ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **30**, 935–947
https://doi.org/10.1093/eurjpc/zwad004

FULL RESEARCH PAPER
Prevention in practice

Optimal or standard control of systolic and diastolic blood pressure across risk factor categories in patients with chronic coronary syndromes

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Received 7 November 2022; revised 9 December 2022; accepted 2 January 2023; online publish-ahead-of-print 7 January 2023

Aims Guidelines have lowered blood pressure (BP) targets to <130/80 mmHg. We examined the benefit of intensive control for each BP component, vs. the burden of other modifiable risk factors, in patients with chronic coronary syndromes (CCS).

Methods and results The CLARIFY registry (ISRCTN43070564) enrolled 32 703 patients with CCS, from 2009 to 2010, with a 5-year follow-up. Patients with either BP component below European guideline safety boundaries (120/70 mmHg) were excluded, leaving 19 167 patients (mean age: 63.8 ± 10.1 years, 78% men) in the present analysis. A multivariable-adjusted Cox proportional hazards model showed a gradual increase in cardiovascular risk (cardiovascular death, myocardial infarction, or stroke) when the number of uncontrolled risk factors (active smoking, no physical activity, low-density lipoprotein cholesterol ≥100 mg/dL, and diabetes with glycated haemoglobin ≥7%) increased [adjusted hazard ratio (HR): 1.34; 95% confidence interval (CI): 1.17–1.52, 1.65 (1.40–1.94), and 2.47 (1.90–3.21) for 1, 2, and 3 or 4 uncontrolled risk factors, respectively, vs. 0], without significant interaction with BP. Although uncontrolled systolic (≥140 mmHg) and diastolic (≥90 mmHg) BP were both associated with higher risk than standard BP, standard BP was associated with higher risk than optimal control for only the diastolic component (adjusted HR: 1.08; 95% CI: 0.94–1.25 for systolic BP 130–139 vs. 120–129 mmHg and 1.43; 95% CI: 1.27–1.62 for diastolic BP 80–89 vs. 70–79 mmHg).

Conclusions Our results suggest that the optimal BP target in CCS may be ≤139/79 mmHg and that optimizing the burden of other risk factors should be prioritized over the further reduction of systolic BP.

Lay summary We aimed to compare the benefit associated with strict vs. standard control of blood pressure with the potential benefit of controlling other modifiable risk factors in patients with chronic coronary syndromes (CCS).

- Our analysis conducted in nearly 20 000 patients from the CLARIFY registry (a prospective international cohort of patients with CCS) showed that the benefit associated with strict blood pressure (BP) control (BP < 130/80 mmHg) was marginal and only driven by the diastolic component of blood pressure, whereas having one or more uncontrolled other risk factors was associated with a gradually increasing risk, for all underlying BP levels.

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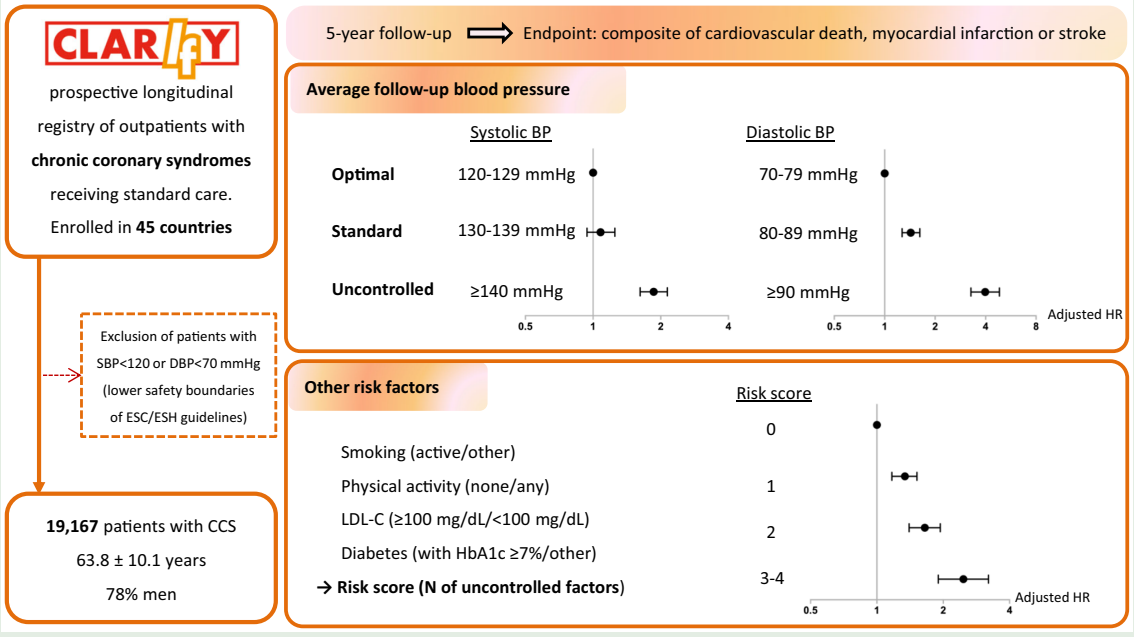
- Patients with CCS should be treated to achieve BP <140/80 mmHg. However, our results suggest that optimizing the burden of other risk factors (lipid-lowering therapy, exercise, smoking cessation, diabetes control) may need to be prioritized before considering further reduction of systolic BP.

Structured Graphical Abstract

Key Question
Are the benefits of optimized BP control presentfor both systolic and diastolic components, and how do they compare relative to reducing the burden of other modifiable risk factors in patients with CCS?
Key Finding
In patients with CCS, the benefit associated with strict BP control is driven only by the diastolic BP component, whereas having one or more other uncontrolled risk factors is associated with a gradually increasing risk, for all underlying BP levels.
Take Home Message
Patients with CCS should be treated to achieve BP ≤139/79 mmHg. However, our results suggest that optimizing the burden of other risk factors (lipid-lowering therapy, exercise, smoking cessation, diabetes control) may need to be prioritized before considering further reduction of systolic BP.



