Ten-Year (2001–2011) Trends in the Incidence Rates and Short-Term Outcomes of Early Versus Late Onset Cardiogenic Shock After Hospitalization for Acute Myocardial Infarction

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Background—Cardiogenic shock (CS) is a serious complication of acute myocardial infarction, and the time of onset of CS has a potential role in influencing its prognosis. Limited contemporary data exist on this complication, however, especially from a population-based perspective. Our study objectives were to describe decade-long trends in the incidence, in-hospital mortality, and factors associated with the development of CS in 3 temporal contexts: (1) before hospital arrival for acute myocardial infarction (prehospital CS); (2) within 24 hours of hospitalization (early CS); and (3) ≥24 hours after hospitalization (late CS).

Methods and Results—The study population consisted of 5782 patients with an acute myocardial infarction who were admitted to all 11 hospitals in central Massachusetts on a biennial basis between 2001 and 2011. The overall proportion of patients who developed CS was 5.2%. The proportion of patients with prehospital CS (1.6%) and late CS (1.5%) remained stable over time, whereas the proportion of patients with early CS declined from 2.2% in 2001–2003 to 1.2% in 2009–2011. In-hospital mortality for prehospital CS increased from 38.9% in 2001–2003 to 53.6% in 2009–2011, whereas in-hospital mortality for early and late CS decreased over time (35.9% and 64.7% in 2001–2003 to 15.8% and 39.1% in 2009–2011, respectively).

Conclusions—Development of prehospital and in-hospital CS was associated with poor short-term survival and the in-hospital death rates among those with prehospital CS increased over time. Interventions focused on preventing or treating prehospital and late CS are needed to improve in-hospital survival after acute myocardial infarction. (*J Am Heart Assoc*. 2017;6:e005566. DOI: 10.1161/JAHA.117.005566.)

Key Words: acute myocardial infarction • cardiogenic shock timing • hospital prognosis • population-based study

Cardiogenic shock (CS) is a serious complication of acute myocardial infarction (AMI).[1–6] The frequency of CS has either slightly declined or remained unchanged over time, with reported rates ranging from 3% through 10%, depending, in part, on the definitions used to define CS and the characteristics of the populations studied.[7–11] Although the hospital case-fatality rates associated with CS have encouragingly

declined over time, CS remains a major cause of death among patients hospitalized with AMI.[7–11]

Understanding the magnitude and impact of the timing of CS, and factors associated with the time of onset of CS, are crucial to identifying patients at increased risk for this serious clinical complication and enhancing their prognosis. Previous studies have shown that a minority of patients with AMI developed CS before hospital admission, whereas the majority developed this complication during their acute hospitalization, especially during the first 24 hours.[7,9,12–16] The pathophysiology, hospital management, and outcomes associated with CS are likely to be different for patients who develop this complication prehospital or at varying time intervals during hospitalization for AMI. However, data in this area are very limited or from the distant past.[7,14–16]

In several previous publications from our population-based coronary heart disease surveillance system among residents of central Massachusetts, we examined trends in the incidence and hospital case-fatality rates associated with in-hospital CS among patients hospitalized with AMI.[4–6,8] The objectives of the present study were to describe relatively contemporary decade-

Clinical Perspective

What is New?

- The results of this community-wide study provide insights into the magnitude of CS, the timing of its occurrence, and its impact on in-hospital death rates among patients hospitalized with AMI overall and over time.
- The proportion of patients who developed prehospital or late (≥24 hours after hospital admission) CS remained stable, whereas the proportion of patients who developed early CS increased and subsequently decreased between the most distant and recent study years.
- The in-hospital death rates were 46%, 33%, and 54%, respectively, for those with prehospital, early, and late CS.

What are the Clinical Implications?

- Clinicians should remain diligent about the prevention of this significant clinical syndrome and treat patients with AMI who develop this condition as soon as possible, especially those who develop CS later during their acute hospital stay.
- We found differences in the sociodemographic and clinical factors associated with the timing of CS, which reinforces the need for a more-detailed assessment of possible predisposing factors that may lead to the development of this serious clinical syndrome at varying time intervals after hospitalization for AMI.

long trends (2001–2011) in the incidence and in-hospital death rates associated with the timing of CS (prehospital, early during hospitalization, and late) in patients hospitalized with AMI and explore factors associated with the timing of CS.

