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ORIGINAL SCIENTIFIC PAPER
Acute Coronary Syndromes

Initial systolic blood pressure associates with systemic inflammation, myocardial injury, and outcomes in patients with acute coronary syndromes

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Aims

Outcomes after acute coronary syndromes (ACS) are determined by baseline risk profiles, including initial systolic blood pressure (sBP) levels. Herein, we aimed to characterize ACS patients stratified by initial sBP levels and study their relation to inflammation, myocardial injury and post-ACS outcomes.

Methods and results

We analysed 4724 prospectively recruited ACS patients according to invasively assessed sBP (<100, 100–139, and ≥140 mmHg) at admission. Biomarkers of systemic inflammation [high-sensitivity C-reactive protein (hs-CRP)] and myocardial injury [high-sensitivity cardiac troponin T (hs-cTnT)] were measured centrally. Major adverse cardiovascular events (MACE; composite measure of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) were externally adjudicated. Leukocyte counts, hs-CRP, hs-cTnT, and creatine kinase (CK) levels decreased from low to high sBP strata ($p_{trend} < 0.001$). Patients with sBP < 100 mmHg developed more often cardiogenic shock (CS; $P < 0.001$), and had a 1.7-fold increased multivariable-adjusted MACE risk at 30 days (HR 1.68, 95% CI 1.05–2.69, $P = 0.031$) which did not persist at one year (HR 1.38, 95% CI 0.92–2.05, $P = 0.117$). Those with sBP < 100 mmHg and CS showed a higher leukocyte count ($P < 0.001$), an increased neutrophil-to-lymphocyte-ratio ($P = 0.031$), and higher hs-cTnT and CK levels relative to those without CS ($P < 0.001$ and $P = 0.002$, respectively), whereas hs-CRP levels did not differ. Patients who developed CS had a 3.6- and 2.9-fold increased MACE risk at 30 days (HR 3.58, 95% CI 1.77–7.24, $P < 0.001$) and at one year (HR 2.94 95% CI, 1.57–5.53, $P < 0.001$), which was intriguingly attenuated after controlling for distinct inflammatory profiles.

Conclusion

In patients with ACS, proxies of systemic inflammation and myocardial injury are inversely associated with initial sBP levels, with highest biomarker levels observed in those <100 mmHg. If linked to high levels of cellular inflammation, these patients are prone to develop CS and are at high MACE and mortality risk.

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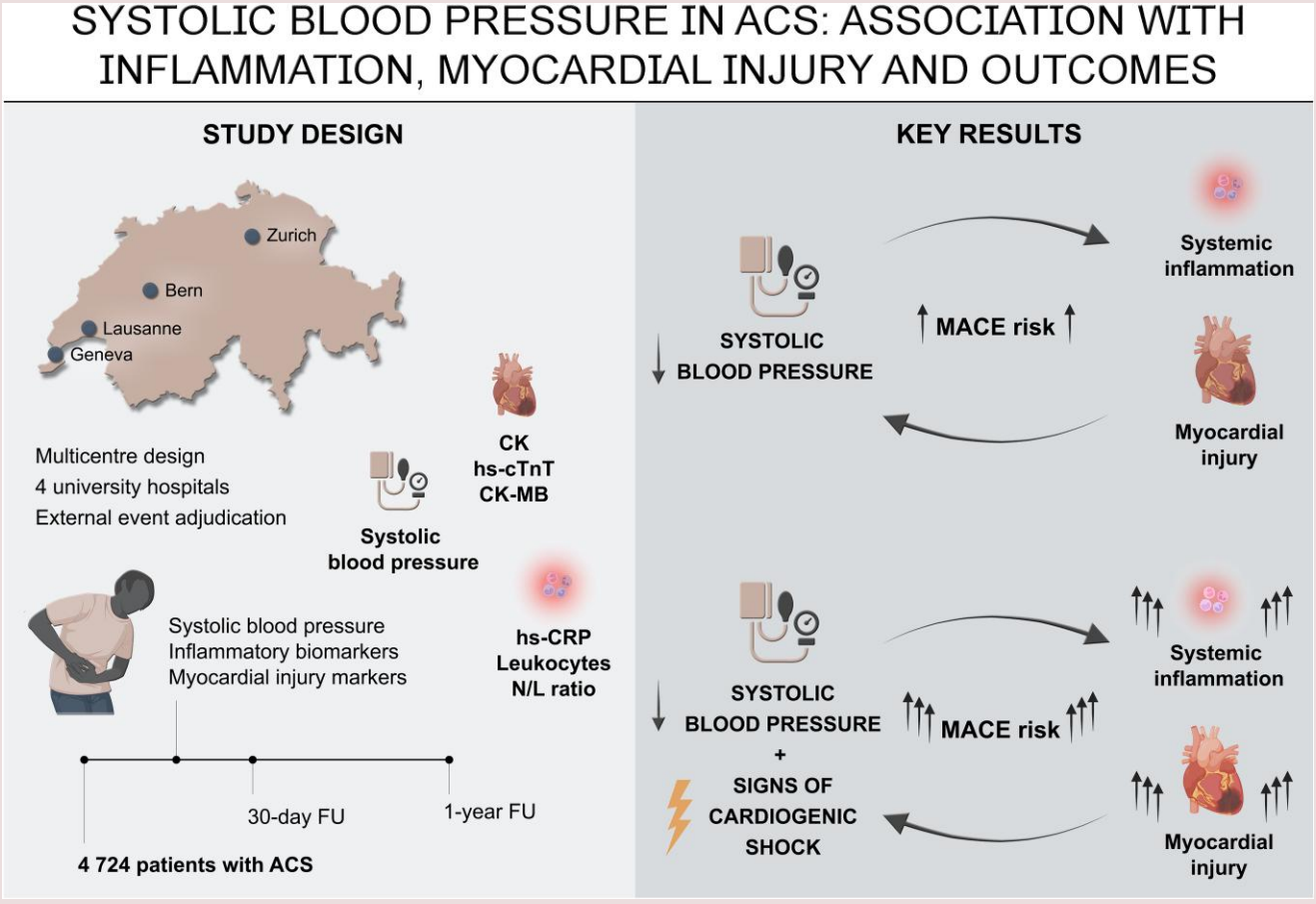
Graphical Abstract



Keywords Acute coronary syndromes • Systolic blood pressure • Cardiogenic shock • Systemic inflammation • C-reactive protein

Introduction

Cardiovascular (CV) diseases remain the leading cause of death globally, of which the majority are due to chronic and acute coronary syndromes (ACS).[1] The etiology of ACS is multifactorial and also involves traditional CV risk factors, such as arterial hypertension, dyslipidaemias, and diabetes. While chronic elevation of systolic blood pressure (sBP) represents a key risk factor for CV events, normal or elevated sBP in the early phase after ACS reflects maintained left ventricular (LV) function. Conversely, low sBP levels—such as in patients at risk for or with established cardiogenic shock (CS)—might be associated with systemic inflammation, the extent of myocardial injury, and thus the risk for major adverse CV events (MACE). Indeed, sBP levels inform established risk scores [e.g. Global Registry of Acute Coronary Events (GRACE), thrombolysis in myocardial infarction (TIMI)] and hence may guide the identification of patients at high risk of CS and thus poor outcomes after the index ACS.[2,3]

Over the past six decades, largely owing to the introduction and broad availability of primary percutaneous coronary intervention and antithrombotic as well as lipid-lowering therapies,[4–6] post-ACS outcomes improved markedly.[7] Yet, mortality remains high, particularly in those presenting with hemodynamic instability, reduced LV ejection fraction (LVEF), or CS.[8] Indeed, while in hemodynamically stable ACS patients in-hospital mortality declined to less than 5%, those presenting with signs of hemodynamic instability remain at an unacceptably high 30-day mortality of up to 40% despite contemporary management.[7–11]

Hence, a more comprehensive characterization of patients according to sBP levels, specifically as it relates to myocardial injury, systemic inflammation, and MACE risk, may help to identify clinical features linked to high susceptibility for the development of CS and thus poor outcomes after the index ACS. For instance, systemic inflammation triggers some, but not all forms of ACS, and markedly influences in-hospital and mid- to long-term prognosis after the acute event.[12,13] Further, inflammatory processes are key modulators of infarct size, impinge on LV function and thus post-ACS outcomes. In parallel, some anti-inflammatory strategies targeting NLRP3-associated pathways showed promising results in patients at high CV risk,[14–16] collectively suggesting a crosstalk between hemodynamic instability, myocardial injury, systemic inflammation, and MACE risk.

Herein, we aimed to characterize baseline characteristics and outcomes of contemporary patients with ACS stratified by their invasively measured sBP levels at presentation (<100 mmHg, 100–139 mmHg, and ≥140 mmHg, respectively), with a particular focus on systemic inflammation and myocardial injury.

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Methods

Study population

The Special Program University Medicine (SPUM)—ACS Biomarker study (ClinicalTrials.gov number, NCT01000701) is a prospective, multicenter cohort study in which patients with ACS presenting to one of the four participating university hospitals (Zurich, Bern, Lausanne, and Geneva) were recruited between 2009 and 2017. The design of the study has been reported previously.[17,18] Briefly, female and male patients aged 18 years or older presenting within five days after pain onset with the main diagnosis of ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS) were included. All patients had scheduled follow-up visits at 30 days (phone call) and at one year (clinical visit). All MACEs occurring within one year after the index ACS event were adjudicated by an independent committee comprising experienced expert cardiologists. Treating physicians were advised to apply guideline-based therapy regimens, including statin therapy, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II (ATII) receptor blockers, beta blockers, and antiplatelet therapy with aspirin and $P2Y_{12}$ receptor inhibitors, as appropriate. In the present study, a total of 4724 patients with complete data on sBP levels were included (*Figure 1*). All patients gave written informed consent to the use of their data for research, the study conformed with the Declaration of Helsinki and was approved by the Cantonal Ethics Committee.

