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ORIGINAL RESEARCH

Early Intra-Aortic Balloon Support for Heart Failure-Related Cardiogenic Shock

A Randomized Clinical Trial

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ABSTRACT

BACKGROUND The impact of intra-aortic balloon pump (IABP) on survival and successful bridging to heart replacement therapies (HRT) in patients with heart failure–cardiogenic shock (HF-CS) remains unclear.

OBJECTIVES The purpose of this study was to evaluate the effect of early IABP use vs standard care on 60-day survival or successful bridging to HRT.

METHODS In the multicenter, prospective Altshock-2 (Study on Early Intra-aortic Balloon Pump Placement in Acute Decompensated Heart Failure Complicated by Cardiogenic Shock), patients with Society for Cardiovascular Angiography and Interventions stage B, C, or D HF-CS and suitable for HRT were randomized to receive early IABP plus standard care (IABP group) or standard care (control group). The primary endpoint was survival or successful bridge to HRT at 60 days. Secondary endpoints included overall survival, maximum inotropic score, and maximum sequential organ failure assessment score.

RESULTS In total, 53 patients were randomized to IABP and 48 to standard care. Patients were Society for Cardiovascular Angiography and Interventions stage B (28%, n = 28), C (57%, n = 56), and D (15%, n = 16). At the prespecified interim analysis, the trial was stopped because of futility. The primary endpoint was reached in 43 patients (81%) in the IABP group and 36 patients (75%) in the control group (HR: 0.72; 95% CI: 0.31-1.68; $P = 0.45$). A total of 37 patients (37%) underwent HRT within the 60-day follow-up. Four patients were escalated in the study group (7.5%) vs 2 in the control group (4.2%). Additionally, 6 patients (13%) initially assigned to standard care crossed over to IABP. Complications were comparable between groups.

CONCLUSIONS Routine early IABP plus standard care, compared with standard care, did not significantly improve survival or successful bridging to HRT in patients with HF-CS. (Study on Early Intra-aortic Balloon Pump Placement in Acute Decompensated Heart Failure Complicated by Cardiogenic Shock [Altshock-2]; NCT04369573)
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CS = cardiogenic shock

HF = heart failure

HRT = heart replacement therapies

HTX = heart transplant

IABP = intra-aortic balloon pump

LVAD = left ventricular assist device

PP = per protocol

SCAI = Society for Cardiovascular Angiography and Interventions

tMCS = temporary mechanical circulatory support

Cardiogenic shock (CS) remains a clinical challenge with in-hospital mortality reaching up to 50%.[1] Previous studies have primarily examined CS in acute coronary syndrome (ACS),[2-6] but randomized trials on temporary mechanical circulatory support (tMCS) in CS unrelated to ACS are lacking. The domain of heart failure (HF)-related CS has been recognized as a growing space in this context; these patients represent a unique physiologic phenotype compared with ACS patients, which may lead to a different response to device therapy.[7,8] Prior evidence emphasized that intra-aortic balloon pump (IABP) is not recommended for patients with ACS-CS, but it is associated with a high likelihood of bridge to durable left ventricular assist device (LVAD) or heart transplant (HTX) without the need for escalation to more potent tMCS devices, when implanted in HF-CS patients.[9-11] The routine use of IABP in ACS with CS and without mechanical complication has been downgraded to Class IIIb (not recommended) in the recent guidelines on ST-segment elevation ACS of the European Society of Cardiology.[12] However, patients with HF-CS differ significantly, making it questionable to extrapolate IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) data to non-ACS-related CS in HF patients. In a small randomized trial exploring the role of IABP compared with inotropes in decompensated HF and low output state, an improvement in mixed-venous oxygen saturation was reported, along with more patients bridged to heart transplant or LVAD.[11]

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Moreover, as a longstanding practice, the procedure is safe, less invasive, and has a lower impact on coagulation and blood rheology compared with other short-term MCS devices.[13-17] Therefore, a prospective randomized controlled trial was prompted to evaluate the early use of IABP in HF-CS patients. We designed Altshock-2 (Study on Early Intra-aortic Balloon Pump Placement in Acute Decompensated Heart Failure Complicated by Cardiogenic Shock)[18] to test the hypothesis that routine early IABP implantation in HF-CS results in a lower mortality and higher successful bridge to heart replacement therapies (HRT) (HTX or durable LVAD) over standard care.

METHODS

STUDY DESIGN AND PARTICIPANTS. Altshock-2 is a national, multicenter, randomized, open-label trial conducted in Italy (NCT04369573) that is part of the Italian Altshock-2 program (national trial on HF-CS and national registry of all consecutive CS patients; NCT04295252). This study was approved by the local ethics committee of Milano Area 3 of the ASST Grande Ospedale Metropolitano Niguarda and by the ethics committee at each participating center (Supplemental Appendix, Supplemental Table 1). The trial was conducted in compliance with the ethical principles based on the Helsinki Declaration. Written informed consent was obtained from all patients before random assignment. However, in accordance with EU Regulation 536/2014, in the case of potentially eligible subjects unable to express their consent ("noncompetent" patients) at the time of enrollment, each study site could decide whether to use deferred consent (procedure described in the protocol section of the Supplemental Appendix) to enroll the patient. The acceptance and usage of the deferred consent procedure was facultative for each study site and had to be approved by its ethics committee. The CONSORT guidelines were followed for reporting the findings[19] (**Figure 1**). The design of the trial has been previously published, and the protocol is available in the Supplemental Appendix.[18] A data and safety monitoring board (DSMB) monitored the trial, and an independent clinical event classification committee was established for a blinded assessment of clinical events.