Summary of the key background and findings of this analysis from CLARIFY, the prospective, observational, longitudinal registry of patients with stable coronary artery disease. BP, blood pressure; CCS, chronic coronary syndromes; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Keywords CLARIFY registry • Chronic coronary syndromes • Hypertension • Blood pressure target • Risk factors

Introduction

In recent years, hypertension guidelines have lowered the pharmacological intervention threshold for blood pressure (BP) in high-risk patients, such as those with chronic coronary syndromes (CCS), to a systolic BP of ≥130 mmHg and a diastolic BP of ≥80 mmHg (US guidelines[1]) or 85 mmHg (European guidelines,[2]) with an optimal BP target of <130/80 mmHg. The European guidelines however advise against lowering BP below the so-called lower safety boundaries (i.e. 120 mmHg for systolic BP and 70 mmHg for diastolic BP), below which an increased risk has been reported, especially in patients with CCS whose coronary perfusion may be compromised in the low BP range.[3–5] The benefit of such restrictive BP targets in patients with CCS in real life is debated, while many patients remain uncontrolled according to the 'standard' 140/90 mmHg threshold[6] and may have several other uncontrolled risk factors. Indeed, no BP target trial was conducted in patients with CCS. The lowered threshold of 130/80 mmHg largely results from the reduced rate of cardiovascular events observed in the intensive arm (<120 mmHg) of the Systolic Blood Pressure Intervention Trial (SPRINT),[7] which included few patients with CCS (20% of the patients had a previous cardiovascular disease of any vascular bed). More data are needed to help physicians decide which interventions should be prioritized to obtain individual risk reduction and whether lower BP targets are associated with consistent benefits for both systolic and diastolic components in patients with CCS.

In this study, we sought to assess the respective effects of intensive lowering of diastolic and systolic BP vs. a global management of risk factor burden in patients with CCS.

Methods

Study design and participants

The prospective, observational, longitudinal registry of patients with stable coronary artery disease (CLARIFY; ISRCTN43070564) enrolled 32 703 patients from 45 countries between 26 November 2009 and 30 June 2010. The design and overall results have been described previously.[8,9] Briefly, this international registry enrolled patients with stable CCS in whom coronary artery disease had been objectively documented by either previous myocardial infarction (>3 months), previous coronary revascularization procedure (>3 months), coronary angiography (>50% stenosis), or myocardial ischaemia provoked by functional testing in symptomatic individuals. Exclusion criteria were hospital admission for cardiovascular reasons (including revascularization) in the past 3 months, planned revascularization, or conditions compromising participation or 5-year follow-up (including severe other cardiovascular diseases such as advanced heart failure, valve disease, or history of valve repair or replacement).

Participation in the study did not affect routine clinical care and investigation, and participants were managed according to usual practice. No specific tests or treatments were mandated by the study protocol. The study was performed in accordance with the Declaration of Helsinki and was approved by local ethics committees and institutional review boards, as appropriate. All subjects provided written informed consent.

Data collection

Following the recruitment of eligible subjects, data were collected using standardized electronic case report forms at baseline and annually for up to 5 years. At each yearly visit, information on symptoms, results of clinical examinations and the main clinical and biological tests, treatments, and clinical outcomes were recorded. Office BP was measured in seated subjects after a rest of 5 min. Physical activity was evaluated and categorized into four levels as follows: no physical activity, only light physical activity on most weeks, vigorous physical activity ≥20 min once or twice a week, and vigorous physical activity ≥20 min three or more times per week. Smoking status was classified as active, former (with the date of cessation), and never smoker.

Completeness, consistency, and correctness of data were verified, managed, and analysed centrally by an independent academic statistics centre (Robertson Centre for Biostatistics, University of Glasgow, UK). Approximately 5% of the sites were randomly selected for audit and quality control, and 100% of their data were verified from source documents during site visits. Where applicable, registries could be used to retrieve the patient's vital status.

Blood pressure and risk factor categories

BP was calculated as the arithmetic mean of all values measured throughout follow-up, from the baseline visit to the visit before an event or to the end of follow-up if no event occurred. The main analyses were performed after the exclusion of patients with either BP component below the lower safety boundaries of the European guidelines (i.e. systolic BP <120 mmHg or diastolic BP <70 mmHg). However, analyses conducted in the total population (including patients with low BP values) are also presented in Supplementary material online.

BP components were analysed separately. Patients were categorized into three subgroups for each BP component: systolic BP ≥140, 130–139, and 120–129 mmHg, and diastolic BP ≥90, 80–89, and 70–79 mmHg, corresponding to uncontrolled, standard, and optimal BP, respectively. In the population including patients with low BP, the optimal BP groups were defined as systolic BP ≤129 mmHg and diastolic BP ≤79 mmHg, respectively.

A risk score was calculated (between 0 and 4) based on the evaluation of smoking (1: active smoker; 0: never or former), physical activity (1: no physical activity; 0: any physical activity), level of low-density lipoprotein cholesterol (LDL-C) [1: ≥ 100 mg/dL (2.59 mmoL/L); 0: < 100 mg/dL], diabetes [1: diabetes and glycated haemoglobin (HbA_{1c}) ≥ 7%; otherwise 0]. For all analyses, Scores 3 and 4 were grouped into the highest risk-score category.

Smoking and physical activity were captured from the first available information (i.e. at baseline for most patients). LDL-C and HbA_{1c} were calculated as the average of all available values until the primary outcome or until the end of follow-up, whichever occurred first. BP and risk-score categories were analysed separately or cross-classified. The reference categories were optimal BP, a risk score of 0, or the intersection of both, depending on the analysis.

Statistical analyses

Continuous variables are summarized as mean with standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables are presented as numbers and percentages.

The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. Event rates at 5 years were calculated as Kaplan–Meier estimates with a 95% confidence interval (CI). Cox proportional hazards models were used to assess the association between each BP category, risk-score category, or combined BP and risk-score categories and the composite outcome. In addition to crude hazard ratios (HRs), adjusted HRs were estimated after adjustment for potential confounding factors, selected *a priori* as potential confounders, namely age, sex, geographical region, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, peripheral artery disease at baseline, previous stroke or transient ischaemic attack, previous hospital admission for (or symptoms of) heart failure, atrial fibrillation or flutter, body mass index, any antiplatelet therapies, statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers. Interactions between BP components and risk-score categories were tested by the introduction of product terms. Data were analysed as recorded without imputation for missing data. Statistical analyses were performed using R (3.4.1).

Results

Baseline characteristics

Data from 19 167 adult patients with CCS, systolic BP ≥120 mmHg, and diastolic BP ≥70 mmHg were included in the analysis (*Figure 1*). Patient baseline characteristics are reported in *Table 1* for the total population and by systolic and diastolic BP categories. The mean age at inclusion was 63.8 ± 10.1 years, 78% were men, 25% had diabetes, 12% were current smokers, 42% had LDL-C ≥100 mg/dL (2.59 mmoL/L), and 15% declared practising no physical activity. Mean baseline systolic and diastolic BPs were 134.8 ± 15.3 and 79.8 ± 8.8 mmHg, respectively. The mean number of available BP measurements per patient throughout follow-up was 4.9 ± 1.6. The mean average systolic and diastolic BPs during follow-up were 133.9 ± 10.2 and 78.9 ± 5.6 mmHg, respectively.

