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ORIGINAL SCIENTIFIC PAPER

Five-year risk of heart failure and death following myocardial infarction with cardiogenic shock: a nationwide cohort study

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Aims More patients survive myocardial infarction (MI) with cardiogenic shock (CS), but long-term outcome data are sparse. We aimed to examine rates of heart failure hospitalization and mortality in MI hospital survivors.

Methods and results First-time MI patients with and without CS alive until discharge were identified using Danish nationwide registries between 2005 and 2017. One-, 5-, and 1- to 5-year rates of heart failure hospitalization and mortality were compared using landmark cumulative incidence curves and Cox regression models. We identified 85 865 MI patients of whom 2865 had CS (3%). Cardiogenic shock patients were of similar age as patients without CS (median age years: 68 vs. 67), and more were men (70% vs. 65%). Cardiogenic shock was associated with a higher 5-year rate of heart failure hospitalization compared with patients without CS [40% vs. 20%, adjusted hazard ratio (HR) 2.90 (95% confidence interval (CI) 2.67–3.12)]. The increased rate of heart failure hospitalization was evident after 1 year and in the 1- to 5-year landmark analysis among 1-year survivors. All-cause mortality was higher at 1 year among CS patients compared with patients without CS [18% vs. 8%, adjusted HR 3.23 (95% CI 2.95–3.54)]. However, beyond the first year, the mortality for CS was not markedly different compared with patients without CS [12% vs. 13%, adjusted HR 1.15 (95% CI 1.00–1.33)].

Conclusion Among MI hospital survivors, CS was associated with a markedly higher rate of heart failure hospitalization and 1-year mortality compared with patients without CS. However, among 1-year survivors, the remaining 5-year mortality was similar for MI patients with and without CS.

Keywords Myocardial infarction • Cardiogenic shock • Long-term prognosis • Heart failure • Mortality

Introduction

Cardiogenic shock (CS) complicates 5–8% of all cases with myocardial infarction (MI) and remains the leading cause of in-hospital mortality in MI.[1–5] Even though in-hospital mortality of CS still exceeds 30–50%,[3,6,7] mortality has decreased during last decades.[2,6,8–10] In light of the improved in-hospital survival and consequential increasing number of hospital survivors, it is of great importance to focus on long-term outcomes of MI patients with CS.

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Data on the association between CS and the long-term risks of heart failure or death are sparse, as previous studies have been of limited size and/or follow-up.[11–14] Further longitudinal data are needed to understand the post-discharge consequences of CS and to improve long-term outcomes. One study reported a doubled 1-year risk of the combined endpoint of death and heart failure hospitalization for CS compared with patients without CS.[12] Other studies reported an increased risk of 1-year death after discharge for CS compared with patients without CS, though CS was not associated with increased mortality if patients survived more than 1 year.[11–13,15]

We hypothesized that CS may have an impact on heart failure hospitalization rate and/or death beyond the short-term course based on the initial presentation with severe in-hospital heart failure, organ hypoperfusion, and potentially irreversible myocardial damage.[1] We conducted a nationwide cohort study to examine the association between CS and rates of heart failure hospitalization and death among MI patients discharged alive for up to 5 years of follow-up.

Methods

Design and setting

We conducted this cohort study from 2005 through 2017 with data from nationwide Danish registries.[16] The Danish National Health Service provides universal tax-funded health care, guaranteeing access to general practitioners and hospitals, and partial reimbursement of prescribed medication.[16] The unique 10-digit Danish Civil Personal Registry number, assigned to all Danish citizens at birth and to residents upon immigration, allows unambiguous linkage of registries and information on all Danes.[17]

First-time myocardial infarction with cardiogenic shock

The Danish National Patient Registry was used to identify all persons with a first-time admission for MI without a history of heart failure from 1 January 2005 through 31 December 2017.[18] Only patients alive until after discharge were included. The Danish National Patient Registry contains data on all hospital admissions since 1977 and on all hospital outpatient specialist clinic and emergency room contacts since 1995. Each admission is assigned one primary diagnosis code and one or more secondary codes classified according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.

