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ORIGINAL ARTICLE

Pre-admission beta-blocker therapy and outcomes in cardiogenic shock: Insights from the Altshock-2 Registry

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Abstract

Aims We aimed to assess the impact of pre-admission beta-blocker (BB) therapy on the clinical characteristics, in-hospital treatment and outcomes of patients with cardiogenic shock (CS).

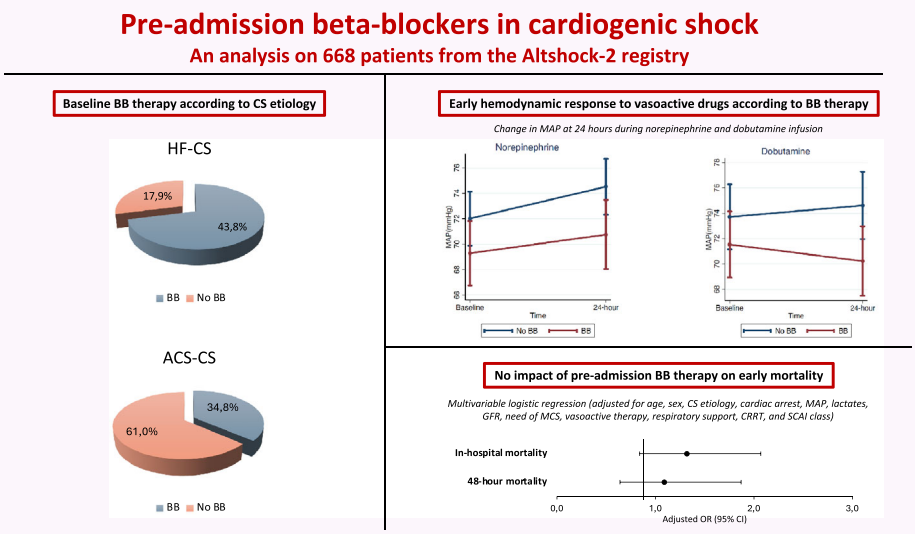
Methods All patients enrolled in the multicentre prospective Altshock-2 registry since March 2020 with available data on pre-admission BB therapy were included. Clinical characteristics, in-hospital management, haemodynamic parameters and clinical outcomes were compared in patients with versus without BB therapy. The primary endpoint was in-hospital mortality.

Results A total of 668 patients were included [median age 66 (56–74) years, male sex 76.5%]: 299 patients (44.8%) with and 369 patients (55.2%) without previous BB therapy. Patients receiving pre-admission BB therapy had more frequently heart failure-related CS (43.8% vs. 17.9%) and less frequently cardiac arrest at presentation (20.1% vs. 27.8%, P = 0.027). Levosimendan was used less frequently and dobutamine was used more frequently in patients with baseline BB therapy (P = 0.033 and P = 0.043, respectively). Differences in the early haemodynamic response to vasoactive drugs were observed between patients with and without previous BB therapy, with a significant impact of baseline BB on mean arterial pressure (MAP) response during norepinephrine infusion (P = 0.012) and with dobutamine having a reduced response in MAP and heart rate in patients receiving BBs before admission (P = 0.023 and P = 0.001, respectively). In-hospital mortality was not significantly different between the BB and no-BB groups (40% vs. 33.7%; adjusted odds ratio 1.32, 95% confidence interval 0.84–2.07, P = 0.224). Similarly, baseline BB therapy was not independently associated with 48 h mortality (12.7% vs. 14.6%; adjusted odds ratio 1.09, 95% confidence interval 0.64–1.87, P = 0.749). The lack of association between baseline BB therapy and mortality was also confirmed at inverse probability of treatment weighting-adjusted analysis.

Conclusions In a real-world, contemporary cohort of patients with CS, previous BB therapy influenced the haemodynamic response to vasoactive drugs, but it was not associated with in-hospital mortality.

Graphical Abstract

Among 668 with cardiogenic shock included in the multicentre prospective Altshock-2 registry, 299 patients (44.8%) received pre-admission beta-blocker therapy. Previous beta-blocker therapy influenced the early hemodynamic response to vasoactive drugs, but it was not associated with in-hospital mortality.



Keywords Cardiogenic shock; beta-blockers; inotropes; mortality; vasopressors

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Introduction

Cardiogenic shock (CS) is a syndrome with clinical and biochemical evidence of tissue hypoperfusion, which can lead to multi-organ failure and death in a high percentage of patients (30%–60%).[1] Its management is based on the immediate stabilization of haemodynamic parameters with the use of inotropes/vasopressors and possible escalation to mechanical circulatory supports (MCSs), in addition to the management of the primary aetiology.[2] However, the most commonly used inotropes/vasopressors act by stimulating β-adrenergic receptors and their action could be less effective in patients with previous β-blocker therapy, which is very common in patients with pre-existing cardiovascular disease, particularly in presence of heart failure (HF); actually, acute decompensation of HF is among the most common causes of CS.[3,4] Moreover, β-blockers (BBs) have a negative inotropic and chronotropic effect that could be deleterious in unstable patients. On the other side, in the setting of acute HF needing inotropic support, BBs have been shown to reduce the rate of vasopressor/inotrope-induced ventricular arrhythmias and the rates of premature ventricular contractions.[5] BBs at admission and discharge also resulted in lower mortality at 31 days in these patients.[6] Recently, the first data on BBs impact in patients hospitalized for CS were published[7,8]: in particular, in a subgroup analysis of the Dobutamine Compared with Milrinone (DOREMI) trial, patients with CS who were treated with BBs in the 24 h prior to initiating inotropic therapy, had fewer deaths and resuscitated cardiac arrest in the early resuscitation period, although this difference was no longer present at hospital discharge. Moreover, BB therapy was not associated with an impaired haemodynamic response to milrinone or dobutamine.[9] In the multicentre FRENSHOCK registry, the discontinuation of previous BBs therapy resulted in increased 1 month all-cause mortality and a trend towards increased 1 year all-cause mortality.[10]

The aim of the present study was to compare the clinical characteristics, in-hospital therapeutic strategies and outcomes of CS patients enrolled in the multicentre Altshock-2 registry based on pre-admission BB therapy.

Methods

Study design

The Altshock-2 registry (NCT04295252) is a multicentre, prospective, observational registry enrolling consecutive patients admitted for CS at 12 Italian centres since March 2020. CS was defined and staged according to the Society for Cardiovascular Angiography and Interventions (SCAI) criteria.[11–13]

In accordance with the EU Regulation 536/2014, all competent patients provided written informed consent, whereas consent was waived for patients who were not competent on admission. The study was conducted in accordance with ethical principles based on the Declaration of Helsinki,[14] International Conference on Harmonization for Good Clinical Practice and the current ethical rules. The Strengthening the Reporting of Observational Studies in Epidemiology Guidelines was followed for reporting study findings.[15] Only patients with known baseline use or non-use of BBs therapy were considered for the present analysis. Patients' characteristics, in-hospital data and clinical outcomes of all consecutively enrolled patients were collected and registered in an electronic case report form through the RedCap® platform. Laboratory, echocardiographic and haemodynamic variables, as well as the SCAI shock stages according to the updated classification, were also reported.[13]