Compared to patients with uncontrolled systolic BP, patients with standard or optimal control of systolic BP tended to be younger, more likely to be men, without diabetes, current or former smokers, with a higher baseline incidence of myocardial infarction and percutaneous coronary intervention, lower average high-density lipoprotein cholesterol, and LDL-C levels, were more physically active, and had a lower risk score. Compared to patients with uncontrolled diastolic BP, patients with controlled (standard or optimal) diastolic BP tended to be older, leaner, diabetic, and non-smokers, with a higher baseline incidence of myocardial infarction, with lower average levels of LDL-C, and had a lower risk score. When patients with systolic BP <120 mmHg or diastolic BP <70 mmHg were included, data were available for 25 606 patients (mean age 63.9 ± 10.4 years, 78% men); their baseline characteristics are presented in Supplementary material online, *Table S1*.

Clinical outcomes

After a median follow-up of 5.0 years (IQR: 4.8–5.1), 1312 patients (6.8%) met the composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke occurred in 678 (3.5%), 415 (2.2%), and 294 (1.5%) patients, respectively.

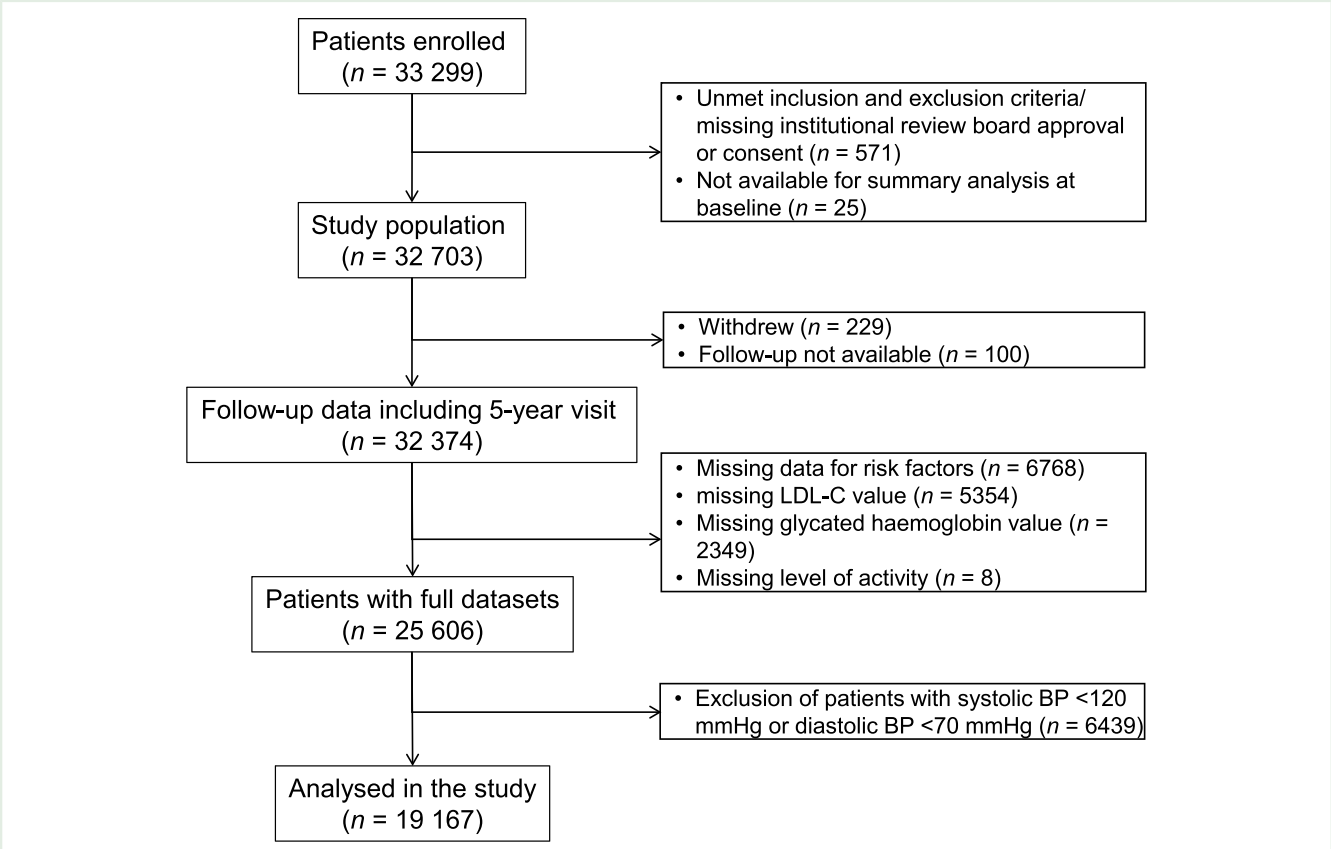


Figure 1 Flow diagram of the study population. BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.

Kaplan–Meier estimated event rates, crude HR, and multivariable-adjusted HR per risk score and BP categories are given in *Table 2*. Compared to patients with a risk score of 0 (no uncontrolled risk factor outside BP), patients with one or more uncontrolled risk factors displayed a gradual increase in risk for the composite outcome, with an adjusted HR of 1.34 (95% CI: 1.17–1.52) for a risk score of 1, 1.65 (1.40–1.94) for a score of 2, and 2.47 (1.90–3.21) for a score of 3 or 4.

The risk associated with a standard control of systolic BP (130–139 mmHg) did not differ from that associated with an optimal control (120–129 mmHg), with an adjusted HR of 1.08 (95% CI: 0.94–1.25), whereas patients with uncontrolled systolic BP (≥140 mmHg) had a higher risk, with an adjusted HR of 1.86 (95% CI: 1.62–2.14) compared with optimal control. In contrast, compared with optimal control of diastolic BP, both standard control of diastolic BP (80–89 mmHg) and uncontrolled diastolic BP (≥90 mmHg) were associated with higher risks, with adjusted HR of 1.43 (95% CI: 1.27–1.62) and 3.98 (95% CI: 3.27–4.84), respectively. Results were very similar when stratified by gender (see Supplementary material online, *Tables S2* and *S3*).

When patients with low BP values (<120 mmHg for systolic BP and <70 mmHg for diastolic BP) were included in the analyses, results were similar, but the lack of benefit associated with strict systolic BP control was even clearer [adjusted HR for standard vs. optimal systolic BP, 0.97 (95% CI: 0.87–1.09)], and the benefit associated with optimal diastolic BP was smaller [adjusted HR for standard vs. optimal diastolic BP, 1.23 (95% CI: 1.11–1.37)]. The same gradually increasing risk with uncontrolled risk factors (apart from BP) was observed in both study populations (see Supplementary material online, *Table S4*).

Cross-classifications of blood pressure and risk-score categories

There was no interaction between BP components and risk score ($P = 0.06$ for systolic BP and $P = 0.54$ for diastolic BP), therefore the gradual increase in risk associated with uncontrolled risk factors was true at all underlying BP levels (*Figures 2* and *3*). Likewise, the lack of benefit associated with optimal vs. standard control of systolic BP (*Figure 2*) and the lower risk associated with optimal compared with standard diastolic BP were true across all risk-score categories (*Figure 3*). Uncontrolled diastolic BP was associated with an approximately fourfold higher risk of the composite outcome compared with optimal diastolic BP (*Table 2*), a consistent finding across all risk-score categories (*Figure 3*).