Among patients with first-time MI, CS was defined by a diagnosis code of CS and/or by medical treatment with vasoactive drugs in relation to the MI admission. The ICD-10 codes are provided in Supplementary material online, *Table S1*. Patients treated with vasoactive drugs, but without a diagnosis code for CS, were excluded if they had a diagnosis code for other shock during admission. The reporting of CS and important intensive procedures stabilized from 2005, why this was chosen as the study start, and 2017 represented the end of our database. A flowchart of the inclusion and exclusion criteria is provided in *Figure 1*. We used validated definitions of MI (positive predictive value: 97%)[19] and CS (positive predictive value: 94%).[20]

Outcomes: heart failure hospitalization and mortality

Heart failure hospitalization and all-cause death were the study outcomes. We defined heart failure hospitalization as any inpatient contact registered with heart failure as primary or secondary diagnosis, following the index admission for MI. We used a validated definition of heart failure hospitalization (positive predictive value: 76–81%).[19,21] Data on all-cause mortality were obtained from the Danish Civil Registration System until the end of 2018.[17] Since 1968, this registry provides daily electronic updates of changes in vital status and migration for the entire Danish population.[17]

Covariates

Data on age, sex, and marital status were collected from the Danish Civil Registration System.[17] We obtained data on comorbidities from the Danish National Patient Registry in a 10-year period preceding MI admission using both primary and secondary in- and outpatient diagnosis codes. We included comorbidities with a potential impact on long-term risks of heart failure or death,[11,12] and used validated definitions.[19,22] Data on out of hospital cardiac arrest (OHCA) in relation to MI admission were obtained from the Danish Cardiac Arrest Registry[23] and the Danish National Patient Registry. Data on OHCA were available in the database until 2015. The Danish National Prescription Registry was used to obtain data on filled prescriptions within 180 days before the MI admission for concomitant pharmacotherapy.[24] We identified in-hospital procedure codes of coronary angiography (CAG), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and mechanical circulatory during admission. High validity has been reported for the use of cardiac procedures in a validation study.[25] All codes are provided in Supplementary material online, *Table S1*.

Statistical analyses

Baseline characteristics were described as frequencies and percentages or medians with interquartile range as appropriate. Baseline differences between MI patients with and without CS were tested using the χ^2 test for categorical variables and Wilcoxon for continuous variables. Cumulative incidence functions and one Kaplan–Meier functions were used to estimate and compare 5-year rates of heart failure hospitalization or death in cohorts of patients with and without CS. For the heart failure hospitalization outcome, we accounted for competing risk of non-heart failure death by use of the Aalen–Johansen estimator. We compared the rates of heart failure hospitalization and mortality in patients with and without CS with use of Gray's test and log-rank, respectively. Crude and multivariable cause-specific Cox proportional hazards models were created for the outcomes comparing CS patients to patient without CS. In the adjusted models, we included information on age, sex, marital status, calendar year of diagnosis, revascularization status (PCI or CABG during admission), and comorbidities (peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, hypertension, atrial fibrillation/flutter, venous thromboembolism, kidney disease, liver disease, diabetes, cancer). Cox proportional hazard assumptions were not fulfilled in the 5-year analyses, why we repeated the analyses for heart failure hospitalization and death in landmark analyses from 0 to 1 year and 1 to 5 years after discharge. Only patients who survived the first-year post-discharge were included in the 1- to 5-year landmark analyses. We estimated 1- to 5-year risk of death stratified upon heart failure status within 1 year in order to examine the effect of heart failure upon long-term risk of death. The landmark was chosen in a clinically relevant perspective and to compare with existing literature. We then examined factors associated with 1-year outcomes among patients with CS including age, sex, comorbidities, and in-hospital procedures. Finally, we examined the association between calendar year and (i) 1-year rate of heart failure hospitalization and (ii) 1-year mortality in adjusted Cox models in subgroups of patients with and without CS. All assumptions of the Cox model were tested and found valid unless otherwise indicated. The analyses were performed using SAS version 9.4 and R version 3.5.1.

