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ORIGINAL RESEARCH

Impact of Center Volume on Outcomes in Myocardial Infarction Complicated by Cardiogenic Shock: A CULPRIT-SHOCK Substudy

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BACKGROUND: Little is known about the impact of center volume on outcomes in acute myocardial infarction complicated by cardiogenic shock. The aim of this study was to investigate the association between center volume, treatment strategies, and subsequent outcome in patients with acute myocardial infarction complicated by cardiogenic shock.

METHODS AND RESULTS: In this subanalysis of the randomized CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial, study sites were categorized based on the annual volume of acute myocardial infarction complicated by cardiogenic shock into low-/intermediate-/high-volume centers (<50; 50–100; and >100 cases/y). Subjects from the study/compulsory registry with available volume data were included. Baseline/procedural characteristics, overall treatment, and 1-year all-cause mortality were compared across categories. n=1032 patients were included in this study (537 treated at low-volume, 240 at intermediate-volume, and 255 at high-volume centers). Baseline risk profile of patients across the volume categories was similar, although high-volume centers included a larger number of older patients. Low-/intermediate-volume centers had more resuscitated patients (57.5%/58.8% versus 42.2%; $P<0.01$), and more patients on mechanical ventilation in comparison to high-volume centers. There were no differences in reperfusion success despite considerable differences in adjunctive pharmacological/device therapies. There was no difference in 1-year all-cause mortality across volume categories (51.1% versus 56.5% versus 54.4%; $P=0.34$).

CONCLUSIONS: In this study of patients with acute myocardial infarction complicated by cardiogenic shock, considerable differences in adjunctive medical and mechanical support therapies were observed. However, we could not detect an impact of center volume on reperfusion success or mortality.

Key Words: acute myocardial infarction ■ cardiogenic shock ■ center volume ■ extracorporeal cardiac life support ■ intensive care

In the field of invasive cardiology, as with many other disciplines in medicine and surgery, the impact of center volume and experience as well as individual operator volume on subsequent outcomes is often discussed. In general, the data suggest that higher volume/experience leads to improved management, so that pooling more procedures at fewer centers would subsequently improve outcomes in specific patient populations. In this regard, it has previously been suggested that higher center/operator volume

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CLINICAL PERSPECTIVE

What Is New?

- We addressed the issue of center volume in relation to outcomes in patients with cardiogenic shock early after myocardial infarction, and found no difference in 1-year all-cause mortality across a wide range of cardiogenic shock cases from <50 to >100 cases per year.
- The treatment of cardiogenic shock differed between hospitals according to case volume, with highly significant differences in use of P2Y12 and GP IIb/IIIa inhibitors as well as the use of mechanical cardiac support.

What Are the Clinical Implications?

- These findings call for a harmonization of all aspects in cardiogenic shock care ranging from adjunctive medical therapy to mechanical devices, but also challenge the perception that higher annual volume equals better care, when patients are treated in experienced centers dedicated to the treatment of myocardial infarction and its immediate complications.

Nonstandard Abbreviations and Acronyms

CULPRIT-SHOCK	Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock

translates into better outcome for patients with elective and urgent percutaneous coronary intervention (PCI).[1–5] Consequently, treatment of myocardial infarction is often organized in networks of several hospitals to improve procedural aspects, a strategy endorsed by European and American guidelines.[6,7]

Cardiogenic shock with or without cardiac arrest complicating myocardial infarction is associated with a very high mortality, which exceeds 40% in most series.[8–10] To improve the survival of affected patients, many smaller hospitals without invasive treatment capabilities as well as hospitals organized in networks have protocols in place for the transfer of patients with cardiogenic shock to dedicated hubs with more resources. However, little is known about the association between center volume, PCI, and medical management strategies and subsequent outcome in this patient population.

Based on a subanalysis from the CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial, the aim of this study was to analyze the associations between cardiogenic shock center volume and baseline/procedural characteristics, overall use of treatment options, and 1-year all-cause mortality in patients with myocardial infarction complicated by cardiogenic shock.

METHODS

The data supporting the findings presented in this study are available from the Stiftung Institut für Herzinfarktforschung, Ludwigshafen am Rhein, Germany upon reasonable request.

Setting

The design of the CULPRIT-SHOCK trial has been reported previously.[11] In short, CULPRIT-SHOCK was an open-label, multicenter trial randomizing patients with myocardial infarction complicated by cardiogenic shock and multivessel coronary artery disease to culprit-lesion-only PCI (and potentially staged revascularization) versus immediate multivessel PCI. Patients not eligible for randomization could be entered into the CULPRIT-SHOCK registry. Both were approved by local ethics committees and institutional review boards, and in all subjects written informed consent was obtained.

