Implementation of a Comprehensive ST-Elevation Myocardial Infarction Protocol Improves Mortality Among Patients With ST-Elevation Myocardial Infarction and Cardiogenic Shock

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Mortality in patients with STEMI-associated cardiogenic shock (CS) is increasing. Whether a comprehensive ST-elevation myocardial infarction (STEMI) protocol (CSP) can improve their care delivery and mortality is unknown. We evaluated the impact of a CSP on incidence and outcomes in patients with STEMI-associated CS. We implemented a 4-step CSP including: (1) Emergency Department catheterization lab activation; (2) STEMI Safe Handoff Checklist; (3) immediate catheterization lab transfer; (4) and radial-first percutaneous coronary intervention (PCI). We studied 1,272 consecutive STEMI patients who underwent PCI and assessed for CS incidence per National Cardiovascular Data Registry definitions within 24-hours of PCI, care delivery, and mortality before (January 1, 2011, to July 14, 2014; n = 723) and after (July 15, 2014, to December 31, 2016; n = 549) CSP implementation. Following CSP implementation, CS incidence was reduced (13.0% vs 7.8%, p = 0.003). Of 137 CS patients, 43 (31.4%) were in the CSP group. CSP patients had greater IABP-Shock II risk scores (1.9 ± 1.8 vs 2.8 ± 2.2, p = 0.014) with otherwise similar hemodynamic and baseline characteristics, cardiac arrest incidence, and mechanical circulatory support use. Administration of guideline-directed medical therapy was similar (89.4% vs 97.7%, p = 0.172) with significant improvements in trans-radial PCI (9.6% vs 44.2%, p < 0.001) and door-to-balloon time (129.0 [89:160] vs 95.0 [81:116] minutes, p = 0.001) in the CSP group, translating to improvements in infarct size (CK-MB 220.9 ± 156.0 vs 151.5 ± 98.5 ng/ml, p = 0.005), ejection fraction (40.8 ± 14.5% vs 46.7 ± 14.6%, p = 0.037), and in-hospital mortality (30.9% vs 14.0%, p = 0.037). In conclusion, CSP implementation was associated with improvements in CS incidence, infarct size, ejection fraction, and in-hospital mortality in patients with STEMI-associated CS. This strategy offers a potential solution to bridging the historically elusive gap in their care. **(Am J Cardiol 2020;134:1−7)**

Cardiogenic shock (CS) is a common complication of ST-elevation myocardial infarction (STEMI), occurring in 5% to 13% of patients, and causes significant morbidity and mortality.[1−3] There is a wealth of data supporting the importance of timely reperfusion through percutaneous coronary intervention (PCI) and its association with improved survival in patients with STEMI and CS.[4−7] Moreover, there is suggestion that a delay in door-to-balloon time (D2BT) results in increased mortality, supporting that rapid PCI may further improve outcomes in these patients. However, despite advances in STEMI care and national improvements in D2BT, mortality is increasing amongst those with STEMI and CS.[3] A recent study by Kochar et al.[8] demonstrated that patients with STEMI and CS had worse first medical contact-to-device time, were less likely to be revascularized, and had 10-fold higher in-hospital mortality compared to those without CS. In addition, implementation of the American Heart Association (AHA) Mission: Lifeline STEMI Systems Accelerator initiative, a regional system of care intervention aimed at improving D2BT, was associated with minimum improvement in D2BT in patients with STEMI and CS. As such, it remains unclear if the care of these critically ill patients is modifiable and if systems of care can be developed to reliably and quickly respond to them.[9] We recently showed the complementary impact on mortality of guideline-directed medical therapy (GDMT), use of trans-radial access (TRA) for primary PCI, and lower D2BT in patients with STEMI.[10] The value of systems of care focusing on improving these key issues for patients with STEMI and CS is unknown. Accordingly, we implemented a 4-step comprehensive STEMI protocol (CSP) aimed at systematically targeting these tenets of STEMI care and investigated its impact on (1) the incidence of CS in all patients with STEMI and (2) care delivery and outcomes in patients with STEMI and CS.

Heart and Vascular Institute, Cleveland Clinic Foundation, Cleveland, Ohio. Manuscript received June 22, 2020; revised manuscript received and accepted August 4, 2020.

See page 6 for disclosure information.

