 (0.98, 1.51) | 1.74 (1.40, 2.17) | <0.0001 | 1.10 (0.73, 1.64) | 0.98 (0.79, 1.22) | 1.00 (-) | 0.95 (0.80, 1.12) | 1.27 (1.01, 1.59) | 0.1269 |
| Stroke | Baseline BP | unadjusted | 0.90 (0.66, 1.23) | 1.00 (-) | 0.96 (0.75, 1.24) | 0.93 (0.71, 1.22) | 1.39 (1.08, 1.79) | 0.0071 | 0.93 (0.47, 1.82) | 1.13 (0.84, 1.50) | 1.00 (-) | 0.85 (0.69, 1.05) | 1.16 (0.91, 1.48) | 0.0895 |
| | | model 2 | 0.93 (0.68, 1.27) | 1.00 (-) | 0.95 (0.73, 1.22) | 0.87 (0.66, 1.15) | 1.26 (0.98, 1.64) | 0.0572 | 0.73 (0.37, 1.43) | 1.00 (0.74, 1.34) | 1.00 (-) | 0.89 (0.72, 1.10) | 1.26 (0.97, 1.63) | 0.0699 |
| | Last BP | unadjusted | 1.05 (0.77, 1.43) | 1.00 (-) | 0.99 (0.77, 1.28) | 1.42 (1.09, 1.85) | 1.90 (1.46, 2.47) | <0.0001 | 1.25 (0.72, 2.16) | 1.28 (0.97, 1.69) | 1.00 (-) | 1.12 (0.91, 1.38) | 1.60 (1.22, 2.10) | 0.0121 |
| | | model 2 | 1.02 (0.75, 1.39) | 1.00 (-) | 0.98 (0.76, 1.26) | 1.38 (1.06, 1.79) | 1.78 (1.36, 2.33) | <0.0001 | 0.88 (0.50, 1.53) | 1.15 (0.87, 1.52) | 1.00 (-) | 1.18 (0.96, 1.46) | 1.77 (1.34, 2.33) | 0.0017 |
| Hospitalisation for heart failure | Baseline BP | unadjusted | 1.09 (0.90, 1.32) | 1.00 (-) | 0.90 (0.76, 1.06) | 1.19 (1.01, 1.40) | 1.21 (1.02, 1.44) | 0.0017 | 1.55 (1.09, 2.22) | 1.04 (0.85, 1.27) | 1.00 (-) | 0.98 (0.86, 1.13) | 1.54 (1.32, 1.79) | <0.0001 |
| | | model 2 | 0.97 (0.81, 1.18) | 1.00 (-) | 0.81 (0.69, 0.96) | 0.93 (0.79, 1.10) | 0.95 (0.80, 1.13) | 0.1384 | 1.41 (0.98, 2.03) | 1.01 (0.83, 1.24) | 1.00 (-) | 0.89 (0.77, 1.02) | 1.05 (0.89, 1.23) | 0.0358 |
| | Last BP | unadjusted | 1.21 (1.01, 1.46) | 1.00 (-) | 0.97 (0.83, 1.14) | 1.28 (1.09, 1.52) | 1.55 (1.30, 1.84) | <0.0001 | 1.53 (1.09, 2.14) | 1.20 (1.00, 1.45) | 1.00 (-) | 1.22 (1.06, 1.40) | 2.49 (2.13, 2.92) | <0.0001 |
| | | model 2 | 1.22 (1.01, 1.46) | 1.00 (-) | 0.94 (0.81, 1.11) | 1.25 (1.05, 1.47) | 1.57 (1.32, 1.87) | <0.0001 | 1.31 (0.93, 1.86) | 1.26 (1.04, 1.52) | 1.00 (-) | 1.05 (0.92, 1.21) | 1.90 (1.61, 2.24) | <0.0001 |

BP=blood pressure. The p-value reported represents the heterogeneity of the association of BP with each outcome across the BP categories.

*Cardiovascular death, myocardial infarction, or stroke.