As illustrated in *Figures 2* and *3*, the highest level of cardiovascular risk was observed for patients with uncontrolled diastolic BP (≥90 mmHg) and a risk score of 3 or 4 (event rate 31.4%; 95% CI: 19.2–48.9). The categories with the next-to-highest risk, displaying event rates above 20% during 5-year follow-up, were patients with uncontrolled diastolic BP and a risk score of 2 (event rate 22.2%; 95% CI: 16.2–30.1) and patients with uncontrolled systolic BP and a risk score of 3 or 4 (event rate 20.2%; 95% CI: 14.6–27.5).

Discussion

This observational study, conducted in a large, contemporary, prospective registry of patients with CCS, with both BP components above the so-called *lower safety boundaries* of the European

Table 1 Demographic and baseline characteristics of the patients, for the total population and each average blood pressure category[a]

	Patients (*n*)	Total population (*n* = 19 167)	Average systolic blood pressure category				Average diastolic blood pressure categories			
			Optimal control (120–129 mmHg) (*n* = 7181)	Standard control (130–139 mmHg) (*n* = 7260)	Uncontrolled (≥140 mmHg) (*n* = 4726)	*P*-value	Optimal control (70–79 mmHg mmHg) (*n* = 10 618)	Standard control (80–89 mmHg) (*n* = 7622)	Uncontrolled ≥90 mmHg) (*n* = 927)	*P*-value
Age (years), mean (SD)	19 162	63.8 (10.1)	62.2 (10.2)	64.2 (10.0)	65.9 (9.7)	<0.001	65.3 (9.9)	62.3 (10.0)	59.5 (10.0)	<0.001
Men, *n* (%)	19 167	15 009 (78)	5877 (82)	5665 (78)	3467 (73)	<0.001	8281 (78)	5991 (79)	737 (80)	0.407
Body mass index (kg/m^2), median (Q1, Q3)	19 153	27.6 (25.1, 30.5)	27.2 (24.9, 30.1)	27.7 (25.2, 30.7)	28.1 (25.5, 31.2)	<0.001	27.2 (24.8, 30.1)	28.0 (25.5, 31.0)	28.7 (26.0, 31.9)	<0.001
Diabetes, *n* (%)	19 166	4820 (25)	1548 (22)	1881 (26)	1391 (29)	<0.001	2870 (27)	1758 (23)	192 (21)	<0.001
Smoking status, *n* (%)							1170 (11)	1028 (13)	153 (17)	<0.001
Current	19 167	2351 (12)	922 (13)	910 (13)	519 (11)	<0.001	5092 (48)	3470 (46)	407 (44)	
Former	–	8969 (47)	3515 (49)	3313 (46)	2141 (45)		4356 (41)	3124 (41)	367 (40)	
Never	–	7847 (41)	2744 (38)	3037 (42)	2066 (44)					
Systolic blood pressure (mmHg), mean (SD)	19 161	134.8 (15.3)	125.1 (9.9)	134.9 (11.2)	149.4 (15.9)	<0.001	131.4 (13.60)	137.4 (15.2)	151.8 (18.5)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	19 161	79.8 (8.8)	77.1 (7.4)	79.7 (8.2)	83.8 (10.0)	<0.001	75.7 (7.1)	83.6 (7.2)	94.5 (8.3)	<0.001
Heart rate (b.p.m.), mean (SD)	19 160	68.3 (10.6)	67.6 (10.0)	68.5 (10.6)	69.1 (11.3)	<0.001	67.3 (10.3)	69.3 (10.6)	72.0 (11.9)	<0.001
Myocardial infarction, *n* (%)	19 165	11 343 (59)	4443 (62)	4278 (59)	2622 (55)	<0.001	6430 (61)	4411 (58)	502 (54)	<0.001
Percutaneous coronary intervention, *n* (%)	19 166	11 208 (58)	4445 (62)	4157 (57)	2606 (55)	<0.001	6049 (57)	4548 (60)	611 (66)	<0.001
Coronary artery bypass graft surgery, *n* (%)	19 165	4481 (23)	1550 (22)	1680 (23)	1251 (26)	<0.001	2585 (24)	1712 (22)	184 (20)	00.001
Transient	19 166	597 (3)	193 (3)	230 (3)	174 (4)	0.009	329 (3)	239 (3)	29 (3)	0.990

Continued

Table 1 *Continued*

	Patients (*n*)	Total population (*n* = 19 167)	Average systolic blood pressure category				Average diastolic blood pressure categories			
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ischaemic attack, *n* (%)										
Stroke, *n* (%)	19 165	756 (4)	268 (4)	268 (4)	220 (5)	0.015	426 (4)	287 (4)	43 (5)	0.377
Hospitalization for heart failure, *n* (%)	19 166	763 (4)	262 (4)	279 (4)	222 (5)	0.012	394 (4)	325 (4)	44 (5)	0.0.80
Symptoms of heart failure, *n* (%)										<0.001
None	19 166	16 389 (86)	6173 (86)	6252 (86)	3964 (84)	<0.001	9520 (89.66)	6197 (81.30)	672 (72.57)	
NYHA class II	–	2353 (12)	880 (12)	838 (12)	635 (13)		946 (8.91)	1199 (15.73)	208 (22.46)	
NYHA class III	–	424 (2)	128 (2)	169 (2)	127 (3)		152 (1.43)	226 (2.97)	46 (4.97)	
Left ventricular ejection fraction (%), mean (SD)	13 727	57.0 (10.3)	56.8 (10.6)	57.1 (10.1)	57.3 (10.4)	0.052	57.2 (10.4)	56.9 (10.2)	55.7 (10.4)	<0.001
HbA_{1c} (%), mean (SD)[b]	5677	6.8 (1.5)	6.6 (1.7)	6.8 (1.3)	6.9 (1.4)	<0.001	6.8 (1.6)	6.8 (1.3)	7.0 (1.6)	0.139
$HbA_{1c} \geq 7\%$, *n* (%)	5677	1958 (35)	577 (29)	778 (36)	603 (40)	<0.001	1165 (34)	710 (35)	83 (37)	0.611
Creatinine (μmoL/L), median (Q1, Q3)	15 644	88 (76, 100)	88 (76, 99)	88 (75, 100)	88 (75, 102)	0.003	88 (75, 100)	88 (76–100)	88 (76, 101)	0.271
eGFR (mL/min/ L;.73 m^2), mean (SD)	13 871	76.0 (18.9)	77.9 (18.5)	75.5 (18.7)	73.7 (19.6)	<0.001	74.9 (18.8)	77.2 (18.9)	78.7 (19.7)	<0.001
Total cholesterol (mmoL/L), mean (SD)	16 974	4.48 (1.08)	4.39 (1.04)	4.50 (1.09)	4.60 (1.11)	<0.001	4.35 (1.02)	4.61 (1.12)	4.91 (1.18)	<0.001
HDL-C (mmoL/ L), mean (SD)[b]	15 690	1.20 (0.32)	1.18 (0.32)	1.20 (0.32)	1.21 (0.33)	<0.001	1.20 (0.32)	1.19 (0.32)	1.18 (0.32)	0.139
LDL-C (mmoL/	15 511	2.55 (0.89)	2.49 (0.85)	2.56 (0.90)	2.63 (0.93)	<0.001	2.45 (0.83)	2.64 (0.93)	2.93 (1.04)	<0.001