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https://doi.org/10.1016/j.amjcard.2020.08.012

Methods

We performed a prospective, registry-based study of consecutive patients with STEMI treated with PCI at our center from January 1, 2011, to December 31, 2016. No patients were excluded. Baseline characteristics, care metrics, adverse events and mortality were adjudicated by the standards of the American College of Cardiology National Cardiovascular Data Registry CathPCI Registry by trained data abstractors.[11] Survival status was ascertained by medical record review and follow-up phone calls as needed. Survival status was complete in 98.7% (n = 1,255) of the population at 30 days and 90.9% (n = 1,156) at 1 year. In those with CS, survival status was complete in 100% (n = 137) and 98.5% (n = 135) at 30 days and 1 year, respectively.

Our 4-step CSP has been described.[12] On July 15,2014, we implemented a CSP intending to minimize STEMI care variability by (1) enabling immediate Emergency Department physician activation of the catheterization laboratory without delay for Cardiology consultation, (2) using a STEMI Safe Handoff Checklist to standardize the early triage of patients including GDMT administration, (3) mandating transfer to an immediately available catheterization laboratory to avoid patient delays, and (4) employing a "radial-first" approach to PCI in suitable patients. Although use, timing, and type of mechanical circulatory support was not protocolized, all patients placed on veno-arterial extracorporeal membrane oxygenation remained in our cardiac intensive care unit rather than being transferred to a cardiothoracic intensive care unit. We identified patients who had CS, per the American College of Cardiology National Cardiovascular Data Registry definition of sustained (> 30 minutes) episode of systolic blood pressure < 90 mm Hg and/or cardiac index < 2.2 L/min/m^2 determined to be secondary to cardiac dysfunction, and/or the requirement of parenteral inotropic or vasopressor agents or mechanical support to maintain blood pressure and cardiac index previously mentioned those specified levels, within 24-hours of PCI.[11] Patients treated from January 1, 2011, to July 14, 2014, were defined as the control group and those treated from July 15, 2014, to December 31, 2016, as the CSP group. First, we assessed for differences in care delivery and incidence of CS in all STEMI patients before and after the implementation of the 4-step CSP. Second, we assessed the impact of the 4-step CSP on these differences and mortality in those with STEMI and CS.

Percentages and means ± standard deviation or median with interquartile range were computed for categorical and continuous variables, respectively. Categorical variables were compared using the Chi-square test or Fisher's exact tests whereas continuous variables were analyzed using the 2-tailed Student's *t* test or the Mann-Whitney U test, when appropriate. Logistic regression was performed to assess for predictors of in-hospital mortality; variables with a p-value <0.10 and those with clinical relevance were included in the final model. We used Kaplan-Meier life tables and the Log-rank test to compare mortality between those within the control and CSP groups. Lastly, we created quality control charts using statistical process control, a method utilizing time series analysis methods to graphically present data variability to support evidence of statistical change.[13] Analyses were performed using R Software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and JMP Pro version 14 (Cary, North Carolina). A p-value <0.05 was considered statistically significant. The authors declare that all supporting data are available within the article. The study protocol was approved by the Cleveland Clinic Foundation Institutional Review Board; need for informed consent was waived.

Results

Of the 1,272 STEMI patients treated with PCI, 723 (56.8%) were in the control group and 549 (43.2%) in the CSP group. Patients in the CSP group were less likely to have a history of previous MI (35.1% vs 21.9%, p <0.001) with no differences in previous revascularization. Baseline characteristics and use of mechanical circulatory support (13.6% vs 10.5%, p = 0.105) were otherwise similar. In the CSP group, there were significant improvements in administration of aspirin, anticoagulant, and $P2Y_{12}$ inhibitor prior to sheath insertion for PCI (74.1% vs 82.5%, p < 0.001) and on admission following PCI (95.6% vs 97.6%, p = 0.049), use of TRA for PCI (19.1% vs 67.0%, p <0.001), median D2BT (106.0 [81:140] vs 89.5 [68:109] minutes, p <0.001), and D2BT at appropriate goal (59.7% vs 84.1%, p <0.001). Receipt of all 3 metrics (GDMT prior to sheath insertion, use of TRA for PCI, and D2BT at appropriate goal) was significantly increased in the CSP group (8.4% vs 47.0%, p < 0.001). The incidence of CS was significantly lower in the CSP group within 24 hours of PCI (13.0% vs 7.8%, p = 0.003) and within 24 hours post-PCI (7.6% vs 4.6%, p = 0.025).