In the initial protocol, patients aged 18 to 75 years with hypotension and hypoperfusion were included according to the standard CS definition.[18] An age limit of 75 years was set for patients to be considered for HRT. On December 16, 2022, a new amendment was approved that made HF-CS patients with Society for Cardiovascular Angiography and Interventions (SCAI) stages B to D eligible according to the updated

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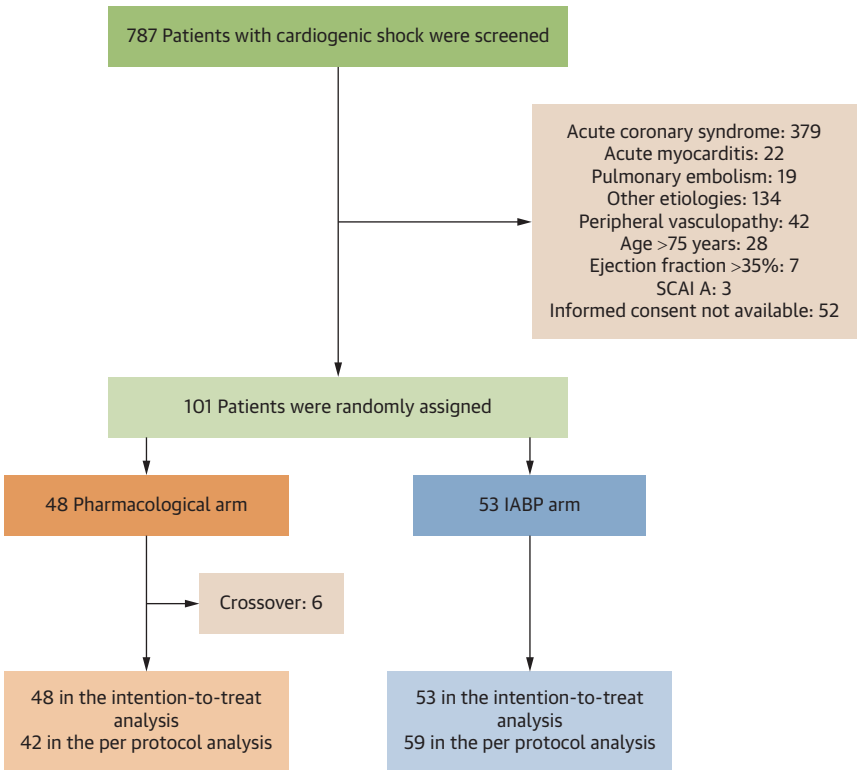
FIGURE 1 Study Flowchart: CONSORT Diagram



Other etiologies include a miscellanea of several causes such as cardiac tamponade, myocardial infarction with nonobstructive coronary arteries, severe cardiac valve regurgitation or stenosis, endocarditis, arrhythmic storms, iatrogenic complications during percutaneous or surgical operations, right ventricle failure after transcatheter edge-to-edge repair, and septic shock. IABP = intra-aortic balloon pump; SCAI = Society for Cardiovascular Angiography and Interventions.

Cardiogenic Shock Working Group (CSWG) definition.[20] The inclusion criteria were modified with a protocol amendment following the updated SCAI criteria, which recognized that patients with SCAI stage B shock represent a particularly vulnerable subset who may be inadvertently overlooked because of the absence of hypotension. Consequently, they are at risk of delayed intervention, potentially progressing to more severe stages of shock. This expanded definition appeared pertinent especially in HF-related shock, condition in which patients frequently present with congestion. If left unaddressed, congestion can exacerbate cardiac output impairment and systemic hypoperfusion, ultimately culminating in end-organ dysfunction.

Patients were excluded if any of the following criteria were detected: septic shock with evident septic focus; severe peripheral vascular disease; CS secondary to cardiac and noncardiac surgery; acute myocardial infarction within 1 month; suspected or documented myocarditis; pulmonary embolism; chronic end-stage organ dysfunction that would preclude HTX/durable LVAD; ominous prognosis (life expectancy <1 year); any other significant disease or disorder which, in the opinion of the investigator, may have either put the participant at risk because of participation in the trial or influenced the result of the trial or the participant's ability to participate in the trial; pregnant or lactating women; or women planning pregnancy during the course of the trial. Inclusion and exclusion criteria are detailed in the Supplemental Appendix and Supplemental Table 2.

RANDOMIZATION AND MASKING. Eligibility was evaluated by the attending physician after the first visit and after confirmation of the diagnosis. The patient, properly informed about the study, was able to decide to sign the informed consent and the privacy form. Patients with HF-CS were randomized 1:1 to early vs standard care with vasoactive agent. Patients underwent central randomization using a permuted block randomization list with varying size, performed with the use of a web-based

randomization system, developed by Aleph SRL using LAMP (Linux/Apache/MariaDB/PHP) servers and HTML/CSS/PHP/SQL coding languages. Because of the nature of the procedure, random assignment was not blinded for the physicians and the staff.