Endpoints

The primary endpoint of this study was in-hospital mortality. Secondary outcomes were 48 h mortality, length of hospitalization, left ventricular assist device (LVAD) implantation and heart transplantation during the index admission. The in-hospital therapeutic management and haemodynamic parameters at admission and at 24 h were also evaluated.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (*SD*) or median and interquartile range (IQR), as appropriate, and were compared with the Student *T*-test or Mann–Whitney *U*-test, respectively. Categorical variables are presented as numbers and percentages and were compared with the χ^2 or Fisher test, as appropriate. Baseline characteristics, in-hospital data, repeated haemodynamic parameters and clinical outcomes were compared between the patients with previous BBs therapy before hospitalization and those without BBs therapy before hospitalization. The association between BB use and the change in mean arterial pressure (MAP) and heart rate (HR) between admission and 24 h was analysed with repeated measures mixed models, that were performed separately in patients treated with different inotropes/vasopressors (epinephrine, norepinephrine, dobutamine and levosimendan). Univariable and multivariable binary logistic regression analyses were performed to evaluate the impact of previous BB therapy on in-hospital mortality and 48 h mortality. The following clinically relevant variables in the context of CS were included in the multivariable analyses: age, sex, CS aetiology, cardiac arrest at presentation, MAP at admission, lactates at admission, glomerular filtration rate (GFR) at admission, need of MCS during hospitalization, need of vasoactive treatment during hospitalization, need of respiratory support during hospitalization, need of continuous renal replacement therapy (CRRT) during hospitalization and SCAI classification at admission. Results of the analyses are reported as unadjusted or adjusted odds ratio (OR) with 95% confidence interval (CI). No imputation was performed for missing values. Propensity score methodology with inverse probability of treatment weighting (IPTW) was also performed to account for bias between patients with versus without previous BB therapy.[16–18] Propensity scores predicting each patient's probability of receiving pre-admission BB were estimated with multivariable logistic regression including the following variables: age, sex, CS aetiology, cardiac arrest at presentation, MAP at admission, lactates at admission, GFR at admission, need of MCS during hospitalization, need of vasoactive treatment during hospitalization, need of respiratory support during hospitalization, need of CRRT during hospitalization and SCAI classification at admission. Stabilized weights were computed from propensity scores by means of IPTW. The weight for pre-admission BB was the inverse of the respective propensity score, whereas the weight for the lack of pre-admission BB therapy was the inverse of 1-propensity score. Logistic regression models evaluating the impact of BB versus no-BB on in-hospital and 48 h mortality were weighted using IPTW.

Subgroup analyses were also performed to evaluate the impact of previous BB therapy on in-hospital mortality in the following subgroups of interest: sex, age $\geq$75 years versus $\leq$75 years, CS aetiology [acute coronary syndrome (ACS) vs. non-ACS], cardiac arrest at presentation, need of temporary MCSs, need of vasoactive drugs, need of invasive or non-invasive respiratory support, need of CRRT, lactates $\geq$2 mmoL/L versus $\leq$2 mmoL/L, GFR $<$ 30 mL/min versus $\geq$ 30 mL/min, MAP $<$ 60 mmHg versus $\geq$ 60 mmHg and SCAI classifications A–C versus D–E.

Analyses were performed with SPSS V 29.0 (SPSS, Chicago, Illinois, USA) and STATA software version 16 (STATA Corp., College Station, Texas, USA). Statistical significance was set at the two-tailed 0.05 level.

Results

Baseline characteristics and clinical presentation

Out of 725 patients enrolled in the Altshock-2 registry, a total of 668 patients (92.1%) with available data on pre-admission

Table 1 Baseline characteristics according to baseline BB therapy.

Characteristics	Overall cohort (N = 668)	Previous BB therapy (N = 299)	No previous BB therapy (N = 369)	P value
Demographics				
Age (n = 666)	66 (56–74)	68 (59–76)	64 (53–73)	<**0.001**
BMI, kg/m^2 (n = 643)	25.7 (23.2–28.4)	26 (23.6–29.4)	25.4 (23.1–27.8)	0.050
Male sex (n = 511)	511 (76.5)	233 (77.9)	273 (74)	0.433
Ethnicity (n = 565)				0.352
White	525 (92.9)	228 (93.1)	297 (92.8)	
Hispanic	10 (1.8)	5 (2)	5 (1.6)	
Asian	8 (1.4)	1 (0.4)	7 (2.2)	
Black	10 (1.8)	6 (2.5)	4 (1.2)	
Other	12 (2.1)	5 (2)	7 (2.2)	
Medical history				
Previous COVID-19 (n = 652)	40 (6.1)	23 (7.9)	17 (4.7)	0.087
Smoking (n = 662)	169 (25.5)	57 (19.3)	112 (30.5)	**0.001**
Hypertension (n = 667)	360 (54)	194 (65.1)	166 (45)	<**0.001**
Diabetes (n = 668)	201 (30.1)	108 (36.1)	93 (25.2)	**0.002**
Dyslipidaemia (n = 667)	278 (41.7)	160 (53.7)	118 (32)	<**0.001**
Stroke or TIA (n = 666)	43 (6.5)	30 (10.1)	13 (3.5)	<**0.001**
Peripheral artery disease (n = 664)	117 (17.6)	77 (26.1)	40 (10.8)	<**0.001**
Atrial fibrillation (n = 666)	155 (23.3)	117 (39.3)	38 (10.3)	<**0.001**
CKD (n = 665)	152 (22.9)	113 (38)	39 (10.6)	<**0.001**
Anaemia (n = 668)	76 (11.4)	49 (16.4)	27 (7.3)	<**0.001**
Liver disease (n = 668)	33 (4.9)	20 (6.7)	13 (3.5)	0.060
Thyroid disease (n = 667)	94 (14.1)	60 (20.1)	34 (9.2)	<**0.001**
Prior PCI (n = 666)	163 (24.5)	113 (37.9)	50 (13.6)	<**0.001**
Prior CABG (n = 665)	60 (9)	46 (15.5)	14 (3.8)	<**0.001**
ICD (n = 667)	93 (13.9)	83 (27.9)	10 (2.7)	<**0.001**
CRT-D (n = 666)	43 (6.5)	38 (12.7)	5 (1.4)	<**0.001**
HF hospitalization (n = 656)	98 (16.5)	72 (29.3)	26 (7.5)	<**0.001**
Prior LVEF, % (n = 359)	40 (25–55)	35 (25–48)	50 (40–60)	<**0.001**
Cancer (n = 666)	85 (12.8)	43 (14.4)	42 (11.4)	0.246
Waiting list for HT (n = 663)	21 (3.2)	19 (6.4)	2 (0.5)	<**0.001**
Drug history				
Periodic levosimendan (n = 663)	25 (3.8)	20 (6.7)	5 (1.4)	<**0.001**
ACE-I (n = 666)	108 (16.2)	68 (22.9)	40 (10.8)	<**0.001**
ARB (n = 665)	80 (12)	51 (17.2)	29 (7.9)	<**0.001**
Sacubitril/valsartan (n = 664)	73 (11)	68 (22.9)	5 (1.4)	<**0.001**
Loop diuretic (n = 665)	257 (38.6)	197 (66.1)	60 (16.3)	<**0.001**
MRA (n = 663)	167 (25.2)	139 (47)	28 (7.6)	<**0.001**
SGLT2-i (n = 215)	29 (13.5)	28 (32.9)	1 (0.8)	<**0.001**
CCB (n = 662)	75 (11.3)	37 (12.6)	38 (10.3)	0.362
Anti-arrhythmic (n = 664)	93 (14)	74 (24.9)	19 (5.2)	<**0.001**
Oral anticoagulant (n = 666)	165 (24.8)	123 (41.3)	42 (11.4)	<**0.001**
Ivabradine (n = 664)	22 (3.3)	14 (4.7)	8 (2.2)	0.067
SAPT (n = 665)	233 (35)	154 (51.9)	79 (21.5)	<**0.001**
DAPT (n = 663)	62 (9.4)	45 (15.2)	17 (4.6)	<**0.001**
Statin (n = 202)	68 (33.7)	45 (56.2)	23 (18.9)	<**0.001**
Oral antidiabetics (n = 663)	113 (17)	66 (22.3)	47 (12.8)	**0.001**
Insulin (n = 660)	79 (12)	53 (18)	26 (7.1)	<**0.001**
CS aetiology (n = 668)				<**0.001**
ACS-CS	329 (49.3)	104 (34.8)	225 (61)	
HF-CS	197 (29.5)	131 (43.8)	66 (17.9)	
Acute myocarditis	17 (2.5)	2 (0.7)	15 (4)	
PE	15 (2.2)	4 (1.3)	11 (3)	
Other	110 (16.5)	58 (19.4)	52 (14.1)	
Cardiac arrest at presentation (n = 627)	153 (24.4)	56 (20.1)	97 (27.8)	**0.027**