Biomarkers

EDTA-blood was drawn from the radial or femoral sheath prior to the procedure, centrifuged and plasma was stored at -80°C until further processing. High-sensitivity C-reactive protein (hs-CRP), high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were measured centrally in the core laboratory (University Hospital Zurich, Zurich, Switzerland) using electrochemiluminescence or particle-enhanced turbidimetric immunoassays (all obtained from Roche Diagnostics, Boehringer Mannheim, Indianapolis, IN, USA).

Systolic blood pressure levels, definition of cardiogenic shock and study endpoints

Patients were stratified into three groups according to their sBP as assessed invasively by aortic measurement prior to coronary angiography after placement of the femoral or radial sheet in the cardiac catheterization laboratory. These strata (i.e. <100 mmHg, 100–139 mmHg, ≥140 mmHg) were predefined according to current guidelines and established risk scores.[2,19] Patients with sBP <100 mmHg were further classified into patients with or without clinical signs of CS. CS was defined as Killip Class IV or the use of vasopressors, intra-aortic balloon pump or percutaneous left ventricular assist device. The primary endpoint of the present study was a composite endpoint [MACE; defined as the composite of non-fatal myocardial infarction (MI), non-fatal stroke and CV death]. The secondary endpoint was CV mortality.

Statistical analysis

Continously coded baseline characteristics of the three blood pressure groups were compared using analysis of variance for normally distributed data and the Kruskal–Wallis test if data were skewed. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Normal distribution was evaluated by the Shapiro–Wilk test. To control for the rise in type I errors due to multiple comparisons, Bonferroni post-hoc testing was used. If not stated otherwise, baseline data are shown as mean and standard deviation, or as median and interquartile range if skewed. Given the multicenter study design of SPUM-ACS, creatine kinase (CK) and CK-MB values were standardized according to the upper limit of normal of each study center's laboratory. In sensitivity analyses, a general linear model controlling for symptom onset-to-door (STD) time across levels of the categorical variable (i.e. sBP groups) was fit to assess the impact of STD time on inflammatory biomarkers. Subgroup analyses in patients stratified by ACS type, location of the infarct-related artery (IRA), and use of antiplatelet or lipid-lowering drugs were performed. Survival analyses were done using the Kaplan–Meier method and by fitting crude and multivariable-adjusted Cox proportional hazard regression models, accounting for established clinical risk factors.[20,21] We used four different Cox models: a crude model, a model adjusted for sex (categorical) and age (continuous), a third model that included sex (categorical), age (continuous), body mass index (BMI, continuous), history of diabetes mellitus (DM, categorical), total cholesterol levels (continuous), NT-proBNP levels (continuous) and use of antihypertensive drugs (i.e. ACE inhibitors, ATII receptor blockers, beta blockers, or calcium channel blockers; categorical) and a fourth and fully adjusted model adjusted for sex (categorical), age (continuous), BMI (continuous), history of DM (categorical), total cholesterol levels (continuous), NT-proBNP levels (continuous), use of antihypertensive drugs (categorical), centrally measured hs-cTnT and hs-CRP levels (both continuous), prehospital delay (defined as STD time ≥90 min; categorical) and ACS type (STEMI vs. NSTE-ACS; categorical). Hazard ratios (HRs) along with 95% confidence intervals were calculated using bootstrapping with 1000 replicates. Statistical significance was established at two-tailed $P < 0.05$ throughout and is given to two significant figures, unless $P < 0.001$. All analyses were performed using SPSS Statistics version 28.0.1.1 (14, IBM Corp, Armonk NY). The Kaplan–Meier curves were created in R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population

Of all 4787 patients with ACS, a total of 4724 were included in the final study sample (*Figure 1*). Median age was 63.5 (52.5–72.5) years, with 20.6% ($n = 971$) being female. While the majority ($n = 2852$, 60.4%) presented with sBP levels ranging between 100 and 139 mmHg, 1474 and 398 patients presented with sBP ≥140 mmHg and <100 mmHg, respectively. Baseline characteristics of all patients and stratified by sBP levels are summarized in *Table 1*. Those presenting with sBP <100 mmHg were less likely to have a history of hypertension (47.7 vs. 52.7 vs. 66.1%, *adj.* $P < 0.001$), to be on ATII receptor blockers (26.8 vs. 29 vs. 35.2% respectively, *adj.* $P < 0.001$) and were less frequently receiving statin-therapy prior to admission (36 vs. 43 vs. 40.9% respectively, *adj.* $P = 0.046$). The relative proportion of STEMIs decreased from low to high sBP strata, with those presenting with <100 mmHg most likely having a final diagnosis of STEMI (70.1%, $n = 279$, *Table 1*). Overall, 87.4% of patients presented at Killip class I, 8.1% at II, 2.1% at III and 2.3% at IV, with class 4 being primarily observed in those with sBP <100 mmHg (13.3%, 100–139 mmHg: 1.6%; and ≥140 mmHg: 0.8%, *adj.* $P < 0.001$). Across all sBP strata, the right coronary artery (RCA) was more frequently the IRA in those with sBP <100 mmHg (39.1 vs. 32.5 vs. 31.3% respectively, *adj.* $P = 0.004$, *Table 1*).

Pre- and in-hospital management differs across sBP groups

The proportion of patients undergoing resuscitation prior to admission was highest among those with sBP <100 mmHg, followed by normo- and hypertensives (11.3 vs. 3.9 vs. 1.8% respectively, *adj.* $P < 0.001$, *Table 2*). Of note, hypotensive patients arrived faster at the hospital after symptom onset than their normotensive or hypertensive counterparts, with a median of 143 min compared to 180 min in normotensive and 201 min in hypertensive patients (*adj.* $P = 0.0020$). Vasopressor use was most prevalent in those with sBP <100 mmHg, (10.3%), and only occurred in 2.3 and 1.1% in normo- and hypertensives, respectively (*adj.* $P < 0.001$, *Table 2*). At discharge, all patients received $P2Y_{12}$ receptor antagonists according to current guidelines and almost all patients were discharged on both aspirin and statins. Interestingly, there were significant differences in the prescriptions of ACE inhibitors and ATII receptor blockers. More patients with sBP <100 mmHg were on ACE inhibitors than normo- and hypertensives (76.1 vs. 73.9 vs. 70%, *adj.* $P = 0.0070$), while ATII receptor blockers were predominantly used in those with sBP ≥140 mmHg (*adj.* $P < 0.001$, *Table 2*).

Systemic inflammation and myocardial injury associates with low sBP

Plasma levels of centrally measured hs-CRP followed a step-wise decline across sBP groups with highest levels observed in patients with sBP

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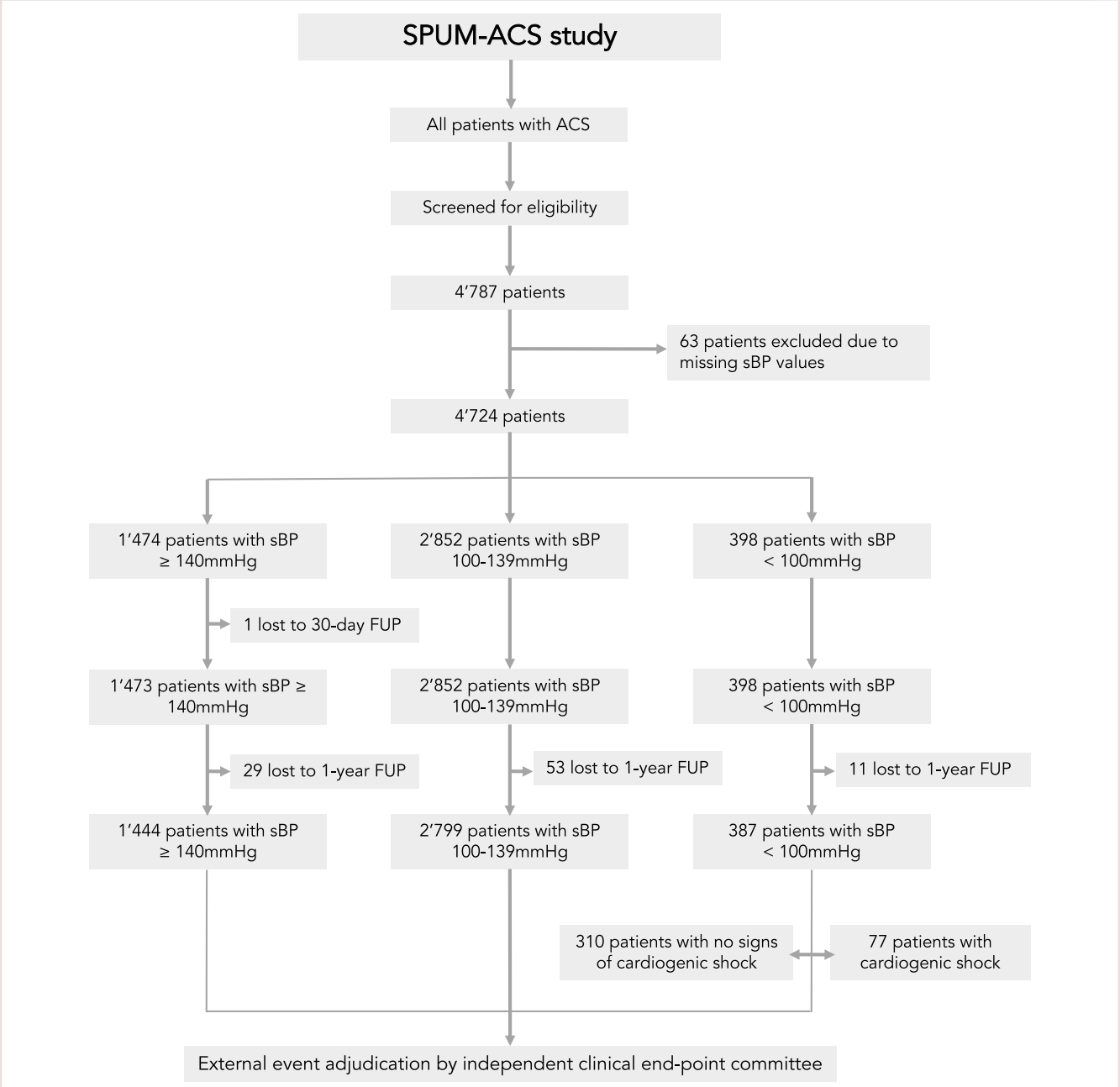

Figure 1 Flowchart of the present study. Patients were stratified according to their systolic blood pressure invasively assessed at the time of acute presentation. Cardiogenic shock was defined as Killip Class IV, use of vasopressors or mechanical support. Abbreviations: FUP = follow-up; sBP = systolic blood pressure; SPUM-ACS = Special Program University Medicine—Acute Coronary Syndromes.