PROCEDURES. HF-CS patients admitted between June 30, 2020, and October 23, 2024, were included. Inotropes were allowed to a maximum inotropic score of 20, then escalation was mandatory. In patients assigned to receive the IABP, the device was to be placed immediately after randomization. Implantation was performed according to the clinical setting (either bedside or in the cardiac catheterization laboratory) following the institutional standard operating procedures. The pump was used with the auto pilot system as primary choice; whichever technology was available (Arrow or Getinge) was used. The catheter size was chosen according to patient height, as per instructions for use. A Swan-Ganz catheter was recommended but not mandatory. Anticoagulation for patients randomized to IABP arm required prophylactic doses of heparin, unless otherwise necessary. Therapeutic management after enrollment, with specific reference to drugs, dosage titration, and IABP weaning, complied with local clinical practice suggesting limiting the dose and the duration of vasoactive medications as tissue perfusion is restored, to decrease myocardial oxygen consumption and the risk of arrhythmias. Escalation to mechanical ventilation and other tMCS was considered in patients who did not reach 5 of 8 of the following goals by 8 hours from enrollment: heart rate <100 beats/min, mean arterial pressure >65 mm Hg, oxygenation saturation from mixed venous blood >60%, PaO_2 >60 mm Hg, lactates <3 mmol/L, wedge pressure <18 mm Hg or E/E' <14, inotropic score <20, and diuresis >0.5 mL/kg/h. Weaning from inotropic and vasoactive agents was strongly suggested in the IABP arm if clinical stabilization was achieved. Crossover was discouraged.

OUTCOMES. The primary endpoint was the effect of early IABP vs standard care according to local practice on 60-day survival or 60-day successful bridge to HRT, defined as the number (percentage) of patients who survived with native heart recovery or after being bridged to HRT by the end of the follow-up period.

Secondary endpoints were maximum inotropic score, maximum duration of inotropic therapy, and maximum sequential organ failure assessment score.

The safety endpoints were the occurrence of bleeding events (Bleeding Academic Research Consortium ≥3), the occurrence of vascular complications, and the occurrence of systemic and cerebral embolic phenomena.

EARLY INTERRUPTION OF TRIAL. The first patient was enrolled on June 30, 2020. The independent DSMB oversaw patient safety in the trial and performed a formal interim analysis after the enrollment and complete follow-up of 100 patients. The DSMB conducted a preplanned interim analysis of the trial data; the results were thoroughly reviewed in teleconference meetings on September 24, 2024, and October 7, 2024. Analysis of the results by the DSMB suggested that the experimental treatment was not providing any meaningful benefit compared with the control. It also appeared quite unlikely that the trial would meet its primary endpoint, even if recruitment (which appeared also to show a declining trend) continued to completion. Thus, the members of the DSMB unanimously recommended stopping the trial on October 9, 2024 for futility, to avoid wasting resources and exposing participants to unnecessary interventions.

STATISTICAL ANALYSIS. The proportion estimated to reach the primary endpoint, ie, survival at 60 days or 60-day successful bridge to HRT, was estimated to be 0.75 of the IABP group and 0.55 of the standard group. With a type I error α-value set to 0.05 and a power 1-β set to 0.8, a total of 200 subjects should have been enrolled in the trial, 100 of whom would have been randomized to IABP and 100 to standard care. The trial was designed to be a group sequential design with one interim analysis. This means that a preliminary assessment of the trial for efficacy was performed after 100 of 200 planned participants (50 randomized to IABP and 50 to standard reference management) had completed the trial.

The following populations were defined and used in the analysis and/or presentation of the trial data: intent-to-treat (ITT) population, with treatment classification for ITT analysis was based on the randomized treatment; and per-protocol (PP) population, with the PP population defined as all ITT patients assigned to IABP without major protocol violations. Specifically, subjects were excluded from the PP population for inclusion/exclusion criteria violations. The PP definition for each patient was finalized before database lock and study unblinding. The primary and secondary efficacy analyses were based on the ITT population. Analyses based on the PP population were considered supportive. All protocol-defined endpoints were measured from the time of randomization.

Descriptive statistics of baseline characteristics of patients randomized to IABP and those randomized to the standard care group were reported. Continuous variables were summarized by median (Q1-Q3) and categorical variables as frequencies and percentages. Comparisons of in-hospital management therapies

and at-discharge prescriptions across study groups were carried out using the Pearson chi-square test, or the Fisher exact test when expected frequencies were lower than 5. The primary endpoint, 60-day survival or successful bridge to HRT, was analyzed in the ITT population and represented in a Kaplan-Meier plot. After testing the hazard proportionality assumption, an unadjusted Cox proportional-hazards model was fitted to summarize the effect of the intervention at 60 days on the primary endpoint. Secondary endpoints and adverse events were compared between patients randomized to IABP and those randomized to the standard care group using chi-square or Fisher exact test for categorical variables and Student's *t*-test for continuous variables. Subgroup analyses were performed according to age, sex, time between symptom onset and coronary care unit arrival, mean arterial pressure, arterial lactate level, left ventricular ejection fraction, and SCAI classification. The type I error (α) was set at 0.05. The analysis was performed using R software version 4.4.1 (R Foundation).