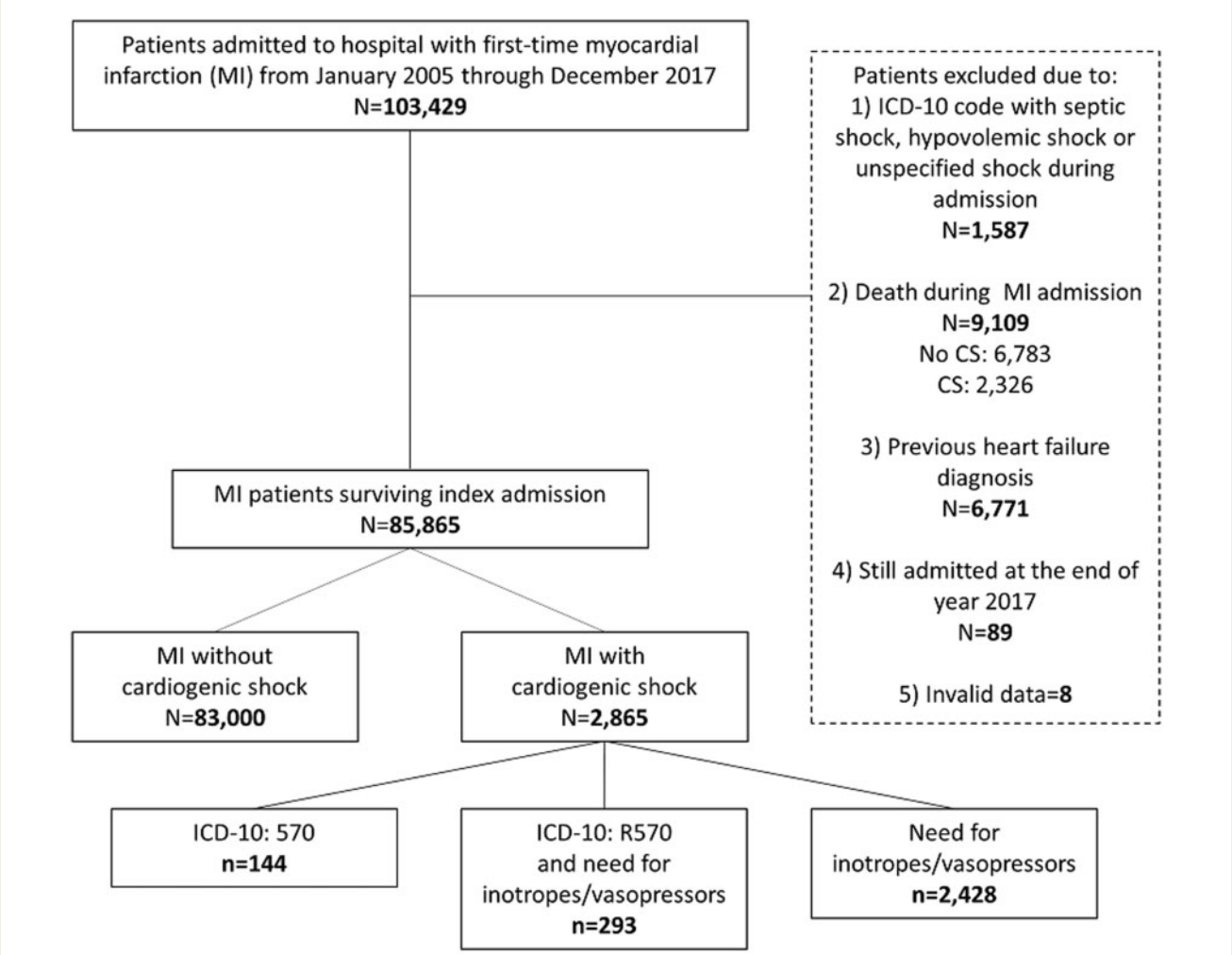

Figure 1 Flowchart of the study population. CS, cardiogenic shock; ICD-10, International Classification of Diseases, 10th revision; MI, myocardial infarction.

Sensitivity analyses

We estimated cumulative incidence functions of first use of loop diuretics after discharge (as a marker of heart failure symptoms) with competing risk of death. Heart failure medication (renin–angiotensin–aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, diuretics) redeemed within first year were identified among 1-year survivors. Moreover, 1- to 5-year landmark analyses were conducted accounting for heart failure medication redeemed within first year after discharge—in addition to the variables mentioned previously; this was done to evaluate whether heart failure medication modified the association between in-hospital CS and outcomes beyond first year. The landmark analyses were repeated for the outcomes: (i) heart failure hospitalization defined by only a primary diagnosis code and (ii) any in- or outpatient heart failure hospital contact (to test the completeness). Finally, we examined any difference in outcomes in subgroups of CS patients (either ICD-10: R570 or need for vasoactive drugs).

Ethics approval

This study complies with the Declaration of Helsinki. Register studies do not require ethical permission in Denmark. The use of data for the study was approved by the Danish Data Protection Agency (Capital Region of Denmark Approval number: P-2019-396).

Results

Patient characteristics

After applying our selection criteria, 85 865 MI patients were included in the study (*Figure 1*); 2865 patients had CS during hospitalization (3%). Compared with patients who died during admission, those who survived until discharge were of younger age, had lower comorbidity burden, and were more often revascularized (Supplementary material online, *Table S2*). Baseline characteristics of the hospital survivors according to CS during admission are displayed in *Table 1*. Of the hospital survivors, CS patients were of similar age as patients without CS (median age: 68 vs. 67), more often men (70% vs. 65%), and had a slightly higher comorbidity burden.

