Potential impact of the 2017 ACC/AHA guideline on high blood pressure in normotensive patients with stable coronary artery disease: insights from the CLARIFY registry

Emmanuelle Vidal-Petiot[1,2], **Emmanuel Sorbets**[3,4,5], **Deepak L. Bhatt**[6], **Gregory Ducrocq**[2,7], **Yedid Elbez**[7], **Roberto Ferrari**[8], **Ian Ford**[9], **Jean-Claude Tardif**[10], **Michal Tendera**[11], **Kim M. Fox**[3], and **Philippe Gabriel Steg**[2,3,7]*, on behalf of the CLARIFY investigators

[1]Physiology Department, AP-HP, Hôpital Bichat, INSERM U1149, Centre de Recherche sur l'Inflammation, 46, rue Henri Huchard, 75018 Paris, France; [2]Sorbonne Paris Cité, Paris Diderot University, Paris, France; [3]NHLI Imperial College, Dovehouse Street, London SW3 6LP ICMS, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; [4]Paris 13 University, Sorbonne Paris Cité, Bobigny, France; [5]Cardiology Department, AP-HP, Hôpital Avicenne, 125 rue de Stalingrad, 93000 Bobigny, France; [6]Harvard Medical School, Brigham and Women's Hospital Heart and Vascular Center, 75 Francis street, Boston, MA 02115, USA; [7]Cardiology Department, AP-HP, Hopital Bichat, FACT (French Alliance for Cardiovascular Trials), an F-CRIN network, INSERM U1148, Laboratory for Vascular Translational Science, 46, rue Henri Huchard, 75018 Paris, France; [8]Cardiological University Centre of Ferrara, University of Ferrara, Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy; [9]Robertson Centre for Biostatistics, Boyd Orr Building, University Avenue, University of Glasgow, Glasgow, G12 8QQ UK; [10]Department of Medicine, Montreal Heart Institute, Université de Montreal, 5000 Belanger street, Montreal H1T1C8, PQ, Canada; and [11]Medical University of Silesia, School of Medicine in Katowice, Departement of Cardiology and Structural Heart Disease, Katowice, Poland

Aims	The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline on high blood pressure (BP) lowered the threshold defining hypertension and BP target in high-risk patients to 130/80 mmHg. Patients with coronary artery disease and systolic BP 130–139 mmHg or diastolic BP 80–89 mmHg should now receive medication to achieve this target. We aimed to investigate the relationship between BP and cardiovascular events in 'real-life' patients with coronary artery disease considered as having normal BP until the recent guideline.
Methods and results	Data from 5956 patients with stable coronary artery disease, no history of hypertension or heart failure, and average BP <140/90 mmHg, enrolled in the CLARIFY registry (November 2009 to June 2010), were analysed. In a multivariable-adjusted Cox proportional hazards model, after a median follow-up of 5.0 years, diastolic BP 80–89 mmHg, but not systolic BP 130–139 mmHg, was associated with increased risk of the primary endpoint, a composite of cardiovascular death, myocardial infarction, or stroke (hazard ratio 2.15, 95% confidence interval 1.22–3.81 vs. 70–79 mmHg and 1.12, 0.64–1.97 vs. 120–129 mmHg). No significant increase in risk for the primary endpoint was observed for systolic BP <120 mmHg or diastolic BP <70 mmHg.
Conclusion	In patients with stable coronary artery disease defined as having normal BP according to the 140/90 mmHg threshold, diastolic BP 80–89 mmHg was associated with increased cardiovascular risk, whereas systolic BP 130–139 mmHg was not, supporting the lower diastolic but not the lower systolic BP hypertension-defining threshold and treatment target in coronary artery disease.
ClinicalTrials identifier	ISRCTN43070564.

* Corresponding author. Tel +33 1 40 25 86 68, Fax +33 1 40 25 88 65, Email: gabriel.steg@aphp.fr

Introduction

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline defined hypertension as a blood pressure (BP) ≥130/80 mmHg.[1] Following that change, patients with or at high risk for cardiovascular disease, with systolic BP between 130 and 139 mmHg or diastolic BP between 80 and 89 mmHg, previously considered as non-hypertensive patients, should now receive BP-lowering treatment for their newly defined hypertension, with a target of <130/80 mmHg. In normotensive patients with coronary artery disease, treated or not with BP-lowering antianginal medication, the new target is now a BP <130/80 mmHg. This lowered threshold largely results from the reduced rate of cardiovascular events observed in the intensive arm of the Systolic Blood Pressure Intervention Trial (SPRINT) trial.[2] However, patients in SPRINT were carefully followed-up in the setting of a randomized trial, and unattended automated BP measurements yielded values approximately 7 mmHg lower than average daytime ambulatory measurement,[3] and expected to be approximately 15 mmHg lower than standard office BP measurement.[4,5] Whether translating the results of SPRINT to real-life patients with standard office BP measurements will result in a lower cardiovascular event rate is debated.[6,7] Furthermore, very few patients in SPRINT had previous coronary artery disease and were normotensive. The potential impact of the 2017 ACC/AHA guideline on high BP in real-life patients with coronary artery disease requires careful attention.