RESULTS

PATIENTS. From June 2020 through October 2024, a total of 787 patients underwent screening and 101 were enrolled at 7 centers. Informed consent was obtained from all patients before randomization. The final analysis included 53 patients in the IABP group and 48 in the standard care group (Figure 1).

Patients' characteristics at baseline appeared to be well balanced between the groups (Table 1). The median age of the patients was 60 years (Q1-Q3: 54-65 years), and 80% were men. The median arterial lactate level was 1.85 mmol/L (Q1-Q3: 1.15-2.45 mmol/L), median systolic blood pressure was 90 mm Hg (Q1-Q3: 85-100 mm Hg), and median left ventricular ejection fraction was 20% (Q1-Q3: 15%-24%). Median left ventricular end-systolic volume was 180 mL (Q1-Q3: 129-226 mL), whereas end-diastolic volume was 214 mL (Q1-Q3: 175-294 mL); median left atrial volume was 107 mL (Q1-Q3: 87-145 mL). Almost 60% of the patients had a non-ischemic cardiomyopathy. A total of 30 patients (30%) had cardiac resynchronization therapy and 62 (61.3%) had an implantable cardioverter-defibrillator. Medications at admission are reported in the Supplemental Appendix and Supplemental Table 3.

Two-thirds of patients were admitted in SCAI C stage and almost 30% in SCAI B. Before the December 2022 amendment, 12 patients without hypoperfusion were included as a protocol deviation. A total of 71 patients (70.3%) had right ventricular failure upon

TABLE 1 Demographic and Clinical Characteristics of the Patients at Baseline and Timing of Randomization

	SoC (n = 48)	IABP + SoC (n = 53)
Age, y	60 (55-64)	60 (51-65)
Male	41 (85)	40 (75)
BMI, kg/m^2	25.4 (21.9-27.6)	25.3 (22.5-28.9)
Medical history		
Hypertension	19 (40)	16 (30)
Dyslipidemia	29 (60)	21 (40)
Diabetes	11 (23)	15 (28)
Atrial fibrillation	20 (42)	22 (42)
Previous stroke/TIA	4 (8.3)	5 (9.4)
Peripheral arterial vasculopathy	5 (10)	1 (1.9)
Chronic kidney disease	24 (50)	23 (43)
Asthma/COPD	5 (10)	6 (11)
Thyroid disease	13 (27)	13 (25)
History of malignancy	6 (13)	7 (13)
Device therapy		
CRT[a]	16 (33)	14 (27)
ICD	30 (63)	32 (60)
Baseline characteristics		
SBP, mm Hg	87 [81-95]	90 [85-100]
DBP, mm Hg	55 [50-60]	60 [50-68]
MAP, mm Hg	67 [59-71]	69 [62-79]
CVP, mm Hg	13 [8-18]	11 [7-17]
HR, beats/min	93 [78-100]	95 [80-111]
Arterial lactate levels, mmol/L	1.70 [1.10-2.25]	1.95 [1.30-2.55]
Creatinine, mg/dL	1.50 [1.10-2.70]	1.40 [1.20-1.80]
AST, U/L	22 [15-95]	34 [20-75]
ALT, U/L	27 [14-97]	37 [22-66]
Left ventricular ejection fraction, %	20 [15-25]	18 [15-23]
LVEDV, mL	219 [161-307]	214 [186-270]
LVESV, mL	193 [103-243]	177 [143-203]
LAV, mL/m^2	108 [89-126]	107 [87-155]
Presenting with cardiac arrest	0 (0)	0 (0)
Signs of hypoperfusion		
SvO_2 <60%	36 (75)	34 (64)
Oliguria <0.5 mL/kg/h	9 (19)	15 (28)
Arterial lactates >2 mmol/L	20 (42)	24 (45)
Etiology		
Nonischemic	26 (54)	36 (68)
Ischemic	22 (46)	17 (32)
SCAI-CSWG stage at admission		
B	16 (33)	12 (23)
C	26 (54)	31 (58)
D	6 (13)	10 (19)
SOFA score	6 (4-8)	6 (4-7)
Inotropic score	5 (3-5)	4 (3-5)
Transfer from		
Same hospital	29 (63)	35 (67)
Other hospital	17 (37)	17 (33)
Timing of randomization		
Time between symptoms onset and arrival at CCU, h	8 (4-24)	8 (3-24)
Time between CCU arrival and enrollment, h	2 (1-14)	3 (1-5)

Values are median (Q1-Q3), n (%), or mean [range]. [a]9 patients in the standard care group and 9 in the IABP group had cardiac resynchronization therapy (CRT) defibrillators.

ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; BP = blood pressure; CCU = coronary care unit; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CVP = central venous pressure ICD = implantable cardioverter-defibrillator; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MAP = mean arterial pressure; SCAI-CSWG = Society for Cardiovascular Angiography and Interventions Cardiac Shock Working Group; SoC = standard of care; SOFA = sequential organ failure assessment. SvO_2 = oxygenation saturation from mixed venous blood; TIA = transient ischemic attack.