Table 1 Baseline characteristics for patients surviving until discharge after myocardial infarction

	MI		*P*-value
	No cardiogenic shock, *n* (%)	Cardiogenic shock, *n* (%)	
Total	83 000 (100)	2865 (100)	—
Male gender	53 491 (64.5)	1999 (69.8)	<0.0001
Median age (IQR)	68 (58–78)	67 (58–75)	<0.0001
Median admission length (days) (IQR)	4 (3–7)	10 (5–18)	<0.0001
Median follow-up time (years) (IQR)	3.3 (0.8–5.0)	0.7 (0.1–4.4)	<0.0001
Age (years)			
<50	9463 (11.4)	303 (10.6)	
50–59	15 626 (18.8)	533 (18.6)	
60–69	20 898 (25.2)	852 (29.7)	
70–79	19 951 (24.0)	835 (29.1)	
≥80	17 062 (20.6)	342 (11.9)	
Living alone	27 734 (33.4)	913 (31.9)	0.09
OHCA[a]	1045 (1.5)	816 (33.1)	<0.0001
Comorbidities			
Peripheral vascular disease	5132 (6.2)	262 (9.1)	<0.0001
Cerebrovascular disease	7638 (9.2)	283 (9.9)	0.22
COPD	4172 (5.0)	201 (7.0)	<0.0001
Hypertension	17 091 (20.6)	612 (21.4)	0.32
Atrial fibrillation/flutter	4850 (5.8)	201 (7.0)	0.01
Chronic kidney disease	1950 (2.4)	181 (6.3)	<0.0001
Liver disease	845 (1.0)	37 (1.3)	0.15
Venous thromboembolism	2061 (2.5)	58 (2.0)	0.12
Diabetes[b]	10 927 (13.2)	475 (16.6)	<0.0001
Cancer	6521 (7.9)	208 (7.3)	0.24
Subtypes of MI			
STEMI	19 667 (23.7)	873 (30.5)	<0.0001
NSTEMI	36 055 (43.4)	505 (17.6)	<0.0001
MI unspecified	27 278 (32.9)	1487 (51.9)	<0.0001
Revascularization therapy			
Coronary angiography	66 949 (80.7)	2327 (81.2)	0.46
PCI	47 631 (57.4)	1718 (60.0)	0.01
Coronary bypass	7352 (8.9)	509 (17.8)	<0.0001
Medical therapy before hospitalization[c]			
Anti-platelet drugs[d]	20 820 (25.1)	753 (26.3)	0.14
Calcium channel blockers	16 145 (19.5)	650 (22.7)	<0.0001
ACE-I/ARBs	24 518 (29.5)	977 (34.1)	<0.0001
Beta-blockers	14 926 (18.0)	526 (18.4)	0.60
Mineralocorticoid-receptor antagonists	1446 (1.7)	54 (1.9)	0.57
Diuretics	19 460 (23.5)	722 (25.2)	0.03
Statins	19 302 (23.3)	782 (27.3)	<0.0001
Anti-diabetics	9381 (11.3)	398 (13.9)	<0.0001

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases, 10th revision; IQR, interquartile range; MI, myocardial infarction; OHCA, out of hospital cardiac arrest; PCI, percutaneous coronary intervention.
[a]Data on OHCA is available between 2005 and 2015.
[b]Defined by an ICD-10 code with diabetes or use of anti-diabetics defines as a redeemed prescription within 180 days before admission.
[c]Defined as a redeemed prescription within 180 days before admission.
[d]Defined as either acetylsalicylic acid or clopidogrel.

Table 2 In-hospital procedures in acute myocardial infarction-related cardiogenic shock from 2005 to 2017

	Total, *n* (%)	<50 years, *n* (%)	50–59 years, *n* (%)	60–69 years, *n* (%)	70–79 years, *n* (%)	≥80 years, *n* (%)	*P* for trend
Total	2865 (100)	303 (100)	533 (100)	852 (100)	835 (100)	342 (100)	
Cardiac procedures							
CAG	2327 (81.2)	280 (92.4)	479 (89.9)	735 (86.3)	640 (76.6)	193 (56.4)	<0.0001
PCI	1718 (60.0)	235 (77.6)	390 (73.2)	522 (61.3)	428 (51.3)	143 (41.8)	<0.0001
CABG	509 (17.8)	36 (11.9)	100 (18.8)	194 (22.8)	155 (18.6)	24 (7.0)	0.1260
Mechanical circulatory support							
IABP	315 (11.0)	41 (13.5)	71 (13.3)	104 (12.2)	82 (9.8)	17 (5.0)	<0.0001
LV assist device	101 (3.5)	19 (6.3)	29 (5.4)	29 (3.4)	19 (2.3)	5 (1.5)	<0.0001
ECMO[a]	8 (0.3)	<4	<4	<4	<4	<4	—
Intensive care							
RRT	402 (14.0)	44 (14.5)	66 (12.4)	127 (14.9)	141 (16.9)	24 (7.0)	0.3982
Mechanical ventilation	2437 (85.1)	279 (92.1)	480 (90.1)	756 (88.7)	686 (82.2)	236 (69.0)	<0.0001

CABG, coronary artery bypass grafting; CAG, coronary angiography; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular; PCI, percutaneous coronary intervention; RRT, renal replacement therapy.
[a]According to rules of use of data from the Danish National Patient Register, it is not allowed to report <3 observations.