Center Volume Substudy

For this subanalysis, study sites were categorized based on their annual volume of cardiogenic shock cases into low-volume (<50 cardiogenic shock cases per year, ≈1 case per week), intermediate-volume (50–100 cardiogenic shock cases per year, ≈1–2 cases per week), and high-volume (>100 cardiogenic shock cases per year, more than 2 cases per week) centers. Information on annual volume of cardiogenic shock cases and other center characteristics was self-reported by each study site based on hospital data and *International Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD*) codes.

Subjects enrolled in the main study and registry were then allocated to the low-volume versus intermediate-volume versus high-volume center group based on the study site in which the subjects were enrolled and treated. There were no secondary transfers after enrollment. Variables of interest were baseline, presentation and procedural characteristics, overall treatment, and outcome. For the latter, 1-year all-cause mortality was assessed. If the information on the cardiogenic shock center volume was missing for a study site, patients enrolled at this site were excluded from the analysis.

Statistical Analysis

Continuous variables are presented as mean (±SD) or median (interquartile range) and compared using

the Kruskal–Wallis test; categorical variables are presented as counts (frequencies) and compared using the Pearson χ^2 test. For the outcome of 1-year all-cause mortality, all deaths that occurred within 365 days after randomization (patients from the randomized controlled trial) or after screening (patients from the registry) were considered. The Kaplan–Meier method was used to estimate survival functions in subjects enrolled at low-volume versus intermediate-volume versus high-volume centers. To investigate the association between center volume and 1-year all-cause mortality, a Cox regression model was fitted adjusted for age, male sex, family history of coronary artery disease, previous congestive heart failure, known peripheral artery disease, mechanical ventilation, resuscitation within 24 hours, left bundle-branch block, known renal insufficiency, and atrial fibrillation. These variables were selected based on clinical expertise and knowledge from previous analyses. Hazard ratios (HR) and 95% CI were calculated based on this multivariable-adjusted Cox regression model. All subjects enrolled in the main study or the registry and with available information on cardiogenic shock center volume of the enrollment site were included in this analysis, irrespective of allocated treatment group or actual treatment. Two-sided *P* values <0.05 was considered to be statistically significant. All analyses were performed using SAS statistical package, version 9.4,[12] and R version 3.5.3 (R-package *ggplot2*) was used for data visualization.[13,14]

RESULTS

Center Characteristics

Information on cardiogenic shock center volume was available for 74 out of 83 study sites, and a total of 1032 patients, including registry and randomized patients, were included in this substudy (Figure 1). Among these sites, 39 centers enrolling 537 patients were categorized as low-volume centers, 22 centers enrolling 240 patients were categorized as intermediate-volume centers, and 13 centers enrolling 255 patients were categorized as high-volume centers. Other center characteristics were similarly distributed as cardiogenic shock volume, such that high-volume centers also performed more angiographies per year, more PCI (overall, urgent, and chronic total occlusion) per year, had more cardiogenic shock cases treated with mechanical circulatory support per year, and had a higher intensive care unit capacity (overall beds and cardiology beds; Figure 2). However, high-volume centers tended to receive more patients as referrals from other centers than low- or intermediate-volume centers (in 63.1% of the high-volume centers, >50% of the patients are transfers versus 16.5%/5.8%; *P*<0.001).