A total of 137 patients presented with STEMI and CS, with 94 (68.6%) patients in the control group and 43 patients (31.4%) in the CSP group (Table 1). Patients in the CSP group had higher IABP-Shock II risk scores (1.9 ± 1.8 vs 2.8 ± 2.2, p = 0.014); baseline characteristics were otherwise similar (Table 1). There were no differences in presenting hemodynamic parameters, initial serum lactate or creatinine, the incidence of cardiac arrest previous to PCI, left main or left anterior descending culprit vessel, or multivessel coronary artery disease.

Administration of GDMT on admission (89.4% vs 97.7%, p = 0.172) was similar with significant improvements in the use of TRA for PCI (9.6% vs 44.2%, p < 0.001), median D2BT (129.0 [89:160] vs 95.0 [81:116] minutes, p = 0.001), and D2BT at appropriate goal (38.5% vs 72.1%, p < 0.001) in the CSP group (Figure 1). Quality control charts depicting semi-annual variation in the (A) administration of GDMT upon admission and (B) use of TRA for PCI and case-by-case variation in (C) D2BT are included in Figure 2. Receipt of all 3 metrics was significantly increased in the CSP group (1.1% vs 20.9%, p < 0.001); conversely, significantly fewer met no metrics (28.7% vs 11.6%, p <0.001). Use of mechanical circulatory support, including type of device, was similar between groups (Table 2).

There were no differences in adverse outcomes between groups (Table 2). Patients in the CSP group had a

Table 1
Baseline characteristics, presentation, and angiographic findings of STEMI patients with cardiogenic shock before and after implementation of a comprehensive STEMI protocol

Variable	No protocol (n = 94)	Protocol (n = 43)	p Value
Age (years)	65.5 ± 11.9	62.9 ± 13.2	0.264
Men	57 (61%)	28 (65%)	0.706
Body mass index (kg/m^2)	28.2 ± 5.7	30.5 ± 7.3	0.079
White	67 (77%)	29 (74%)	0.822
Current or former smoker	37 (39%)	13 (30%)	0.343
Hypertension	71 (76%)	34 (79%)	0.828
Dyslipidemia	71 (76%)	33 (77%)	1.000
Diabetes mellitus	32 (34%)	22 (51%)	0.057
Previous myocardial infarction	38 (40%)	10 (23%)	0.056
Previous percutaneous coronary intervention	24 (26%)	13 (30%)	0.679
Previous coronary artery bypass grafting	8 (9%)	1 (2%)	0.272
Previous heart failure	28 (30%)	10 (23%)	0.538
Previous valve surgery	3 (3%)	1 (2%)	1.000
Previous cerebrovascular disease	19 (20%)	8 (19%)	0.826
Previous peripheral arterial disease	19 (20%)	9 (21%)	1.000
Chronic kidney disease			0.438
Glomerular filtration rate > 60 ml/min/1.73 m^2	49 (57%)	20 (54%)	
Glomerular filtration rate 30−60 ml/min/1.73 m^2	30 (35%)	11 (30%)	
Glomerular filtration rate < 30 ml/min/1.73 m^2	3 (4%)	4 (11%)	
Hemodialysis	4 (5%)	2 (5%)	
Chronic lung disease	14 (15%)	6 (14%)	1.000
Presentation			
Heart rate (beats per minute)	94.6 ± 31.7	95.6 ± 30.2	0.886
Systolic blood pressure (mm Hg)	105 [89.5:129]	109 [105:128]	0.832
Cardiac arrest	50 (53%)	21 (48.8%)	0.714
Creatinine (mg/dl)	1.28 ± 1.02	1.63 ± 1.38	0.134
Hemoglobin (g/dl)	13.1 ± 2.5	13.5 ± 2.8	0.494
Serum lactate (mmol/L)	4.1 ± 3.5	4.9 ± 4.1	0.272
Angiographic Findings			
Culprit coronary artery			0.968
Left main or left anterior descending	49 (52%)	23 (54%)	
Left circumflex	19 (20%)	9 (21%)	
Right coronary	26 (28%)	11 (26%)	
Fluoroscopy time (minutes)	27.3 ± 18.5	31.9 ± 26.3	0.308
Fluoroscopy dose (mGy)	1670 [847:2899]	1678 [1020:2491]	0.052
Contrast volume (ml)	204.0 ± 105.5	170.7 ± 78.8	0.066