In the present *post hoc* analysis, we evaluated the association between BP level and cardiovascular outcomes, including cardiovascular mortality, in patients with normal BP (<140/90 mmHg) and stable coronary artery disease from the CLARIFY registry. These patients represent the epitome of high-risk patients to whom the lowered pharmacological intervention threshold in the recent ACC/AHA guideline applies. Our goal was to determine whether there is an increased risk associated with systolic and diastolic BP values higher than 130 and 80 mmHg (vs. 120–129 and 70–79 mmHg, respectively) in the individuals classified as having normal BP according to the previous guidelines.

Methods

Study design and participants

The prospective, observational, longitudinal registry of patients with stable coronary artery disease (CLARIFY; ISRCTN43070564; www.clarify-registry.com) enrolled 32 703 patients from 45 countries between November 2009 and June 2010.[8,9] Patients were included if they had at least one of the following: documented myocardial infarction ≥3 months before enrolment, angiographic demonstration of >50% coronary stenosis, 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. Exclusion criteria were hospital admission for cardiovascular reasons in the past 3 months, planned revascularization, or conditions

compromising the participation or 5-year follow-up (including severe other cardiovascular disease such as advanced heart failure, severe valve disease, or history of valve repair or replacement). At baseline and at each yearly visit for up to 5 years, symptoms, clinical examination, results of the main clinical and biological tests, treatment, and clinical outcomes were recorded; office BP was measured in seated subjects after a 5-min rest, using the same arm throughout the study, with no pre-specified device. The registry was observational, with no recommendations on clinical management, and therefore, reflects routine practice. Events were accepted as reported by physicians and were not adjudicated. However, all events were source-verified during audits and several measures were implemented to ensure data quality, including onsite monitoring visits of 100% of the data in 5% of centres selected at random; regular telephone contact with investigators to limit missing data and loss to follow-up; and centralized verification of the electronic case report forms for completeness, consistency, and accuracy. The study was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained in all countries. All patients gave written informed consent.

This analysis was restricted to patients without any history of hypertension, and with an average systolic and diastolic BP during follow-up below 140 and 90 mmHg, respectively (Supplementary material online, Figure S1). Patients with congestive heart failure (defined as previous hospitalization for heart failure, or symptoms of heart failure, or a left ventricular ejection fraction <45%) were excluded.

Blood pressure subgroups

Data were analysed using the arithmetic mean of all BP values measured throughout follow-up, from the baseline visit to the visit before an outcome event or, in patients without an event, up to the last visit. All analyses were performed for systolic BP and diastolic BP separately. Patients were categorized into three subgroups for each BP component: systolic BP <120, 120–129 (reference), and 130–139 mmHg, and diastolic BP <70, 70–79 (reference), and 80–89 mmHg.

Study outcomes

The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. Secondary outcomes were each component of the primary outcome.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), depending on the distribution of the data; categorical data are presented as count and percentage. Event rates at 5 years are presented as the Kaplan–Meier estimates with 95% confidence intervals (CIs). Cox proportional hazards models were used to evaluate the relationship between BP categories and cardiovascular outcomes. In addition to crude hazard ratios (HRs), adjusted HRs were estimated after adjustment for covariates selected a priori as potential confounding factors, namely age, sex, geographic region, ethnicity, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes, low- and high-density lipoprotein cholesterol level, body mass index, and glomerular filtration rate [at baseline, estimated with the chronic kidney disease Epidemiology Collaboration (CKD-EPI) equation], peripheral artery disease, stroke, and transient ischaemic attack (any time before enrolment), and baseline

medication (aspirin, statin, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium channel blocker, and diuretic). An intermediate adjustment for age and gender was also performed.

Interactions between average systolic or diastolic BP and covariate age (>75 vs. ≤75 years), diabetes, and chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2, using the CKD-EPI equation) at baseline were tested. In addition, interactions between systolic and diastolic BP were also tested.

Statistical analyses were performed using SAS (version 9.3). A P-value <0.05 was used to signify statistical significance using two-sided testing, with no correction for multiple comparisons.