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 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

Table S3: Interaction analyses

| Outcome | | Covariate | Interaction p-value |
|------------------|-----|---|--------------------------------|
| Primary endpoint | SBP | Age ≤ 75 vs > 75 years | 0.0176 |
| | | Diabetes | 0.6596 |
| | | Previous stroke or transient ischaemic attack | 0.2190 |
| | | Heart failure | 0.6494 |
| | | Previous revascularization | 0.3634 |
| | | Chronic kidney disease | 0.9141 |
| Primary endpoint | DBP | Age ≤ 75 vs > 75 years | 0.0180 |
| | | Diabetes | 0.1363 |
| | | Previous stroke or transient ischaemic attack | 0.0592 |
| | | Heart failure | 0.0929 |
| | | Previous revascularization | 0.8685 |
| | | Chronic kidney disease | 0.5852 |

DBP=diastolic blood pressure; SBP=systolic blood pressure.

Figure S1: Flow diagram of study population

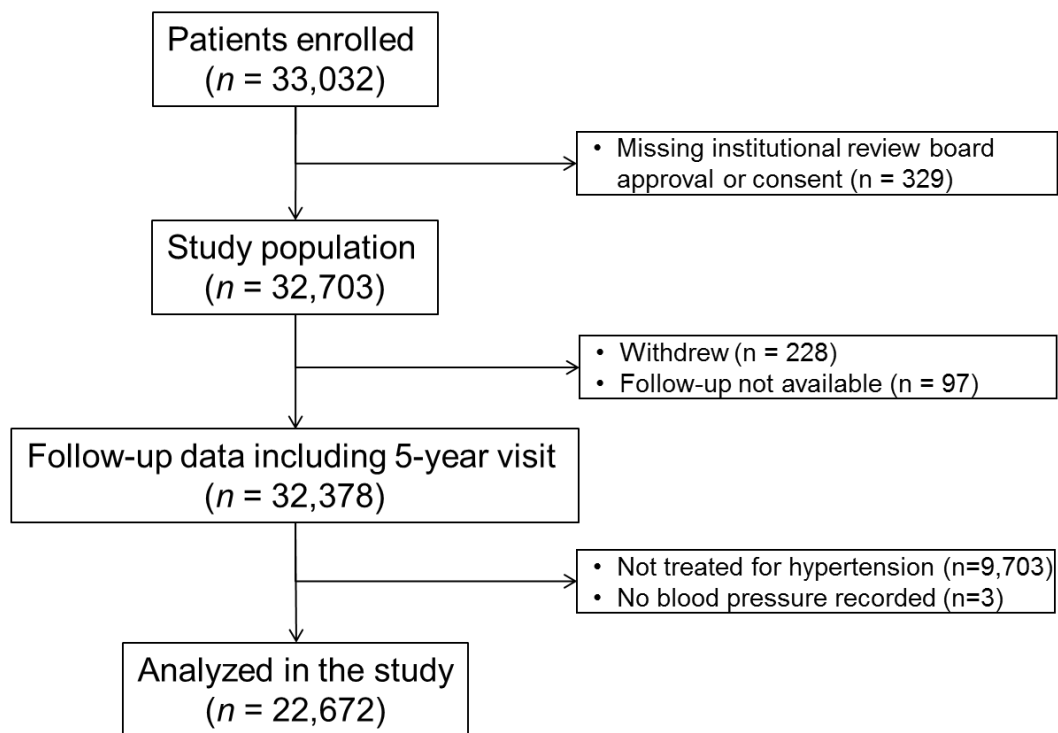
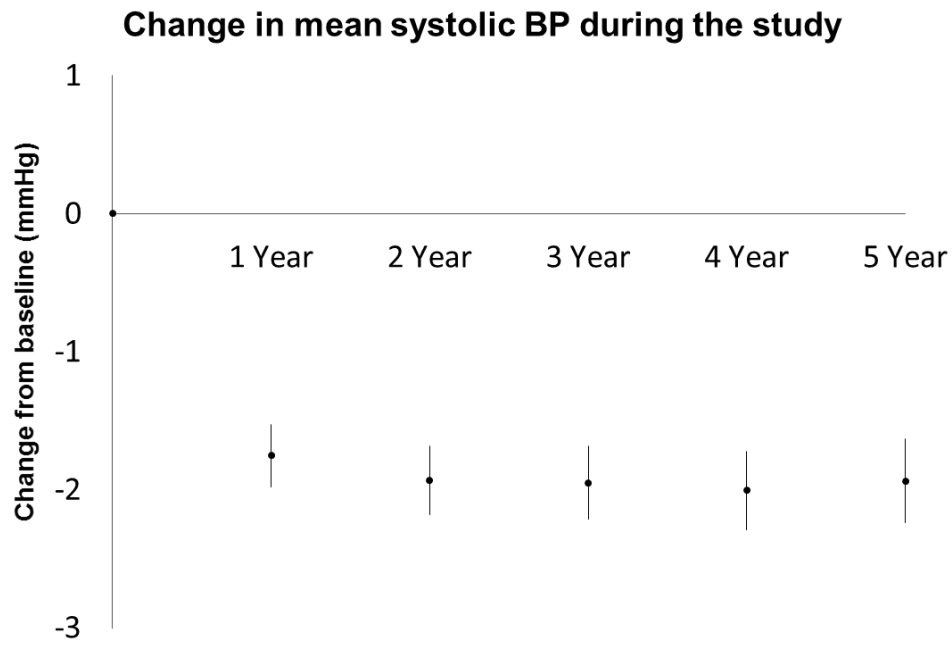