Methods

The Worcester Heart Attack Study is an ongoing population-based investigation that is examining long-term trends in the descriptive epidemiology of AMI among residents of the Worcester, Massachusetts, metropolitan area hospitalized at all medical centers in central Massachusetts on an approximate biennial basis.[2,3,17,18] All data collected from the hospital medical records of patients with independently validated AMI in this population-based clinical/epidemiological investigation are independently reviewed by experienced physician and nurse reviewers and validated to the extent possible. This is in contrast to information that is recorded in an administrative database, which is often neither independently reviewed nor validated in a standardized manner.

Computerized printouts of patients discharged from all greater Worcester hospitals with possible AMI (International Classification of Disease, Ninth Revision codes: 410–414, 786.5) were identified and cases of AMI were independently validated using predefined criteria.[2,3,17,18] We reviewed the medical records of all consecutive geographically eligible (eg, resident of central Massachusetts) patients who were hospitalized for AMI at all 11 central MA medical centers during the years under study. Diagnoses of ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) were made using standardized criteria.[19]

Trained nurses and physicians abstracted information on patients' demographic and clinical characteristics and hospital treatment practices through the review of hospital medical records. These factors included patients' age, sex, race/ethnicity, mode of transportation, hospital length of stay, history of previously diagnosed comorbidities and cardiac procedures, AMI type (STEMI versus NSTEMI) and order (initial versus previous), clinical signs and symptoms, and laboratory findings on admission.[20,21] Information on the development of important in-hospital complications, including atrial fibrillation,[22] CS,[6] heart failure,[23] and stroke,[24] was collected.

Patients with a systolic blood pressure of <80 mm Hg in the absence of hypovolemia and associated with cyanosis, cold extremities, changes in mental status, persistent oliguria, or congestive heart failure, as recorded in hospital medical records, were defined as having CS.[4–6] The definition of CS remained the same during all periods studied. This disorder was defined so that patients with classic signs and symptoms of this clinical syndrome would be included. Data on cardiac index or left ventricular ejection fraction findings were not included as part of our working definition for CS in this study. In the present analysis, because the exact time of onset of AMI was not possible to be precisely determined, CS was categorized into 3 distinct groups based on time of admission: prehospital; early (during the first 24 hours after admission); and late shock (≥24 hours after hospital admission).

Data on the receipt of 3 coronary diagnostic and interventional procedures (cardiac catheterization, percutaneous coronary intervention [PCI], and coronary artery bypass grafting [CABG]), intra-aortic balloon pump (IAPB) support, and various pharmacotherapies during hospitalization, including angiotensin converting inhibitors/angiotensin receptor blockers, aspirin, beta-blockers, and lipid-lowering agents, were obtained. Patients with a diagnosis of AMI associated with an interventional procedure were not included in this study.

Statistical Analysis

We estimated the incidence of CS for the 3 temporally characterized groups (prehospital, early, and late) in a standard manner. We compared patient characteristics, hospital management practices, in-hospital clinical

complications, and in-hospital case-fatality rates (CFRs) in the 3 CS groups using chi-square tests for categorical variables and ANOVA tests for continuous variables.

In examining factors associated with the development of CS at different time points, we used a multivariable multinomial logistic regression model (with patients who did not develop CS serving as the reference group), including age, sex, ambulance transportation, previously diagnosed comorbidities, past cardiac procedures, and AMI type and order. Because we were unable to determine the relationship between the timing of development of other clinical complications during hospitalization and the onset of CS, we did not include other clinical complications in this regression model.

In examining the association between the timing of CS and in-hospital death rates, we used multivariable logistic regression models to control for the effects of several sociodemographic and clinical factors of prognostic importance. These factors were chosen based on the findings from previously published studies and because they differed between our primary comparison groups of patients with CS at a *P* value of <0.20. These factors included age, sex, study year, hospital transportation, previously diagnosed comorbidities (eg, angina, diabetes mellitus, heart failure, hypertension, and stroke), past cardiac procedures (PCI, CABG), AMI type (STEMI versus NSTEMI) and order (initial versus prior), other clinical complications that patients may have developed during their acute hospitalization (eg, atrial fibrillation, heart failure, and stroke), and hospital length of stay.

All analyses were performed using SAS software (version 9.3; SAS Institute Inc, Cary, NC). This study was approved by the institutional review board at the University of Massachusetts Medical School (Worcester, MA).