Role of the funding source

Results

A total of 5956 patients with stable coronary artery disease, without any history of hypertension, and with average BP <140/90 mmHg, were included in the analysis. Baseline characteristics of the patients are given for total population and by average follow-up systolic BP subgroups in *Table 1*, and by average follow-up diastolic BP subgroups in *Table 2*. Baseline medications are reported in Supplementary material online, *Tables S1 and S2*, and the number of patients in each subgroup of systolic BP, cross-classified with subgroups of diastolic BP, is reported in Supplementary material online, *Table S3*. Mean age at baseline was 61.0 ± 10.8 years, 4973 (83%) were men, and 1031 (17%) had diabetes. Mean average systolic and diastolic BPs were 122.7 ± 12.4 and 74.1 ± 9.8 mmHg, respectively. Compared with patients with systolic BP 130–139 mmHg, those with a lower systolic BP tended to be younger, leaner, less likely to have diabetes, and to have lower total cholesterol and triglyceride levels. Compared with patients with diastolic BP 80–89 mmHg, those with a lower diastolic BP tended to be older, leaner, more likely to be female, to have diabetes, and tended to have lower total cholesterol and triglyceride levels.

After a median follow-up of 5.0 years (IQR 4.2–5.1), 145 patients (2.7%, 95% CI 2.3–3.2) met the primary composite outcome. Cardiovascular death occurred in 114 (2.1%, 95% CI 1.8–2.6) patients, myocardial infarction (fatal or not) in 48 patients (0.9%, 95% CI 0.7–1.2), and stroke (fatal or not) in 29 (0.5%, 95% CI 0.4–0.7) patients.

Kaplan–Meier crude event rates and multivariable adjusted HRs are reported in the *Take home figure* for the primary outcome, and in *Table 3* for systolic BP subgroups and *Table 4* for diastolic BP subgroups, for secondary outcomes. Age and sex-adjusted HRs are reported along unadjusted and fully adjusted HRs in Supplementary material online, *Tables S4 and S5*. Compared with the reference group for systolic BP (120–129 mmHg), the risk for the primary outcome was not increased in the 130–139 mmHg subgroup, with an adjusted HR for the primary outcome of 1.12 (95% CI 0.64–1.97). There was no evidence of an increased risk in

the <120 mmHg systolic BP either, with an adjusted HR of 1.16 (95% CI 0.65–2.05). Similar results were observed for each separate component of the primary endpoint.

In contrast, compared with the reference group of patients with a diastolic BP of 70–79 mmHg, the adjusted HR for the primary outcome was 2.15 (95% CI 1.22–3.81) for diastolic BP 80–89 mmHg. A significant increase in the risk for cardiovascular death or stroke was also observed for diastolic BP 80–89 mmHg compared with 70–79 mmHg. There was no statistical evidence for increased risks for the primary outcome or secondary outcomes in the lowest diastolic BP subgroup (<70 mmHg) after adjustment for covariates.

Interaction analyses are given in the Supplementary material online, *Tables S6 to S8*. No significant effect-modification of age, diabetes, or chronic kidney disease at baseline was detected on the association between systolic BP or diastolic BP and primary or secondary outcomes. Interactions between systolic and diastolic BP were nonsignificant, with P-values of 0.33, 0.39, 0.20, and 0.87 for the primary endpoint, cardiovascular death, myocardial infarction, and stroke respectively, suggesting that the increased risk observed for a diastolic BP between 80 and 89 mmHg compared with 70–79 mmHg remained across all systolic BP subgroups.

Discussion

This observational study conducted in a large population of patients with coronary artery disease, no history of hypertension, and average follow-up BP <140/90 mmHg, treated according to standard care, showed that a systolic BP between 130 and 139 mmHg was not associated with an increased cardiovascular risk compared with a systolic BP between 120 and 129 mmHg. However, the risk associated with a diastolic BP between 80 and 89 mmHg was significantly greater than that of a diastolic BP between 70 and 79 mmHg. Although observational, our data do not support initiation of BP-lowering therapy (or more-intensive treatment in those receiving antianginal BP-lowering drugs) in patients newly defined as hypertensive according to the 2017 AHA/ACC guideline because of a systolic BP between 130 and 139 mmHg.

The CLARIFY registry provides a unique population of patients with stable coronary artery disease, including nearly 6000 normotensive patients, as defined from the 140/90 mmHg threshold, a third of whom were in the 130-139 mmHg range, to study the relationship between BP and cardiovascular events. Indeed, evidence supporting the new definition of hypertension and lower targets in patients with coronary artery disease is lacking. BP-intervention trials included a large majority of hypertensive patients, and very few trials until SPRINT lowered systolic BP below 130 mmHg, with overall no significant reduction in cardiovascular events except stroke below this threshold.[10] In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial,[11] which tested trandolapril vs. placebo in patients with stable coronary artery disease and normal or slightly reduced left ventricular function (more than half of whom were normotensive), patients in the treatment arm reached a mean BP below 130 mmHg, which was not associated with a reduced rate of cardiovascular events. However, the BP difference between the two groups was only 3 mmHg. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and SPRINT trials,