<100 mmHg ($p_{trend} < 0.001$), which remained robust after adjusting for STD time ($p_{adj} < 0.001$). Accordingly, leukocyte counts decreased from low to high sBP strata ($p_{trend} < 0.001$), whereas the neutrophil-to-lymphocyte-ratio (NLR) did not differ ($p_{trend} = 0.102$, *Figure 2A*). Similarly, proxies of myocardial injury, such as hs-cTnT and CK plasma levels, decreased with increasing sBP levels (both $p_{trend} < 0.001$; *Figure 2B*), a difference that was consistently observed after adjusting for STD time ($p_{adj} = 0.023$ and $p_{adj} = 0.003$, respectively). Notably, a positive correlation between hs-CRP and hs-cTnT levels was identified ($\rho = 0.218$, $P < 0.001$), with an even more pronounced correlation between hs-CRP and standardized CK levels ($\rho = 0.44$, $P = 0.007$). Subgroup analyses suggested that these associations were independent of statin use (see Supplementary material online, *Table S1*), with similar results obtained in patients irrespective of ACS type (see Supplementary material online, *Table S2*), antiplatelet therapy (see Supplementary material online, *Tables S3–4*), and IRA-location (see Supplementary material online, *Table S5*).

Systolic blood pressure levels independently associate with post-ACS outcomes

At 30 days, MACE occurred most frequently in those with sBP <100 mmHg (8.8 vs. 3.8 vs. 3.6%, *adj. P* < 0.001; *Figure 3*). At 30 days, those

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Table 1 Baseline characteristics of all patients stratified by initial sBP levels

	All patients $n = 4724$	<100 mmHg $n = 398$	100–139 mmHg $n = 2852$	≥140 mmHg $n = 1474$	*P*-value
Patient characteristics					
Age (years)	63.5 (52.5–72.5)	62.3 (52–72.7)	62.6 (53.5–72)	65.5 (56.3–75)	< 0.001
% Female ♀	20.6% ($n = 971$)	16.6% ($n = 66$)	19.7% ($n = 563$)	23.2% ($n = 342$)	0.0030
BMI (kg/m^2)	26.6 (24.8–29.3)	26.1 (23.9–28.7)	26.4 (24.1–29.3)	27.1 (24.5–30)	< 0.001
Previous medical history					
HTN history	56,4% ($n = 2666$)	47.7% ($n = 190$)	52.7% ($n = 1502$)	66.1% ($n = 974$)	< 0.001
DM history	17.1% ($n = 768$)	16.4% ($n = 63$)	16.0% ($n = 435$)	19.5% ($n = 270$)	0.020
Previous MI	12.2% ($n = 577$)	9.8% ($n = 39$)	11.8% ($n = 336$)	13.7% ($n = 202$)	0.056
Medication at presentation					
Aspirin	44.3% ($n = 1350$)	39.7% ($n = 95$)	43.5% ($n = 788$)	46.8% ($n = 467$)	0.084
ACE inhibitor	23.0% ($n = 700$)	23.0% ($n = 55$)	23.1% ($n = 418$)	22.7% ($n = 227$)	0.27
ATII receptor blocker	30.8% ($n = 939$)	26.8% ($n = 64$)	29.0% ($n = 524$)	35.2% ($n = 351$)	< 0.001
Beta blocker	35.1% ($n = 1071$)	30.1% ($n = 72$)	34.9% ($n = 631$)	36.9% ($n = 368$)	0.10
Diuretics	24.7% ($n = 752$)	25.5% ($n = 61$)	22.9% ($n = 415$)	27.7% ($n = 276$)	0.073
P2Y12 receptor inhibitor	11.5% ($n = 350$)	7.5% ($n = 18$)	12.1% ($n = 219$)	11.3% ($n = 113$)	0.11
Statin	41.7% ($n = 1270$)	36.0% ($n = 86$)	43.0% ($n = 778$)	40.9% ($n = 406$)	0.046
Cardiac function					
LVEF (%)	51 (43–59)	50 (40–60)	50 (45–60)	55 (45–60)	< 0.001
Heart rate (b.p.m.)	76.84 ± 15.81	76.3 ± 18.55	76.55 ± 15.42	77.55 ± 15.74	0.054
Systolic BP (mmHg)	128 (118–149)	92 (86–96)	121 (111–130)	152 (145–163)	< 0.001
Diastolic BP (mmHg)	75.66 ± 14.9	56.95 ± 10.13	72.84 ± 11.33	86.18 ± 14.68	< 0.001
Cardiometabolic risk factors					
Total cholesterol (mmol/L)	4.9 ± 1.23	4.77 ± 1.21	4.89 ± 1.2	4.97 ± 1.27	0.032
HDL-C (mmol/L)	1.18 ± 0.35	1.13 ± 0.36	1.18 ± 0.34	1.2 ± 0.37	< 0.001
LDL-C (mmol/L)	3.13 ± 1.1	3.06 ± 1.08	3.13 ± 1.09	3.16 ± 1.13	0.38
Triglycerides (mmol/L)	1.01 (0.61–1.47)	1.04 (0.68–1.62)	0.99 (0.67–1.5)	1.07 (0.71–1.6)	0.0040
Glucose (mmol/L)	6.44 (6.3–10.19)	6.8 (5.8–8.51)	6.5 (5.6–7.9)	6.3 (5.5–7.74)	< 0.001
HbA1c (%)	5.8 (5.7–6.95)	5.8 (5.5–6.4)	5.7 (5.5–6.2)	5.8 (5.5–6.5)	< 0.001
Creatinine (μmol/L)	77 (66–87)	83 (68–102)	76 (66–89)	77 (66–91)	< 0.001
Inflammatory and myocardial injury markers					
White blood cell count (WBC, G/L)	9.6 (8.53–12.55)	11.2 (8.64–14.45)	9.73 (7.6–12.2)	9.07 (7.1–11.3)	< 0.001
Neutrophil-to-lymphocyte ratio	4.53 (2.94–7.05)	5.37 (3.11–9.16)	4.65 (2.85–7.96)	4.15 (2.54–6.58)	0.10
CRP, high-sensitivity (mg/L)	2.9 (1.1–6.95)	3.1 (1.3–9.7)	2.8 (1.2–7.9)	3 (1.4–7.65)	< 0.001
Troponin T, high-sensitivity (ng/L)	197 (85–728)	204 (59–1010)	203 (59–672)	186 (58–581)	< 0.001
NT-proBNP (ng/L)	341 (126–980)	251 (84–1527)	302 (101–1097)	422 (133–1324)	< 0.001
Creatine Kinase (x ULN)	1.13 (0.65–2.78)	1.13 (0.61–3.15)	1.18 (0.59–2.75)	1.06 (0.54–2.34)	< 0.001
CK-MB (x ULN)	1.93 (0.75–4.15)	2.53 (1.21–7.68)	2.05 (0.93–6.3)	1.63 (0.8–4.6)	0.29
ACS type					
STEMI	53.1% ($n = 2509$)	70.1% ($n = 279$)	54.5% ($n = 1555$)	45.8% ($n = 675$)	< 0.001
IRA					
LAD	44.5% ($n = 1961$)	40.4% ($n = 154$)	45.1% ($n = 1201$)	44.6% ($n = 606$)	0.40
LCx	19.9% ($n = 878$)	18.1% ($n = 69$)	19.7% ($n = 526$)	20.8% ($n = 283$)	0.67
RCA	32.7% ($n = 1439$)	39.1% ($n = 149$)	32.5% ($n = 865$)	31.3% ($n = 425$)	0.0040
LMCA	1.7% ($n = 73$)	1.8% ($n = 7$)	1.5% ($n = 39$)	2.0% ($n = 27$)	0.47
SVG	1.2% ($n = 54$)	0.5% ($n = 2$)	1.2% ($n = 33$)	1.4% ($n = 19$)	0.42

Data are shown as mean and standard deviation or median and interquartile range if skewed. Categorical data are shown as numbers and percentages. Creatine kinase and creatine kinase-MB were normalized to the upper limit of normal (ULN) of each laboratory. Percentages may not total 100 owing to rounding. Abbreviations: ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ATII = angiotensin II; BMI = body mass index; BP = blood pressure; CK-MB = creatine kinase-MB; CRP = C-reactive protein; DM = diabetes mellitus; HDL-C = high-density lipoprotein-cholesterol; HbA1c = haemoglobin A1c; HTN = hypertension; IRA = infarct-related artery; LAD = left anterior descending coronary artery; LCx = left circumflex artery; LDL-C = low-density lipoprotein-cholesterol; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RCA = right coronary artery; STEMI = ST-elevation myocardial infarction; SVG = saphenous vein graft (bypass).