TABLE 2 In-Hospital Management of Cardiogenic Shock and At Discharge Prescriptions

	SoC (n = 48)	IABP + SoC (n = 53)	*P* Value
Inotropes			
Any inotrope	33 (69)	34 (64)	0.63
Epinephrine	30 (63)	30 (57)	0.99
Norepinephrine	5 (10)	4 (7.5)	0.99
Dobutamine	19 (40)	24 (45)	0.56
Dopamine	7 (15)	6 (11)	0.62
Enoximone	1 (2.1)	0 (0)	0.48
Milrinone	6 (13)	4 (7.5)	0.51
Levosimendan	7 (15)	9 (17)	0.74
Vasodilators			
Any vasodilator	31 (65)	37 (70)	0.58
Sodium nitroprusside	29 (60)	36 (68)	0.43
Nitroglycerin	4 (8.3)	4 (7.5)	0.99
Respiratory support			
Mechanical ventilation	21 (44)	18 (34)	0.31
Noninvasive ventilation	18 (38)	15 (28)	0.32
Other procedures			
Swan-Ganz catheter	20 (42)	24 (45)	0.71
Medical treatment at discharge[a]			
Beta-blockers	16 (44)	18 (42)	0.82
ACE inhibitors	5 (15)	5 (12)	0.65
ARBs	6 (19)	5 (13)	0.54
Sacubitril/valsartan	12 (33)	17 (40.5)	0.49
Diuretics	24 (77)	29 (69)	0.56
Potassium-sparing diuretics	24 (70)	21 (50)	0.15
SGLT2 inhibitors	13 (38)	11 (25)	0.19
Insulin	6 (17)	7 (16)	0.66
$P2Y_{12}$ inhibitors	1 (2.8)	3 (7)	0.45
Anticoagulants	21 (60)	24 (56)	0.64

Values are n (%). [a]Among survivors.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; SGLT2 = sodium-glucose cotransporter 2.

admission (defined as tricuspid annular plane systolic excursion ≤17 mm).

Details of in-hospital management are provided in **Table 2**. Swan-Ganz catheter was used in 44 patients (43%). Use of any inotropic agent and vasodilators were comparable between the 2 arms. Anticoagulation was recommended for IABP, but these patients usually have multiple factors driving the need for antithrombotic therapies beyond the specific IABP protocol; indeed, 78 patients (77.2%) were on antithrombotic therapy with antiplatelets or anticoagulants on admission and details are provided in the Supplemental Appendix and Supplemental Table 3.

Among the 53 patients assigned to the IABP group, the device was placed successfully in all cases (100%). Additionally, 6 patients (13%) initially assigned to standard care crossed over to IABP. In the IABP group, 4 patients (7.5%) required escalation to another MCS compared with 2 patients (4.2%) in the standard care group.

PRIMARY AND SECONDARY ENDPOINTS. The primary endpoint, 60-day survival or 60-day successful bridge to HRT, occurred in 43 patients (81%) in the IABP group and 36 patients (75%) in the standard care group (HR: 0.72; 95% CI: 0.31-1.68; $P = 0.45$) (**Figure 2**). Causes of death are reported in Supplemental Table 4. Similar results were achieved in the PP analysis that considered 6 patients escalated to IABP: the primary endpoint was 78% in the IABP group compared with 79% in the standard care group ($P > 0.9$), with an HR of 0.99 (95% CI: 0.42-2.31).

In total, 18 patients (18%) underwent HTX and 19 (19%) patients LVAD. Overall, 16 patients in the standard care group (33%) and 21 (39.6%) in the IABP group were bridged to HRT, with neutral effect of the IABP intervention ($P = 0.52$). Death after HTX occurred in 4 patients and after LVAD in 3 patients.

The results of subgroup analyses are shown in **Figure 3**.

The secondary endpoint analysis is reported in **Table 3**. There were no statistically significant differences in the secondary endpoints (maximum inotropic score, maximum sequential organ failure assessment score, treatment escalation, and adverse events).

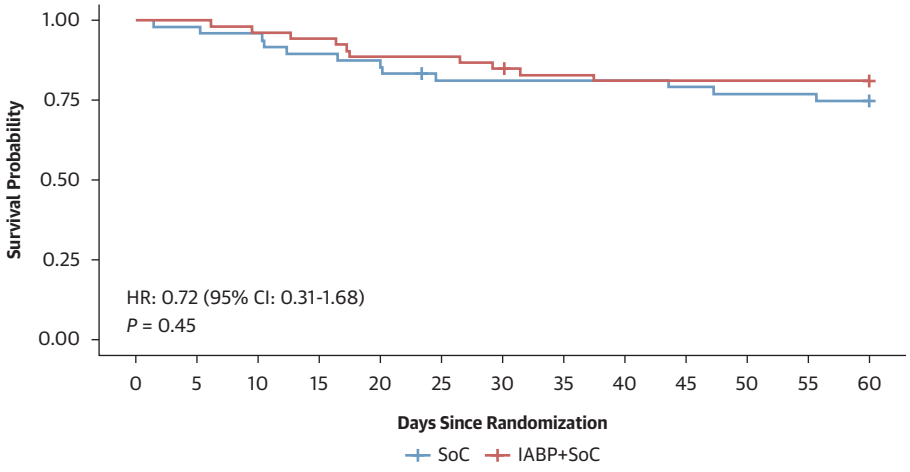
Renal replacement therapy was required in 3 patients in the standard care group (6.2%) and in 1 patient in the IABP group (1.9%; $P = 0.26$).