Results

The study population consisted of 5782 patients hospitalized with AMI at the 11 tertiary care and community medical centers in central Massachusetts on a biennial basis between 2001 and 2011. The average age of this study population was 70 years old and 56.6% were men.

Trends in Incidence Rates According to Timing of CS

The overall proportion of residents of the Worcester metropolitan area who were hospitalized for AMI at all central MA medical centers who developed CS was 5.2%; there was a slightly increasing trend in the frequency of CS in this population between 2001–2003 (5.1%) and 2005–2007 (6.0%) and a decreasing trend thereafter to 4.4% in

2009–2011. The proportion of patients who developed either prehospital (1.6%) or late CS (1.5%) remained relatively unchanged over time (Figure 1). The proportion of patients who developed early CS increased between 2001–2003 (2.2%) and 2005–2007 (2.9%) and declined thereafter to 1.2% in 2009–2011.

Among the 1853 patients who were diagnosed with a STEMI, 2.5% developed CS before admission, 4.3% during the first day of hospitalization, and 2.1% after this time; these proportions were 1.2% at each of these 3 time points among the 3929 patients who developed an NSTEMI (*P*<0.001).

Trends in Hospital Death Rates According to Timing of CS

The overall in-hospital CFR associated with CS was 42.7%. The overall in-hospital 2CFRs for patients with prehospital, early, and late CS were 45.7%, 32.8%, and 54.1%, respectively. The in-hospital CFRs associated with prehospital CS increased from 38.9% in 2001–2003 to 53.6% in 2009–2011 (Figure 2), whereas the in-hospital CFRs associated with early or late CS declined (35.9% and 64.7% in 2001–2003 to 15.8% and 39.1% in 2009–2011, respectively) over this period.

Among patients who were diagnosed with an STEMI, 46.8% of those who developed CS before admission (n=47) died during their acute hospitalization compared with 77.2% of those who developed CS during the first 24 hours of admission (n=79) and 53.9% of the 39 who developed CS thereafter (*P*<0.001). Among patients with an NSTEMI, 55.6% of the 45 who developed CS before admission died, 50.0% of the 46 who developed CS during the first 24 hours of admission died, whereas 39.1% of the 46 who developed CS thereafter died (*P*<0.001).
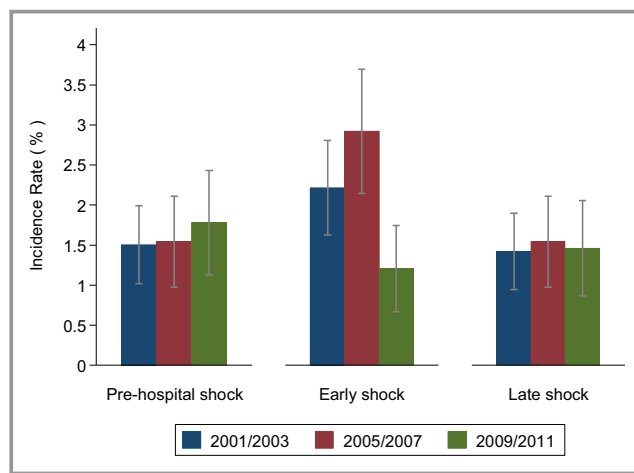

Figure 1. Temporal trends (2001–2011) in the incidence rates of cardiogenic shock.
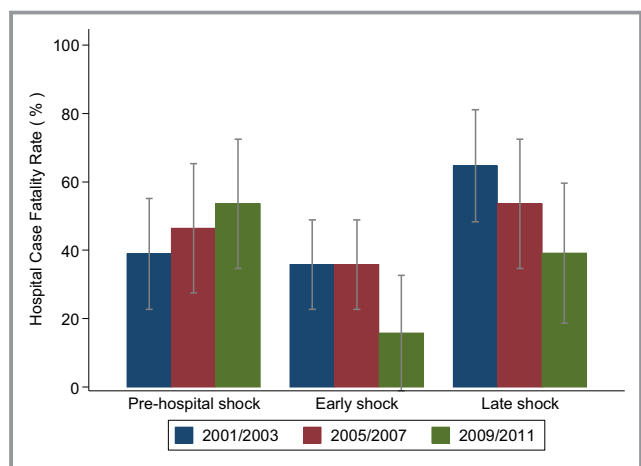
Figure 2. Temporal trends (2001–2011) in in-hospital case-fatality rates associated with cardiogenic shock.