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Table 2 Management characteristics of ACS patients stratified by initial sBP levels

	All patients $n = 4724$	<100 mmHg $n = 398$	100–139 mmHg $n = 2852$	≥140 mmHg $n = 1474$	*P*-value
In-hospital management					
GRACE 2.0 Risk Score	0.087 (0.06–0.13)	0.141 (0.93–0.3)	0.089 (0.06–0.14)	0.073 (0.05–0.12)	< 0.001
Killip Classification					
Class I	87.4% ($n = 4024$)	74.9% ($n = 293$)	88.6% ($n = 2468$)	88.4% ($n = 1263$)	< 0.001
Class II	8.1% ($n = 375$)	8.7% ($n = 34$)	8.0% ($n = 223$)	8.3% ($n = 118$)	0.88
Class III	2.1% ($n = 96$)	3.1% ($n = 12$)	1.8% ($n = 49$)	2.5% ($n = 35$)	0.12
Class IV	2.3% ($n = 108$)	13.3% ($n = 52$)	1.6% ($n = 44$)	0.8% ($n = 12$)	< 0.001
Resuscitation prior to admission	3.8% ($n = 181$)	11.3% ($n = 45$)	3.9% ($n = 110$)	1.8% ($n = 26$)	< 0.001
STD (minutes)	180 (105–420)	143 (85–300)	180 (105–420)	201 (109–475)	0.0020
STI (minutes)	313 (188–710)	240 (156–456)	303 (184–684)	391 (209–805)	< 0.001
PCI duration (minutes)	30 (19–45)	32 (19–49)	29 (19–45)	29 (18–46)	0.37
Hospitalization (days)	4 (3–6)	5 (3–6)	4 (3–6)	4 (3–6)	0.75
Vasopressor use	2.6% ($n = 122$)	10.3% ($n = 41$)	2.3% ($n = 65$)	1.1% ($n = 16$)	< 0.001
Mechanical support					
IABP	2.6% ($n = 125$)	10.3% ($n = 41$)	2.1% ($n = 60$)	1.6% ($n = 24$)	< 0.001
Percutaneous LVAD	0.4% ($n = 21$)	0.8% ($n = 3$)	0.4% ($n = 11$)	0.5% ($n = 7$)	0.73
Discharge destination					
Other hospital	44% ($n = 2041$)	41.6% ($n = 156$)	43.9% ($n = 1234$)	44.8% ($n = 651$)	0.52
Rehabilitation center	10.6% ($n = 491$)	13.3% ($n = 50$)	10.7% ($n = 301$)	9.6% ($n = 140$)	0.11
Home	45.4% ($n = 2105$)	45.1% ($n = 169$)	45.4% ($n = 1275$)	45.5% ($n = 661$)	0.99
Discharge medication					
Aspirin	99.1% ($n = 4611$)	98.7% ($n = 371$)	99.1% ($n = 2796$)	99% ($n = 1444$)	0.65
ACE inhibitor	72.9% ($n = 3391$)	76.1% ($n = 286$)	73.9% ($n = 2085$)	70% ($n = 1020$)	0.0070
ATII receptor blocker	15.6% ($n = 726$)	9.6% ($n = 36$)	13.8% ($n = 390$)	20.6% ($n = 300$)	< 0.001
Beta blocker	78.5% ($n = 3655$)	78.5% ($n = 295$)	78% ($n = 2200$)	79.6% ($n = 1160$)	0.51
Diuretics	23.7% ($n = 1105$)	26.3% ($n = 99$)	22.8% ($n = 643$)	24.9% ($n = 363$)	0.15
P2Y12 receptor inhibitor	100% ($n = 4429$)	100% ($n = 363$)	100% ($n = 2695$)	100% ($n = 1371$)	0.99
Statin	97.9% ($n = 4558$)	97.3% ($n = 366$)	97.8% ($n = 2758$)	98.4% ($n = 1434$)	0.34

Data are shown as mean and standard deviation or median and interquartile range if skewed. Categorical data are shown as numbers and percentages. Data on hospitalization refer to patients discharged home. Percentages may not total 100 owing to rounding. GRACE 2.0 Score refers to 1-year mortality risk estimates. Abbreviations: ACE = angiotensin-converting enzyme; ATII = angiotensin II; GRACE = global registry of acute coronary events; IABP = intra-arterial balloon pump; LVAD = left ventricular assist device; PCI = percutaneous coronary intervention; STD = symptom onset-to-door time; STI = symptom onset-to-intervention time; PCI = percutaneous coronary intervention.

with sBP <100 mmHg had a 2.4-fold increased MACE risk (HR 2.39, 1.63–3.50, $P < 0.001$) as compared to normotensives, an association consistently observed after adjusting for sex and age (HR 2.45, 1.67–3.59, $P < 0.001$). The risk of MACE was lower after controlling for clinical risk factors, including BMI, history of DM, total cholesterol, NT-proBNP, and the use of antihypertensive drugs (HR 1.96, 1.24–3.08, $P = 0.0040$) and persisted after further adjusting for hs-CRP, hs-cTnT levels, STD time, and ACS type (HR 1.68, 1.05–2.69, $P = 0.031$, *Table 3*). At 1 year, patients with sBP <100 mmHg were at 1.7-fold increased risk of MACE (HR 1.70, 1.24–2.35, $P = 0.001$), which remained similar in magnitude after adjusting for sex and age (HR 1.76, 1.27–2.42, $P < 0.001$). Adjustment for the above-mentioned risk factors led to a slightly attenuated association (HR 1.51, 1.03–2.21, $P = 0.036$), and was not significant after further controlling for levels of both hs-CRP, hs-cTnT, and STD time as well as ACS type (HR 1.38, 0.92–2.05, $P = 0.117$, *Table 3*). Importantly, the high risk of MACE was mainly driven by the high multivariable-adjusted risk of CV mortality at 30 days (HR 3.34, 1.73–6.45, $P < 0.001$) and 1 year (HR 2.17, 1.19–3.94, $P = 0.011$), respectively (*Table 3*), with no significant differences in any other MACE components (i.e. non-fatal MI and non-fatal stroke) (see Supplementary material online, *Table S6*).

Systemic inflammation and myocardial injury are most pronounced in patients with sBP <100 mmHg presenting in cardiogenic shock

When comparing patients with sBP <100 mmHg and CS with those without clinical signs thereof, the former were older (66.46 vs. 61.47 years, $P = 0.002$), had lower LVEF (40.73 vs. 50.07%, $P < 0.001$), and showed higher heart rates (85.18 vs. 73.99 b.p.m., $P < 0.001$). Moreover, patients in CS had higher glucose and higher creatinine levels (both $P < 0.001$, *Table 4*). Regarding systemic inflammation and myocardial injury, patients with CS had a higher leukocyte count ($P < 0.001$) and higher NLRs ($P = 0.031$), while hs-CRP levels did not differ among patients with sBP <100 mmHg with or without CS (*Figure 4*; Supplementary material online, *Table S7*). Furthermore, patients with CS had significantly higher

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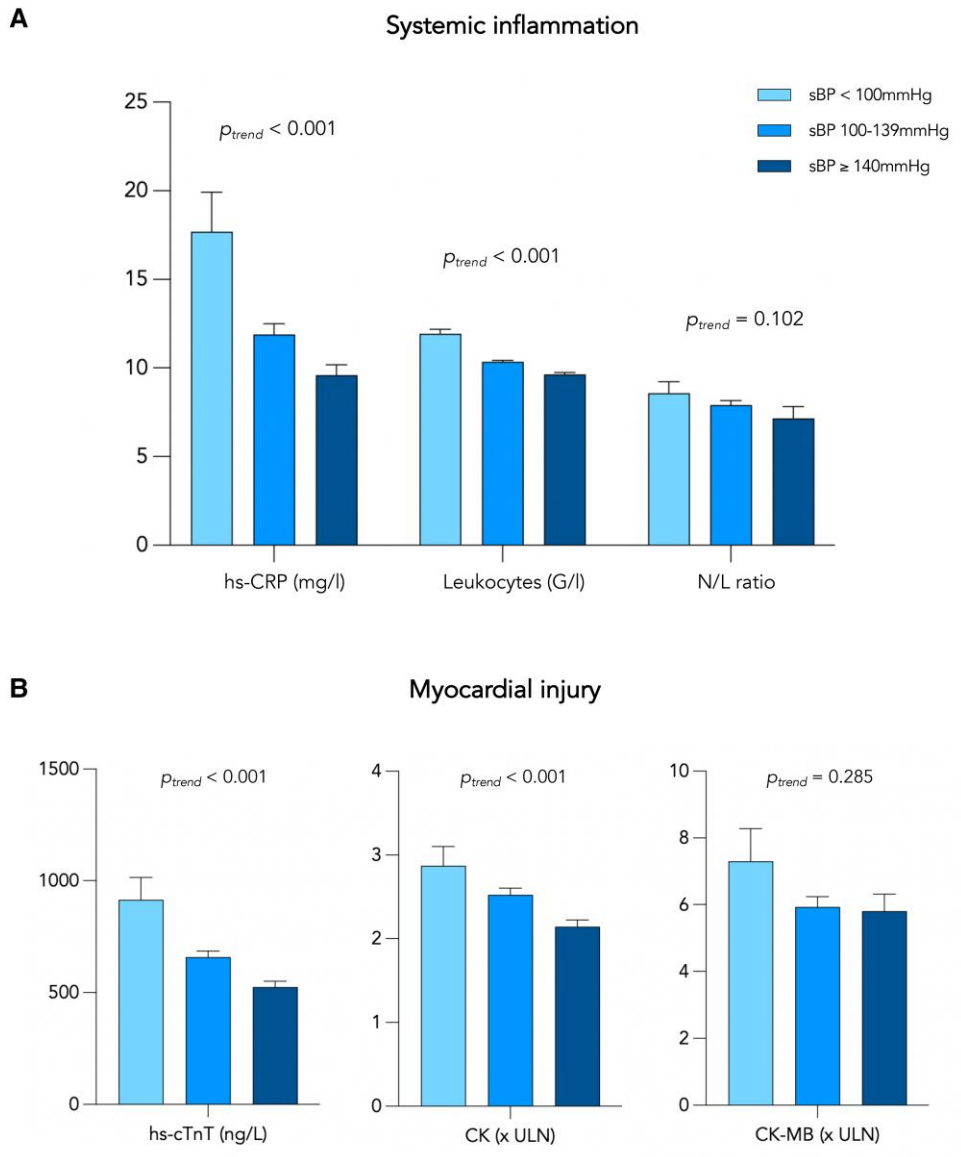