Continued

Table 1 *Continued*

	Patients (*n*)	Total population (*n* = 19 167)	Average systolic blood pressure category				Average diastolic blood pressure categories			
			Optimal control (120–129 mmHg) (*n* = 7181)	Standard control (130–139 mmHg) (*n* = 7260)	Uncontrolled (≥140 mmHg) (*n* = 4726)	*P*-value	Optimal control (70–79 mmHg mmHg) (*n* = 10 618)	Standard control (80–89 mmHg) (*n* = 7622)	Uncontrolled ≥90 mmHg) (*n* = 927)	*P*-value
L), mean (SD)[b]										
LDL-C ≥ 100 mg/dL, *n* (%)	15 511	6462 (42)	2277 (39)	2451 (42)	1734 (45)	<0.001	3254 (37)	2768 (46)	440 (58)	<0.001
Fasting triglycerides (mmoL/L), mean (SD)	15 995	1.62 (0.88)	1.58 (0.85)	1.63 (0.88)	1.67 (0.92)	<0.001	1.55 (0.83)	1.69 (0.91)	1.83 (1.00)	<0.001
Physical activity, *n* (%)						<0.001				0.078
No physical activity weekly	19 167	2886 (15)	1009 (14)	1139 (16)	738 (16)		1624 (15)	1129 (15)	133 (14)	
Light physical activity most weeks	–	9704 (51)	3576 (50)	3654 (50)	2474 (52)		5344 (50)	3863 (51)	497 (54)	
≥20 min vigorous physical activity 1–2 a week	–	3453 (18)	1357 (19)	1302 (18)	794 (17)		1883 (18)	1393 (18)	177 (19)	
≥20 min vigorous physical activity ≥3 times a week	–	3124 (16)	1239 (17)	1165 (16)	720 (15)		1767 (17)	1237 (16)	120 (13)	
Risk score, *n* (%)						<0.001				<0.001
0	19 167	7522 (39)	3020 (42)	2811 (39)	1691 (36)		4485 (42)	2780 (36)	257 (28)	
1	–	8168 (43)	2991 (42)	3111 (43)	2066 (44)		4348 (41)	3373 (44)	447 (48)	
2	–	2915 (15)	1015 (14)	1101 (15)	799 (17)		1513 (14)	1222 (16)	180 (19)	
3 or 4	–	562 (3)	155 (2)	237 (3)	170 (4)		272 (3)	247 (3)	43 (5)	

eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NYHA, New York Heart Association; SD, standard deviation; Q, quartile.
[a]Some percentages do not add up to 100% because of rounding.
[b]Cholesterol and HbA_{1c} values are the averages of all available values until an event or until the end of follow-up.

Table 2 Relationship between risk score, blood pressure components, and the composite outcome of cardiovascular death, myocardial infarction, or stroke

	Patients (*n*)	Events (*n*)	Event rate (95% CI)[a]	Unadjusted HR (95% CI)	*P*-value[b]	Adjusted HR (95% CI)[c]	*P*-value
Risk score							
0	7522	418	5.96 (5.42–6.56)	1.00	<0.001	1.00	<0.001
1	8168	571	7.66 (7.07–8.30)	1.29 (1.13–1.46)		1.34 (1.17–1.52)	
2	2915	253	9.35 (8.29–10.55)	1.61 (1.37–1.88)		1.65 (1.40–1.94)	
3 or 4	562	70	13.95 (11.15–17.37)	2.45 (1.89–3.16)		2.47 (1.90–3.21)	
Systolic blood pressure							
120–129 mmHg (optimal)	7181	387	5.74 (5.20–6.34)	1.00	<0.001	1.00	<0.001
130–139 mmHg (standard)	7260	440	6.58 (6.00–7.21)	1.14 (0.99–1.31)		1.08 (0.94–1.25)	
≥140 mmHg (uncontrolled)	4726	485	11.47 (10.53–12.49)	2.08 (1.82–2.38)		1.86 (1.62–2.14)	
Diastolic blood pressure							
70–79 mmHg (optimal)	10 618	630	6.43 (5.95–6.94)	1.00	<0.001	1.00	<0.001
80–89 mmHg (standard)	7622	546	7.77 (7.15–8.43)	1.24 (1.11–1.40)		1.43 (1.27–1.62)	
≥90 mmHg (uncontrolled)	927	136	17.03 (14.54–19.90)	3.02 (2.50–3.64)		3.98 (3.27–4.84)	

CI, confidence interval; HR, hazard ratio.
[a]Event rates are indicated as Kaplan–Meier estimates.
[b]The *P*-value reported represents the heterogeneity of the association of blood pressure or risk score with the outcome across the different categories of the variable
[c]Adjusted for age, sex, geographical region, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, peripheral artery disease at baseline, previous stroke or transient ischaemic attack, previous hospital admission for (or symptoms of) heart failure, atrial fibrillation or flutter, body mass index, any antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers.

guidelines (hence a systolic BP ≥120 mmHg and a diastolic BP ≥70 mmHg),[2] showed that optimal systolic BP (120–129 mmHg) was not associated with improved cardiovascular outcome compared to standard control (130–139 mmHg). In contrast, optimal diastolic BP (70–79 mmHg) was associated with a lower risk of the composite of cardiovascular death, myocardial infarction, or stroke compared with 80–89 mmHg, even after adjustment for multiple confounders. Our study also confirmed that uncontrolled BP (>140/90 mmHg) was associated with higher cardiovascular risk, which reached fourfold that of optimal BP for the diastolic component. These observations were consistent across all cardiovascular risk levels and in both men and women. Furthermore, each additional uncontrolled modifiable risk factor other than BP was associated with a gradually higher cardiovascular risk, without interaction with systolic or diastolic BP levels.