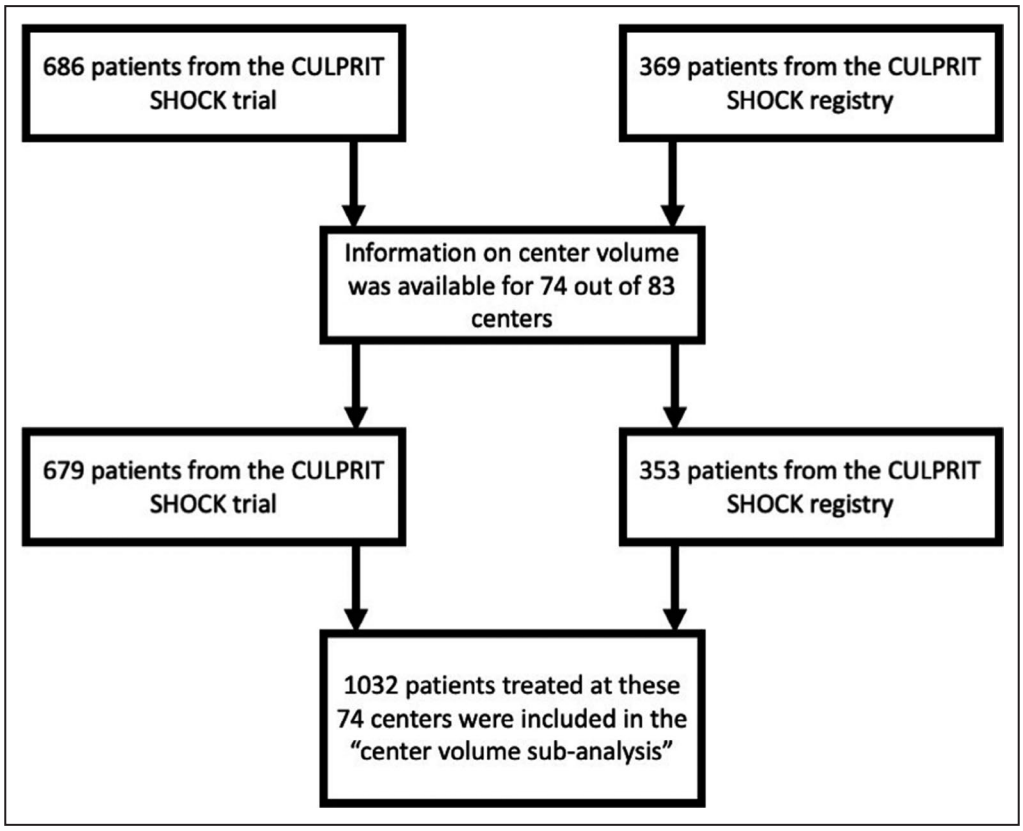

Figure 1. Study flow chart.
CULPRIT-SHOCK indicates Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock.

Patient Characteristics

Patients enrolled at intermediate-volume centers were younger, had less peripheral artery disease, and were less likely to present with previous β-blocker therapy. Additionally, the prevalence of a family history of coronary artery disease differed across center volume. However, most other baseline characteristics were equally distributed between the 3 groups (Table 1).

Regarding presentation characteristics, patients enrolled at low- or intermediate-volume centers were more likely to receive mechanical ventilation and to have had prior resuscitation, whereas patients enrolled at high-volume centers had more severely depressed TIMI (Thrombolysis in Myocardial Infarction trial) flow before revascularization. There were no significant differences in regard to the number of diseased vessels, culprit-lesion artery, hemodynamics, renal function, or hypoperfusion (Table 2).

Treatment

Adjunctive medical therapies as well as mechanical circulatory support differed significantly between patients enrolled at low- versus intermediate- versus high-volume centers (Figure 3).

Patients enrolled in intermediate-volume centers were less likely to receive PCI via radial access and more likely to receive more contrast dye and have longer fluoroscopy time as compared with patients enrolled at low- or high-volume centers; but there were no differences in PCI procedural success, defined as either TIMI-III flow in the culprit artery or complete revascularization. Mechanical circulatory support was more often used in patients enrolled in low- or intermediate-volume centers. Among patients treated with mechanical circulatory support at high-volume centers, extracorporeal membrane oxygenation was the most frequently used device, and the percentage of use was higher compared with patients treated with mechanical circulatory support at low- or intermediate-volume centers (21.2% [35/165] versus 39.8% [35/88] versus 46.9% [23/49], $P<0.01$).

Patients enrolled at low-volume centers were more likely to be treated with unfractionated heparin, glycoprotein IIb/IIIa inhibitors, and ticagrelor, whereas