Figure 2 Inflammatory (**A**) and myocardial injury markers (**B**) in all patients according to sBP strata. Values are plotted as mean ± SEM. *P*-values were calculated by linear trend analysis. Abbreviations: CK = creatine kinase; CK-MB = creatine kinase-MB; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; N/L ratio = neutrophil-to-lymphocyte-ratio; sBP = systolic blood pressure; SEM = standard error of the mean; ULN = upper limit of normal.

levels of NT-proBNP ($P < 0.001$), hs-cTnT ($P < 0.001$), and CK ($P = 0.002$, *Table 4*, *Figure 4*) and presented more often in STEMI (85.4 vs. 66.1%, $P < 0.001$). Notably, among those with CS, the IRA was more frequently the left anterior descending coronary artery (50 vs. 37.9%, $P = 0.049$), and less so the RCA (27.5 vs. 42.2%, $P = 0.017$, *Table 4*). At 30 days, those with sBP <100 mmHg and CS had a 3.6-fold multivariable-adjusted MACE risk (HR 3.58, 1.77–7.24, $P < 0.001$, reference: sBP <100 mmHg without CS), an association that was attenuated, yet persisted after adjusting for differences in hs-cTnT, hs-CRP, STD time, and ACS type (HR 2.91, 1.34–6.32, $P = 0.007$). Similarly, multivariable-adjusted risk of MACE was increased by 194% (HR 2.94, 1.57–5.53, $P < 0.001$) at 1 year, which was attenuated after controlling for hs-CRP, hs-cTnT, STD time, and ACS type (HR 2.14, 1.06–4.3, $P = 0.033$, *Table 5*, *Figure 5*). Expectedly, the high risk of MACE was driven by the risk of CV mortality, with a multivariable-adjusted HR of 5.52 (2.41–12.65, $P < 0.001$) and 5.96 (2.63–13.52, $P < 0.001$) at 30 days and 1 year, respectively (*Table 5*). This association was slightly attenuated after adjusting for hs-CRP, hs-cTnT, prehospital delay, and ACS type, yielding an HR of 4.74 (1.91–11.78, $P < 0.001$) and 4.74 (1.91–11.78, $P < 0.001$) at 30 days and 1 year, respectively (*Table 5*).

Discussion

Here, we show for the first time that (i) inflammatory phenotypes of patients with ACS differ according to initial sBP levels, (ii) those with sBP <100 mmHg and CS express marked cellular inflammation compared to those without CS, and (iii) biomarkers of systemic

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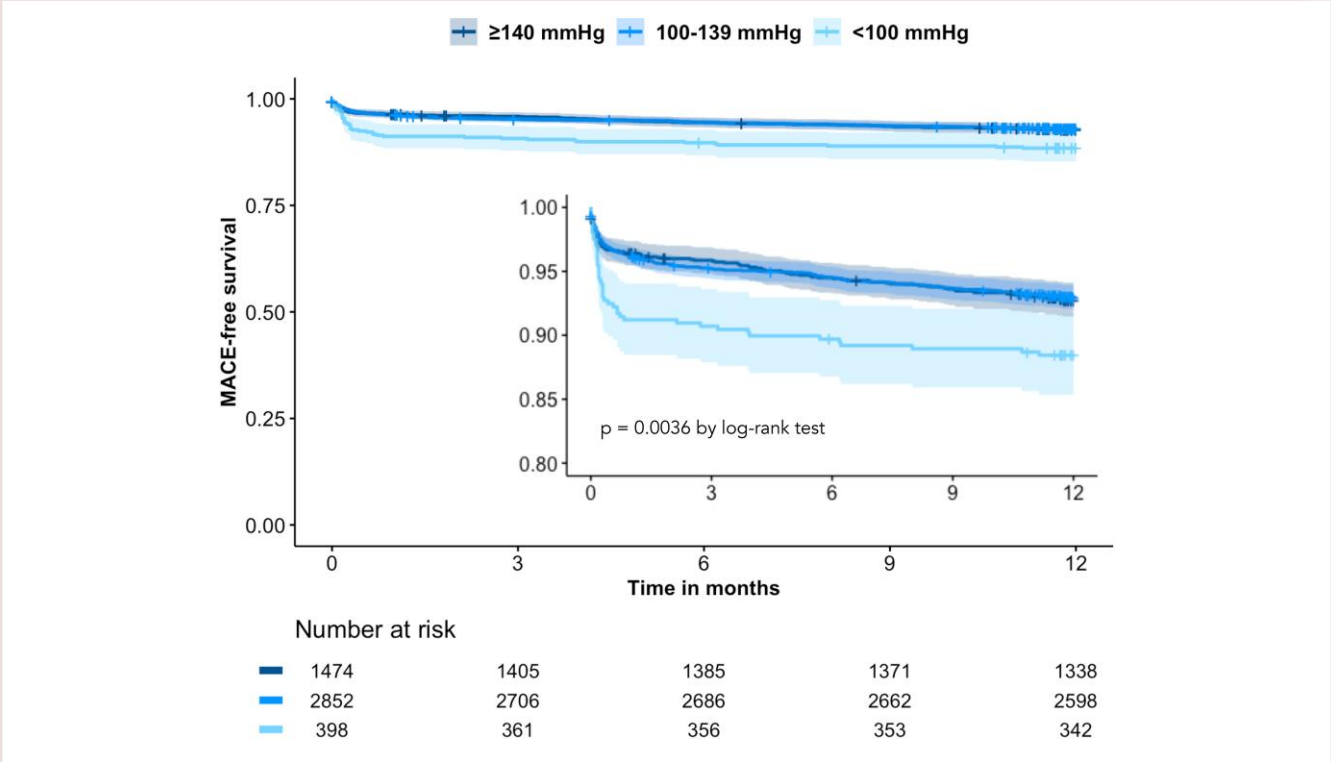

Figure 3 Kaplan–Meier survival analysis of all ACS patients stratified by initial sBP levels for MACE-free survival up to 1 year. Abbreviation: MACE = major adverse cardiovascular events.

inflammation and myocardial injury as well as MACE and mortality risk associate inversely with initial sBP levels.

Seminal studies have implicated systemic and in particular local inflammation as key triggers of ACS.[22,23] Inflammatory mechanisms reduce fibrous cap thickness and in turn plaque stability, thereby paving the way for plaque rupture, thrombosis and eventually ACS.[24] Indeed, components of cell-mediated immunity such as macrophages and T-cells are intricately linked to ACS pathogenesis, with macrophages producing extracellular matrix degrading enzymes, and certain T-cell subsets being involved in the rupture or erosion of atherosclerotic plaques.[25,26] Although inflammatory processes may not be the sole driver of the transition from stable to acute atherothrombotic events,[27] the vast majority of patients with ACS present with increased levels of systemic inflammation, as assessed by CRP,[28] with high concentrations showing a strong association with cardiac contractile decline and MACE risk.[30–32,23,29]

A previous report by Shlomai *et al.* provided hints that sBP levels at presentation may determine MACE risk post-ACS.[33] Beyond confirming these findings, we herein show that systemic inflammation decreases from low to high sBP strata, providing an observational link between sBP and systemic inflammation. Notably, patients presenting with sBP <100 mmHg had accentuated signs of cellular as well as humoral inflammation, as reflected by dramatically increased leukocyte counts, NLR, and hs-CRP levels. Although higher leukocyte counts might occur transiently due to '*stress leukocytosis*',[34] the higher hs-CRP levels clearly point toward increased levels of systemic inflammation, given the markedly delayed kinetics of hepatic CRP production. Indeed, a previous study using a model of myocardial infarction suggested a sharp incline of CRP no sooner than 24 h after acute inschaemia.[35] In line, differences in hs-CRP levels between sBP groups were consistently observed after adjustment for the time elapsed between symptom onset and acute presentation ($p_{adj} < 0.001$). This finding is thought-provoking, as patients with sBP <100 mmHg were actually characterized by a shorter time-window between symptom onset and presentation, and yet inflammatory parameters were highest in this patient population.