Similar results for the risk associated with components of BP have been found in previous analyses of normotensive[10] and treated hypertensive patients[4] from the CLARIFY registry. However, patients with low BP values had not been excluded from these studies, and as such low BP values are associated with a steep increase in cardiovascular risk,[4] patients with at least one BP component <120/70 mmHg may have erased the potential benefits associated with optimal BP control. In the present study, we show that when systolic BP was within the optimal range, as defined in the 2018 European guidelines (120–129 mmHg), and with a diastolic BP >70 mmHg, cardiovascular risk was not lower compared to standard control of systolic BP. Of note, when analyses were performed without the exclusion of patients with low BP ($n = 25\,608$ patients, as shown in Supplementary material online), the conclusion was reinforced, with an even clearer lack of benefit associated with optimal systolic BP (≤129 mmHg) and a smaller benefit associated with optimal diastolic BP (≤79 mmHg), as one could expect from the previously described J-curve phenomenon in patients with very low BP values.[4]

The optimal BP target has long been debated. All guidelines issued between 2011 and 2014 recommend a systolic BP target <140 mmHg in most non-frail adults.[11–14] In 2015, the SPRINT, conducted in patients at high risk but mostly in primary prevention, demonstrated that an intensive systolic BP target (<120 mmHg) reduced cardiovascular events and mortality compared with a standard systolic BP target (<140 mmHg).[7] Following the publication of SPRINT, BP guidelines lowered the target to <130/80 mmHg for most if not all patients—the 10 mmHg shift of systolic BP above the SPRINT target being due to considerations regarding BP measurement.[1,2] Indeed, in SPRINT, office BP measurement protocol was highly standardized, unattended, and yielded values lower than those expected when measured in routine practice.[15,16] Although these stricter BP targets include patients with CCS, data from interventional trials specifically designed to define the optimal BP target in this population are lacking.

In the absence of a randomized BP target trial in patients with CCS, most of the evidence regarding the optimal BP target in these patients comes from observational data or retrospective analyses of interventional trials. In a *post hoc* analysis of the Treating to New Targets (TNT) trial, which warned against a J-curve phenomenon in patients with coronary artery disease, the BP value associated with the lowest risk was 146/81, but the authors noted that the curve was relatively flat across the 120–140 mmHg range for systolic BP, in line with our results.[17] A *post hoc* analysis of the International Verapamil SR-Trandolapril Study (INVEST) also showed that the incidence of the primary outcome of all-cause death, non-fatal myocardial infarction, or non-fatal stroke was similar in patients with systolic BP between 120 and 130 mmHg or between 130 and 140 mmHg.[3] In patients with coronary artery disease and diabetes from the same trial, Cooper-DeHoff *et al.* found similar results for systolic BP, namely a 'tight' BP control <130 mmHg was not associated with better outcomes than usual (130–140 mmHg) control.[18] In a *post hoc* analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 Trial, Bangalore *et al.* found that after an acute coronary syndrome, the average follow-up systolic

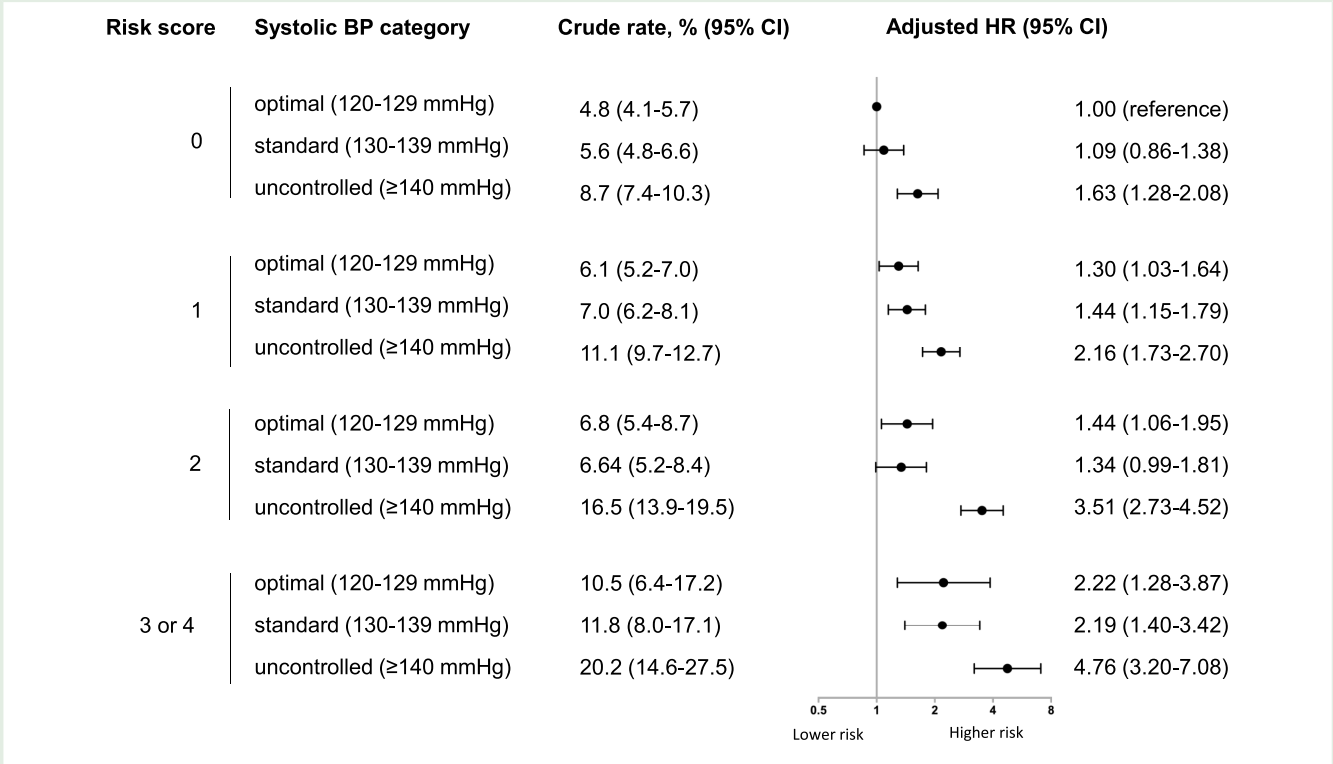

Figure 2 Relationship between systolic BP categories, cross-classified with risk-score, and the composite outcome of cardiovascular death, myocardial infarction, or stroke. Crude event rates are indicated as Kaplan–Meier estimates. Adjusted HR: adjusted for age, sex, geographical region, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, peripheral artery disease at baseline, previous stroke or transient ischemic attack, previous hospital admission for (or symptoms of) heart failure, atrial fibrillation or flutter, body mass index, any antiplatelet, statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers. BP, blood pressure; CI, confidence interval; HR, hazard ratio.