Note: Data are presented as n (% on available) and as median (IQR). Bold values represent significant P values.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ACS-CS, acute coronary syndrome-cardiogenic shock; ARB, angiotensin receptor blocker; BBs, β-blocker; BMI, body mass index; CABG, coronary artery bypass graft; CCB, calcium-channel blocker; CKD, chronic kidney disease; COVID-19, Coronavirus disease 2019; CRT-D, cardiac resynchronization therapy-defibrillator; CS, cardiogenic shock; DAPT, dual antiplatelet therapy; HF, heart failure; HF-CS, heart failure-cardiogenic shock; HT, heart transplant; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SAPT, single antiplatelet therapy; SGLT2-I, sodium-glucose cotransporter 2 inhibitor; TIA, transient ischaemic attack.

BB therapy were included in the present study: 299 (44.8%) with and 369 (55.2%) without baseline BB therapy. The most common aetiology of CS was ACS (49.3%), followed by HF-CS in 29.5% of patients (*Table* 1). Patients receiving baseline BB therapy had less frequently ACS-CS (34.8%) compared with those without BB therapy (61%). Conversely, HF-CS was observed in 43.8% of patients in the BB group versus 17.9% in the no-BB group ($P < 0.001$). SCAI stages on admission according to BB and no-BB groups are described in *Figure* 1. Overall, most patients presented with SCAI stage C (52.8%). Demographic data and baseline characteristics are summarized in *Table* 1. Patients with BB therapy at baseline were older than patients without BB therapy [68 (IQR 59–76) vs. 64 (IQR 53–73) years, $P < 0.001$] and had more comorbidities, including a higher prevalence of diabetes, prior stroke or transient ischaemic attack, atrial fibrillation, prior myocardial revascularization and chronic kidney disease. Prior HF hospitalization was more common, and pre-admission left ventricular ejection fraction (LVEF) was lower among patients with previous BB therapy; these patients were also treated more frequently with other medications for HF. Patients receiving BBs therapy had less cardiac arrest at presentation (20.1% vs. 27.8%, $P = 0.027$).

Type of invasive monitoring, haemodynamic data, blood gas analysis, laboratory profile, echocardiographic and pulmonary artery catheter (PAC) findings are reported in *Table* 2. Overall, the majority of patients were monitored with invasive arterial line (96.2%) and central venous catheter (91.7%), whereas PAC was used only in 22.7% of patients. On admission, patients previously treated with BB had a slightly lower MAP [70 (IQR 60–80) vs. 71 (IQR 62–85) mmHg, $P = 0.019$] and higher systolic pulmonary artery pressure (PAP), mean PAP, pulmonary vascular resistance and PaO_2/FiO_2 ratio. In contrast, central venous pressure, cardiac output (CO), wedge pressure, lactates and central venous oxygen saturation at presentation were similar in the two groups. Of note, there was no significant difference in HR between the BB and no-BB groups [89 (IQR 73–110) vs. 93 (IQR 79–110) bpm, $P = 0.082$]. On admission, patients treated with BB had lower GFR, higher C-reactive protein and higher N-terminal pro brain natriuretic peptide concentrations. Regarding echocardiographic data, patients with prior BB therapy had higher left ventricular end-diastolic volume, lower tricuspid annular plane systolic excursion and a higher prevalence of severe mitral regurgitation and severe tricuspid regurgitation, whereas median LVEF was not significantly different between the BB and no-BB groups [23 (IQR 15–30) vs. 25 (IQR 17–35) %, $P = 0.327$].

In-hospital therapeutic management

In-hospital management is described in *Table* 3. The maximum inotropic score was similar in the two groups [14 (IQR 5.5–28) vs. 15 (IQR 6–31.1), $P = 0.292$]. The most used adrenergic drug in β-blocked patients was epinephrine (57.7%), while norepinephrine was the most used drug in the BB naïve group (64.4%). Regarding dobutamine administration, it was more used in patients with baseline BB therapy (46.6% vs. 38.9%, $P = 0.043$) and was also used at slightly higher maximum doses in this group of patients compared with patients without baseline BB. Maximum doses of epinephrine and

Figure 1 Society for Cardiovascular Angiography and Interventions (SCAI) class at admission in the whole cohort and according to baseline β-blocker (BB) therapy.