Table I   **Baseline characteristics for the total population and for each subgroup of systolic blood pressure**

	n	Total population (n = 5956)	<120 mmHg (n = 1779)	120–129 mmHg (n = 2532)	130–139 mmHg (n = 1645)	P-value
Age (years)	5955	61.0 (10.8)	58.7 (11.0)	61.1 (10.5)	63.4 (10.6)	<0.0001
Men	5955	4973 (83%)	1474 (82%)	2139 (84%)	1361 (83%)	0.22
Body mass index (kg/m^2)	5949	26.2 (24.09–28.71)	25.5 (23.53–27.78)	26.3 (24.17–28.95)	26.8 (24.62–29.28)	<0.0001
Diabetes	5956	1031 (17%)	279 (16%)	425 (17%)	327 (20%)	0.0034
Smoking status	5956	—	—	—	—	0.13
Current	—	895 (15%)	292 (16%)	378 (15%)	225 (14%)	—
Former	—	2986 (50%)	889 (49%)	1283 (51%)	815 (50%)	—
Never	—	2075 (35%)	599 (33%)	871 (34%)	605 (37%)	—
Systolic blood pressure (mmHg)	5954	122.7 (12.4)	111.8 (9.8)	123.7 (8.9)	132.7 (10.0)	<0.0001
Diastolic blood pressure (mmHg)	5954	74.1 (8.5)	69.8 (8.4)	75.1 (7.7)	77.3 (8.0)	<0.0001
Heart rate (b.p.m.)	4098	65.1 (10.6)	64.5 (10.7)	65.0 (10.4)	66.1 (10.9)	0.0007
Myocardial infarction	5956	3535 (59%)	1123 (63%)	1498 (59%)	914 (56%)	<0.0001
Percutaneous coronary intervention	5955	3991 (67%)	1223 (69%)	1720 (68%)	1048 (64%)	0.0031
Coronary artery bypass graft surgery	5956	1071 (18%)	286 (16%)	451 (18%)	334 (20%)	0.0054
Transient ischaemic attack	5955	91 (2%)	33 (2%)	37 (1%)	21 (1%)	0.36
Stroke	5956	89 (1%)	30 (2%)	38 (2%)	21 (1%)	0.61
Left ventricular ejection fraction (%)	3671	60.1 (7.8)	59.3 (7.9)	60.2 (7.9)	60.7 (7.6)	0.0003
HbA$_{1c}$ (%)	1264	6.5 (1.2)	6.4 (1.3)	6.5 (1.2)	6.6 (1.3)	0.0450
Creatinine (µmol/L)	4459	86 (74–97)	85 (74–96)	86 (74–97)	86 (73–97)	0.40
Total cholesterol (mmol/L)	4753	4.2 (3.6–4.9)	4.1 (3.5–4.8)	4.2 (3.6–4.9)	4.3 (3.7–4.9)	0.0001
HDL cholesterol (mmol/L)	4440	1.14 (0.98–1.38)	1.13 (0.96–1.35)	1.16 (0.99–1.38)	1.17 (0.99–1.40)	0.076
LDL cholesterol (mmol/L)	4239	2.33 (1.87–2.86)	2.30 (1.82–2.81)	2.34 (1.89–2.86)	2.36 (1.90–2.91)	0.0414
Fasting triglycerides (mmol/L)	4452	1.30 (0.95–1.79)	1.20 (0.90–1.68)	1.31 (0.97–1.80)	1.34 (0.97–1.87)	<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.

HbA$_{1c}$, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association.

which randomized patients to an intensive (<120 mmHg) or a standard (<140 mmHg) treatment target, inclusion criteria did not mandate hypertension (only a systolic BP ≥130 mmHg).[2,12] In both trials, approximately 10% of the patients did not receive BP-lowering drugs, and as some patients may have had systolic BP between 130 and 139 mmHg, only a small fraction of the populations were normotensive according to the 140/90 mmHg threshold. In addition, 33% of the ACCORD, and 17% of the SPRINT populations had a previous cardiovascular event, which leaves very few patients with normotension and coronary artery disease. Overall, even though the combined analysis of these trials favoured intensive treatment,[13] no clear conclusion can be drawn on intensive BP-lowering in normotensive patients with coronary artery disease. Noteworthy, in SPRINT, mean age was 7 years older than in CLARIFY, and patients with diabetes or previous stroke were excluded, also limiting the comparison between these two studies. In the Secondary Prevention of Small Subcortical Strokes (SPS3) BP target trial, in which the intensive target systolic BP was <130 mmHg in patients with previous stroke, there was no significant reduction in recurrent stroke, myocardial infarction, or death, but only 25% were normotensive, and 11% had previous coronary artery disease.[14] The randomized Heart Outcomes Prevention Evaluation (HOPE)-3 trial included a large proportion of normotensive patients (62%) and showed no benefit associated with the candesartan–hydrochlorothiazide therapy despite achieved BP below 130 mmHg in the treatment arm; however, this trial included intermediate-risk patients with no cardiovascular disease at baseline.[15]