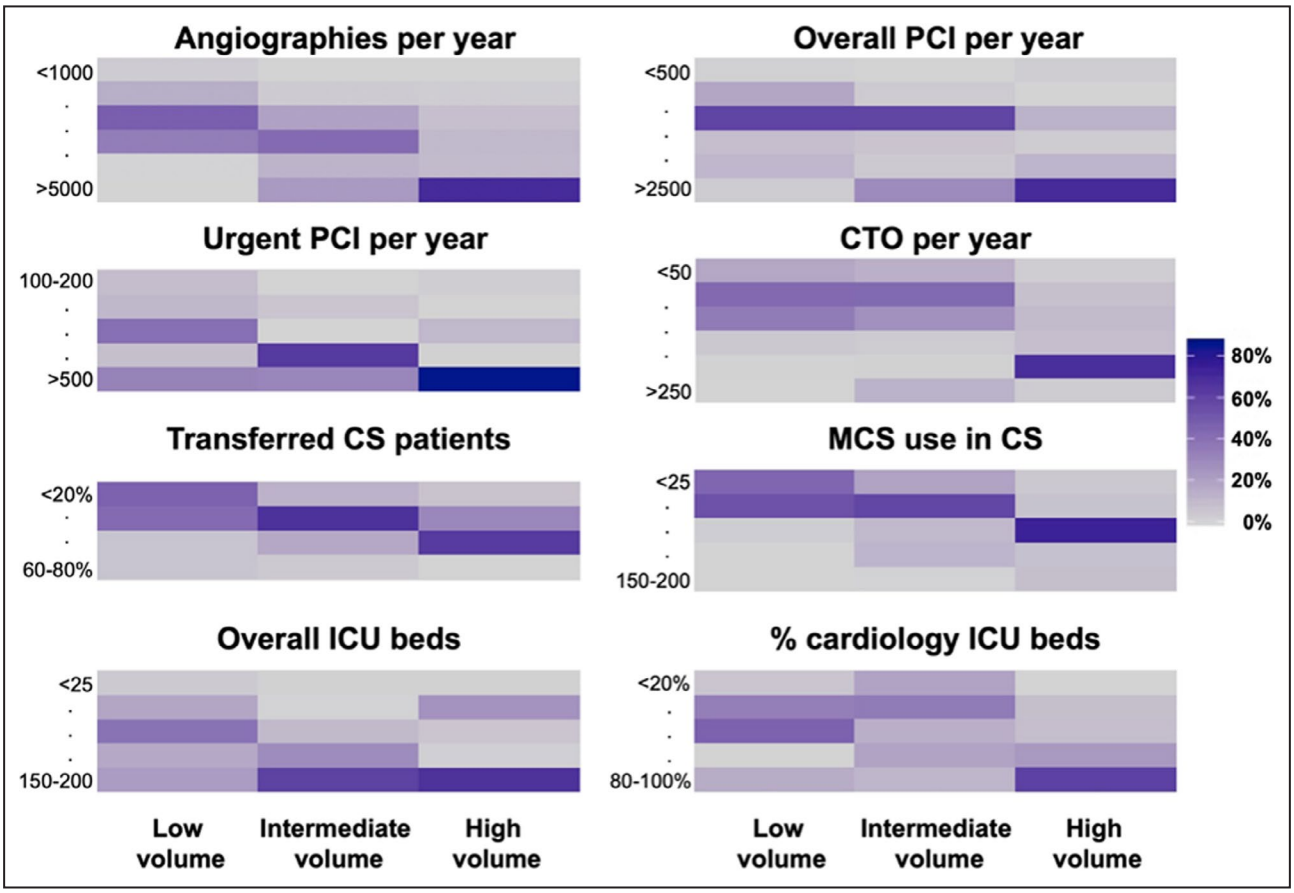

Figure 2. Frequency distribution of invasive coronary procedures, use of mechanical support devices, and intensive care capacity in hospitals according to cardiogenic shock center volume.
CS indicates cardiogenic shock; CTO, chronic total occlusion; ICU, intensive care unit; MCS, mechanical circulatory support; and PCI, percutaneous coronary intervention.

Table 1. Baseline Characteristics Stratified by Center Volume

	Low-volume center (n=537, 52%)	Intermediate-volume center (n=240, 23%)	High-volume center (n=255, 25%)
Demographics			
Age, y	68 (±12)	66 (±13)	69 (±11)
Sex, male	396 (74.4)	187 (78.6)	180 (72.6)
Body mass index, kg/m^2	27.4 (±4.8)	27.5 (±4.4)	27.1 (±4.0)
Cardiovascular risk factors			
Current smoking	161 (31.4)	65 (28.0)	63 (28.6)
Hypertension	319 (61.2)	128 (54.0)	146 (65.5)
Dyslipidemia	186 (35.7)	64 (27.0)	77 (34.8)
Diabetes mellitus	168 (32.3)	64 (27.0)	65 (29.0)
Family history of CAD	82 (16.3)	25 (11.0)	18 (8.2)
Medical history			
Previous myocardial infarction	83 (15.9)	40 (16.9)	40 (17.7)
Previous PCI	92 (17.6)	41 (17.3)	43 (19.0)
Previous CABG	27 (5.1)	11 (4.6)	11 (4.8)
Previous congestive heart failure	41 (7.8)	18 (7.6)	29 (12.8)
Previous stroke	40 (7.6)	15 (6.3)	20 (8.9)
Known peripheral artery disease	59 (11.2)	17 (7.2)	33 (14.5)
Chronic kidney disease	27 (5.2)	16 (6.8)	20 (8.8)
Chronic dialysis	5 (1.0)	3 (1.3)	6 (2.7)
Previous drug therapy			
Aspirin	185 (43.7)	62 (36.7)	70 (40.9)
Clopidogrel	47 (11.3)	17 (10.1)	20 (11.9)
Prasugrel	7 (1.7)	4 (2.4)	4 (2.4)
Ticagrelor	20 (4.8)	3 (1.8)	6 (3.6)
Vitamin K antagonists	23 (5.6)	10 (5.9)	14 (8.3)
β-Blocker	158 (38.7)	53 (31.5)	81 (48.2)
Renin angiotensin system inhibitor	183 (44.9)	69 (41.1)	82 (48.0)
Statin	164 (40.1)	50 (29.9)	61 (36.1)