DISCUSSION

In this randomized trial involving patients with HF-CS, early use of IABP was not associated with improved survival or successful bridge at 60 days compared with standard care (**Central Illustration**).

Despite a substantial increase in the use of IABP over the past decade for these patients, its effectiveness remains controversial. The IABP, which was developed >5 decades ago, was the first device developed for mechanical support of circulation in patients with CS, often when caused by ACS. The early and persistent enthusiasm for its use was on the basis of nonrandomized trials and registry data.[8-17] In recent years, multiple studies have failed to demonstrate the benefit of routine IABP use in patients with acute myocardial infarction. The randomized IABP-SHOCK II trial[3] and the CRISP AMI (Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction) trial[21] failed to show any survival or infarct size-related benefits for IABP both in patients with acute myocardial infarction and CS and in patients without CS, respectively. Moreover, the

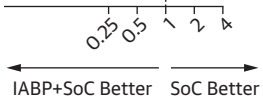
FIGURE 2 Kaplan-Meier Curve for 60-Day Survival or Successful Bridge to HRT



HRT = heart replacement therapy; IABP = intra-aortic balloon pump; SoC = standard of care.

FIGURE 3 Subgroup Analysis of the Primary Endpoint of 60-Day Survival or Successful Bridge to HRT

Subgroup	IABP+SoC	SoC	HR (95% CI)	*P* Value	Interaction *P* Value
Overall	10/53 (19%)	12/48 (25%)	0.72 (0.31-1.68)	0.45	
Age, y					0.25
≤60	2/26 (8%)	5/23 (22%)	0.33 (0.06-1.72)	0.19	
>60	8/27 (30%)	7/25 (28%)	1.02 (0.37-2.82)	0.97	
Sex					0.32
F	1/13 (8%)	2/7 (29%)	0.23 (0.02-2.53)	0.23	
M	9/40 (22%)	10/41 (24%)	0.91 (0.37-2.24)	0.83	
Time Between Symptoms Onset and Arrival at CCU, h					0.90
≤7	4/22 (18%)	5/22 (23%)	0.78 (0.21-2.92)	0.72	
>7	5/23 (22%)	7/23 (30%)	0.70 (0.22-2.20)	0.54	
MAP, mm Hg					0.91
≤70	8/29 (28%)	9/33 (27%)	1.04 (0.40-2.69)	0.94	
>70	2/19 (11%)	1/11 (9%)	1.30 (0.12-14.40)	0.83	
Arterial Lactate Levels, mmol/L					0.25
≤1.80	3/24 (12%)	7/26 (27%)	0.41 (0.11-1.59)	0.20	
>1.80	7/28 (25%)	5/22 (23%)	1.16 (0.37-3.65)	0.80	
Left Ventricular Ejection Fraction, %					0.52
≤20%	5/34 (15%)	7/29 (24%)	0.54 (0.17-1.69)	0.29	
>20%	4/16 (25%)	5/18 (28%)	0.96 (0.26-3.57)	0.95	
SCAI-CSWG Stage at Admission					0.39
B	3/12 (25%)	3/16 (19%)	1.32 (0.27-6.57)	0.73	
C-D	7/41 (17%)	9/32 (28%)	0.57 (0.21-1.54)	0.27	



CCU = coronary care unit; CSWG = Cardiac Shock Working Group; MAP = mean arterial pressure; other abbreviations as in Figures 1 and 2.

TABLE 3 End Points and Adverse Events

	SoC (n = 48)	IABP + SoC (n = 53)	*P* Value
Primary endpoint			
Survival or successful bridge to HRT at 60 d	36 (75)	43 (81)	0.46
Durable LVAD	7 (15)	12 (23)	0.30
HTX	9 (19)	9 (17)	0.82
Secondary endpoints			
Duration of hospitalization, d	35 (20-79)	33 (18-91)	0.94
CCU duration of hospitalization, d	13 (8-25)	15 (9-49)	0.49
Maximum SOFA score	7.00 (5.00-9.00)	6.00 (5.00-7.00)	0.18
Maximum inotropic score	5.0 (4.5-9.5)	5.0 (4.0-10.0)	0.98
Inotropic therapy duration, h	13 (5-30)	13 (4-29)	0.82
Duration of IABP support, d[a]	7 (0- 41)	8 (4- 18)	0.87
Treatment escalation			
Escalation to IABP	6 (13)	–	–
Escalation to Impella	1 (2.1)	1 (1.9)	0.99
Escalation to venoarterial ECMO	1 (2.1)	3 (5.7)	0.62
Adverse events			
Bleeding	4 (8.3)	9 (17)	0.19
Vascular complications	0 (0)	4 (7.5)	0.12
Limb ischemia	0 (0)	2 (3.8)	0.50
Systemic embolism	1 (2.1)	0 (0)	0.48
Major Ventricular Arrhythmia	2 (4.2)	2 (3.8)	0.99
Cardiac arrest	6 (13)	7 (13)	0.92
Characteristic			
Stroke	0 (0)	3 (5.7)	0.24
Sepsis	8 (17)	10 (19)	0.77
Septic shock	8 (17)	4 (7.5)	0.28

Values are n (%) or median (Q1-Q3). [a]Among patients who received IABP.