Patient Characteristics According to Timing of CS

Patients who developed CS were older than those who did not develop shock; patients in the late shock group were the oldest (Table 1). Patients with CS were more likely to have a do not resuscitate order, to have been transferred to all greater Worcester medical centers by ambulance, and to have been previously diagnosed with diabetes mellitus and heart failure (with the exception of the early CS patients), as compared with patients who did not develop CS. Patients who developed late onset CS were more likely to have been previously diagnosed with hypertension and stroke as compared with patients who did not develop this serious clinical complication. However, patients who developed prehospital CS were less likely to have a history of stroke, whereas patients who developed early CS were less likely to have had hypertension and stroke previously diagnosed, as compared with patients who did not develop this complication. Patients who developed early and late onset CS were more likely, whereas patients who developed prehospital CS were less likely, to have undergone cardiac catheterization and a subsequent PCI and/or CABG compared with patients who did not develop this complication.

On admission, patients who developed prehospital and late CS were less likely to have reported chest pain, more likely to have been diagnosed with an STEMI, and had lower systolic and diastolic blood pressure, estimated glomerular filtration rate, and blood cholesterol findings, but higher heart rate and blood glucose levels, as compared with patients who did not develop CS (Table 1).

Factors Associated With the Time of Onset of CS

After multivariable adjustment, patients aged 65 to 74 years were more likely to have developed early CS, whereas patients aged 75 years or older were more likely to have developed late CS, compared with younger patients (Table 2). Patients transported by ambulance were more likely, whereas those with a history of previously diagnosed stroke were less likely, to have developed prehospital and early CS compared with respective comparison groups. Patients with a history of previously diagnosed diabetes mellitus were more likely to have developed prehospital CS compared with those without this comorbid condition. Patients presenting with an STEMI were more likely to have developed CS at all 3 time points examined than patients who developed an NSTEMI.

In-Hospital Management Practices According to Timing of CS

The proportion of patients who were treated with various cardiac medications was significantly lower in patients with prehospital and early CS (with the exception of angiotensin converting inhibitors/angiotensin receptor blockers in early shock patients), but higher in patients who developed CS at a later time (with the exception of beta-blockers) than among patients who did not develop CS (Table 3). The proportion of patients who underwent cardiac interventional procedures was lower in patients who developed prehospital CS, but higher in patients who developed either early or late CS, than patients who did not develop CS. The proportion of patients who received IABP support was higher in all patients who developed CS, and highest in patients who developed CS early during their hospitalization, compared with patients who did not develop CS. Although we were unable to determine whether coronary reperfusion/revascularization therapy occurred before or after the development of CS when these entities occurred on the same hospital day, we did collect information about whether or not a PCI or CABG surgery was performed within 24 hours of hospital arrival.

Among patients with prehospital CS, 38% of patients underwent a PCI compared with 23.5% of patients with late shock. Among patients with an STEMI, these percentages were 55.3% and 41%, respectively, among those with prehospital and late CS; these proportions were 20% and 8.7% among those with an NSTEMI. With regard to CABG surgery, 1.1%, and 2.4% of patients with prehospital and late CS underwent this procedure. These percentages were 0% and 2.6% for patients with an STEMI and 2.2% and 2.2% for patients with an NSTEMI.

In-Hospital Clinical Complications and Death According to Timing of CS

Patients who developed CS at all 3 time points were more likely to have developed other important clinical

Table 1. Patient Characteristics According to Timing of CS in Patients Hospitalized With AMI