Figure S2: Change from baseline of systolic (A) and diastolic (B) BP during follow-up

Values reported for the change in mean systolic (A) or diastolic (B) BP are the mean and corresponding 95% confidence interval at each follow-up visit

BP=blood pressure.

A



B

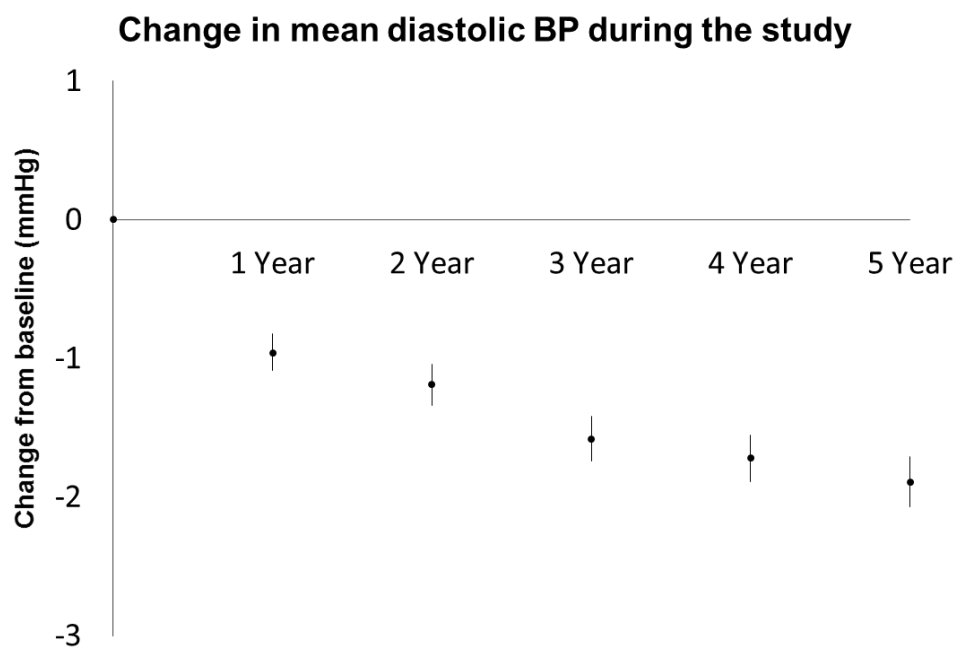
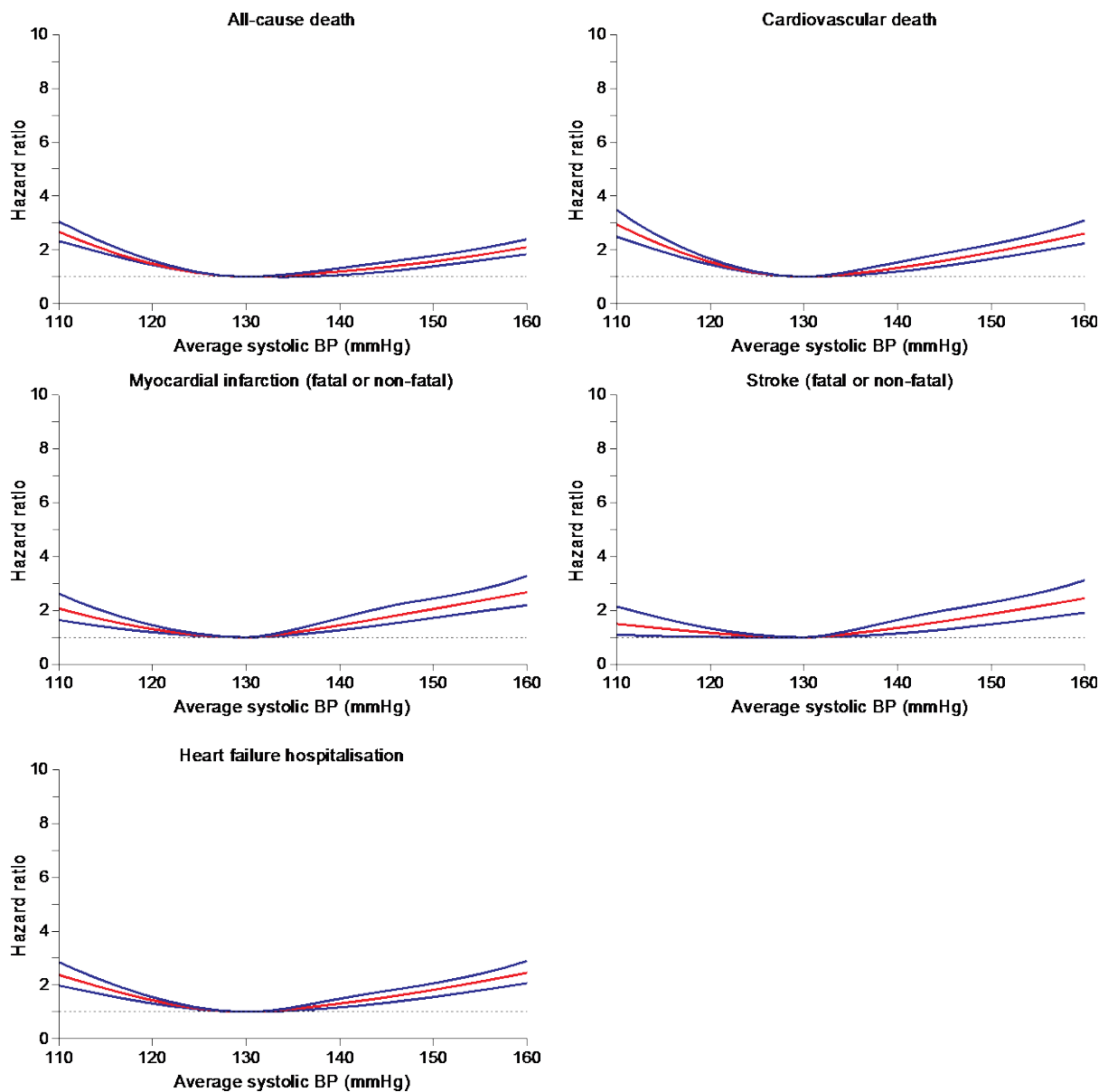


Figure S3: Restricted cubic splines of all secondary outcomes versus average systolic and diastolic BP

Restricted cubic splines are represented for the association between average BP level and all secondary outcomes. The analyses were adjusted for a subset of the variables from model 2 and 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.