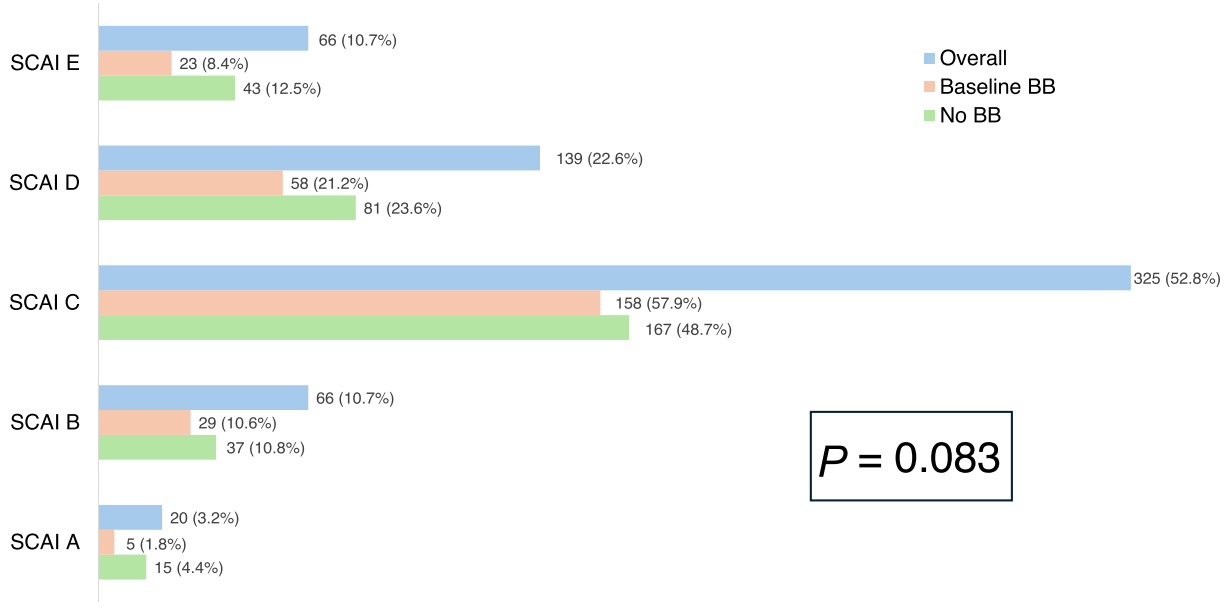


Table 2 Type on invasive monitoring, haemodynamic findings, blood gas analysis, laboratory profile, echocardiographic findings and pulmonary findings according to baseline BB therapy.

Variable	Overall cohort (N = 668)	Previous BB therapy (N = 299)	No previous BB therapy (N = 369)	P value
Type of invasive monitoring				
Invasive arterial pressure (n = 666)	641 (96.2)	281 (94.3)	360 (97.8)	**0.017**
CVC (n = 664)	609 (91.7)	271 (90.9)	338 (92.3)	0.512
Pulmonary artery catheter (n = 665)	151 (22.7)	59 (19.8)	92 (25.1)	0.107
Haemodynamic data on admission				
SBP, mmHg (n = 646)	95 (80–110)	94 (80–110)	100 (82–115)	0.125
MAP, mmHg (n = 644)	70 (60–83)	70 (60–80)	71 (62–85)	**0.019**
HR, bpm (n = 644)	90 (75–110)	89 (73–110)	93 (79–110)	0.082
CVP, mmHg (n = 424)	12 (8–15)	12 (8–16)	11 (8–15)	0.107
Systolic PAP, mmHg (n = 84)	39 (±14)	45 (±17)	36 (±12)	**0.004**
Mean PAP, mmHg (n = 84)	28 (±11)	32 (±12)	26 (±9)	**0.027**
PCWP, mmHg (n = 71)	20 (+7)	22 (+6)	19 (+7)	0.080
Cardiac output, L/min (n = 53)	3.8 (±1)	3.8 (±1.1)	3.9 (±1)	0.950
Cardiac index, L/min/m^2 (n = 57)	1.98 (±0.47)	1.96 (±0.51)	1.99 (±0.46)	0.834
PVR, Woods unit (n = 46)	2.3 (1.5–3.2)	3.1 (2.1–3.9)	2.0 (1.5–2.6)	**0.008**
SVR, dynes*s/cm^5 (n = 39)	1339.1 (1336–1625.5)	1263.2 (916.7–1562.4)	1384.6 (1226.7–1637.6)	0.270
Blood gas analysis on admission				
PaO_2, mmHg (n = 629)	98 (77–140)	96 (78–139)	100 (76–142)	0.653
PaO_2/FiO_2 ratio (n = 595)	250 (159–361)	266 (175–375)	234 (146–350)	**0.010**
$PaCO_2$, mmHg (n = 630)	35 (30–42)	34 (29–41)	35 (30–42)	0.225
HCO_3^-, mmol/L (n = 503)	20 (17–23.1)	20.2 (17–23.9)	20 (17.1–23)	0.666
Lactate, mmol/L (n = 641)	2.6 (1.6–5.3)	2.5 (1.6–5.1)	2.7 (1.6–5.7)	0.308
$SvcO_2$, % (n = 323)	62 (51–71)	60 (50–70)	63 (52–71)	0.132
Laboratory profile on admission				
Haemoglobin, g/dL (n = 638)	12.7 (10.8–14.5)	12 (10.5–13.9)	13.2 (11.4–14.7)	<**0.001**
Platelet count, 10^3/mm^3 (n = 638)	217 (163–277)	195 (154–256)	235 (176–292)	<**0.001**
WBC count, 10^3/mm^3 (n = 637)	12.9 (9.1–17.5)	11.7 (8.5–15.8)	14.1 (9.5–18.4)	<**0.001**
Glycaemia, mg/dL (n = 588)	171 (132–243)	168 (130–227)	180 (134–265)	**0.032**
AST, U/L (n = 519)	101 (34–338)	64 (24–213)	137 (49–420)	<**0.001**
ALT, U/L (n = 457)	71 (27–190)	52 (24–195)	82 (34–185)	**0.037**
Bilirubin, mg/dL (n = 554)	0.8 (0.5–1.5)	1 (0.6–1.7)	0.8 (0.5–1.3)	**0.003**
GFR, ml/min (n = 620)	56 (35–80)	48 (28–68)	64 (43–89)	<**0.001**
CRP, mg/L (n = 512)	3.4 (0.8–11.9)	3.9 (1.1–12.6)	2.8 (0.5–10.2)	**0.032**
Troponin T, ng/L (n = 213)	962 (100–4798)	252 (53–2372)	1760 (176–6653)	<**0.001**
Troponin I, ng/L (n = 379)	2790 (247–36 541)	850 (90–6702)	6637 (527–95 390)	<**0.001**
NT-proBNP, ng/L (n = 189)	8423 (4218–21 456)	9403 (4956–26 996)	6000 (2685–14 968)	**0.001**
Echocardiographic findings on admission				
LVEF, % (n = 541)	25 (16–33)	23 (15–30)	25 (17–35)	0.327
LVEDV, mL (n = 276)	150 (115–200)	169 (120–248)	135 (112–180)	<**0.001**
Severe MR (n = 516)	95 (18.4)	65 (27.4)	30 (10.8)	<**0.001**
Severe TR (n = 490)	64 (13.1)	48 (21.4)	16 (6)	<**0.001**
TAPSE, mm (n = 407)	15 (12–18)	15 (12–17)	16 (12–19)	**0.012**
Pulmonary findings on admission				
Bilateral B-lines (n = 239)	208 (87)	97 (85.8)	111 (88.1)	0.538
Pleural effusion (n = 241)	98 (40.7)	44 (37.9)	54 (43.2)	0.405

Note: Data are presented as n (% on available), as mean (*SD*) and as median (IQR). Bold values represent significant P values.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBs, β-blocker; CRP, C-reactive protein; CVC, central venous catheter; CVP, central venous pressure; GFR, glomerular filtration rate; $HCO3^-$, bicarbonate ion; HR, heart rate; IQR, interquartile range; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MR, mitral regurgitation; NT-proBNP, N-terminal pro brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of arterial oxygen; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; $SvcO_2$, central venous oxygen saturation; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; WBC, white blood cell.

norepinephrine were similar between BB and no-BB groups. Levosimendan was used more frequently in patients without previous BB therapy (41.5% vs. 32.5%, P = 0.033). Sodium nitroprusside was used more frequently in BB patients (39%) as compared with BB naïve patients (30.6%, P = 0.034), and higher doses for longer duration were prescribed in the former group.