	Prehospital CS (n=92)	Early CS (n=125)	Late CS (n=85)	No CS (n=5480)	*P* Value
Age (mean, y)	70.9	71.1	76.1	69.8	<0.01
Age groups, %					
<65 y	26.1	28.0	14.1	33.8	<0.01
65 to 74 y	23.9	29.6	23.5	20.2	
≥75 y	50.0	42.4	62.4	46.0	
Male, %	54.4	60	45.9	56.8	0.19
Any DNR, %	45.7	34.4	37.7	22.9	<0.001
Ambulance transportation, %	84.8	80.8	72.9	67.7	<0.001
Prehospital delay duration (mean, h)	3.0	2.9	5.9	3.8	0.09
Medical history, %					
Angina	13.0	13.6	17.7	14.4	0.83
Diabetes mellitus	46.7	36.0	50.6	30.5	0.002
Heart failure	29.4	19.2	36.5	23.5	0.02
Hypertension	73.9	68.0	88.2	73.8	0.01
Stroke	6.5	3.2	15.3	11.8	0.006
Cardiac procedure history, %					
Catheterization	58.7	81.6	64.7	61.2	<0.001
Percutaneous coronary intervention (PCI)	19.6	21.6	25.9	20.1	0.61
Coronary artery bypass grafting (CABG)	14.1	13.6	16.5	13.5	0.89
Both PCI and CABG	0.0	3.2	2.4	0.7	0.02
Presenting symptoms, %					
Chest pain	54.4	73.6	62.4	73.3	<0.001
Diaphoresis	29.4	33.6	18.8	29.6	0.12
Shortness of breath	60.9	60.8	63.5	55.6	0.22
AMI characteristics					
STEMI, %	51.1	63.2	45.9	30.8	<0.001
Initial	69.6	67.2	52.9	64.7	0.10
Clinical parameters on admission, mean					
Systolic blood pressure, mm Hg	117.1	117.8	130.9	142.3	<0.001
Diastolic blood pressure, mm Hg	68.3	68.0	72.3	77.5	<0.001
Heart rate, beats/minute	86.4	89.2	89.7	85.8	0.17
Laboratory findings on admission, mean					
Blood glucose, mg/dL	225.2	205.0	189.0	169.8	<0.001
Estimated GFR, %	45.9	52.1	47.1	56.6	<0.001
Blood cholesterol, mg/dL	148.3	156	154.3	171.3	<0.001

AMI indicates acute myocardial infarction; CS, cardiogenic shock; DNR, do not resuscitate; GFR, glomerular filtration rate; STEMI, ST-segment elevation myocardial infarction.

complications in comparison to patients who did not develop CS during their index hospitalization; the highest rates of these complications were observed in patients who developed late CS with the exception of third-degree atrioventricular block, which was more likely to occur in patients who developed prehospital CS (Table 4). Similarly, the in-hospital CFR were significantly higher in patients who did, as compared with those who did not, develop CS; the highest in-hospital mortality was observed in the late CS group, followed by patients with prehospital and early CS.

Table 2. Factors Associated With the Timing of CS in Patients Hospitalized With AMI

	Prehospital CS	Early CS	Late CS
	Odds Ratio (95% CIs)		
Age groups, y			
<65	1.00	1.00	1.00
65 to 74	1.55 (0.79–3.07)	2.23 (1.30–3.82)*	2.26 (0.95–5.36)
≥75	0.99 (0.52–1.93)	1.49 (0.87–2.53)	2.93 (1.34–6.40)*
Male	1.18 (0.70–1.99)	0.87 (0.59–1.32)	1.03 (0.61–1.74)
Ambulance transportation	2.89 (1.40–5.95)*	2.21 (1.32–3.69)*	1.14 (0.62–2.08)
Medical history			
Angina	0.81 (0.40–1.64)	0.84 (0.48–1.48)	0.90 (0.47–1.74)
Diabetes mellitus	2.04 (1.21–3.46)*	1.17 (0.75–1.82)	1.68 (0.99–2.86)
Heart failure	1.36 (0.74–2.47)	0.91 (0.54–1.54)	1.40 (0.79–2.48)
Hypertension	0.98 (0.54–1.79)	0.84 (0.53–1.31)	1.53 (0.75–3.11)
Stroke	0.29 (0.09–0.93)*	0.28 (0.10–0.78)*	0.93 (0.45–1.92)
Cardiac procedure history			
Percutaneous coronary intervention	1.17 (0.55–2.50)	1.35 (0.74–2.47)	1.07 (0.52–2.21)
Coronary artery bypass grafting	1.00 (0.49–2.06)	1.24 (0.71–2.19)	1.30 (0.67–2.51)
AMI characteristics			
STEMI	2.66 (1.58–4.49)*	3.57 (2.34–5.44)*	2.93 (1.73–4.96)*
Initial	1.18 (0.65–2.15)	1.01 (0.62–1.64)	0.89 (0.50–1.58)

AMI indicates acute myocardial infarction; CS, cardiogenic shock; STEMI, ST-segment elevation myocardial infarction.
*Statistically significant.