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; and PCI, percutaneous coronary intervention.

patients enrolled in high-volume centers were more likely to receive clopidogrel and bivalirudin.

Outcome

During 365 days after randomization or entering the registry, 535 deaths (51.8%) occurred in the overall study cohort. The estimated 1-year mortality was 50.8% (95% CI, 46.4%–55.0%) in patients enrolled at low-volume centers, 56.4% (95% CI, 49.8%–62.4%) in patients enrolled at intermediate-volume centers, and 54.4% (95% CI, 48.0%–60.3%) in patients enrolled at high-volume centers. After adjustment for relevant confounders, there was no significant difference in the risk of 1-year mortality between patients enrolled in low- versus intermediate-volume centers (HR, 1.15 [95% CI, 0.92–1.43], *P*=0.22) and low- versus high-volume centers (HR, 0.95 [95% CI 0.76–1.20], *P*=0.69) (Figure 4).

DISCUSSION

In this subanalysis from the CULPRIT-SHOCK trial, there were large differences in adjunctive antithrombotic therapies during and after PCI and use of mechanical circulatory support in patients with myocardial infarction complicated by cardiogenic shock treated at low- versus intermediate- versus high-volume centers. Despite these variations, 1-year all-cause mortality was comparable across centers irrespective of annual cardiogenic shock volume.

The only evidence-based treatment improving outcomes in myocardial infarction complicated by cardiogenic shock is early revascularization of the culprit artery.[9,15,16] Nevertheless, cardiogenic shock was almost always an exclusion criterion in acute coronary syndrome trials investigating adjunctive therapies in this field, so that the generated evidence on myocardial infarction itself does not necessarily cover the

Table 2. Presentation Characteristics Stratified by Center Volume

	Low-volume center (n=537, 52%)	Intermediate-volume center (n=240, 23%)	High-volume center (n=255, 25%)
Coronary artery characteristics			
Number of diseased vessels			
Single-vessel disease	76 (14.3)	34 (14.5)	27 (10.9)
Double-vessel disease	171 (32.3)	68 (28.9)	75 (30.4)
Triple-vessel disease	283 (53.4)	133 (56.6)	145 (58.7)
Coronary artery with culprit lesion			
RCA	154 (29.1)	62 (26.7)	68 (27.6)
Left main	51 (9.6)	14 (6.0)	16 (6.5)
LAD	214 (40.4)	108 (46.6)	113 (45.9)
CFX	102 (19.2)	46 (19.8)	48 (19.5)
CABG	9 (1.7)	2 (0.9)	1 (0.4)
TIMI-flow pre-PCI (culprit lesion)			
0	262 (50.5)	147 (62.6)	154 (63.4)
1	68 (13.1)	26 (11.1)	28 (11.5)
2	92 (17.7)	21 (8.9)	37 (15.2)
3	97 (18.7)	41 (17.4)	24 (9.9)
Clinical characteristics			
Mechanical ventilation	333 (63.2)	141 (59.5)	121 (52.6)
Fibrinolysis within 24 h	33 (6.3)	12 (5.0)	16 (7.0)
Resuscitation within 24 h	303 (57.5)	140 (58.8)	97 (42.2)
Systolic blood pressure, mm Hg	106 (±30)	106 (±32)	106 (±31)
Diastolic blood pressure, mm Hg	65 (±20)	65 (±23)	64 (±18)
Heart rate, bpm	91 (±27)	89 (±24)	93 (±28)
ST-elevation or LBBB	375 (73.0)	174 (74.4)	159 (71.3)
Atrial fibrillation	63 (12.2)	22 (9.4)	37 (16.4)
Creatinine, µmol/L	111 (90, 141)	106 (88, 139)	116 (93, 149)
Arterial lactate, mmol/L	5.4 (2.7, 8.9)	5.2 (2.6, 8.7)	4.4 (2.6, 8.1)
Mechanical circulatory support	165 (30.7%)	88 (36.7%)	49 (19.2%)
IABP	70 (42.4%)	29 (33.0%)	21 (42.9%)
Impella 2.5	30 (18.2%)	12 (13.6%)	2 (4.1%)
Impella CP	37 (22.4%)	20 (22.7%)	11 (22.4%)
VA-ECMO	35 (21.2%)	35 (39.8%)	23 (46.9%)
Other	4 (2.4%)	2 (2.3%)	0 (0%)