Nonetheless, in addition to the concept that inflammatory mechanisms may drive hemodynamic instability in patients with ACS, it is equally important to consider the alternative hypothesis that systemic hypoperfusion (owing the loss of cardiac contractile mass) and subsequent neurohumoral activation may accelerate the systemic inflammatory response evoked by myocardial injury.[36] For instance, in the SHOCK trial, almost one-fifth of patients with CS complicating ACS showed clinical signs of severe systemic inflammation,[37] which were intriguingly preceded by a decline in systemic vascular resistance. While the role of inflammation in CS development (and vice versa) is a matter of ongoing investigations, it might well be that both conditions affect each other resulting in an '*inflammation—hemodynamic instability loop*' putting hypotensive patients with high inflammatory burden at particularly high MACE risk (*Graphical Abstract*). Albeit our study's design does not allow to tackle cause-effect relationships, it is striking that differences in hs-CRP levels remained robust in STD-adjusted analysis. Indeed, as noted above, CRP synthesis may take up to 24 h, whilst leukocyte mobilization may occur rapidly in response to biochemical and neuronal cues.[38]

Expectedly, patients with sBP <100 mmHg featured pronounced myocardial injury as reflected by elevated hs-cTnT and CK levels, which coincided with a reduction in LVEF and increase in NT-proBNP levels, as suggested by a previous report.[39] Despite the shorter STD and STI time, patients with sBP <100 mmHg showed a markedly increased 30-day and one-year MACE risk, which was mainly driven by the accentuated CV mortality risk. In contrast, the

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Table 3 Associations of initial sBP levels with risk of adverse outcomes

	<100 mmHg n = 398	100–139 mmHg n = 2852	≥140 mmHg n = 1474	P-value
Time to event	11.6% (n = 46)	7.1% (n = 203)	7.2% (n = 106)	
Time to MACE (days)	7.5 (4–25)	23 (4–170)	31 (3–167)	0.044
Time to CV death (days)	6 (2–18)	18 (4–97)	10.5 (4–120)	0.014
MACE				
30-days MACE	8.8% (n = 35)	3.8% (n = 107)	3.6% (n = 53)	< 0.001
– [a] Crude model	2.39 (1.63–3.5)	reference	0.96 (0.69–1.34)	< 0.001
– [b] Sex/Age model	2.45 (1.67–3.59)		0.86 (0.62–1.2)	< 0.001
– [c] Adjusted model	1.96 (1.24–3.08)		0.8 (0.55–1.17)	0.0040
– [d] Fully adjusted model	1.68 (1.05–2.69)		0.85 (0.58–1.25)	0.031
1-year MACE	11.6% (n = 46)	7.0% (n = 200)	7.2% (n = 106)	0.0050
– [a] Crude model	1.7 (1.24–2.35)	reference	1.03 (0.81–1.3)	0.0010
– [b] Sex/Age model	1.76 (1.27–2.42)		0.92 (0.73–1.16)	< 0.001
– [c] Adjusted model	1.51 (1.03–2.21)		0.92 (0.7–1.2)	0.036
– [d] Fully adjusted model	1.38 (0.92–2.05)		0.94 (0.72–1.24)	0.12
Cardiovascular mortality				
30-days CV mortality	7.0% (n = 28)	1.4% (n = 40)	1.4% (n = 20)	< 0.001
– [a] Crude model	5.15 (3.18–8.34)	reference	0.97 (0.57–1.66)	< 0.001
– [b] Sex/Age model	5.34 (3.29–8.66)		0.81 (0.47–1.38)	< 0.001
– [c] Adjusted model	4.42 (2.38–8.19)		0.59 (0.28–1.26)	< 0.001
– [d] Fully adjusted model	3.34 (1.73–6.45)		0.71 (0.33–1.54)	< 0.001
1-year CV mortality	7.8% (n = 31)	2.6% (n = 73)	2.0% (n = 30)	< 0.001
– [a] Crude model	3.16 (2.07–4.81)	reference	0.79 (0.51–1.22)	< 0.001
– [b] Sex/Age model	3.29 (2.16–5.01)		0.66 (0.43–1.02)	< 0.001
– [c] Adjusted model	2.89 (1.66–5.03)		0.57 (0.33–1)	< 0.001
– [d] Fully adjusted model	2.17 (1.19–3.94)		0.64 (0.37–1.14)	0.011

Time to event is shown as median and interquartile range. Hazard ratios along with bootstrapped 95% confidence intervals for the association of initial sBP levels and risk of MACE (primary endpoint; composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) or cardiovascular death (secondary endpoint) at both 30 days and 1 year are shown (reference: 100–139 mmHg). Abbreviations: MACE = major adverse cardiovascular event; CV = cardiovascular.
[a]Crude regression model;
[b]Includes sex (categorical) and age (continuous);
[c]Includes sex (categorical), age (continuous), body mass index (continuous), history of diabetes mellitus (categorical), total cholesterol (continuous), NT-pro brain natriuretic peptide (continuous), and antihypertensive drugs (i.e. ACE-inhibitors, ATII receptor blockers, beta blockers, and calcium antagonists; categorical);
[d]Includes sex (categorical), age (continuous), body mass index (continuous), history of diabetes mellitus (categorical), total cholesterol (continuous), NT-pro brain natriuretic peptide (continuous), antihypertensive drugs (i.e. ACE-inhibitors, ATII receptor blockers, beta blockers and calcium antagonists; categorical), high-sensitivity cardiac troponin T (continuous), high-sensitivity C-reactive protein (continuous), symptom onset-to-door time (categorical), and ACS type (categorical).

risk of non-fatal stroke and recurrent infarction did not differ neither at 30 days nor at one year.

Of note, not all patients presenting with sBP <100 mmHg were in CS or developed such a condition during hospitalization. Expectedly, hypotensive patients with and without CS differed in several clinical features, including age, LVEF, and heart rate. Interestingly, however, those presenting with CS had significantly higher hs-cTnT, NT-proBNP, CK, and CK-MB levels as compared to those with sBP <100 mmHg without CS. Moreover, among all patients with sBP <100 mmHg, those with signs of CS had markedly elevated signs of cellular inflammation, as reflected by increased leukocyte count and NLR, yet intriguingly showed similar hs-CRP levels as compared to their non-shocked counterparts. As such, although observational in character, it might well be that cellular inflammation contributes to the transition of hypotensive patients to CS and thereby significantly influences clinical outcomes. Indeed, the risk of both MACE and CV mortality was attenuated after controlling for systemic inflammation, arguing in favor of this hypothesis. Whether and in what way this may open novel therapeutic avenues in patients presenting with low sBP levels remains to be further addressed in future investigations.

Of note, the vast majority of contemporary risk scores builds on sBP values determined at the time of acute presentation. For instance, the GRACE score, as well as the TIMI risk score for STEMI is informed by sBP levels, with values <100 mmHg adding substantially to the risk estimates of the latter.[2,3,17,40,41] Herein, we show that a significant interplay between sBP levels and systemic inflammation exists, with the latter not only representing a well-established modulator of plaque formation, rupture and arterial thrombosis,[16,42,43] but likely also determining hemodynamic stability after the acute event.[37] Of note, hepatic CRP synthesis is mainly regulated by interleukins downstream of the NLRP3-pathway, including IL-1ß, IL-6, and IL-18, which were found to be individually associated with increased MACE risk.[12,29,30,32,44,45] In line with this interpretation, an attenuated MACE risk was observed in patients with sBP <100 mmHg after adjustment for the systemic

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Table 4 Baseline characteristics of ACS patients with initial sBP <100 mmHg with or without cardiogenic shock

	All hypotensive patient (<100 mmHg) *n* = 398	No signs of cardiogenic shock *n* = 316	Signs of cardiogenic shock *n* = 82	*P*-value
Patient characteristics				
Age (years)	62.5 ± 12.77	61.47 ± 12.82	66.46 ± 11.84	0.0020
% Female ♀	16.6% (*n* = 66)	15.5% (*n* = 49)	20.7% (*n* = 17)	0.26
BMI (kg/m^2)	26.59 ± 3.93	26.59 ± 3.81	26.57 ± 4.44	0.98
Cardiac function				
LVEF (%)	48.38 ± 12.16	50.07 ± 11.24	40.73 ± 13.37	< 0.001
Heart rate (b.p.m.)	76.3 ± 18.55	73.99 ± 17.42	85.18 ± 30.13	< 0.001
Systolic BP (mmHg)	89.69 ± 8.69	91.01 ± 7.61	84.59 ± 10.56	< 0.001
Diastolic BP (mmHg)	56.95 ± 10.13	58.06 ± 9.83	52.68 ± 10.21	< 0.001
Cardiometabolic risk factors				
Total cholesterol (mmol/L)	4.77 ± 1.21	4.81 ± 1.2	4.59 ± 1.26	0.15
HDL-C (mmol/L)	1.13 ± 0.36	1.13 ± 0.35	1.14 ± 0.39	0.77
LDL-C (mmol/L)	3.06 ± 1.08	3.1 ± 1.1	2.88 ± 1.03	0.11
Triglycerides (mmol/L)	1.04 (0.53–3.39)	1.04 (0.68–1.65)	1.03 (0.68–1.54)	0.62
Glucose (mmol/L)	7.89 ± 3.79	7.4 ± 3.11	9.71 ± 5.25	< 0.001
HbA1c (%)	5.8 (5.6–8.3)	5.8 (5.5–6.4)	5.8 (5.5–6.2)	0.23
Creatinine (µmol/L)	91.92 ± 44.1	86.94 ± 40.76	110.83 ± 50.96	< 0.001
Inflammatory and myocardial injury markers				
White blood cell count (WBC, G/L)	11.93 ± 4.6	11.25 ± 4.06	14.57 ± 5.58	< 0.001
Neutrophil-to-lymphocyte ratio	5.37 (3.5–9.36)	5.15 (2.9–8.48)	6.31 (3.86–11.85)	0.031
CRP, high-sensitivity (mg/L)	17.69 ± 41.86	16.06 ± 39.25	24.19 ± 5 0.82	0.15
Troponin T, high-sensitivity (ng/L)	204 (46–295)	155 (55–771)	356 (130–1910)	< 0.001
NT-proBNP (ng/L)	2111.4 ± 5932	1475.49 ± 3520	4743.36 ± 11060	< 0.001
Creatine Kinase (x ULN)	1.13 (0.64–2.12)	1.09 (0.56–3.14)	1.64 (0.72–3.56)	0.0020
CK-MB (x ULN)	2.53 (0.63–2.17)	2.5 (1.22–7.45)	3.21 (0.9–9.04)	0.41
ACS type				
STEMI	70.1% (*n* = 279)	66.1% (*n* = 209)	85.4% (*n* = 70)	< 0.001
IRA				
LAD	40.4% (*n* = 154)	37.9% (*n* = 114)	50% (*n* = 40)	0.049
LCx	18.1% (*n* = 69)	17.9% (*n* = 54)	18.8% (*n* = 15)	0.87
RCA	39.1% (*n* = 149)	42.2% (*n* = 127)	27.5% (*n* = 22)	0.017
LMCA	1.8% (*n* = 7)	1.3% (*n* = 4)	3.8% (*n* = 3)	0.15
SVG	0.5% (*n* = 2)	0.7% (*n* = 2)	0% (*n* = 0)	0.47

Data are shown as mean and standard deviation or median and interquartile range if skewed. Creatine kinase and creatine kinase-MB were standardized to the upper limit of normal (ULN) of each laboratory. Abbreviations: ACS = acute coronary syndrome; BMI = body mass index; BP = blood pressure; CK-MB = creatine kinase-MB; CRP = C-reactive protein; HbA1c = haemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; IRA = infarct-related artery; LAD = left anterior descending artery; LCx = left circumflex artery; LDL-C = low-density lipoprotein-cholesterol; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RCA = right coronary artery; STEMI = ST-elevation myocardial infarction; SVG = saphenous vein graft (bypass).

inflammatory burden reflected by hs-CRP, thus highlighting important crosstalks between sBP levels and systemic inflammation.