significantly smaller infarct size (peak creatine kinase-MB 220.9 ± 156.0 ng/ml vs 151.1 ± 98.5, p = 0.005) and greater postinfarct ejection fraction (40.8 ± 14.5% vs 46.7 ± 14.6%, p = 0.037). Although there was no difference in length of stay, there was a trend toward increased rate of discharge to home (Table 3). In-hospital mortality (30.9% vs 14.0%, p = 0.037) was significantly reduced in patients in the CSP group. In a multivariable model including age, gender, race, chronic kidney disease, peripheral vascular disease, diabetes mellitus, use of drug eluting stent, and $P2Y_{12}$ inhibitor, CSP was an independent predictor for hospital survival (OR: 5.6, 95% CI: 1.2 to 11.1, p = 0.035). Although numerically lower in the CSP group, the mortality reduction was non-significant at one-year (42.9% vs 34.2%, p = 0.113, Figure 3).

Discussion

In this study, we demonstrated that implementation of a 4-step CSP was associated with a reduction in the incidence of STEMI-associated CS by 40%. Amongst those with STEMI and CS, patients in the CSP group had improved guideline-recommended care delivery including > 4-fold increase in the use of TRA for PCI and > 25% reduction in D2BT. These improvements translated to a significant reduction in infarct size by > 30% and in-hospital mortality by > 50%. Although there was a trend towards less major bleeding, need for blood transfusion and overall trans-femoral access remained high due to substantial use of mechanical circulatory support. These findings quantify the positive impact of a formalized STEMI protocol on clinical outcomes in patients with CS, who are among the most critically ill patients encountered in patient care. However, despite these early improvements, long-term mortality remained severe.

Numerous previously studied strategies have not improved outcomes in patients with STEMI and CS, including use of intra-aortic balloon pumps,[14] percutaneous left ventricular assist devices,[15–17] and multivessel revascularization.[18] To date, the only proven strategy to reduce mortality in patients with STEMI and CS is early reperfusion.[7] Recent studies, demonstrating improved outcomes among