The higher risk observed for diastolic BP of 80–89 mmHg compared with 70–79 mmHg is in line with meta-analyses of more- vs. less-intensive BP-lowering trials, even those conducted before SPRINT.[16,17] However, no such trial with a mean achieved BP in both groups across the 80 mmHg threshold was conducted in patients with coronary artery disease. In a recent post hoc analysis from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized AssessmeNt Study in ACE iNtolerant participants with cardiovascular Disease TRANSCEND patients with achieved systolic BP between 120 and 139 mmHg, a diastolic BP of 80–89 mmHg compared with 70–79 mmHg, was associated with a higher risk for stroke and hospitalization for heart failure.[18]

Although there are observational data on optimal BP targets in hypertensive patients with coronary artery disease,[19,20] no observational study was conducted specifically in normotensive patients with coronary artery disease. However, in the post hoc analysis of the Treating to New Targets (TNT) trial,[21] which included 10 001 patients with coronary artery disease, 46% of whom were normotensive at baseline, the relationship between systolic or diastolic BP and a composite endpoint of cardiovascular events showed a J-curve,

Table 2 Baseline characteristics for each subgroup of diastolic blood pressure

	n	<70 mmHg (n = 1200)	70–79 mmHg (n = 3523)	80–89 mmHg (n = 1233)	P-value
Age (years)	5955	62.9 (11.1)	61.2 (10.7)	58.8 (10.5)	<0.0001
Men	5955	942 (79%)	2984 (85%)	1047 (85%)	<0.0001
Body mass index (kg/m^2)	5949	25.6 (23.42–28.17)	26.2 (24.159–28.720)	26.8 (24.676–29.055)	<0.0001
Diabetes	5956	238 (20%)	609 (17%)	184 (15%)	0.0060
Smoking status	5956	—	—	—	0.0268
Current	—	158 (13%)	524 (15%)	213 (17%)	—
Former	—	599 (50%)	1798 (51%)	589 (48%)	—
Never	—	443 (37%)	1201 (34%)	431 (35%)	—
Systolic blood pressure (mmHg)	5954	116.2 (13.5)	123.0 (11.6)	128.0 (10.4)	<0.0001
Diastolic blood pressure (mmHg)	5954	64.9 (7.0)	74.5 (6.6)	82.0 (5.8)	<0.0001
Heart rate (b.p.m.)	4098	63.6 (10.4)	65.0 (10.6)	66.6 (10.8)	<0.0001
Myocardial infarction	5956	723 (60%)	2089 (59%)	723 (59%)	0.71
Percutaneous coronary intervention	5955	776 (65%)	2360 (67%)	855 (69%)	0.0494
Coronary artery bypass graft surgery	5956	257 (21%)	632 (18%)	182 (15%)	0.0001
Transient ischaemic attack	5955	23 (2%)	51 (1%)	17 (1%)	0.46
Stroke	5956	18 (2%)	51 (1%)	20 (2%)	0.91
Left ventricular ejection fraction (%)	3671	59.2 (7.9)	60.2 (7.8)	60.3 (7.8)	0.0075
HbA$_{1c}$ (%)	1264	6.7 (1.3)	6.4 (1.2)	6.5 (1.3)	0.0019
Creatinine (μmol/L)	4459	86 (74–97)	86 (74–97)	84 (72–97)	0.22
Total cholesterol (mmol/L)	4753	4.0 (3.5–4.7)	4.2 (3.6–4.8)	4.4 (3.8–5.1)	<0.0001
HDL cholesterol (mmol/L)	4440	1.13 (0.97–1.38)	1.16 (0.97–1.38)	1.14 (0.99–1.35)	0.76
LDL cholesterol (mmol/L)	4239	2.20 (1.77–2.70)	2.34 (1.90–2.83)	2.47 (1.98–3.07)	<0.0001
Fasting triglycerides (mmol/L)	4452	1.21 (0.90–1.62)	1.30 (0.95–1.80)	1.40 (1.00–1.89)	<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.
HbA$_{1c}$, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association.

with nadir values of 146 and 81 mmHg, respectively. There was no interaction with hypertension, suggesting similar results in normotensive patients. These results concur with the present observations, showing a benefit of BP reduction down to a threshold lower than the standard 90 mmHg for diastolic BP but not lower than the 140 mmHg threshold for systolic BP.

The rationale for more-intensive treatment in high-risk patients is the greater absolute risk reduction as baseline cardiovascular risk increases.[22–24] Patients with established coronary artery disease are clearly one such high-risk group. However, the benefits of more-intensive BP control have not been consistently observed in patients with coronary artery disease,[10] potentially because low BP—particularly low diastolic BP—may also be deleterious in this population, as described in several observational studies.[20,25–27]