Bpm indicates beats per minute; CABG, coronary artery bypass graft; CFX, circumflex artery; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LBBB, left bundle-branch block; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction; and VA-ECMO, veno-arterial extracorporeal membrane oxygenation therapy.

subpopulation of patients with myocardial infarction complicated by cardiogenic shock. Consequently, the management of patients with cardiogenic shock is much less driven by evidence-based recommendations.

This study describes a marked variation in the management of patients with myocardial infarction complicated by cardiogenic shock based on annual center volume. This ranges from technical aspects of the PCI (eg, arterial access) to use of mechanical circulatory support and choice of adjunctive antithrombotic therapy. However, this was not associated with differences in outcome, because PCI procedural success and 1-year all-cause mortality were comparable across centers with a low- versus intermediate versus high annual volume of cardiogenic shock cases.

Our findings differ from 2 previous studies on this topic, although variations in study design might explain the observed differences. In a US-based administrative database, Shaefi et al did observe a higher in-hospital mortality in patients with cardiogenic shock treated at hospitals with lower annual case volume.[17] Although this study covers a large sample of patients, there was no adjustment for cardiogenic shock–specific confounders such as prior resuscitation, and patients who died in a nursing home or hospice care were

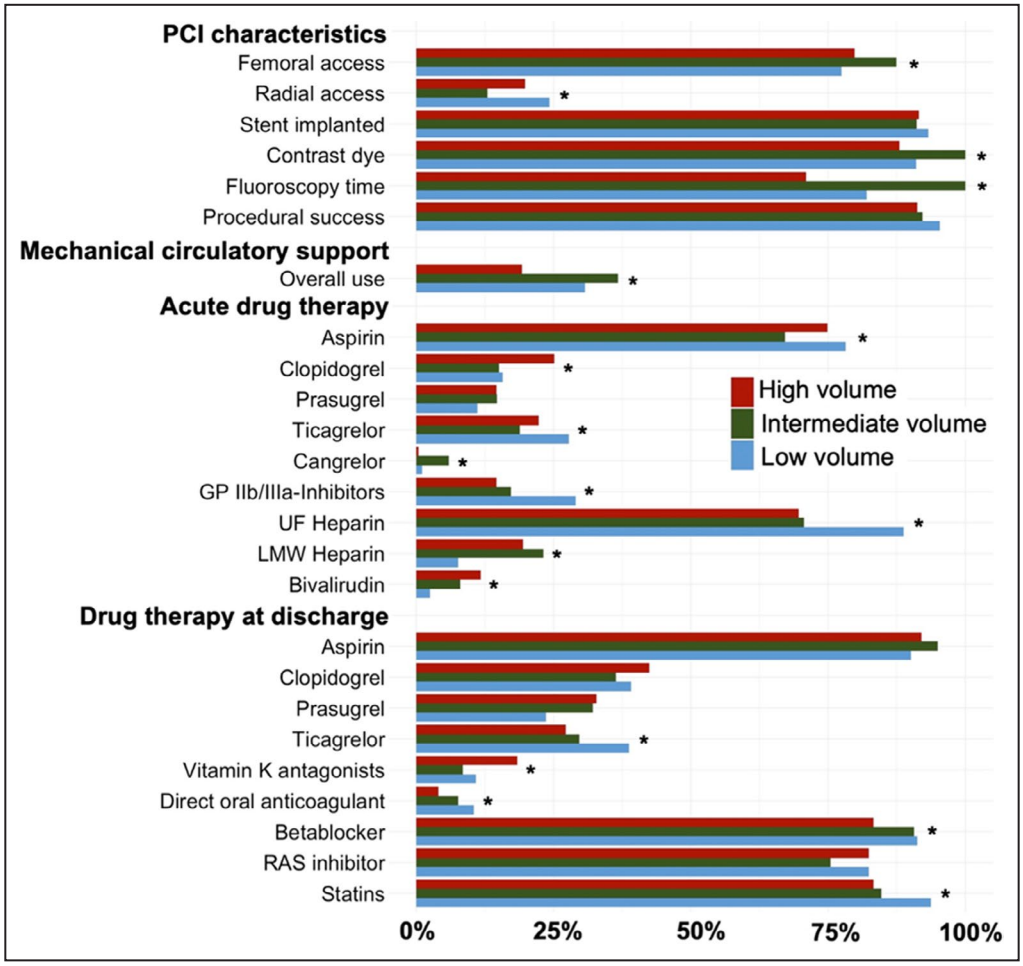

Figure 3. Use of treatment stratified by center volume.
Contrast dye and fluoroscopy time are shown as relative values comparing low-/high-volume centers vs intermediate-volume centers. GP IIb/IIIa-Inhibitors, glycoprotein IIb/IIIa inhibitors; LMW heparin, low-molecular weight heparin; PCI, percutaneous coronary intervention; RAS inhibitor, renin-angiotensin-aldosterone inhibitor; and UF heparin, unfractionated heparin. * Statistical difference.

excluded.[17] Hence, differences in cardiogenic shock severity and the proportion of patients discharged to care facilities may help to explain the difference between our findings and those of Shaefi et al. Based on a national PCI registry in Japan, Kubo et al evaluated the volume-outcome association of cardiogenic shock in patients undergoing PCI.[18] Here, the authors report that lower annual PCI volume was independently associated with worse outcome.[18] In this study, cardiogenic shock was mostly defined via hypotension (not hypoperfusion) and overall mortality was very low, at 13%, suggesting a somewhat selected population differing from a real-world consecutive cardiogenic shock cohort.[18] Therefore, the findings might be more applicable to patients with less severe/developing cardiogenic shock as described by the recent Society for Cardiovascular Angiography and Interventions cardiogenic shock classification.[19–21] Additionally, hospital volume was defined based on annual PCI procedures with <640 procedures performed over 3 years in the lowest category; so this study supports the volume–outcome association previously described for urgent PCI, rather than conflicting with our findings.

Ultimately, the following conclusions can be drawn from this study: Reperfusion success and 1-year outcomes did not differ across the spectrum of experience or center volume. This being said, most adjunctive therapies differed depending on center volume, including antithrombotic therapy, renal replacement, and even the use of mechanical support. The lack of evidence-based treatment protocols might potentially explain the high mortality in the overall cardiogenic shock population and in this study.[22] Additionally, the treatment heterogeneity underscores the urgent need for standardized protocols and accelerated research to answer the open questions (eg, what are the best adjunctive treatments in cardiogenic shock?). In the future, dedicated treatment protocols might help to