BP=blood pressure.

Systolic BP



Diastolic BP

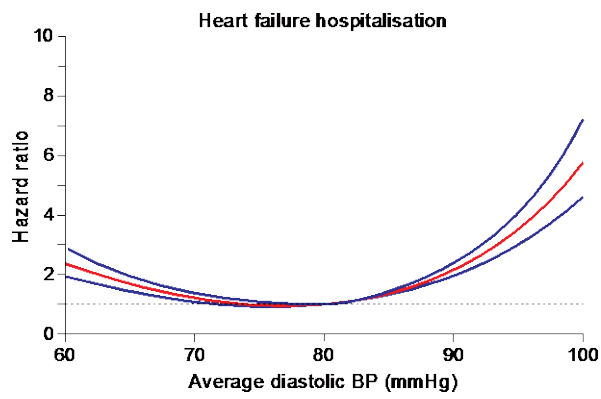
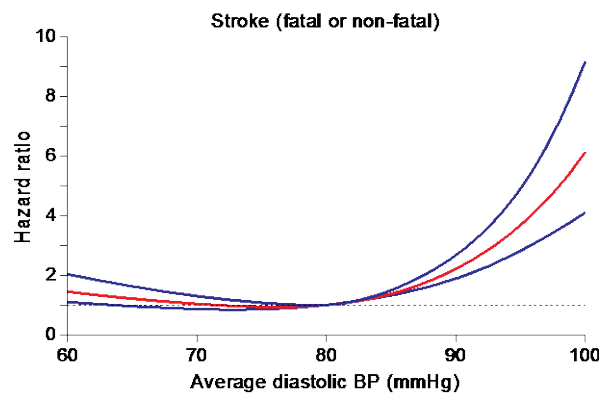
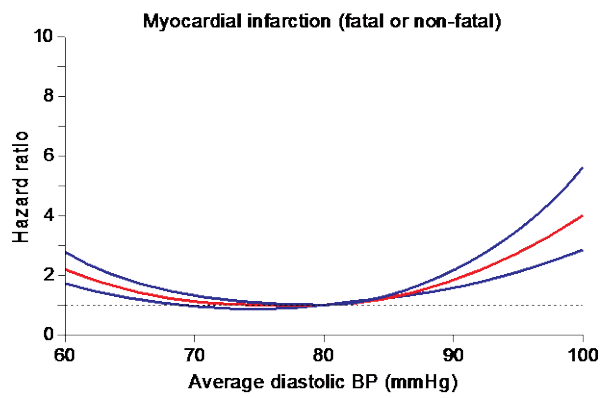
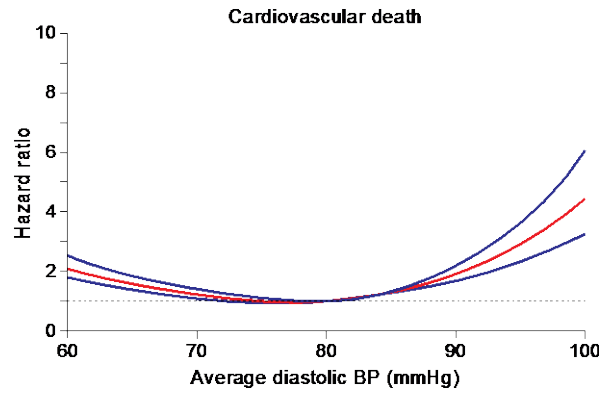
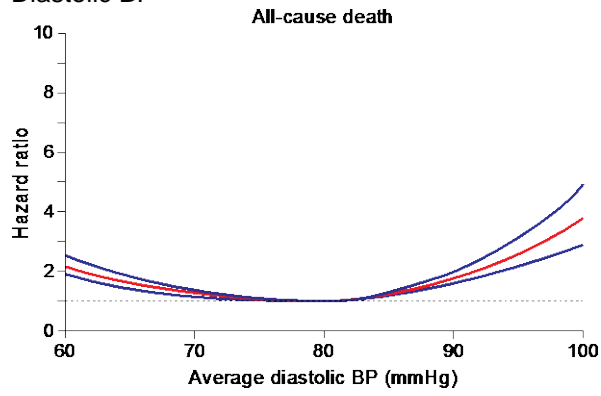
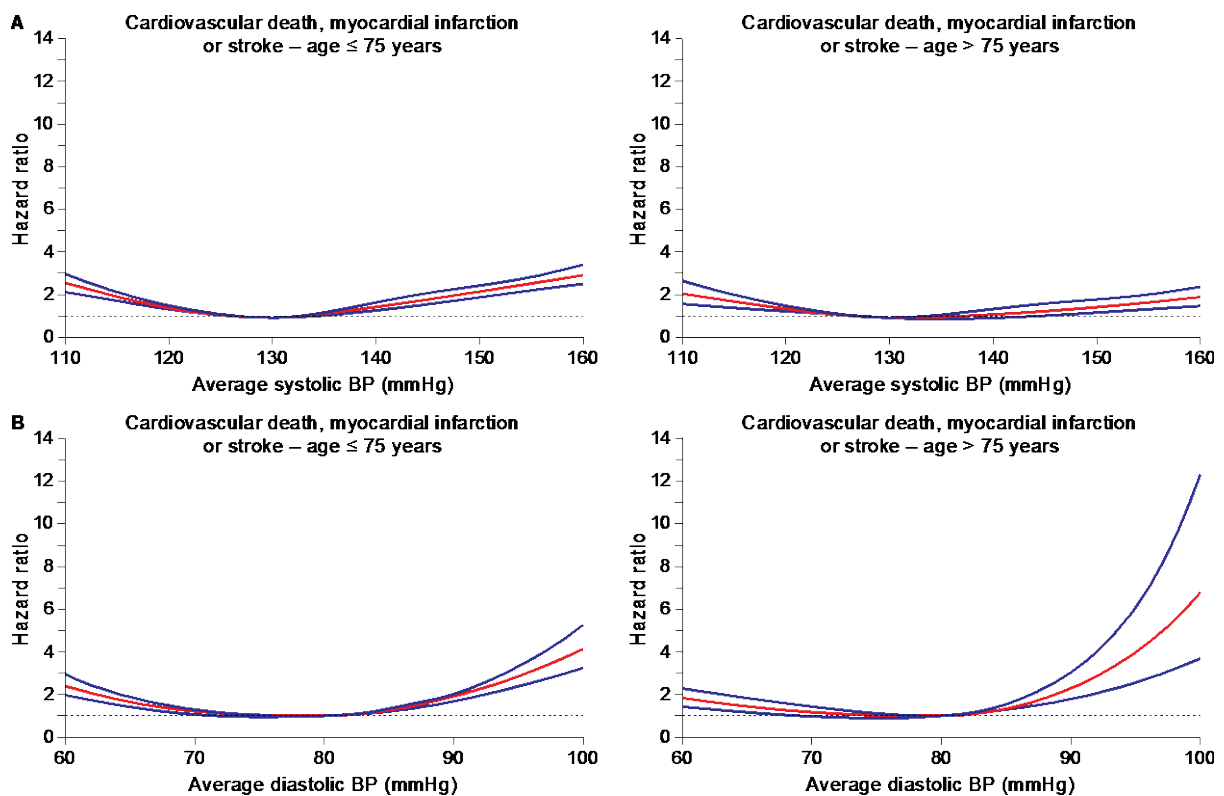


Figure S4: Restricted cubic splines of the primary outcome versus average (A) systolic and (B) diastolic BP in the patients younger or older than 75 years.

Restricted cubic splines are represented for the association between average BP level and primary composite outcome of cardiovascular death, myocardial infarction, or stroke, for subgroups of patients ≤ 75 years or >75 years. The analyses were adjusted for a subset of the variables from model 2 and 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.

BP=blood pressure.



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