Overall, short-term MCS devices were used in 64.9% of patients, but their use was significantly lower in the BB group (57.6%) as compared with the no-BB group (70.7%, $P < 0.001$; *Table* 3).

Effect of baseline BBs use on early response to vasoactive drugs

Figures 2 and 3 show changes in MAP and HR between admission and 24 h in patients with and without pre-admission

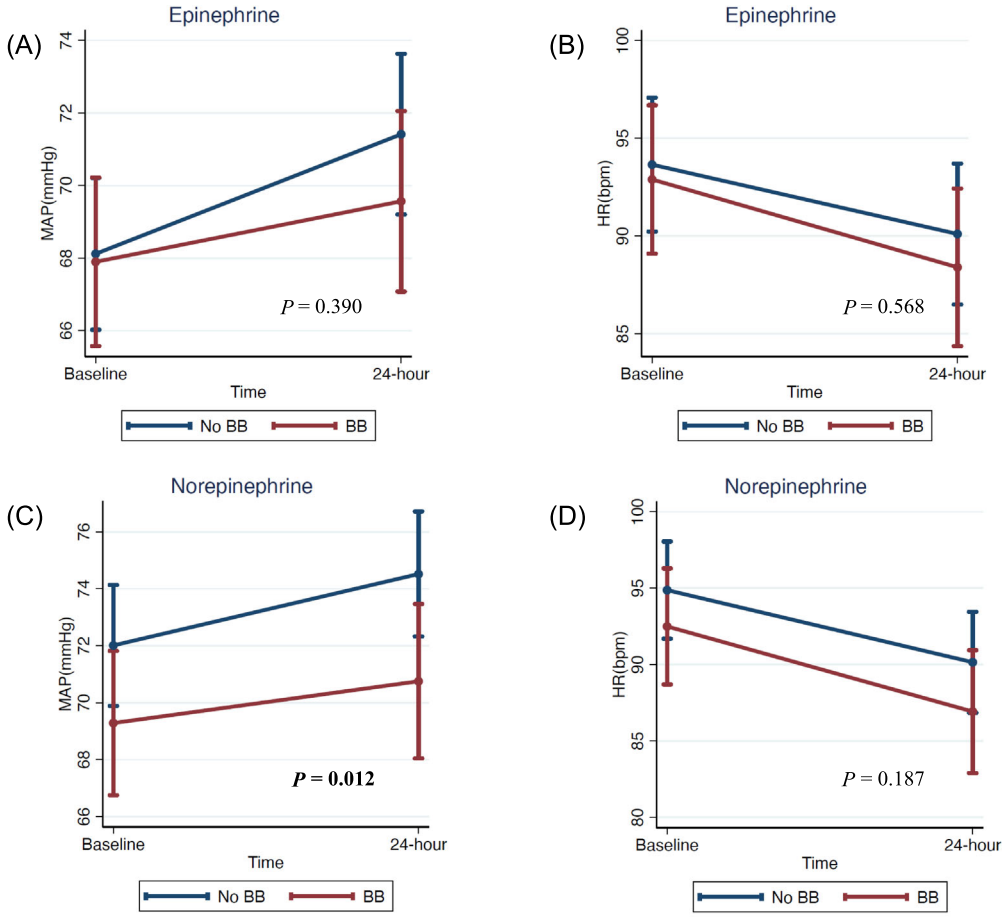
Table 3 Therapeutic management stratified according to baseline BB therapy.

	Overall cohort (*N* = 668)	Previous BB therapy (*N* = 299)	No previous BB therapy (*N* = 369)	*P* value
Vasoactive drugs				
Overall vasoactive medication (*n* = 662)	617 (93.2)	277 (93.6)	340 (92.9)	0.728
Max inotropic score	14.5 (5.7–30)	14 (5.5–28)	15 (6–31.1)	0.292
Epinephrine[a]	351 (56.9)	157 (57.7)	194 (57.1)	0.928
Max dose, γ/kg/min	0.10 (0.05–0.13)	0.10 (0.05–0.12)	0.10 (0.05–0.14)	0.986
Median time of epinephrine infusion, h	72 (24–160)	72 (25–144)	72 (24–174)	0.614
Levosimendan[a]	231 (37.4)	90 (32.5)	141 (41.5)	**0.033**
Max dose, γ/kg/min	0.10 (0.05–0.10)	0.10 (0.05–0.10)	0.10 (0.05–0.10)	0.145
Median time of levosimendan infusion, h	38 (24–48)	44 (24–48)	36 (24–48)	0.277
Norepinephrine[a]	373 (60.5)	154 (55.6)	219 (64.4)	**0.035**
Max dose, γ/kg/min	0.15 (0.10–0.30)	0.15 (0.10–0.30)	0.15 (0.10–0.30)	0.403
Median time of norepinephrine, h	48 (18–106)	48 (24–120)	48 (14–96)	0.277
Dobutamine[a]	261 (42.3)	129 (46.6)	132 (38.9)	**0.043**
Max dose, γ/kg/min	5 (3–5.6)	5 (4–6)	4.7 (3–5)	**0.014**
Median time of dobutamine infusion, h	48 (23–120)	48 (24–120)	48 (14–120)	0.564
Dopamine[a]	77 (12.5)	42 (15.2)	35 (10.3)	0.065
Max dose, γ/kg/min	4 (2.5–5)	3.2 (2.5–4.5)	4 (3–5)	0.173
Median time of dopamine infusion, h	48 (12–138)	72 (24–192)	24 (3–87)	**0.010**
Enoximone[a]	15 (2.4)	9 (3.2)	6 (1.8)	0.222
Max dose, γ/kg/min	2.79 (±1.46)	3.23 (±1.40)	2.27 (±1.48)	0.254
Median time of enoximone infusion, h	47 (±30)	33 (23)	61 (31)	0.103
Milrinone[a]	29 (4.7)	15 (5.4)	14 (4.1)	0.441
Max dose, γ/kg/min	0.49 (±0.20)	0.46 (±0.19)	0.52 (±0.22)	0.467
Median time of milrinone infusion, h	132 (48–366)	120 (96–384)	190 (18–360)	0.622
Sodium nitroprusside[a]	212 (34.4)	108 (39)	104 (30.6)	**0.034**
Max dose, γ/kg/min	0.5 (0.3–0.9)	0.6 (0.4–1.0)	0.40 (0.25–0.80)	**0.009**
Median time of sodium nitroprusside, h	96 (36–240)	120 (70–245)	72 (24–240)	**0.013**
Temporary mechanical circulatory support				
Overall tMCS (*n* = 663)	430 (64.9)	170 (57.6)	260 (70.7)	**<0.001**
IABP[b]	346 (80.5)	138 (81.2)	208 (80)	0.671
IABP duration, h	96 (48–168)	96 (48–168)	96 (48–172)	0.617
Impella[b]	94 (21.9)	32 (18.8)	62 (23.8)	0.272
Impella duration, h	117 (49–176)	129 (72–194)	96 (48–176)	0.374
ECMO[b]	128 (29.8)	48 (28.2)	80 (30.8)	0.636
ECMO duration, h	87 (48–170)	72 (46–157)	96 (48–191)	0.577
Other supports				
Need of respiratory support (*n* = 659)	503 (76.3)	210 (71.9)	293 (79.3)	**0.018**
NIV[c]	193 (38.4)	91 (43.3)	102 (34.8)	**0.036**
NIV duration, h	48 (14–96)	47 (11–96)	48 (20–96)	0.615
Mechanical ventilation[c]	359 (71.4)	140 (66.7)	219 (74.7)	0.064
Mechanical ventilation duration, h	96 (42–240)	72 (36–240)	108 (48–240)	0.089
CRRT (*n* = 658)	141 (21.4)	65 (22.3)	76 (20.8)	0.642
CRRT duration, h	86 (38–205)	96 (36–195)	76 (41–231)	0.848

Note: Data are presented as n (% on available), as mean (*SD*) and as median (IQR). Bold values represent significant *P* values.
Abbreviations: BBs, β-blocker; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; h, hour; IABP, intra-aortic balloon pump; NIV, non-invasive ventilation (both continuous positive airway pressure and bilevel ventilation); tMCS, temporary mechanical circulatory support.
[a]Percentage among patients treated with overall vasoactive medications.
[b]Percentage among patients treated with overall tMCS.
[c]Percentage among patients treated with respiratory support.