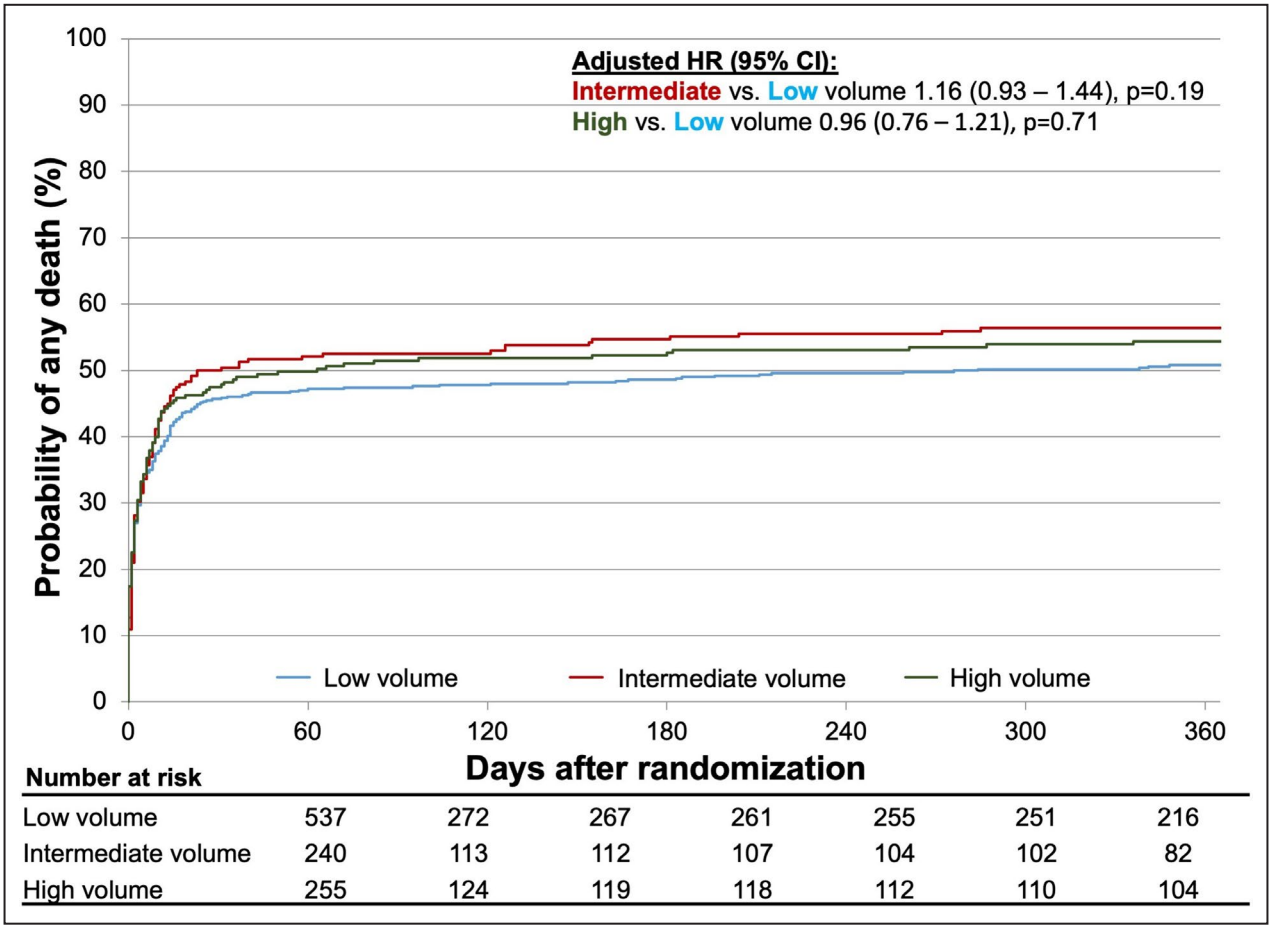

Figure 4. Outcome stratified by center volume.
HR indicates hazard ratio.

improve outcomes in these patients (eg, via guiding the use of mechanical circulatory support towards patients who might benefit the most). In this regard, 2 recent studies have already reported encouraging results for standardized team-based care for cardiogenic shock.[23,24] Additionally, the National Cardiogenic Shock Initiative reported promising results based on an algorithm focusing on left ventricular unloading for the treatment of cardiogenic shock, indicating that a more targeted application of these devices could potentially improve survival of affected patients.[25]

Nevertheless, our study should not be interpreted as an opportunity to further decentralize the care for patients with cardiogenic shock, because all participating centers in this study had 24/7 availability for coronary angiography/intervention, access to level 3 intensive care unit, which is a minimum requirement as per current guidelines,[16] but also selected based on scientific interest and level of care by the steering committee. Hence, all participating centers are considered *Level 1 Cardiogenic Shock Care* Centers,[26] which provide the needed expertise and treatment options for this patient population, and thus mainly differ in overall case volume, but not in individual expertise.

Rather, this study should be understood as a reminder that more work is needed in this field, and a call for a harmonization of the therapeutic approach to myocardial infarction complicated by cardiogenic shock.

Limitations

This study is based on the largest randomized trial and its accompanying registry in the field of cardiogenic shock, with near-complete data capture regarding center volume and complete follow-up of enrolled patients. The great depth of available data allowed us to provide a clear picture of patient characteristics, management, and