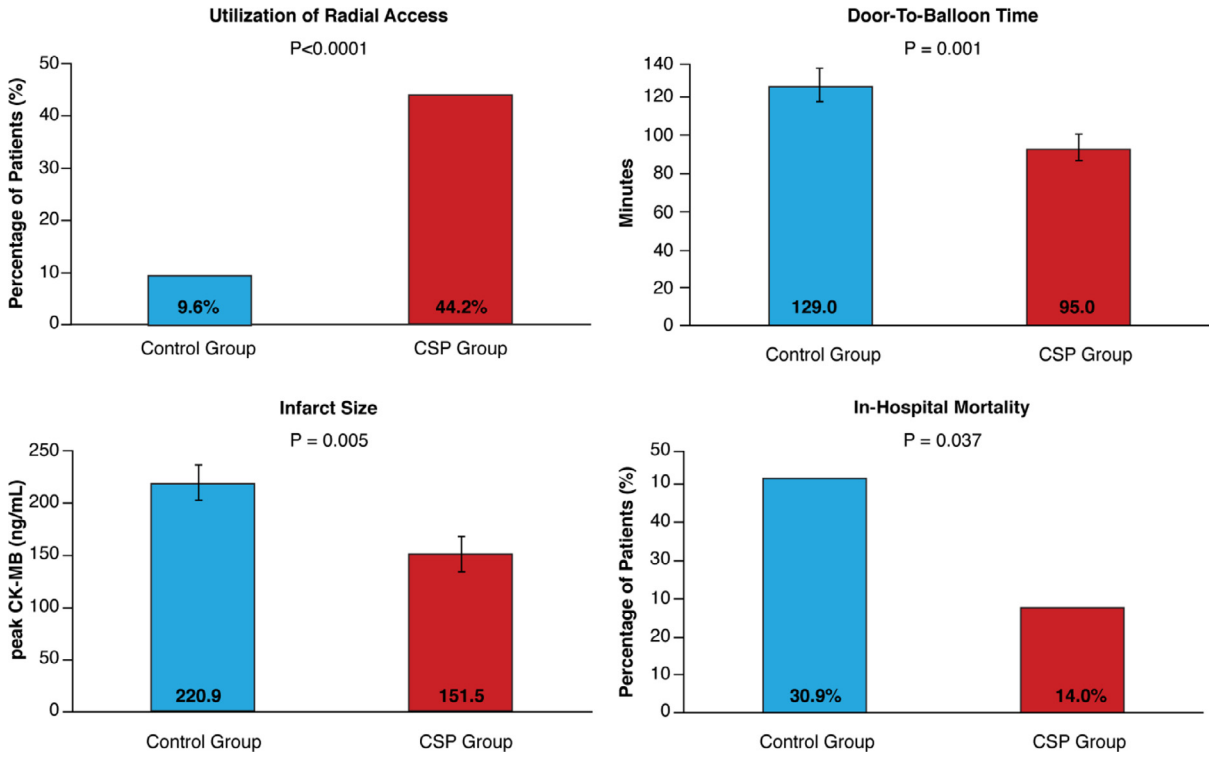

Figure 1. Improvements in utilization of radial access during percutaneous coronary intervention, door-to-balloon time, infarct size, and in-hospital mortality following implementation of a comprehensive STEMI protocol amongst patients with cardiogenic shock.

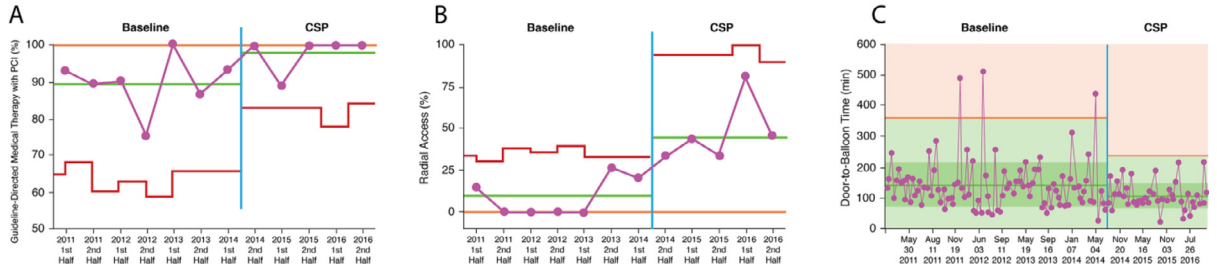

Figure 2. Quality control chart depicting improvements in (A) administration of guideline-directed medical therapy upon admission (89.4% vs 97.7%), (B) use of radial access for primary PCI (9.6% vs 44.2%), and (C) door-to-balloon time (129.0 vs 95.0 minutes) following implementation of the comprehensive STEMI protocol.

patients who underwent prompt reperfusion, called for a systems of care approach to improving D2BT.[19,20] This was studied by Kocher et al[8] who demonstrated that the AHA Mission: Lifeline STEMI Systems Accelerator project did not improve first medical contact-to-device time among patients with STEMI and CS. The authors concluded a "lack of specialized focus on high-risk STEMI patients with CS in the Accelerator program." An AHA scientific statement on the contemporary management of CS advocated for a "model of high-volume hospitals used as hubs for regional systems of care dedicated to CS care."[21,22]

However, our results highlight the importance of the specific manner in which a system of care is applied. Rather than implementing a system which focuses on care delivery specific to patients with STEMI and CS or diverting such patients to regional shock centers, we propose a paradigm shift supporting a systems of care which focuses more broadly on improving care at the STEMI-level. Cumulatively, by employing a comprehensive approach to all patients presenting with STEMI which focuses on early protocol-driven GDMT, increasing adoption of TRA for PCI, enabling rapid access to a cardiac catheterization laboratory, and providing centralized care in a modern cardiac intensive care unit, we were able to both decrease the incidence of STEMI-associated CS and improve care delivery and outcomes amongst this high-risk population. We have further demonstrated an association of our CSP with improved outcomes amongst women presenting with STEMI, another high-risk population subject to care disparities.[12]

As a corollary to this, we found that the strategies previously mentioned improved D2BT resulting in guideline-recommended time to reperfusion for > 70% of patients with STEMI and CS. In a recent study investigating causes of non-system delays, it was shown that almost half of all STEMI patients with CS were excluded from D2BT public reporting with these patients having higher associated mortality even after adjusting for presentation characteristics.[23]

Table 2
In-hospital treatment and outcomes of patients with STEMI and cardiogenic shock before and after implementation of a comprehensive STEMI protocol