BP associated with the lowest risk of a composite outcome of all-cause death and cardiovascular events was 130–140 mmHg.[19]

Similar data were found in high-risk secondary prevention patients in a *post hoc* analysis from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant participants with cardiovascular Disease (TRANSCEND) trial, patients with achieved systolic BP between 120 and 139 mmHg displayed the lowest risk of the primary outcome (cardiovascular death, myocardial infarction, stroke, or hospital admission for heart failure).[20] In a *post hoc* analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, half of whom had CCS, a systolic BP <130 mmHg did not perform better than a systolic BP of 130–140 mmHg.[21]

In a meta-analysis of randomized clinical trials of antihypertensive therapy in patients with CCS, compared with a standard (<140 mmHg) BP target, a <135 mmHg systolic BP was associated with modest reductions in stroke and heart failure but not cardiovascular death, at the cost of an increased risk of hypotension.[22] However, none of these trials were designed to test a BP target and the marginal benefit in the lower BP groups could be driven by the effect of drugs demonstrated to generate cardiovascular protection such as renin–angiotensin system blockers.

Overall, to date, there is little evidence that targeting a systolic BP of <130 mmHg in patients with CCS would reduce markedly their cardiovascular risk. Many different studies with various designs have actually shown a fairly steady risk of cardiovascular events across the 120–140 mmHg range. Our results further highlight the need for future interventional studies testing an intensive vs. standard control of systolic BP in coronary disease.

In contrast with systolic BP, our results support a strict control of diastolic BP, as advised in current guidelines. Data regarding optimal diastolic BP values are more discrepant than for systolic BP. Most observational studies (or *post hoc* analyses from trials) conducted in CCS patients found similar outcomes across the 70–90 mmHg diastolic BP range.[3,19,21,23] However, many of these studies may have been underpowered to highlight a slightly better outcome in the 70–80 than in the 80–90 mmHg diastolic BP range. In their *post hoc* analyses of ONTARGET and TRANSCEND, which included more than 30 000 patients, Bohm *et al.* found results very similar to ours, with the lowest cardiovascular risk associated with a diastolic BP in the 70–80 mmHg range.[20,24] Our results are also in line with the net benefit observed in the subgroup of patients with CCS of the Hypertension Optimal Treatment (HOT) study, which increased as the diastolic BP target decreased from <90 to <80 mmHg.[25]

Finally, a meta-analysis of more vs. less intensive BP lowering trials, including SPRINT, showed that most cardiovascular outcomes were reduced when diastolic BP in the intensive group was <80 mmHg.[26] However, no trial achieving a diastolic BP across the 80 mmHg threshold with treatment groups was conducted in a population with CCS.

Our data from a large, international registry show that most patients with CCS have at least one other uncontrolled risk factor besides BP, when the benefit of treating these has been clearly demonstrated.[27] Even with very loose thresholds for considering a risk factor as

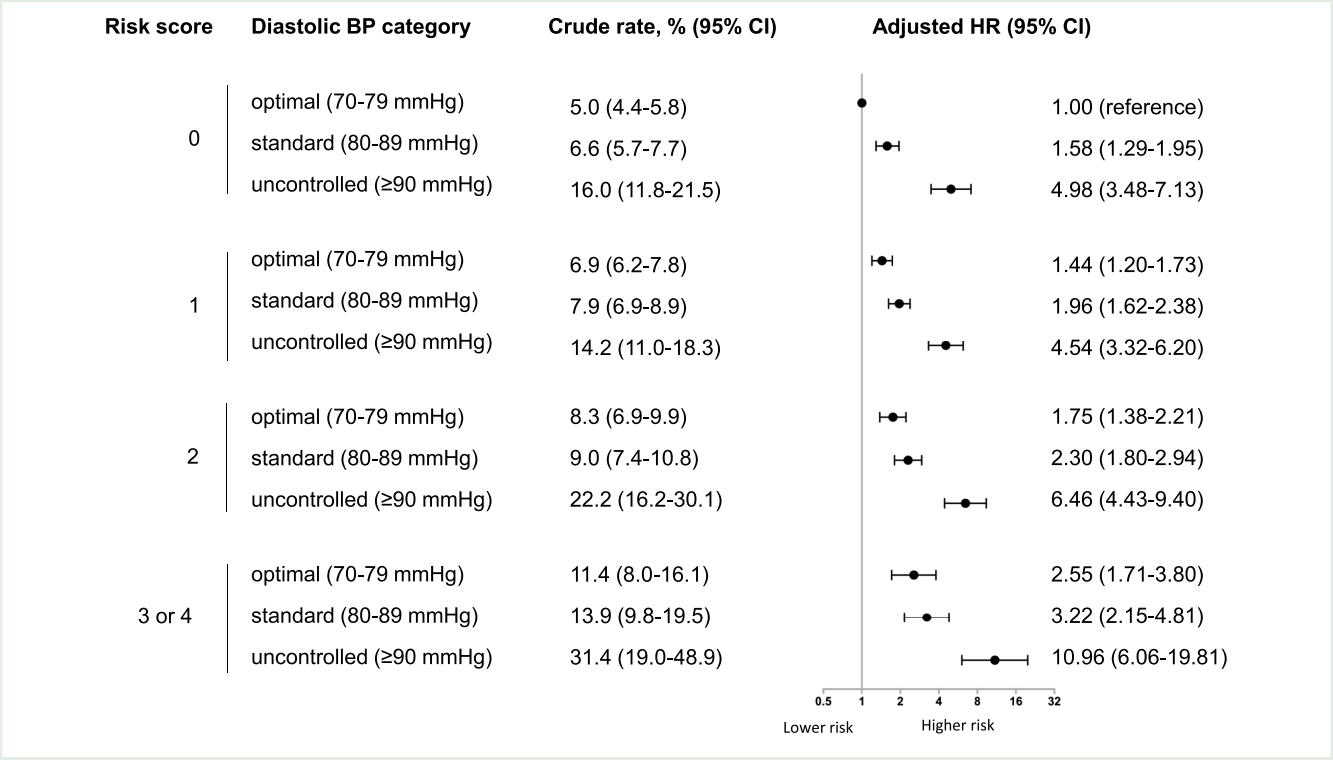

Figure 3 Relationship between diastolic BP categories, cross-classified with risk-score, and the composite outcome of cardiovascular death, myocardial infarction, or stroke. Crude event rates are indicated as Kaplan–Meier estimates. Adjusted HR: adjusted for age, sex, geographical region, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, peripheral artery disease at baseline, previous stroke or transient ischaemic attack, previous hospital admission for (or symptoms of) heart failure, atrial fibrillation or flutter, body mass index, any antiplatelet, statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers. BP, blood pressure; CI, confidence interval; HR, hazard ratio.

uncontrolled [LDL-C ≥ 100 mg/dL (2.59 mmoL/L), no physical activity, active smoking, diabetes, and HbA_{1c} ≥ 7%], more than 60% of the study population had at least one uncontrolled risk factor outside of BP, which underlines the relevance of integrating associated modifiable risk factors in the treatment of hypertensive patients. All key modifiable risk factors used in our model have been associated with worse outcomes in patients with CCS as well as in other primary and secondary prevention populations, and interventional studies have shown a clear benefit associated with their treatment to standard goals.[28–31] Accordingly, in our study, the combination of uncontrolled risk factors was associated with a marked and gradual increase in the risk of the composite of cardiovascular death, myocardial infarction, or stroke.