outcomes. However, we could only consider the available variables in our analysis, so unknown or unmeasured confounding cannot be ruled out. While the data are extremely valid for the participating centers, generalizability to other centers might be limited. Additionally, 9 trial sites did not participate in this substudy, so that patients enrolled at these centers

were not considered, which might have influenced our findings. Data on the duration between onset of shock and treatment were not available for this analysis, so that longer treatment delays (eg, during transfer of patients to high-volume centers) might have influenced the results. Lastly and most importantly, the present study was conducted within the framework of a network of hospitals and investigators with interest and experience in treating cardiogenic shock and doing complex clinical trials. However, the data do reflect the current reality of triage and treatment of patients with cardiogenic shock, because most of the patients in the low- and intermediate-volume hospitals were directly admitted whereas the high-volume centers recruited most of their patients through transfers from surrounding spoke hospitals, which is also highlighted by the more severely depressed TIMI flow in those patients.

CONCLUSIONS

This CULPRIT-SHOCK trial and registry analysis revealed major differences in PCI-related adjunctive antithrombotic therapies and use of mechanical circulatory support between low-, intermediate-, and high-volume centers when treating cardiogenic shock in patients with myocardial infarction. However, the mortality risk was comparable across centers, despite adjustment for several relevant confounders. These observations are provocative and should call for a harmonization of the therapeutic approach to myocardial infarction complicated by cardiogenic shock.

ARTICLE INFORMATION

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