Variable	No protocol (n = 94)	Protocol (n = 43)	p Value
Aspirin	90 (97%)	43 (100%)	0.551
$P2Y_{12}$ inhibitor			< 0.0001
Clopidogrel	71 (76%)	12 (28%)	
Prasugrel	3 (3%)	1 (2%)	
Ticagrelor	11 (12%)	29 (67%)	
None	9 (10%)	1 (2%)	
Unfractionated heparin or bivalrudin	93 (99%)	43 (100%)	1.000
Glycoprotein IIb/IIIa inhibitor	24 (26%)	11 (26%)	1.000
Drug eluting stent	19 (20%)	34 (79%)	< 0.001
Coronary artery bypass grafting	7 (7%)	2 (5%)	0.720
Mechanical circulatory support			0.826
Intra-aortic balloon pump	62 (66%)	29 (67%)	
Impella	2 (2%)	1 (2%)	
Tandem heart	3 (3%)	0 (0%)	
Extracorporeal membrane oxygenation	8 (9%)	5 (12%)	
In-hospital outcomes			
Postprocedure creatinine (mg/dl)	2.10 ± 1.86	2.05 ± 1.67	0.879
Postprocedure hemoglobin (g/dl)	9.30 ± 2.05	10.2 ± 2.06	0.014
Peak troponin T (ng/ml)	8.28 [2.88:13.3]	6.48 [2.66:12.3]	0.144
Peak creatine kinase-MB (ng/ml)	220.9 ± 156.0	151.5 ± 98.5	0.005
Recurrent myocardial infarction	0 (0%)	0 (0%)	n/a
Cerebrovascular accident	2 (2%)	1 (2%)	1.000
Major bleeding	35 (37%)	11 (26%)	0.242
Need for blood transfusion	42 (45%)	17 (40%)	0.710
Access site bleed	22 (23%)	5 (12%)	0.262

Table 3
Discharge characteristics and therapies of STEMI patients with cardiogenic shock before and after implementation of a comprehensive STEMI protocol

Discharge characteristics	No protocol (n = 94)	Protocol (n = 43)	p Value
Postinfarct ejection fraction	40.8 ± 14.5	46.7 ± 14.6	0.037
Postinfarct ejection fraction ≤ 35%	41 (44%)	13 (30%)	0.137
Length of stay (days)	13.0 ± 11.4	13.5 ± 11.2	0.818
Discharged to home	43 (46%)	27 (63%)	0.064
Discharge Therapies			
Aspirin	65 (100%)	35 (95%)	0.129
$P2Y_{12}$ inhibitor			0.141
Clopidogrel	41 (63%)	19 (51%)	
Prasugrel	6 (9%)	2 (5%)	
Ticagrelor	10 (15%)	13 (35%)	
None	8 (12%)	3 (8%)	
ACE inhibitor or angiotensin receptor blocker	41 (63%)	20 (54%)	0.406
Beta blocker	60 (92%)	33 (89%)	0.720
Statin	60 (92%)	34 (92%)	1.000

Although exclusion from public reporting acknowledges the barriers which physicians managing patients with STEMI and CS encounter−−patient comorbidities, management of hemodynamic instability, frequent need for transfer to a tertiary care facility, care process variables−−it supports the premise that CS complicating STEMI is a non-modifiable risk which precludes timely reperfusion. We demonstrated that implementation of a CSP can mitigate these challenges and expedite reperfusion for these high-risk patients. This raises the suggestion of a paradigm shift from acknowledging CS complicating STEMI to be a rigid obstacle to optimal care delivery to supporting the implementation of care processes which enable guideline-recommended D2BT for these patients. Future consideration should be given to creation of national metrics which, similarly to uncomplicated STEMI, assess care delivery for patients with STEMI-associated CS.