In-hospital procedures for cardiogenic shock patients surviving until discharge

The youngest groups of MI patients with CS were more revascularized as displayed in *Table 2*; 92% of patients <50 years underwent CAG and subsequently 60% PCI, whereas only 56% of patients ≥80 years had CAG and 42% of those were treated with PCI (*P* for trend < 0.0001 for use of CAG and PCI according to age group, respectively). More patients were treated with intra-aortic balloon pump (IABP) (11%) than left ventricular (LV) assist device (4%) in the study period. The use of mechanical circulatory devices was more prevalent among the youngest patients (*P* for trend < 0.0001).

Heart failure hospitalization

One-year rate of heart failure hospitalization was three-fold higher for CS patients compared with patients without CS [21% (95% confidence interval (CI) 19–22) vs. 7.8% (95% CI 7.6–7.9), adjusted hazard ratio (HR) 3.25 (95% CI 2.98–3.54)] (*Figure 2*). Over time, no changes in 1-year heart failure hospitalization were observed in the subgroup of patients with CS (*P* for temporal change: 0.58) (Supplementary material online, *Figure S1*), whereas for the subgroup of patients without CS 1-year heart failure hospitalization decreased (*P* for temporal change < 0.0001) (Supplementary material online, *Figure S1*). The 5-year rate of heart failure hospitalization in patients with CS was 28% (95% CI 27–30) compared with 13.5% (95% CI 13.2–13.7) in those without CS. The association remained statistically significant in the multivariable analysis with a HR of 2.90 (95% CI 2.67–3.12). Age groups modified the association between CS and 5-year rate of heart failure hospitalization with less impact of CS with increasing age (*P* for interaction < 0.0001) (Supplementary material online, *Table S3*). In the 1- to 5-year landmark analysis, CS was still associated with a higher rate of heart failure hospitalization compared with patients without CS [13% (95% CI 11–14) vs. 6.8% (95% CI 6.6–7.0), adjusted HR 2.11 (95% CI 1.82–2.45)] (*Figure 3*).

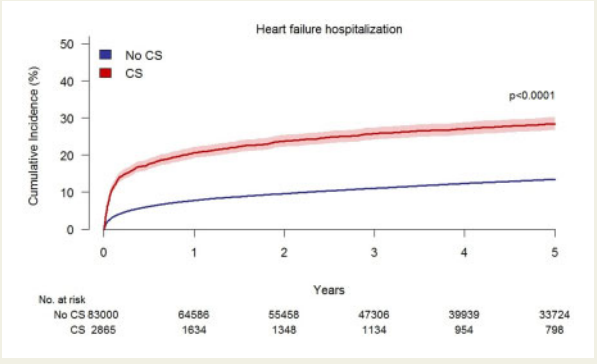

Figure 2 Five-year rate of heart failure hospitalization among myocardial infarction patients surviving until discharge, by cardiogenic shock status. CS, cardiogenic shock.

Among patients with CS, advancing age, diabetes, IABP, and LV assist devices were associated with an increased 1-year HR of heart failure hospitalization (Supplementary material online, *Table S4*).

Mortality

One-year mortality after discharge in CS patients was 18% (95% CI 17–20) compared with 8.1% (95% CI 7.9–8.3) in those without CS with an adjusted HR of 3.23 (95% CI 2.95–3.54) (*Figure 4*). Five years after discharge, the mortality in CS was 28% (95% CI 27–30) compared with 19.9% (95% CI 19.6–20.2) in patients without CS [adjusted HR 2.13 (95% CI 1.98–2.30)]. Over time, 1-year mortality decreased for both subgroups of patients with and without CS

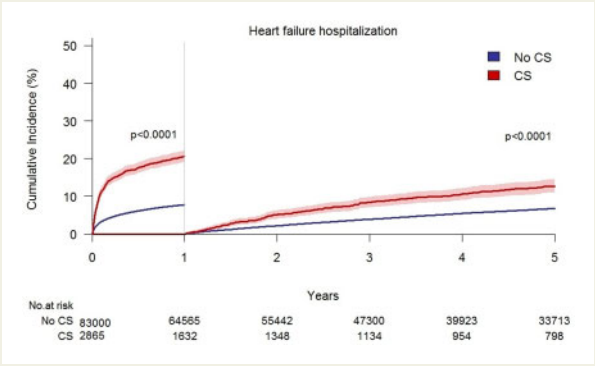

Figure 3 One- and 1- to 5-year rate of heart failure hospitalization, by cardiogenic shock status. CS, cardiogenic shock.