Of note, the results from the present study are consistent with those obtained in treated hypertensive patients from the same registry, in which patients with stable coronary artery disease and treated for hypertension, with an on-treatment systolic BP between 130 and 139 mmHg, did not have an increased risk compared with patients with systolic BP 120–129 mmHg; in contrast, a marked and progressive increase was observed for a systolic BP value >140 mmHg, and for diastolic BP values >80 mmHg, compared with patients with

diastolic BP of 70–79 mmHg. Overall, these results from the CLARIFY registry do not support the lower systolic BP threshold of the 2017 ACC/AHA guideline on high BP in patients with coronary artery disease, whereas the expected cost of implementation of these recommendations would be major.[28–30]

Interestingly, in this population of normotensive patients, no significantly increased risk of cardiovascular events was observed in patients in the lowest BP subgroups, unlike what was previously observed in treated hypertensive patients of the same registry.[20] We cannot rule out that the present study may be underpowered to highlight a so-called 'J-curve' phenomenon. However, another potential explanation for this discrepancy is that during hypertension, autoregulation is shifted rightwards, to a higher pressure range, and patients tend to have increased left ventricular mass, both of which may contribute to the increased risk of adverse events associated with low BP values.[31,32] Therefore, the inflection of the so-called 'J-curve' may occur at lower BP values in normotensive than in hypertensive patients.

Our study has certain limitations. First, CLARIFY is an observational registry, and is therefore, prone to confounding, and possibly to less accurate outcome identification than in randomized controlled trials; only dedicated randomized controlled trials in patients with
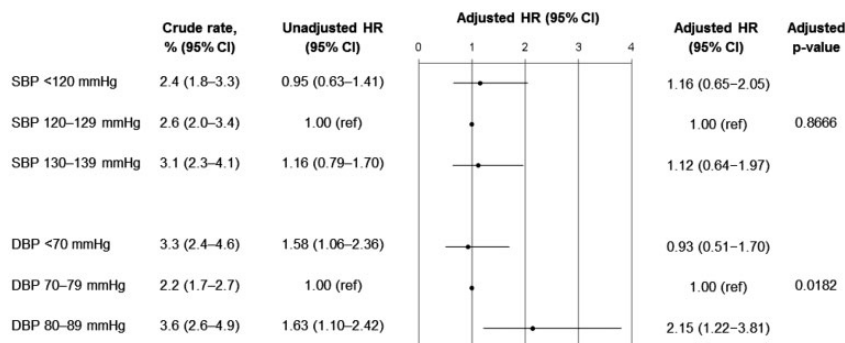
Take home figure Kaplan-Meier estimated crude event rates, HRs (95% confidence interval), and forest plot of adjusted HRs (95% confidence interval) of the primary outcome (cardiovascular death, myocardial infarction, or stroke). The analyses were adjusted for age, sex, geographic region, ethnicity, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes, low- and high-density lipoprotein cholesterol level, body mass index, glomerular filtration rate, peripheral artery disease, stroke, transient ischaemic attack, and baseline medication (aspirin, statin, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium channel blocker, and diuretic).

Table 3   **Event rates and unadjusted and adjusted^a hazard ratios for systolic BP subgroups (secondary outcomes)**

Outcomes	Parameters	Systolic BP subgroup			
		<120 mmHg	120–129 mmHg	130–139 mmHg	*P*-value
Cardiovascular death	*n/N*	33/1779	43/2532	38/1645	
	Crude event rate (%)	2.0 (1.4–2.9)	1.9 (1.4–2.5)	2.7 (1.9–3.7)	0.52
	Unadjusted HR	1.09 (0.69–1.72)	1.00 (–)	1.36 (0.88–2.11)	0.36
	Adjusted HR	1.20 (0.63–2.30)	1.00 (–)	1.19 (0.64–2.20)	0.81
Myocardial infarction	*n/N*	11/1779	20/2532	17/1645	
	Crude event rate (%)	0.7 (0.4–1.3)	0.9 (0.6–1.4)	1.1 (0.7–1.8)	0.58
	Unadjusted HR	0.78 (0.37–1.63)	1.00 (–)	1.31 (0.69–2.50)	0.40
	Adjusted HR	1.16 (0.40–3.39)	1.00 (–)	1.70 (0.62–4.66)	0.57
Stroke	*n/N*	9/1779	13/2532	7/1645	
	Crude event rate (%)	0.5 (0.2–1.0)	0.6 (0.3–1.0)	0.5 (0.2–1.0)	0.98
	Unadjusted HR	0.99 (0.42–2.30)	1.00 (–)	0.83 (0.33–2.08)	0.92
	Adjusted HR	1.67 (0.56–4.99)	1.00 (–)	0.85 (0.24–3.01)	0.52

Event rates (95% CI) are indicated as the Kaplan–Meier estimates.
BP, blood pressure; HR, hazard ratio; *n/N*, number of events/number of patients.
^aAdjusted for age, sex, geographic region, ethnicity, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes, low- and high-density lipoprotein cholesterol level, body mass index, glomerular filtration rate, peripheral artery disease, stroke, transient ischaemic attack, and baseline medication (aspirin, statin, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium channel blocker, diuretic).