It should be noted that although we found that CSP implementation was associated with early survival, this difference dissipated after discharge. The reasons why remain unclear, as a majority of patients in the CSP cohort underwent prompt revascularization and were discharged home with appropriate GDMT and preserved ejection fraction. There are data to suggest that among STEMI patients that

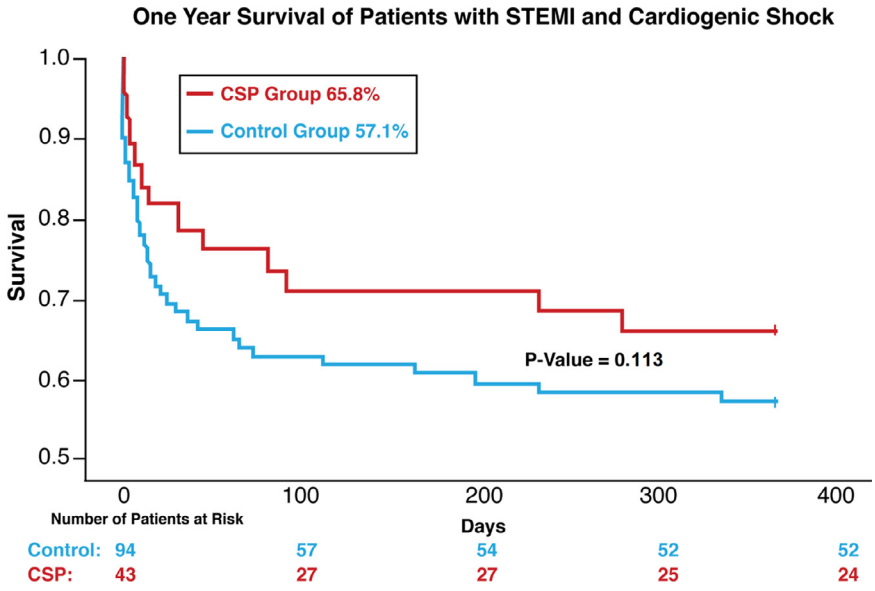

Figure 3. One-year mortality of patients with STEMI and cardiogenic shock before and after implementation of a comprehensive STEMI protocol.

survive the immediate postdischarge period, mortality is largely attributable to non-cardiac causes, namely infection, gastrointestinal bleeding, and malignancy.[24,25] It remains unclear if hospital survivors of STEMI and CS have a greater predilection for these causes of non-cardiac death in comparison to their counterparts with uncomplicated STEMI. Further studies regarding the reasons for long-term mortality and impact of outpatient follow-up upon discharge are warranted.

Our study has certain limitations. First, this is a non-randomized, prepost study with small sample size and thus subject to confounding, including changes in standard of care (greater use of drug eluting stents or novel $P2Y_{12}$ inhibitors). However, the CSP group was a predictor for in-hospital survival in multivariable analysis despite a higher IABP-SHOCK II risk score, a previously validated score strongly correlated with mortality among patients with infarct-related CS,[26] supportive of the positive impact of the program. Second, our study is based at a single STEMI referral center and warrants further validation at similar. Although this may reduce generalizability to regions without a tertiary care center, we did not exclude any patients, and our population should reflect that of any large, urban area in the United States.

In conclusion, implementation of a CSP significantly reduced the incidence of CS among patients with STEMI. Among those with STEMI and CS, care improvements with CSP were associated with improvements in infarct size, ejection fraction, and early mortality. This strategy offers an attractive solution to improve the care of these critically ill patients. However, long-term mortality remains significant in this patient population, highlighting the need for further improvements in care strategies in the outpatient setting.

Author Contributions

A Kumar: Dr. Kumar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Kumar contributed to the conception and design of the study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

CP Huded: Dr. Huded contributed to the the data analysis, the data interpretation, and the critical revision of the manuscript. L Zhou: Dr. Zhou contributed to the data interpretation and the critical revision of the manuscript. C Krittanawong: Dr. Krittanawong contributed to the data interpretation and critical revision of the manuscript. LD Young: Dr. Young contributed to the data interpretation and the critical revision of the manuscript. A Krishnaswamy: Dr. Krishnaswamy contributed to the data interpretation and the critical revision of the manuscript. V Menon: Dr. Menon contributed to the data interpretation and the critical revision of the manuscript. AM Lincoff: Dr. Lincoff contributed to the data interpretation and the critical revision of the manuscript. SG Ellis: Dr. Ellis contributed to the data interpretation and the critical revision of the manuscript. GW Reed: Dr. Reed contributed to the data interpretation and the critical revision of the manuscript. SR Kapadia: Dr. Kapadia contributed to the data interpretation and the critical revision of the manuscript. UN Khot: Dr. Khot contributed to the conception and design of the study, the supervision, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr. Khot is the corresponding author.

Author Disclosures

The authors have no relationships to industry or disclosures pertinent to this study to report.

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