ECMO = extracorporeal membrane oxygenation; HRT = heart replacement therapy; HTX = heart transplant; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; MCS = mechanical circulatory support; other abbreviations as in Table 1.

6-year follow-up of the IABP-SHOCK II trial confirmed no long-term survival benefit. Consequently, routine IABP use is not recommended, and the 2023 European Society of Cardiology guidelines for ACS[12] assign it a Class IIIb recommendation. Real-world data indicate a 50% decline in IABP utilization in ACS patients in the last decade.[22]

The Altshock-2 trial is the largest trial designed to enroll patients with HF-CS to assess the hypothesis of improved survival in HF-CS compared with standard care. Unlike previous studies, it focused on the SCAI B to D HF-CS population.

The inclusion of the SCAI B population was relevant and had a strong pathophysiological rationale.

Different from ACS-CS, acute decompensated heart failure is mechanistically characterized by ventricular afterload mismatch in the absence of preload reserve. Consequently, cardiac output is highly sensitive to fluctuations in afterload/congestion and may improve simply through its reduction. Given its substantial impact on left ventricular afterload with only a modest augmentation in cardiac output, IABP therapy could be optimally suited to clinical scenarios marked by disproportionate afterload/congestion elevation with less severe hemodynamic compromise. The first 12 SCAI-B patients were enrolled by the participating investigators on the clinical grounds that deterioration was impending.

Even if this might be considered an important determinant of the treatment effect, mostly considering the changing criteria with the 2022 amendment, the subgroup analysis did not show any interaction between SCAI phenotype and treatment on survival.

Because of the multiple exclusion criteria and potential candidacy for HRT, recruitment was slow, consistent with previous experiences in selecting suitable candidates for randomization.

The overall survival was higher than expected and initially estimated for standard care (75% in the standard care group vs an estimate of 55% in the original sample size calculation). This may reflect protocol-adopted best practice in hub centers with multidisciplinary teams.

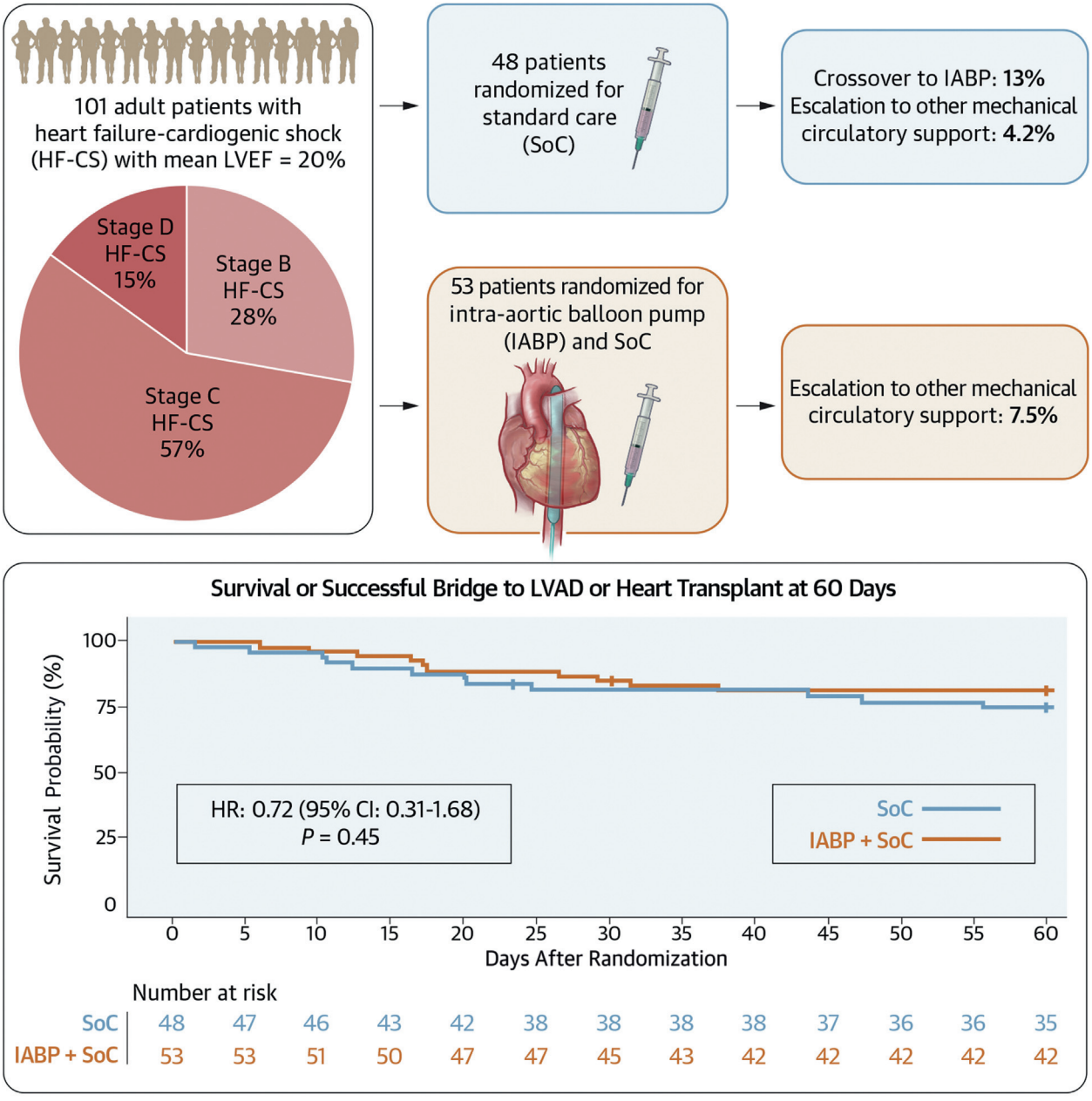
Adverse events were comparable between groups. Interestingly, this study confirmed that complications related to vascular access are lowered by smaller IABP access size compared with other percutaneous devices (3.8% in our study group). However, the rate of bleeding is still highly driven by the medical complexity of the patient and the interaction between organ dysfunction and antithrombotic regimen, as shown by 17% vs 8% severe bleeding for the IABP and standard care groups, respectively, in our data.