In aggregate, among contemporary patients with ACS, proxies of systemic inflammation and myocardial injury decreased from low to high sBP strata, with highest levels observed in those with sBP <100 mmHg. Interestingly, among all patients with sBP <100 mmHg, patients in CS had a distinct inflammatory profile, and were at marked MACE risk, an association that was primarily driven by their high CV mortality risk.

Novelty and limitations

This study is based on a prospective real-world cohort with central biomarker measurements and independent event adjudication not only at 30 days, but also at one year. While the assessment of inflammatory pathways primarily focused on hs-CRP levels, leukocyte counts, as well as the NLR, other biomarkers may also be of interest. Further, levels of hs-cTnT are not only determined by the extent of acute myocardial injury, but are also driven by the time that elapsed between symptom onset and blood sampling. Yet, injury markers

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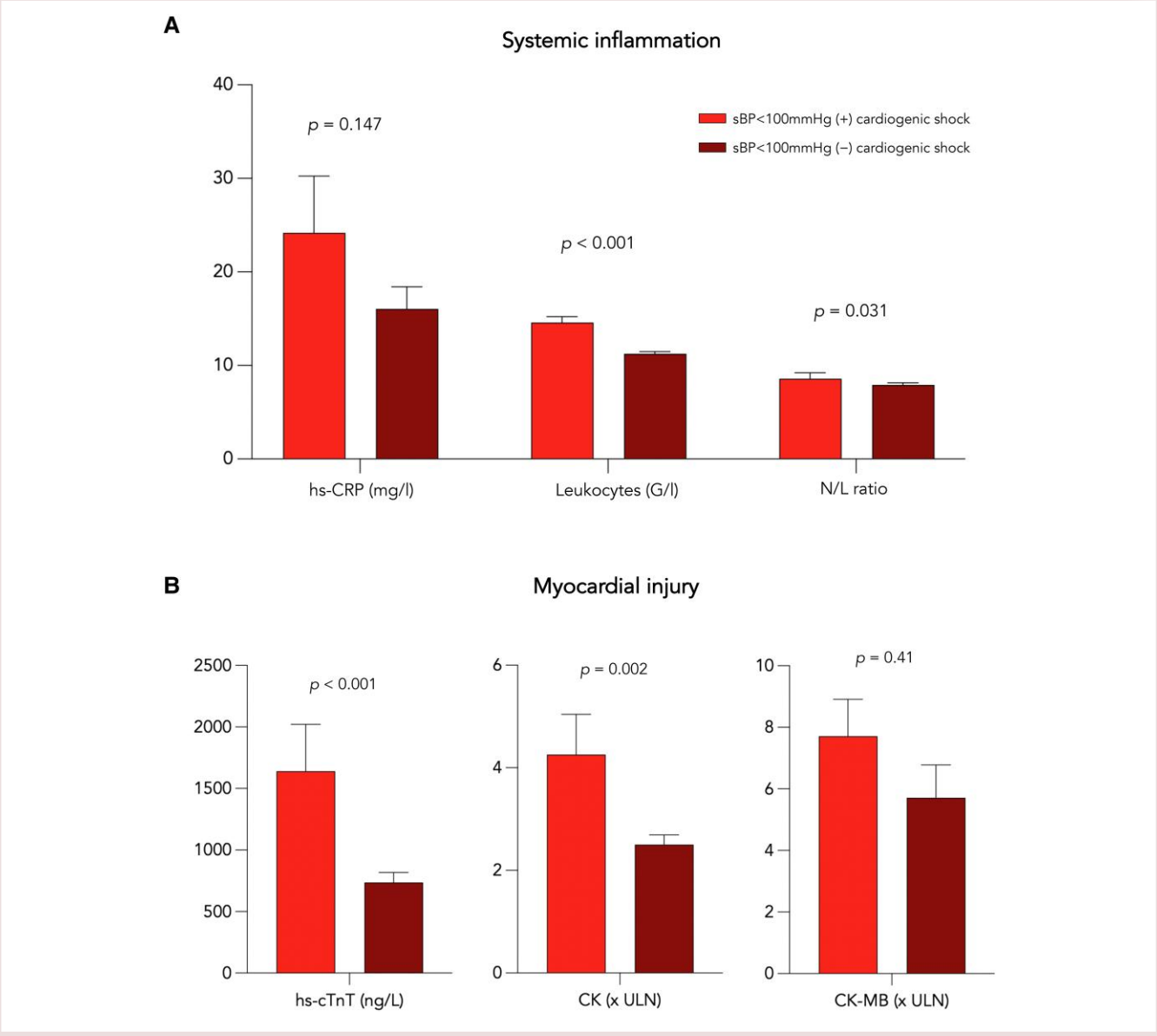

Figure 4 Inflammatory (**A**) and myocardial injury markers (**B**) in patients with sBP < 100 mmHg in the presence or absence of cardiogenic shock. Values are plotted as mean ± SEM. Calculation of p_{trend} was achieved by linear trend analysis. Abbreviations: CK = creatine kinase; CK-MB = creatine kinase-MB; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; N/L ratio = neutrophil-to-lymphocyte-ratio; sBP = systolic blood pressure; SEM = standard error of the mean; ULN = upper limit of normal.

Table 5 Associations of cardiogenic shock with risk of adverse outcomes among all patients with initial sBP <100 mmHg

Parameter	All hypotensive patients (<100 mmHg) *n* = 398	No signs of cardiogenic shock *n* = 316	Signs of cardiogenic shock *n* = 82	*P*-value
Outcomes				
MACE				
30-days MACE	8.8% (*n* = 35)	4.7% (*n* = 15)	24.4% (*n* = 20)	< 0.001
– [a] Crude model		reference	5.68 (2.9–11.09)	< 0.001

Continued

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Table 5 *Continued*

Parameter	All hypotensive patients (<100 mmHg) *n* = 398	No signs of cardiogenic shock *n* = 316	Signs of cardiogenic shock *n* = 82	*P*-value
– [b] Sex/Age model			4.75 (2.42–9.3)	< 0.001
– [c] Adjusted model			3.58 (1.77–7.24)	< 0.001
– [d] Fully adjusted model			2.91 (1.34–6.32)	0.0070
1-year MACE	11.6% (*n* = 46)	7.3% (*n* = 23)	28% (*n* = 23)	< 0.001
– [a] Crude model		reference	4.41 (2.47–7.87)	< 0.001
– [b] Sex/Age model			3.72 (2.08–6.65)	< 0.001
– [c] Adjusted model			2.94 (1.57–5.53)	< 0.001
– [d] Fully adjusted model			2.14 (1.06–4.3)	0.033
Cardiovascular mortality				
30-days CV mortality	7.0% (*n* = 28)	2.8% (*n* = 9)	23.2% (*n* = 19)	< 0.001
– [a] Crude model		reference	9.14 (4.13–20.2)	< 0.001
– [b] Sex/Age model			7.47 (3.37–16.55)	< 0.001
– [c] Adjusted model			5.52 (2.41–12.65)	< 0.001
– [d] Fully adjusted model			4.74 (1.91–11.78)	< 0.001
1-year CV mortality	7.8% (*n* = 31)	3.2% (*n* = 10)	25.6% (*n* = 21)	< 0.001
– [a] Crude model		reference	9.2 (4.33–19.55)	< 0.001
– [b] Sex/Age model			7.54 (3.54–16.06)	< 0.001
– [c] Adjusted model			5.96 (2.63–13.52)	< 0.001
– [d] Fully adjusted model			4.74 (1.91–11.78)	< 0.001

Data are HRs and bootstrapped 95% confidence intervals of cardiovascular death or MACE (composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death) at 30 days and 1 year. Abbreviations: MACE = major adverse cardiovascular event; CV = cardiovascular.
[a]Crude regression model;
[b]Includes sex (categorical) and age (continuous);
[c]Includes sex (categorical), age (continuous), history of diabetes mellitus (categorical) and total cholesterol (continuous);
[d]Includes sex (categorical), age (continuous), history of diabetes mellitus (categorical), total cholesterol (continuous), high-sensitivity cardiac troponin T (continuous), high-sensitivity C-reactive protein (continuous), symptom onset-to-door time (categorical) and ACS type (categorical).