coronary artery disease would provide a definite answer on the optimal BP target in this population. Second, patients underwent casual office BP measurement, which is not as accurate and standardized as the conditions of BP measurement in randomized trials, and especially not as stringent as in the SPRINT trial, where unattended measurement ensured minimizing any white-coat effect. However, routine clinical practice worldwide relies on casual office BP measurements; these 'real-life' observations in a large number of patients should also be taken into consideration when trying to translate scientific data into clinical practice recommendations. In addition, owing to a low number of patients, we were not able to analyse the consequences of very low BP values: <110 mmHg for systolic BP and <60 mmHg for

diastolic BP. This could be of importance, as in patients with cardiovascular disease and increased arterial stiffness, targeting a systolic BP <130 mmHg may not infrequently be at the cost of reaching low systolic and diastolic BP values, the potential harm of which requires further careful consideration and dedicated studies. Furthermore, although our population was selected using the combination of absence of history of hypertension according to the clinician, and an average follow-up BP <140/90 mmHg, it is likely that some patients would have a clinical diagnosis of hypertension if antianginal drugs were withdrawn. However, in the event of routine clinical implementation of the guidelines recommending a lower threshold for antihypertensive treatment, the patients of the present study are those

Table 4 Event rates and unadjusted and adjusted[a] hazard ratios for diastolic BP subgroups (secondary outcomes)

Outcomes	Parameters	Diastolic BP subgroup			
		<70 mmHg	70–79 mmHg	80–89 mmHg	*P*-value
Cardiovascular death	*n/N*	33/1200	52/3523	29/1233	
	Crude event rate (%)	3.0 (2.1–4.2)	1.7 (1.3–2.2)	2.7 (1.9–3.8)	0.0179
	Unadjusted HR	1.87 (1.25–2.90)	1.00 (–)	1.61 (1.02–2.53)	0.01
	Adjusted HR	1.04 (0.54–1.98)	1.00 (–)	2.14 (1.11–4.13)	0.07
Myocardial infarction	*n/N*	14/1200	23/3523	11/1233	
	Crude event rate (%)	1.3 (0.8–2.2)	0.7 (0.5–1.1)	1.0 (0.6–1.9)	0.35
	Unadjusted HR	1.79 (0.92–3.48)	1.00 (–)	1.37 (0.67–2.81)	0.22
	Adjusted HR	0.84 (0.30–2.38)	1.00 (–)	1.35 (0.43–4.22)	0.78
Stroke	*n/N*	7/1200	12/3523	10/1233	
	Crude event rate (%)	0.5 (0.2–1.2)	0.4 (0.2–0.6)	0.9 (0.5–1.7)	0.18
	Unadjusted HR	1.71 (0.67–4.35)	1.00 (–)	2.39 (1.03–5.52)	0.12
	Adjusted HR	1.28 (0.34–4.74)	1.00 (–)	3.67 (1.24–10.86)	0.054

Event rates (95% CI) are indicated as the Kaplan–Meier estimates.
BP, blood pressure; HR, hazard ratio; *n/N*, number of events/number of patients.
[a]Adjusted for age, sex, geographic region, ethnicity, smoking status, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, diabetes, low- and high-density lipoprotein cholesterol level, body mass index, glomerular filtration rate, peripheral artery disease, stroke, transient ischaemic attack, and baseline medication (aspirin, statin, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium channel blocker, diuretic).

whom clinicians would consider eligible for this new recommendation. Finally, our results were obtained in a population of normotensive patients with stable coronary artery disease (CAD), with a fairly small proportion of patients with diabetes (17%), and cannot be extrapolated to normotensive patients at higher cardiovascular risk, or unstable CAD.

Conclusion

In conclusion, this large international cohort study shows that in normotensive patients with stable coronary artery disease, the cardiovascular risk associated with an average systolic BP of 130–139 mmHg is not higher than that of patients with a systolic BP of 120–129 mmHg, and therefore does not support initiation of BP-lowering therapy in this population. Conversely, patients with diastolic BP between 80 and 89 mmHg (and systolic BP <140 mmHg) have a significantly increased risk compared with patients with a diastolic BP of 70–79 mmHg, even after multiple adjustments for potential confounders.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