BB therapy; these changes were assessed separately in patients treated with different vasoactive drugs. Among patients treated with epinephrine, no significant differences were observed between the BB and no-BB groups in terms of change in MAP and HR (*Figure* 2A,B). No difference in HR change was observed between the BB and no-BB groups during norepinephrine infusion (*Figure* 2D). Conversely, there was a significant difference in MAP change between the two groups (*Figure* 2C; *P* = 0.012), with a higher MAP increase at 24 h among BB naïve patients as compared with patients on pre-admission BB therapy. Among patients treated with dobutamine, there were significant differences between the BB and no-BB groups for both haemodynamic parameters (*Figure* 3A,B). In detail, patients on pre-admission BB therapy had a MAP decrease, whereas MAP slightly increased in BB naïve patients (*P* = 0.023). Moreover, a smaller HR decrease was observed in the BB group as compared with the no-BB group (*P* = 0.001). During levosimendan infusion (*Figure* 3C,D), BB patients had a more pronounced MAP decrease (*P* = 0.022) and a slightly less pronounced HR decrease (*P* = 0.047), as compared with BB naïve patients.

Figure 2 Change in haemodynamic parameters between baseline and the first 24 h according to infusion of epinephrine or norepinephrine (A, MAP during epinephrine infusion; B, HR during epinephrine infusion; C, MAP during norepinephrine infusion; D, HR during norepinephrine infusion). MAP and HR values at baseline and at 24 h are reported in the BB (red) and no-BB (blue), along with 95% CI. BB, β-blocker; bpm, beats per minute; CI, confidence interval; HR, heart rate; MAP, mean arterial pressure.



Clinical outcomes

Clinical outcomes are reported in *Table* 4. Patients with previous BB therapy had longer hospital stay [23 (IQR 12–39) vs. 18 (IQR 10–30) days, P = 0.024]. Overall in-hospital mortality was 36.5%, not significantly different between the BB and no-BB groups (40.0% vs. 33.7%, P = 0.101). Similarly, early mortality evaluated at 48 h did not differ between the two groups (12.7% vs. 14.6%, P = 0.473). Overall, 27 patients (6.3%) underwent LVAD implantation, and 30 patients (4.6%) underwent heart transplantation during index admission. The proportion of patients undergoing LVAD implantation was numerically higher, and the proportion of patients undergoing heart transplantation was significantly higher in the BB group (*Table* 4).

At univariable and multivariable analyses, there was no impact of previous BB therapy on 48 h and in-hospital mortality (*Table* 5). This was also confirmed after IPTW adjustment for both 48 h mortality (IPTW-adjusted OR 1.00, 95% CI 0.59–1.69, P = 0.992) and for in-hospital mortality (IPTW-adjusted OR 1.12, 95% CI 0.74–1.70, P = 0.580). At subgroup analyses, (*Table* 6), there was no evidence of significant interaction between previous BB therapy and all the subgroups of interest (all P values for interaction $>$0.100).

Discussion

The aim of this analysis of the Altshock-2 registry was to compare the characteristics, therapeutic strategies and outcomes in CS patients with versus without pre-admission BB therapy. The main findings of our study are as follows: (1) 48 h and in-hospital mortality were similar in BB-treated and BB naïve patients; (2) prior BB therapy influenced the early haemodynamic response to vasoactive therapy evaluated at 24 hour,

Figure 3 Change in haemodynamic parameters between baseline and the first 24 h according to infusion of dobutamine or levosimendan (A, MAP during dobutamine infusion; B, HR during dobutamine infusion; C, MAP during levosimendan infusion; D, HR during levosimendan infusion). MAP and HR values at baseline and at 24 h are reported in the BB (red) and no-BB (blue), along with 95% CI. BB, β-blocker; bpm, beats per minute; CI, confidence interval; HR, heart rate; MAP, mean arterial pressure.

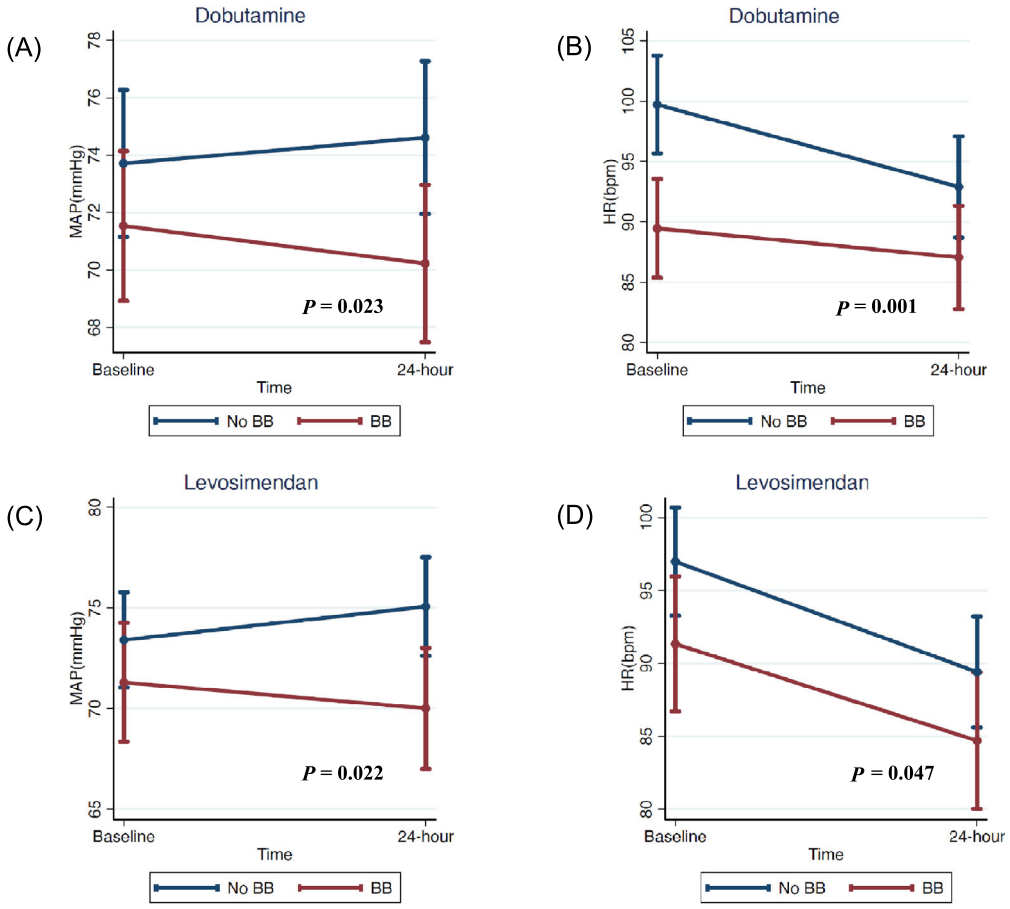


Table 4 Clinical outcomes according to baseline BB therapy.