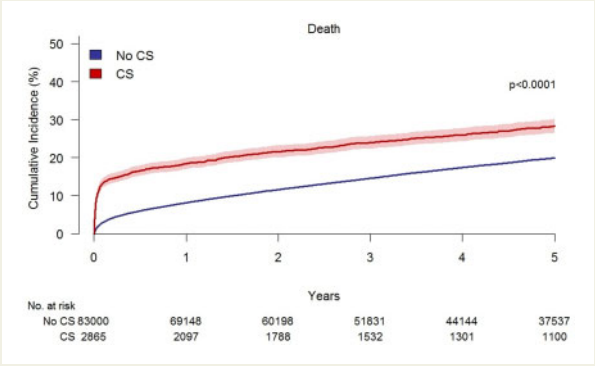

Figure 4 Five-year mortality among myocardial infarction patients surviving until discharge, by cardiogenic shock status. CS, cardiogenic shock.

(*P* for temporal change < 0.05) (Supplementary material online, *Figure S1*). Age modified the association between CS and 5-year death with decreasing association with increasing age as reported in Supplementary material online, *Table S2* (*P* for interaction < 0.0001). In the 1- to 5-year landmark analysis, all-cause mortality risks in patients with and without CS were not significantly different [12% (95% CI 11–14) vs. 12.8% (95% CI 12.6–13.1)] (*Figure 5*), however, the HR was 1.15 (95% CI 1.00–1.33) in the adjusted analysis comparing patients with and without CS. The 1-year MI survivors with and without CS had similar age (median age, years: 65 vs. 66) and comorbidity burden (Supplementary material online, *Table S5*). However, unaffected by CS status, patients with heart failure hospitalization within first year after discharge had markedly higher mortality from landmark at 1 year and forward compared with patients without heart failure [with heart failure: CS: 31% (95% CI 26–35), no CS: 35% (95% CI 34–37), without heart failure: CS: 20% (95% CI 18–22), no CS: 16% (95% CI 15.9–16.5)] (Supplementary material online, *Figure S2*). Finally, in patients with CS advancing age and several comorbidities were highly associated with greater 1-year mortality, whereas PCI and CABG were associated with lower 1-year mortality (Supplementary material online, *Table S4*).

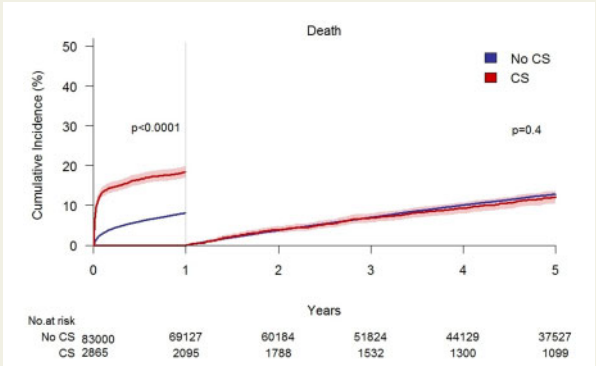

Figure 5 One- and 1- to 5-year mortality, by cardiogenic shock status. CS, cardiogenic shock.

Sensitivity analyses

The likelihood of loop diuretics use 5 years after discharge was markedly higher for CS compared with patients without CS [55% vs. 38%, adjusted HR 2.33 (95% CI 2.20–2.45)]. Among 1-year survivors, more CS patients received two or more heart failure drugs within first year after discharge (59% vs. 39%) (*Table 3*). The associations between CS and the outcomes heart failure hospitalization and death were similar in landmark analyses from 1 to 5 years post-discharge adjusted for heart failure medication [heart failure: HR 1.61 (95% CI 1.38–1.87) and death: HR 1.10 (95% CI 0.96–1.27)]. The increased risk of heart failure hospitalization for CS patients compared with patients without CS was persistent in the analysis with only primary diagnosis coded. The use of both in- and outpatient heart failure increased capture within first year, whereafter no further information was gained (Supplementary material online, *Figure S3*). The results for the sub-cohorts of CS patients restricted to patients with either R570 diagnosis code or need for vasoactive drugs were consistent with the overall results. However, patients with an R570 diagnosis code were associated with higher rates of heart failure hospitalization and mortality compared to patients only defined by need for vasoactive drugs (Supplementary material online, *Table S6*).

Discussion

We observed a persistent increased cumulative incidence of heart failure hospitalization until 5 years after discharge comparing patients with and without CS. One-year mortality was doubled for CS compared with patients without CS; however, beyond 1 year after discharge, the mortality was not markedly different between patients with and without CS. Over time, we observed no difference in heart failure hospitalization for patients with CS, whereas for patients without CS a discrete decrease was observed. Unaffected by CS status, mortality decrease with time.