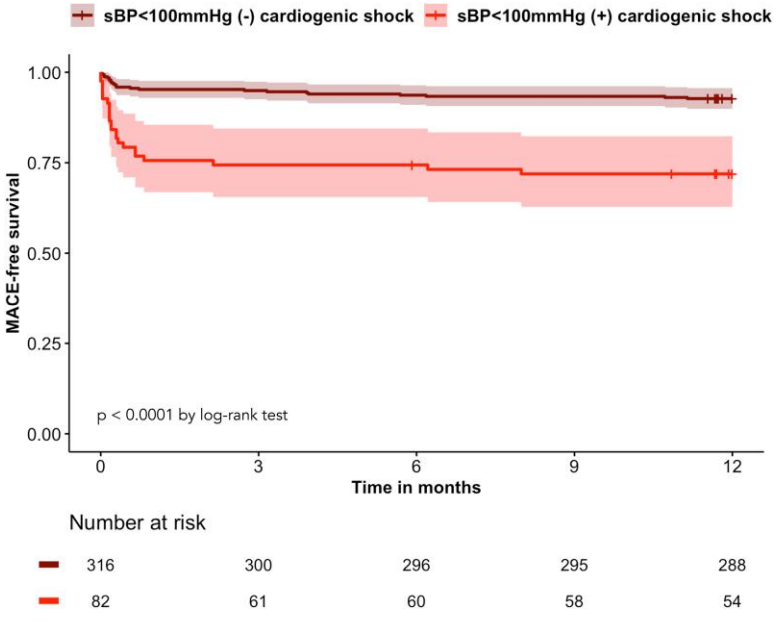

Figure 5 Kaplan–Meier estimates for 1-year MACE-free survival in ACS patients with sBP <100 mmHg in the presence (+) or absence (-) of cardiogenic shock. Abbreviation: MACE = major adverse cardiovascular event; sBP = systolic blood pressure.

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decreased consistently from low up to high sBP strata, while prehospital delays increased across sBP groups, providing high internal validity of these findings. Finally, the present study has several limitations inherent to any cohort study, including the risk of residual confounding and a potential selection bias.

Author's contributions

P.A.W., S.K., and T.F.L. conceived and S.K. and T.F.L. supervised the study. P.A.W. analysed the data; P.A.W. and S.K. wrote the initial version of the manuscript. All the authors vouch for the data and analyses reported. All co-authors revisited the work critically for important intellectual content and approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the integrity of any part of the work presented are appropriately investigated and resolved.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

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Data availability

The study dataset will be made available to other researchers upon reasonable request to the corresponding authors, subject to institutional and ethical committee approvals.

References

1. European Society of Cardiology. Cardiovascular disease statistics 2019 (executive summary). *Eur Heart J* 2020;**41**:12–85.
2. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, *et al.* TIMI Risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation. *Circulation* 2000;**102**:2031–2037.
3. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, *et al.* Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.
4. European Society of Cardiology. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J* 2021;**42**:2298–2298.
5. Rakowski T, Dudek D, van 't Hof A, Ten Berg J, Soulat L, Zeymer U, *et al.* Impact of acute infarct-related artery patency before percutaneous coronary intervention on 30-day outcomes in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention in the EUROMAX trial. *Eur Heart J Acute Cardiovasc Care* 2018;**7**:514–521.
6. Batra G, Renlund H, Kunadian V, James SK, Storey RF, Steg PG, *et al.* Effects of early myocardial reperfusion and perfusion on myocardial necrosis/dysfunction and inflammation in patients with ST-segment and non-ST-segment elevation acute coronary syndrome: results from the PLATelet inhibition and patients Outcomes (PLATO) trial. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:336–349.
7. Lüscher TF, Obeid S. From Eisenhower's heart attack to modern management: a true success story!. *Eur Heart J* 2017;**38**:3066–3069.
8. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J* 2019;**40**:2671–2683.
9. Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, *et al.* One-year outcomes after PCI strategies in cardiogenic shock. *N Engl J Med* 2019;**380**:1876–1877.
10. Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, *et al.* PCI Strategies in acute myocardial infarction with cardiogenic shock. *N Engl J Med* 2018;**378**:1358–1361.
11. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, *et al.* Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
12. Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE, *et al.* Inflammatory markers at the site of ruptured plaque in acute myocardial infarction. *Circulation* 2005;**111**:1355–1361.
13. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;**35**:1782–1791.
14. Ridker PM, Everett BM, Thuren T, MacFayden JG, Chang WH, Ballantyne C, *et al.* Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
15. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, *et al.* Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;**383**:1838–1847.
16. Kraler S, Wenzl FA, Lüscher TF. Repurposing colchicine to combat residual cardiovascular risk: the LoDoCo2 trial. *Eur J Clin Invest* 2020;**50**:e13424.
17. Wenzl FA, Kraler S, Ambler G, Weston C, Herzog SA, Räber L, *et al.* Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. *Lancet* 2022;**400**:744–756.
18. Kraler S, Wenzl FA, Georgiopoulos G, Obeid S, Liberale L, von Eckardstein A, *et al.* Soluble lectin-like oxidized low-density lipoprotein receptor-1 predicts premature death in acute coronary syndromes. *Eur Heart J* 2022;**43**:1849–1860.

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19. The task force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2019;**39**:3021–3104.
20. Winzap PA, Davies A, Klingenberg R, Obeid S, Roffi M, Mach F, *et al.* Diabetes and baseline glucose are associated with inflammation, left ventricular function and short- and long-term outcome in acute coronary syndromes: role of the novel biomarker Cyr 61. *Cardiovasc Diabetol* 2019;**18**:142.
21. Grinberg T, Hammer Y, Wiessman M, Perl L, Ovdat T, Tsafrir O, *et al.* Management and outcomes over time of acute coronary syndrome patients at particularly high cardiovascular risk: the ACSIS registry-based retrospective study. *BMJ Open* 2022;**12**:e060953.
22. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, *et al.* The prognostic value of C-reactive protein and Serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;**331**:417–424.
23. Brunetti ND, Troccoli R, Correale M, Pellegrino P L, Di Biase M. C-reactive protein in patients with acute coronary syndrome: correlation with diagnosis, myocardial damage, ejection fraction and angiographic findings. *Int J Cardiol* 2006;**109**:248–256.
24. Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. *Circulation* 2017;**136**:1155–1166.
25. Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis. *Nat Rev Cardiol* 2020;**17**:387–401.
26. Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J Clin Invest* 1994;**94**:2493–2503.
27. Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, *et al.* Targeting cardiovascular inflammation: next steps in clinical translation. *Eur Heart J* 2021;**42**:113–131.
28. Cristell N, Cianflone D, Durante A, Ammirati E, Vanuzzo D, Banfi M, *et al.* High-Sensitivity C-reactive protein is within normal levels at the very onset of first ST-segment elevation acute myocardial infarction in 41% of cases: a multiethnic case-control study. *J Am Coll Cardiol* 2011;**58**:2654–2661.
29. Rossi VA, Denegri A, Candreva A, Klingenberg R, Obeid S, Räber L, *et al.* Prognostic value of inflammatory biomarkers and GRACE score for cardiac death and acute kidney injury after acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:445–452.
30. Kunkel JB, Josiassen J, Helgestad OKL, Schmidt H, Holmvang L, Jensen LO, *et al.* Inflammatory response by 48 h after admission and mortality in patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2023. online ahead of print.
31. Reindl M, Reinstadler SJ, Feistritzer H-J, Klug G, Tiller C, Mair J, *et al.* Relation of inflammatory markers with myocardial and microvascular injury in patients with reperfused ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:640–649.
32. Seropian IM, Sonnino C, Van Tassell BW, Biasucci LM, Abbate A. Inflammatory markers in ST-elevation acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2016;**5**:382–395.
33. Shlomai G, Kopel E, Goldenberg I, Grossman E. The association between elevated admission systolic blood pressure in patients with acute coronary syndrome and favorable early and late outcomes. *J Am Soc Hypertens* 2015;**9**:97–103.
34. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, *et al.* The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain Behav Immun* 2001;**15**:199–226.
35. Liebetrau C, Hoffmann J, Dörr O, Gaede L, Blumenstein J, Biermann H, *et al.* Release kinetics of inflammatory biomarkers in a clinical model of acute myocardial infarction. *Circ Res* 2015;**116**:867–875.
36. Samsky MD, Morrow DA, Proudfoot AG, Hochman JS, Thiele H, Rao SV. Cardiogenic shock after acute myocardial infarction. *JAMA* 2021;**326**:1840.
37. Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, *et al.* Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Arch Intern Med* 2005;**165**:1643–1650.
38. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science* 2013;**339**:161–166.
39. Frydland M, Møller JE, Lindholm MG, Hansen R, Wiberg S, Lerche Helgestad OK, *et al.* Biomarkers predictive of late cardiogenic shock development in patients with suspected ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:557–566.
40. Fox KAA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, *et al.* Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014;**4**:e004425.
41. Weichwald S, Candreva A, Burkholz R, Klingenberg R, Räber L, Heg D, *et al.* Improving 1-year mortality prediction in ACS patients using machine learning. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:855–865.
42. Wang H, Liu Z, Shao J, Lin L, Jiang M, Wang L, *et al.* Immune and inflammation in acute coronary syndrome: molecular mechanisms and therapeutic implications. *J Immunol Res* 2020;**2020**:1–13.
43. Liberale L, Kraler S, Puspitasari YM, Bonetti NR, Akhmedov A, Ministrini S, *et al.* SGLT-2 inhibition by empagliflozin has no effect on experimental arterial thrombosis in a murine model of low-grade inflammation. *Cardiovasc Res Preprint* 2022. online ahead of print.
44. Aday AW, Ridker PM. Antiinflammatory therapy in clinical care: the CANTOS trial and beyond. *Front Cardiovasc Med* 2018;**5**:62.
45. Yang C, Deng Z, Li J, Ren Z, Liu F. Meta-analysis of the relationship between interleukin-6 levels and the prognosis and severity of acute coronary syndrome. *Clinics (Sao Paulo)* 2021;**76**:e2690.

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