	Overall cohort (*N* = 668)	Previous BB therapy (*N* = 299)	No previous BB therapy (*N* = 369)	*P* value
Length of hospitalization, days	20 (11–36)	23 (12–39)	18 (10–30)	**0.024**
48 h mortality	92 (13.8)	38 (12.7)	54 (14.6)	0.473
In-hospital mortality	233 (36.5)	114 (40.0)	119 (33.7)	0.101
LVAD implantation	27 (6.3)	15 (8.9)	12 (4.6)	0.078
Heart transplantation	30 (4.6)	21 (7.1)	9 (2.5)	**0.004**

Note: Data are presented as *n* (%) and as median (IQR). Bold values represent significant *P* values.
Abbreviations: BBs, β-blocker; IQR, interquartile range LVAD, left ventricular assist device.

as baseline BB had a significant impact on MAP change during norepinephrine and on MAP and HR changes during dobutamine or levosimendan.[2] BB therapy is one of the pillars of HF therapy in the presence of reduced LVEF[19]; indeed, we observed that CS patients with baseline BB had more frequently HF-CS and history of HF with lower LVEF, more HF hospitalizations and were more frequently treated with drugs for HF, implantable cardioverter defibrillator or cardiac resynchronization therapy. Although BB use in CS patients requiring inotropic support may seem counterintuitive, analyses of patients with acute HF, as well as a prospective randomized trial, have consistently shown a better outcome when BB therapy is continued or initiated in patients with acute HF.[20–22] These data seem confirmed also in patients

Table 5 Logistic regression analysis to evaluate the impact of previous BB therapy on 48 h and in-hospital mortality.

	Univariable analysis		Multivariable analysis		IPTW-adjusted analysis	
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)[a]	*P* value	IPTW-adjusted OR (95% CI)[a]	*P* value
48 h mortality	1.18 (0.75–1.84)	0.473	1.09 (0.64–1.87)	0.749	1.00 (0.59–1.69)	0.992
In-hospital mortality	1.31 (0.95–1.81)	0.101	1.32 (0.84–2.07)	0.224	1.12 (0.74–1.70)	0.580

Note: Data are presented as OR and 95% CI.
Abbreviations: BB, β-blocker; CI, confidence interval; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; GFR, glomerular filtration rate; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure; OR, odds ratio; SCAI, Society for Cardiovascular Angiography and Interventions.
[a]Covariates included in multivariable analysis are age, sex, CS aetiology, cardiac arrest at presentation, MAP at admission, lactates at admission, GFR at admission, need of MCS during hospitalization, need of vasoactive treatment during hospitalization, need of respiratory support during hospitalization, need of CRRT during hospitalization and SCAI classification at admission.

Table 6 Impact of previous BB therapy on in-hospital mortality in subgroups of interest.

Subgroups	No. of events (%) in previous BB therapy	No. of events (%) without BB therapy	Previous BB therapy vs. no BB therapy within each subgroup, OR (95% CI), *P* value	*P* value for interaction[a]
Sex subgroups				0.717
Male	85/222 (38.3)	82/264 (31.1)	1.38 (0.95–2.01), *P* = 0.095	
Female	29/63 (46)	37/89 (41.6)	1.20 (0.63–2.30), *P* = 0.585	
Age subgroups				0.583
≥75 years	39/78 (50)	39/82 (47.6)	1.10 (0.59–2.05), *P* = 0.758	
<75 years	75/206 (36.4)	80/270 (29.6)	1.36 (0.93–2.00), *P* = 0.118	
CS aetiology subgroups				0.321
ACS-CS	41/102 (40.2)	80/218 (36.7)	1.16 (0.72–1.88), *P* = 0.548	
Non ACS-CS	73/183 (39.9)	39/135 (28.9)	1.63 (1.02–2.63), *P* = **0.043**	
CS presentation subgroups				0.334
Cardiac arrest	23/55 (41.8)	39/96 (40.6)	1.05 (0.54–2.06), *P* = 0.886	
Non-cardiac arrest	87/209 (41.6)	75/237 (31.6)	1.54 (1.05–2.27), *P* = **0.029**	
SCAI subgroups				0.726
A–B–C	58/183 (31.7)	44/208 (21.2)	1.73 (1.10–2.73), *P* = **0.018**	
D–E	50/78 (64.1)	66/122 (54.1)	1.52 (0.85–2.72), *P* = 0.163	
tMCS subgroups				0.353
Yes	61/163 (37.4)	85/250 (34)	1.16 (0.77–1.75), *P* = 0.477	
No	53/120 (44.2)	34/103 (33)	1.61 (0.93–2.77), *P* = 0.089	
Vasoactive drugs subgroups				0.302
Yes	111/265 (41.9)	113/325 (34.8)	1.35 (0.97–1.89), *P* = 0.077	
No	2/18 (11.1)	5/26 (19.2)	0.53 (0.09–3.06), *P* = 0.474	
Respiratory support subgroups				0.286
Yes	90/201 (44.8)	99/285 (34.7)	1.52 (1.05–2.20), *P* = **0.026**	
No	23/78 (29.5)	20/67 (29.9)	0.98 (0.48–2.01), *P* = 0.962	
CRRT subgroups				0.149
Yes	37/64 (57.8)	46/74 (62.2)	0.83 (0.42–1.65), *P* = 0.603	
No	75/216 (34.7)	73/277 (26.4)	1.49 (1.01–2.19), *P* = **0.045**	
Lactates subgroups				0.442
≥2 mmoL/L	77/171 (45)	87/227 (38.3)	1.32 (0.88–1.97), *P* = 0.179	
<2 mmoL/L	34/105 (32.4)	24/112 (21.4)	1.76 (0.96–3.23), *P* = 0.070	
GFR subgroups				0.398
≥30 mL/min	67/196 (34.2)	85/287 (29.6)	1.23 (0.84–1.82), *P* = 0.289	
<30 mL/min	42/76 (55.3)	22/37 (59.5)	0.84 (0.38–1.87), *P* = 0.673	
MAP subgroups				0.259
≥60 mmHg	81/206 (39.3)	83/273 (30.4)	1.48 (1.01–2.17), *P* = **0.042**	
<60 mmHg	30/69 (43.5)	30/69 (43.5)	1.00 (0.51–1.50), *P* = 1.00	

Note: Data are presented as HR and 95% CI. Bold values represent significant *P* values.
Abbreviations: ACS, acute coronary syndrome; BB, β-blocker; CI, confidence interval; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; GFR, glomerular filtration rate; HR, hazard ratio; MAP, mean arterial pressure; tMCS, temporary mechanical circulatory support.
[a]*P* value for interaction = *P* value for interaction between patients with previous BB therapy versus no BB therapy and the subgroup of interest.

with acute HF requiring inotropic support with a lower rate of vasopressor/inotropic-induced ventricular arrhythmias and especially mortality at 31 days in patients on BBs.[5,6] In recent years, evidence about BB use has also accumulated for patients with CS. In a subgroup analysis of DOREMI,[9] Di Santo et al. reported fewer early deaths (within 48 h) in patients

treated with BB [crude relative risk (RR) 0.41, 95% CI 0.18–0.95, $P = 0.03$] while this finding was not confirmed through the entire hospitalization with a non-significant difference regarding in-hospital mortality in patients with versus without BB (crude RR 0.86, 95% CI 0.61–1.23, $P = 0.41$). However, in this analysis it was not known whether BB therapy was maintained or discontinued after hospital admission.