In-hospital procedures

The prevalence of CAG and revascularization in this study is consistent with findings in previous observational studies.[2,6,26] We observed similar use of CAG in MI patients with and without CS ~80%, and a

Table 3 Heart failure medication within first year after discharge among survivors with myocardial infarction until 1 year after discharge

	Myocardial infarction		*P*-value
	No cardiogenic shock, *n* (%)	Cardiogenic shock, *n* (%)	
One-year survivors, total	74 771 (100)	2246 (100)	—
Heart failure medication[a]			
Heart failure medication ≥2	28 837 (38.6)	1314 (58.5)	<0.0001
ACE-I/ARBs	27 367 (36.6)	1158 (51.6)	<0.0001
Heart failure hospitalization[b]	3058 (4.1)	309 (13.8)	<0.0001
Beta-blockers	52 659 (70.4)	1381 (61.5)	<0.0001
Heart failure hospitalization	3493 (4.7)	293 (13.1)	<0.0001
MRAs	3129 (4.2)	306 (13.6)	<0.0001
Heart failure hospitalization	807 (1.0)	113 (5.0)	0.0001
Diuretics	17 013 (22.8)	1105 (49.2)	<0.0001
Heart failure hospitalization	2808 (3.8)	320 (14.3)	<0.0001

ACE-I, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs: mineralocortiocoid-receptor antagonists.
[a]Defined as any reedemed heart failure medical drug during first year after discharge wih first-time myocardial infarction.
[b]Defined as heart failure hospitalization within 1 year after hospital discharge.

similar approach was also seen for the groups concerning PCI. CS patients without CAG were the oldest most comorbid patients, which could explain the deselection of this diagnostic strategy. We observed high compliance to guidelines among the youngest MI patients with CI, whereas the use of CAG and PCI decreased with increasing age.

In patients with persistent hypoperfusion despite standard medical therapy, mechanical circulatory support may be indicated.[27] Since the IABP-SHOCK II trial,[28] use of IABP has decreased, along with a simultaneous increase in use of LV assist device.[3,6] Left ventricular assist device as a therapeutic agent did, however, not prove any superiority compared with IABP;[29] thus, gaps in evidence still exist concerning the best timing and indication for the use of mechanical circulatory support in MI with CS.[30] Younger age was associated with more frequent use of IABP and LV assist device. Increasing age is often followed by high comorbidity burden, complexity of disease, and increased risk of complications, why a great challenge remains in selecting those patients who will benefit from aggressive therapy.

Long-term heart failure hospitalization

Considering the growing number of hospital survivors it is of great importance to add knowledge on the long-term course to improve post-discharge survival and quality of life. Studies with long-term outcome are sparse, especially concerning heart failure, and those that do exist were of limited size and with lack of long-term follow-up.[11–14,31,32] Shah *et al.*[12] reported an increased risk of the composite endpoint of re-hospitalization with heart failure or death within 1 year after discharge with CS compared with patients without CS (33% vs. 24%). Furthermore, culprit-lesion-only PCI was associated with higher risk of re-hospitalization with heart failure within 1 year compared with multi-vessel PCI (5.2% vs. 1.2%).[33] In comparison, we found a persistent doubled rate of first-time heart failure hospitalization for MI patients with CS compared with those without CS; in absolute numbers corresponding to a 20% cumulative incidence 1 year after discharge and 13% from 1 to 5 years. The steep increase in risk of first-time heart failure hospitalization within 1 year of follow-up emphasizes the persistent impact of the acute cardiac condition beyond hospitalization. Consistent with a previous study, markedly more patients with CS redeemed heart failure medication after discharge compared with those without CS.[13] Along with recovery, use of evidence-based heart failure medication may facilitate the diminished long-term risk of heart failure. The long-term association between CS and heart failure hospitalization was persistent despite multiple adjustments (sex, age, comorbidities, heart failure medication, etc.). We did not have data on in-hospital or post-discharge ejection fraction, but do not either consider it appropriate for inclusion in the regression analysis as it indirectly either reflect the CS exposure or a causal intermediate, respectively. The higher rate of heart failure observed in our study compared with prior results may be explained by the improved survival among MI patients with and without CS, thus, a larger number of patients at risk of long-term heart failure. In addition, this study consisted of an unselected nationwide cohort of MI patients, why the results of this study may be more complete than previous findings.

Heart failure hospitalization was unaffected by calendar year of diagnosis for the subgroup of patients with CS despite increase in early revascularization. This finding may be due to increased survival until hospital discharge,[2,6,34] more complexity of disease, and increasing age and comorbidity burden among CS patients carrying multiple risk factors for heart failure.[3] Among patients without CS, heart failure hospitalization decreased slightly, which may be explained the decrease in MI[35] and improved tertiary prevention of heart failure after MI (beta-blockers, aldosterone, renin-angiotensin inhibitors, etc.).[36]

A plausible mechanism underlying the increased risk of heart failure in patients with CS compared with MI patients without CS is based on the significant association between infarct size, residual LV ejection fraction, and long-term heart failure.[37,38] Stone *et al.*[37] proved a graded relationship between infarct size and 1-year risk of heart failure hospitalization unaffected by known risk factors for heart failure (age, diabetes, hypertension, etc.), thus, emphasizing the increased risk of long-term heart failure hospitalization for patients with large MI, e.g. patients with CS in relation to MI.