The results of our multivariable adjusted logistic regression analyses, which controlled for a number of potentially confounding factors of prognostic importance, showed that patients who developed CS before hospital arrival and at any time during hospitalization were significantly more likely to have died compared with those who did not develop CS. Late CS was associated with the highest risk of dying during the hospital stay (adjusted odds ratio, 22.20; 95% CI, 12.25–40.22) followed by prehospital CS (adjusted OR, 9.19; 95% CI, 5.31–15.91) and early CS (adjusted odds ratio, 7.92; 95% CI, 5.04–12.46).

Table 3. Hospital Management Practices According to Timing of CS in Patients Hospitalized with AMI

	Prehospital CS (n=92)	Early CS (n=125)	Late CS (n=85)	No CS (n=5480)	*P* Value
In-hospital medications, %					
ACEi/ARBs	44.6	64.8	65.9	64.8	<0.001
Aspirin	79.4	90.4	97.7	92.0	<0.001
Beta-blockers	64.1	77.6	85.9	90.5	<0.001
Calcium-channel blockers	14.1	12.0	28.2	22.3	<0.005
Lipid-lowering agents	58.7	64.8	76.5	73.7	<0.001
In-hospital cardiac procedures, %					
Catheterization	58.7	81.6	64.7	61.2	<0.001
Percutaneous coronary intervention	44.6	67.2	43.5	43.0	<0.001
Coronary artery bypass grafting	3.3	8.0	12.9	6.3	<0.05
Intra-aortic balloon pump	41.3	60.0	42.4	3.5	<0.001

ACEi indicates angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARBs, angiotensin II receptor blockers; CS, cardiogenic shock.

Table 4. In-Hospital Clinical Complications and Death According to Timing of CS

	Prehospital CS (n=92)	Early CS (n=125)	Late CS (n=85)	No CS (n=5480)	*P* Value
In-hospital complications, %					
Third-degree atrioventricular block	13.0	4.0	5.9	1.4	<0.001
Atrial fibrillation	32.6	44.0	49.4	19.1	<0.001
Heart failure	66.3	76.8	77.7	34.9	<0.001
Stroke	2.2	1.6	3.5	1.6	0.68
Death	45.7	32.8	54.1	7.3	<0.001

CS indicates cardiogenic shock.

Discussion

The results of this study of ≈5800 patients hospitalized with AMI at all 11 medical centers in central Massachusetts between 2001 and 2011 showed that the frequency of prehospital, early, and late CS has remained either unchanged or inconsistently varied during the years under study. The short-term CFRs associated with prehospital CS have increased, whereas the in-hospital CFRs associated with early and late CS have declined, during the years under study. Late CS was associated with the highest risk of dying during hospitalization followed by prehospital and early CS.

Trends in Incidence Rates According to Timing of CS

We showed that the frequency of prehospital CS among patients hospitalized with AMI has remained essentially unchanged (1.6%) during the years under study, results which are consistent with the findings from previous studies.[7,9,15] For example, a study of nearly 300 000 patients with an STEMI who were enrolled in the National Registry of Myocardial Infarction showed that the frequency of CS at the time of hospital admission remained relatively unchanged (2.5%) between 1995 and 2004.[7] Similarly, data from the AMIS (Acute Myocardial Infarction in Switzerland) Plus registry showed that the incidence rates of CS at the time of hospital admission remained stable (2.3%) between 1997 and 2006.[9] Of note, the frequency of prehospital CS in previous studies was slightly higher than that observed in our study, which may be attributed to differences in the respective study populations and working definitions of AMI and CS utilized. Similar relatively stable trends in the incidence rates of CS at the time of hospital presentation were noted in the multicenter GRACE (Global Registry of Acute Coronary Events) study, which included more than 65 000 patients who were

hospitalized with an acute coronary syndrome between 1999 and 2007.[15]

We found that the frequency of late CS remained relatively unchanged (1.5%), whereas the incidence of early-onset CS increased in early years and declined during later study years. A limited number of studies have examined the timing of CS during hospitalization for AMI,[12,13] but none have examined changing trends in the magnitude of this condition according to its timing. In the MILIS (Multicenter Investigation of the Limitation of Infarct Size) study, which included nearly 850 patients with AMI in the 1980s, the incidence of in-hospital CS was 7.1%, and one half of these patients developed shock ≥24 hours after hospital admission.[13] Similarly, in a study of ≈6000 patients hospitalized with AMI in 13 coronary care units in Israel between 1981 and 1983, 2.6% of patients developed CS during their hospitalization and two thirds of these patients developed this complication ≥24 hours after hospital admission.[12] Of note, these studies included a single study time point and data from more-distant years.