In an analysis of the FRENSHOCK registry, Cardelli et al. compared patients who maintained or discontinued BB, but also assessed the impact of an early (within 24 h) initiation of BB therapy in patients with CS.[10] Patients receiving BB at 24 h had a non-significant trend towards lower all-cause mortality at 1 month (adjusted HR 0.61, 95% CI 0.34–1.1, $P = 0.10$). Moreover, compared with patients who discontinued BBs at 24 h, those who did not discontinue BB had lower 1 month mortality (adjusted HR 0.43, 95% CI 0.2–0.92, $P = 0.03$). Lastly, an early introduction of BB therapy after CS was not associated with 1 month mortality (adjusted HR 0.96, 95% CI 0.38–2.4, $P = 0.93$).

In contrast with the DOREMI analysis, we did not find an initial protective action of BB therapy as early mortality (at 48 h) was similar in the BB and no-BB groups (12.7% vs. 14.6%, $P = 0.473$). Similarly to previous analyses by Di Santo et al. and Cardelli et al., in our study in-hospital death was not different between the two groups (40.0% vs. 33.7%, $P = 0.101$). Of note, prior BB therapy was also associated with a lower risk of long-term mortality in a previous study on miscellaneous CS.[8] Taken together, available studies seem to confirm the lack of a significant impact of previous BB therapy on in-hospital mortality in patients with CS, that is reassuring since a non-negligible proportion of CS patients are treated with BB prior to hospital admission, especially those with pre-existing HF. In our study, we also did not find a significant interaction between previous BB therapy and several subgroups of interest based on sex, age or other key variables related to clinical presentation. Regretfully, we do not have data regarding interruption or prosecution of BB therapy in our registry.

Because previous BB therapy may alter the haemodynamic response during infusion of vasoactive drugs,[4,23] we also evaluated the haemodynamic response to different vasoactive therapies in patients with or without baseline BB. In our analysis, levosimendan was more used in BB naïve patients, while dobutamine was more used in patients with prior BB therapy. Evaluating the impact of BB on the early (24 h) haemodynamic response to vasoactive drugs infusion, we observed significant differences between the BB and no-BB groups in terms of changes in MAP and HR during dobutamine infusion, with BB patients showing a MAP decrease while this parameter slightly increased in BB naïve patients, and with a less pronounced HR decrease in the BB group. Slight differences in MAP and HR changes between patients with versus without baseline BB were also observed during levosimendan infusion, as well as a higher MAP increase was observed among BB naïve patients during norepinephrine infusion. The impact of baseline BB on the early MAP response to norepinephrine and dobutamine may be secondary to their competitive effect on adrenergic receptors, thus influencing the catecholamine-related increase in CO and MAP. Interestingly, in a previous small trial enrolling 227 patients with CS, those receiving BB had a lower HR when vasopressors/inotropes were at maximum doses and also lower systolic and diastolic blood pressure.[7] Analysing individual inotropes in the DOREMI trial, there was no difference between the BB and no BB groups with respect to HR and MAP variations in the first 48 h during dobutamine infusion. In the Levosimendan Infusion versus Dobutamine (LIDO) study, the use of BB had significant effects on CO increase because BB attenuated the effect of dobutamine on CO, but did not reduce that of levosimendan.[24]

Of note, the pharmacological properties of different BB generations may impact on the haemodynamic response to vasoactive agents. In fact, administering dobutamine in patients previously exposed to metoprolol tartrate or carvedilol markedly attenuated its effects on invasive haemodynamic parameters (including PAP and wedge pressure decline), especially with carvedilol.[4] However, the type of BB used was not assessed in our study nor in the other analyses focused on CS patients.

In our study, the lower use of MCS and the higher rate of heart transplantation observed in the BB group may reflect differences in patient profiles at baseline. Patients with previous BB therapy had a higher prevalence of chronic HF and more advanced structural heart disease. This may be reflected in a larger percentage of those already on the waiting list for heart transplantation at the time of admission. Therefore, these patients may have been considered less suitable for temporary MCS due to their advanced disease or this may have favoured an early transition to durable therapies such as heart transplantation. Additionally, the lower frequency of cardiac arrest at presentation among BB users may have influenced the clinical decision-making regarding the need for immediate short-term MCS.

Limitations

Our study has several limitations. First, the present registry represents a real-world picture of contemporary management of CS. However, patients were treated according to protocols that may vary between enrolling centres, thus potentially creating some bias in data interpretation. Furthermore, some variables had a non-negligible number of missing values, which could have influenced the study results. Second, we reported the impact of BB as a class effect because we did not have data on BB type and dose, although the actual BB type may have an impact when evaluating the response to vasoactive therapy. Third, although it is very

likely that background BB therapy was interrupted on admission due to CS in order to avoid its negative inotrope effect, this detail was not specifically collected as well as the timing of BB interruption. Fourth, although we adjusted the impact of BB on mortality for relevant covariates including CS aetiology, the different proportion of patients with history of HF and HF-CS in the BB versus no-BB groups still represents an important confounder and might have influenced the study findings. Finally, in the analysis on the changes in MAP and HR during vasoactive therapy in response to the presence or absence of BB therapy, some confounding factors such as the use of MCS could have influenced the findings. Furthermore, we could not evaluate the impact on other invasive haemodynamic parameters (such as CO) because PAC was used in a minority of patients.

Conclusions

In a contemporary, prospective, real-world, multicentre cohort of patients with CS, baseline BB therapy influenced the haemodynamic response to vasoactive drugs, such as dobutamine and norepinephrine, but was not associated with early mortality at 48 h or in-hospital mortality. These findings potentially supporting the safety of prior BB use in this high-risk population are, however, hypothesis-generating only. Future dedicated studies should explore whether the maintenance or early reintroduction of BB after stabilization could improve outcomes and assess the role of specific BB subtypes in modulating the haemodynamic responses and clinical trajectories in CS.

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Conflict of interest statement

Dr. Pagnesi has received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. Dr. Sacco and Dr. Morici received institutional grant support from Getinge Global US; Dr. Sacco received speaker honoraria from AstraZeneca and Menarini. Dr. Marini received consulting/speaker honoraria from AstraZeneca, Orion and Abiomed. Dr. Pappalardo is a consultant for Abiomed. Dr. Metra has received consulting honoraria as a member of trial committees or advisory boards for Abbott Vascular, Actelion, Amgen, Bayer, Edwards Therapeutics, Servier, Vifor Pharma and Windtree Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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