The lack of interaction between risk score and BP components in our study is in line with meta-analyses of randomized BP trials, which showed that lowering BP provides similar relative risk reduction at all underlying cardiovascular risk levels.[32] However, the absolute risk reduction will be greater for the same relative risk reduction when baseline risk is higher, as illustrated by the event rates in our cross-sectional analyses.

Beyond the optimal management of each individual risk factor, the importance of their clustering is increasingly recognized. Previous studies conducted in patients with CCS have similarly shown that with each added risk factor, there is a progressive increase in the incidence of cardiovascular events.[33,34] Interestingly, despite the well-known very high risk associated with diabetes, patients with Type 2 diabetes from a large Swedish cohort study who had five risk factors (elevated HbA_{1c}, elevated LDL-C, smoking, elevated BP, and albuminuria) within target ranges appeared to have little or no excess risk of death, myocardial infarction, or stroke, compared with the general population.[35]

Strength and limitations

The main limitation of our study is its observational design, so our results can only be considered hypothesis-generating. In addition, some confounding factors may not have been accounted for. Whether targeting an intensive BP target, especially a systolic BP of <130 mmHg, will improve cardiovascular outcomes in patients with coronary diseases can only be answered by a dedicated interventional trial. Also, we divided BP components into 10-mmHg categories and summarized information on the four other main modifiable risk factors in a single categorical variable. This approach allowed to cross-classify the variables and is useful to translate the results into clinical practice, but is not as accurate as a continuous analysis of each variable separately, and prevents direct comparison of the effect magnitude of each factor. In addition, in this large, international, contemporary registry conducted across 45 countries, BP measurement was not as standardized as it was in the SPRINT trial for instance. However, information on office BP levels, as measured in real-life conditions including in non-expert centres, and their associations with outcomes also carry valuable information when evaluating the potential worldwide effect of guidelines in routine clinical practice as opposed to the carefully controlled setting of a randomized trial. Another strength of this analysis is the exclusion of patients with low BP values (<120/70 mmHg). The exclusion of these patients, who have poorer outcomes, from our analyses ensures that the absence of benefit associated with the optimal systolic BP level was not driven by patients with very low systolic and/or diastolic BP levels.

Conclusions

Both standard control of systolic BP (130–139 mmHg) and diastolic BP (80–89 mmHg) were associated with markedly reduced cardiovascular risks compared with uncontrolled BP (>140/90 mmHg). However, only optimal diastolic BP (70–79 mmHg), but not optimal systolic BP (120–129 mmHg), was associated with a lower risk of cardiovascular events compared with standard control. These findings were consistent across all risk factor categories. Conversely, each additional uncontrolled risk factor was associated with higher cardiovascular risk, without significant interaction with BP, highlighting the importance of the combined effect of key clinical risk factors. This suggests that all patients with CCS should have a BP ≤139/79 mmHg. Once this is achieved, management of other potentially still uncontrolled risk factors—including appropriate lipid-lowering therapy, smoking cessation, control of diabetes, and increased physical activity—may need to be prioritized before considering further reduction of systolic BP ≤129 mmHg.

Authors' contributions

E.V.-P. designed the study, interpreted the data, designed tables and figures, and wrote the first draft and subsequent iterations of the manuscript; Y.E. and J.M. did the statistical analyses, interpreted the data, designed tables and figures, and reviewed and provided critical comments on the manuscript; G.D. interpreted the data and provided critical comments on the manuscript, I.F. conceived and initiated the CLARIFY registry, coordinated the database acquisition and management, and provided critical comments on the manuscript. M.T., R.F., and J.-C.T. conceived and initiated the CLARIFY registry, coordinated the study and collected data in their respective countries, and reviewed and provided critical comments on the manuscript. K.M.F. and P.G.S. initiated and coordinated the CLARIFY registry, designed the study, interpreted the data, and provided critical comments on the manuscript. All authors gave final approval for submission of the manuscript.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

All analyses for this manuscript were performed independently of the sponsor at FACT and Hôpital Bichat, Paris, France. Editorial support, limited to editing, checking content and language, and formatting, was provided by Sophie Rushton-Smith, PhD (MedLink Healthcare Communications), and was funded by the authors.

Funding

The CLARIFY registry was supported by Servier.

Conflict of interest: E.V.-P. reports non-financial support and personal fees from Servier, outside the submitted work. Y.E. reports consulting fees for statistical support related to this study from Assistance Publique-Hopitaux de Paris and consulting fees unrelated to this study from Bristol-Myers Squib. J.M. reports a research grant from Fédération Française de Cardiologie, outside the submitted work. G.D. reports honoraria for lectures and consulting fees from Abbott, Amgen, Astra Zeneca, Bayer, BMS, Novo Nordisk, Sanofi. I.F. reports grants and personal fees from Servier, during the conduct of the study. M.T. reports personal fees from Servier, during the conduct of the study; and personal fees from Bayer, Janssen-Cilag, Kowa, PERFUSE Group, and Servier, outside the submitted work. R.F. discloses grants and personal fees from Servier International and Novartis, and personal fees from Merck Serono, Lupin, Reddys Ltd, and SunPharma outside the submitted work. J.-C.T. reports grants from Servier, during the conduct of the study, and grants from Amarin, Ceapro, Esperion, Ionis, Novartis and RegenXBio, grants and personal fees from Astra Zeneca and Pfizer, personal fees from HLS Pharmaceuticals and Pendopharm, grants, personal fees and minor equity interest from Dalcor Pharmaceuticals, outside the submitted work. In addition, J.-C.T. has patent genetic markers for predicting responsiveness to therapy with HDL-raising or HDL mimicking agent pending, and a patent Methods for using low dose colchicine after myocardial infarction pending assigned to the Montreal Heart Institute. K.M.F. reports personal fees and other support from Servier, during the conduct of the study, personal fees and other support from Celixir and AstraZeneca, outside the submitted work. In addition, he is the Director of Vesalius Trials. P.G.S. reports grants and personal fees from Servier, during the conduct of the study; grants and personal fees from Bayer, Sanofi, and Amarin, and personal fees from Amgen, AstraZeneca Bristol Myers Squibb, Boehringer-Ingelheim, PhaseBio, Pfizer, Novartis, Regeneron Pharmaceuticals, Novo Nordisk, Idorsia, Janssen, Merck, Myokardia, outside the submitted work. P.G.S. also reports participation on Data Safety Monitoring Boards or Advisory Boards for Servier, Sanofi, PHRI, and Monash University.

Data availability

Requests from qualified investigators for data from the CLARIFY registry will be considered by its Executive Steering Committee upon request.

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