If we combined our data for patients with early- and late-onset CS, our findings are in agreement with the results from previous studies, which have shown that the incidence of in-hospital CS has declined over time.[9,15] In the AMIS Plus registry, the frequency of in-hospital CS decreased from 10.6% in 1997 to 2.7% in 2006.[9] Similarly, there was a declining trend in the frequency of in-hospital CS between 1999 and 2007 (5.1% versus 3.6%) in the GRACE study.[15] Data from 3 national French registries of more than 7500 patients hospitalized with AMI in 1995, 2000, and 2005 also showed declines in the prevalence of CS over time from 6.9% in 1995 to 5.7% in 2005.[25] However, data from the National Registry of Myocardial Infarction showed that the incidence of this complication during hospitalization remained unchanged (6.1%) or even slightly increased between 1995 and 2004[7]; of note, this latter study only included patients with an STEMI. It remains important to more fully understand the clinical epidemiology and pathophysiological processes underlying the timing of CS, including their underlying pathogenesis, which has implications for the enhanced prevention, diagnosis, management, and prognosis of these patients.

Trends in Hospital Death Rates According to Timing of CS

We found that the in-hospital CFRs associated with prehospital CS increased between 2001–2003 and 2009–2011 (38.9% to 53.6%), which is consistent with findings from the GRACE study.[15] In contrast, the AMIS Plus registry showed that the CFRs associated with CS at the time of hospital presentation declined between 1997 and 2006 (62.8% to 47.7%).[9]

The worsening trend in short-term death rates for patients who developed prehospital CS in our study is unclear, but of concern. Whereas the in-hospital CFRs improved over time for those with in-hospital CS, perhaps as a result of early and more-effective treatment approaches, patients suffering prehospital CS experienced poorer outcomes. One potential explanation for this observation is that patients hospitalized with AMI in recent years have a greater burden of comorbid conditions present coupled with less-than-optimal care-seeking behaviors and prolonged prehospital delay times.[8] Another possible reason for our finding, which is supported by the observation that fewer patients with prehospital CS underwent an invasive procedure during their hospitalization than did participants free from prehospital CS, is that patients with prehospital CS were deemed to be too sick and at too high risk at the time of hospital admission to receive selected therapies.

Our study reinforces the need for more attention to be directed to patients who develop CS in the prehospital setting in clinical guidelines, research, and clinical practice and emphasis placed on the more-aggressive use of early revascularization in these high-risk patients.[26–31] The use of IABP is recommended,[31,32] and although newer interventional devices have provided better hemodynamic support than the use of conventional IABP, none of these devices have yet been shown to favorably improve survival compared with the use of IABP.[33,34]

The in-hospital CFRs associated with early or late CS in the present study declined between 2001–2003 and 2009–2011, which are consistent with the results of previous studies.[7,9,15] In the AMIS Plus study, the hospital CFRs for CS developing during hospitalization for AMI declined from 60.9% to 48.9% between 1997 and 2006.[9] Similarly, declines in the hospital death rates associated with CS were observed in the National Registry of Myocardial Infarction between 1995 and 2004 (60.3% to 47.9%)[7] and in 3 nation-wide French registries of more than 7500 patients hospitalized with AMI in 1995, 2000, and 2005.[25]

Previous studies have suggested that the declining trend in mortality associated with CS complicating AMI was mainly attributed to the early and aggressive use of evidence-based medications and coronary interventions, including the use of balloon pumps.[7–11,25,26,28,35] However, a recent report from the National Cardiovascular Database Registry Cath-PCI registry, which included more than 56 000 patients with CS complicating AMI who underwent a PCI within 24 hours from acute symptom onset, showed that the hospital death rate for this patient group increased between 2005–2006 (27.6%) and 2011–2013 (30.6%).[36] This finding highlights the importance of additional research into the use of various therapeutic approaches to improve the short-term outcomes for patients who develop CS.