Overall, 7.5% and 4.2% of the patients in the IABP and standard care groups, respectively, required escalation to other tMCS (Impella or venoarterial extracorporeal membrane oxygenation). This issue is frequently encountered in CS trials[6,23] that, by definition, should allow for the multistate journey of patients through multiple opportunities for MCS and HTX. Whether a "conservative" preliminary approach with standard treatment or IABP and, eventually, escalation to other MCS is safe warrants specific consideration, ie, comprehensive evaluation by the shock team of a chance that the patient can follow a trajectory tailored to their needs.

The field of native heart recovery is expanding, focusing on extended and potent left ventricular unloading that can reverse the functional, geometric, and molecular mechanisms of HF.[24]

Although probably sufficient in some patients, our study shows that early IABP should not be by default the routine MCS device, because it provides support that is only comparable and not superior to the use of inotropes. Rather, the field needs a new algorithm

CENTRAL ILLUSTRATION **Early Intra-Aortic Balloon Pump in Heart Failure Complicated by Cardiogenic Shock**



The routine early use of IABP plus standard care, compared to standard care alone, did not result in significantly better survival or successful bridge to LVAD or heart transplantation in patients with HF-CS.

Morici N, et al. JACC. 2025;85(16):1587–1597.

CS = cardiogenic shock; HF = heart failure; HRT = heart replacement therapies; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; SoC = standard care; SCAI = Society for Cardiovascular Angiography and Interventions.

that provides the thresholds for escalating from intravenous inotropes to tMCS (including IABP, transaortic axial flow pumps, venoarterial extracorporeal membrane oxygenation, or ECPella), as well as criteria for progression to HRT for those candidates who are not improving within several days of initial support.

STUDY LIMITATIONS. First, heterogenous etiologies must be considered. HF-CS is a broad definition for various etiologies that may show different responses to investigational treatment. Yet in this study, all patients had longstanding left ventricular dysfunction, had optimized guideline-directed medical therapy, to the extent possible, and were of the clinical phenotype of "refractoriness," because we selected only patients who had deterioration driven by the progression of primary disease and not a reversible precipitating event. Second, access to HRT was variable. In this patient group, access to HTX is necessarily regulated by national allocation policies, which are unique for each country. Indeed, individual patient characteristics (size, blood group, immunization, pulmonary pressure) are also very important to receiving a donor heart. Conversely, LVAD is easily available, but a lack of equipoise with HTX projects to an implantation strategy that is often deferred beyond 60 days after admission. Third, best practices and standard operating procedures of IABP management were not protocolized, including the lack of standardization of anticoagulation in the IABP arm. The implantation of any tMCS is not sufficient to assume that patients are being treated similarly, because the pump setting, medical therapy, and weaning procedure are key for success and very difficult to reproduce across different patients. In particular, the IABP response likely depends on optimizing several patient- and device-related factors, particularly its ability to augment diastolic blood pressure. However, we did not collect these data, and the protocol lacked guidelines for optimizing IABP function. Fourth, invasive monitoring was low in our population (about 40%), and we cannot exclude that implementation could have driven improved patient management. Finally, informed consent remains a major challenge in intensive care studies in Europe, but all Altshock-2 trial participants signed the informed consent.

CONCLUSIONS

Our study demonstrates that early IABP implantation does not improve 60-day survival or bridge to HRT in HF-CS compared with standard care.

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KEY WORDS heart failure-cardiogenic shock, heart replacement therapies, intra-aortic balloon pump

APPENDIX For an expanded Methods section, supplemental tables, and study protocol, please see the online version of this paper.