Consistent with a prior study, advancing age, diabetes, IABP, and LV assist device were significantly associated with increased risk of heart failure hospitalization within 1 year in patients with CS.[14] Patients who were treated with mechanical circulatory devices may represent the most deranged subgroup of patients with CS, thus, among those who survive until discharge, the need for mechanical circulatory device may act as a proxy for severity of disease.

Long-term mortality

Consistent with our findings, previous studies demonstrated an increased mortality 1 year after discharge comparing patients with and without CS (23% vs. 7–16%).[11–13,15] Only one study based on 99 CS patients from the French registry, Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) 2005 Registry, had more than 1 year of follow-up.[13] Consistent with our findings, survival was similar for patients with and without CS beyond the first year in a landmark analysis from 1 to 5 years after MI [1- to 5-year survival: 76% vs. 82%, adjusted HR 1.06 (0.64–1.74)].[13] Similar findings were observed in two studies containing MI patients with CS aged >65 years, where equal mortality risks were observed after 3–6 months.[12,15] Over time, 1-year mortality decreased for patients with and without CS; changes that may be explained by the increasing use of early revascularization,[39] and improved tertiary prevention.[36]

Cardiogenic shock is a low-cardiac-output state causing severe myocardial dysfunction, ischaemia, inflammation, and end-organ hypoperfusion.[1] The initial decreased cardiac contractility causes a complex pathophysiological response including compensatory vasoconstriction and a counter-acting vasodilatation caused by systemic inflammatory response syndrome.[1] Along with the severe myocardial damage and subsequent residual LV ejection fraction, these mechanisms may explain the increased 1-year mortality, among those patients who survive until hospital discharge. Despite lack of clarity, the similar mortality between MI patients with and without CS beyond 1 year may be explained by the selection of patients who have overcome the initial systemic derangement in absence of the most severe affected subset of MI patients; i.e. those with severe myocardial dysfunction due to CS along with subsequent in-hospital complications as renal failure, mechanical complications, and long intensive care treatment.

Cardiogenic shock survivors at 1 year after discharge had reduced comorbidity burden and younger age than the total cohort of CS patients; thus, emphasizing the selection of patients with CS who survive until 1 year as more 'healthy survivors' with more transient ischaemia and lesser probability of long-term cardiac dysfunction and mortality. This selection of 1-year CS survivors of CS may also explain why patients with CS and a heart failure hospitalization within first year after MI was associated with a lower mortality than those without CS and with heart failure hospitalization, since those with the most reduced ejection fraction died earlier. Still, heart failure hospitalization was associated with increased mortality beyond 1 year of follow-up for both patients with and without CS, but we cannot infer any link between in-hospital CS and increased mortality beyond first year.

Among others, advancing age, peripheral vascular disease, renal disease, and hypertension were associated with increased 1-year mortality, whereas PCI and CABG were associated with lower 1-year mortality.[40]

Strengths and limitations

The potential of selection bias is minimized with a well-defined nationwide cohort in a country providing tax-financed universal healthcare with complete mortality data.[16,17] The positive predictive value for the diagnosis codes with MI, CS, and vasoactive drugs are above 90% in the Danish National Patient Registry.[19,20] Considering the 50% in-hospital mortality, the prevalence of CS in this study is comparable with existing literature with an in-hospital CS prevalence of ~5–10%.[1,2,6] The positive predictive value for heart failure hospitalization was 76–81%.[19,21] The symptoms of heart failure are often non-specific (fatigue, swelling, dyspnoea), thus, we cannot exclude the potential of misclassification of heart failure status. However, all sensitivity analyses led in the same direction as the primary heart failure outcome. The subtypes of MI have high positive predictive value, but low completeness in the Danish National Patient Registry.[19] Furthermore, we do not have data on lactate levels, cardiac index, duration of shock, and ejection fraction in the registry. We note that multivariable adjustments changed the effect estimates marginally but we cannot exclude unmeasured or residual confounding. Due to the observational nature of this study, no causal relation can be inferred from the results. The results of this study may be applicable to other industrial Western countries with similar approach to guideline-based treatment of myocardial infarction (MI), CS, and heart failure.

Conclusions

Among MI hospital survivors, CS was associated with a markedly higher early and late rate of heart failure hospitalization compared with patients without CS. In addition, the presence of CS was associated with increased 1-year all-cause mortality, whereas beyond the first year, mortality was similar for MI patients with and without CS.

Supplementary material

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

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