References

1. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**:e127–e248.
2. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. Sprint Research Group A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
3. Drawz PE, Pajewski NM, Bates JT, Bello NA, Cushman WC, Dwyer JP, Fine LJ, Goff DC Jr, Haley WE, Krousel-Wood M, McWilliams A, Rifkin DE, Slinin Y, Taylor A, Townsend R, Wall B, Wright JT, Rahman M. Effect of intensive versus standard clinic-based hypertension management on ambulatory blood pressure: results from the SPRINT (Systolic Blood Pressure Intervention Trial) ambulatory blood pressure study. *Hypertension* 2017;**69**:42–50.
4. Myers MG, Valdivieso M, Kiss A. Use of automated office blood pressure measurement to reduce the white coat response. *J Hypertens* 2009;**27**:280–286.
5. Filipovsky J, Seidlerova J, Kratochvil Z, Karnosova P, Hronova M, Mayer O Jr. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood Press* 2016;**25**:228–234.
6. Bakris G, Sorrentino M. Redefining hypertension—assessing the new blood-pressure guidelines. *N Engl J Med* 2018;**378**:497–499.
7. Lüscher TF. What is a normal blood pressure? *Eur Heart J* 2018;**39**:2233–2240.
8. Steg PG, Greenlaw N, Tendera M, Tardif JC, Ferrari R, Al-Zaibag M, Dorian P, Hu D, Shalnova S, Sokn FJ, Ford I, Fox KM; Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) Investigators. Prevalence of anginal symptoms and myocardial ischemia and their effect on clinical outcomes in outpatients with stable coronary artery disease: data from the International Observational CLARIFY Registry. *JAMA Intern Med* 2014;**174**:1651–1659.
9. Sorbets E, Greenlaw N, Ferrari R, Ford I, Fox KM, Tardif JC, Tendera M, Steg PG; CLARIFY Investigators. Rationale, design, and baseline characteristics of the CLARIFY registry of outpatients with stable coronary artery disease. *Clin Cardiol* 2017;**40**:797–806.
10. Zanchetti A, Thomopoulos C, Parati G. Randomized controlled trials of blood pressure lowering in hypertension: a critical reappraisal. *Circ Res* 2015;**116**:1058–1073.
11. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;**351**:2058–2068.
12. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–1585.
13. Aggarwal R, Steinkamp J, Chiu N, Petrie B, Mirzan H. Intensive blood pressure targets for diabetic and other high-risk populations: a pooled individual patient data analysis. *Hypertension* 2018;**71**:833–839.
14. SPS3 Study Group, Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;**382**:507–515.
15. Lonn EM, Bosch J, Lopez-Jaramillo P, Zhu J, Liu L, Pais P, Diaz R, Xavier D, Sliwa K, Dans A, Avezum A, Piegas LS, Keltai K, Keltai M, Chazova I, Peters RJ, Held C, Yusoff K, Lewis BS, Jansky P, Parkhomenko A, Khunti K, Toff WD, Reid CM, Varigos J, Leiter LA, Molina DI, McKelvie R, Pogue J, Wilkinson J, Jung H, Dagenais G, Yusuf S ; HOPE Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;**374**:2009–2020.
16. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. *J Hypertens* 2014;**32**:2296–2304.
17. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. *J Hypertens* 2016;**34**:613–622.
18. Bohm M, Schumacher H, Teo KK, Lonn E, Mahfoud F, Mann JFE, Mancia G, Redon J, Schmieder R, Weber M, Sliwa K, Williams B, Yusuf S. Achieved diastolic blood pressure and pulse pressure at target systolic blood pressure (120-140 mmHg) and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Eur Heart J* 2018; doi: 10.1093/eurheartj/ehy287.
19. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;**144**:884–893.
20. Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, Tendera M, Tavazzi L, Bhatt DL, Steg PG; CLARIFY Investigators. 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* 2016;**388**:2142–2152.
21. Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, LaRosa JC; Treating to New Targets Steering Committee and Investigators. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J* 2010;**31**:2897–2908.
22. Blood Pressure Lowering Treatment Trialists Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;**384**:591–598.
23. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk—overview and meta-analyses of randomized trials. *J Hypertens* 2014;**32**:2305–2314.
24. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. *J Am Coll Cardiol* 2017;**69**:2446–2456.
25. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987;**1**:581–584.

26. McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: implications for blood pressure control. *J Am Coll Cardiol* 2016;**68**: 1713–1722.

27. Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, Mancia G, Redon J, Schmieder RE, Sliwa K, Weber MA, Williams B, Yusuf S. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet* 2017;**389**:2226–2237.

28. Vaucher J, Marques-Vidal P, Waeber G, Vollenweider P. Population impact of the 2017 ACC/AHA guidelines compared with the 2013 ESH/ESC guidelines for hypertension management. *Eur J Prev Cardiol* 2018;**25**: 1111–1113.

29. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *J Am Coll Cardiol* 2018;**71**:109–118.

30. Ioannidis JPA. Diagnosis and treatment of hypertension in the 2017 ACC/AHA guidelines and in the real world. *JAMA* 2018;**319**:115–116.

31. Polese A, De Cesare N, Montorsi P, Fabbiocchi F, Guazzi M, Loaldi A, Guazzi MD. Upward shift of the lower range of coronary flow autoregulation in hypertensive patients with hypertrophy of the left ventricle. *Circulation* 1991;**83**: 845–853.

32. Rabkin SW, Shiekh IA, Wood DA. The impact of left ventricular mass on diastolic blood pressure targets for patients with coronary artery disease. *Am J Hypertens* 2016;**29**:1085–1093.