Factors Associated With the Time of Onset of CS

We found that older patients, patients transported by ambulance, those with a history of previously diagnosed diabetes mellitus, and patients who presented with an STEMI were more likely to develop CS compared with respective comparison groups. These findings are consistent with the results from previous studies[9,13–15] On the other hand, patients who had a history of previously diagnosed stroke were less likely to have developed prehospital and early CS. In the GRACE study, the frequency of having a previous stroke was higher in patients who developed in-hospital CS than in patients who did not develop CS[15] whereas results from the SPRINT (Systolic Blood Pressure Intervention Trial) study found that a history of stroke was an independent predictor for the development of in-hospital CS.[12]

The results of our study reinforce the need for a more-detailed examination of the factors associated with CS, including the role of other factors, such as prehospital management practices, patient's sociodemographic characteristics, comorbid conditions, size of the acute infarct, and impact of coronary reperfusion therapy, to provide insights into clinical practice guidelines to assist in the secondary prevention of this serious complication. This is a complicated undertaking given the heterogeneity of patients who develop CS and possible differing underlying mechanisms involved that lead to the development of this serious clinical syndrome.

Our findings also emphasize the relevance of educating paramedics to promptly recognize the development of CS and initiate treatment of this condition during ambulance transport to a nearby hospital for the management of AMI.

In-Hospital Management According to Timing of CS

Our study found that the proportion of patients who were treated with various cardiac medications was lower in patients with prehospital and early CS, but higher in patients who developed late-onset shock in comparison to patients who did not develop CS. Of note, several of these medications are often withheld because of the presence of hypotension,[37] and we were unable to determine the relationship between timing of treatments given during hospitalization and the development of CS. The proportion of patients who underwent cardiac procedures was lower in patients who experienced prehospital CS, but higher in patients who developed either early or late CS, than was observed in patients who did not develop CS. Similar findings were reported from a study of more than 10 000 patients in the Euro-Heart-Survey ACS between 2000 and 2001.[11] We also found considerable differences in the frequency of use of early PCI and CABG surgery in patients with prehospital versus late CS and according to the type of

AMI. Patients who developed prehospital shock were more likely to have undergone a PCI during the first 24 hours of hospital admission than patients who developed late-onset CS whereas patients who developed late onset CS were more likely to have undergone early CABG surgery than patients who developed prehospital CS. Given the observational nature of this study, however, and the difficulties in interpreting the relationship between occurrence of CS and the timing of coronary revascularization, caution should be exercised in the interpretation of these data. Future studies should more systematically examine the relation between the timing of these revascularization procedures and the onset of CS, given the potential benefits associated with the use of these interventional procedures.

On the other hand, our findings differ from the results of several previous studies. For example, in the AMIS Plus study, patients with CS, regardless of timing, were less likely to have received effective cardiac medications, and were more likely to have received IABP support, compared with patients without this complication.[9] Furthermore, in this study, patients who developed CS on hospital admission were more likely (45.4% versus 39.0%), whereas patients who developed this complication during hospitalization were less likely (24.6% versus 39.0%), to have undergone a PCI compared with those who did not develop this complication.[9] In the GRACE study, patients with CS both on admission and during hospitalization were less likely to have received effective cardiac medications, but were more likely to have undergone a PCI and IABP, compared with patients without this complication.[15]

In-Hospital Clinical Complications and Death According to Timing of CS

In the present study, patients who developed CS at all 3 time points were at significantly higher risk for developing other important clinical complications and dying during their index hospitalization for AMI compared with patients who did not develop CS. Indeed, patients who developed late CS were at more than 20 times higher risk for dying, followed by patients with prehospital shock (9 times), and those who developed CS early during their acute hospitalization (8 times), than patients who did not develop this complication.

Our results are consistent with findings from the AMIS Plus registry and the GRACE study, which showed that the CFRs associated with in-hospital CS were higher than that associated with prehospital CS.[9,15] One possible explanation is that patients with late CS are more likely to be older, to have more comorbidities present, and to develop other clinical complications compared with patients with prehospital CS. The development of late CS is likely attributed to the failure of the initial treatments prescribed that protect against the adverse

hemodynamic consequences of a large infarction and associated mechanical complications, whereas prehospital CS may be attributed to arrhythmias or stunned myocardium that could heal after prompt treatment. In contrast, a report from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial registry (1993–1997) showed that short-term mortality was higher in patients with early (<24 hours) versus late CS (≥24 hours; 62.6% versus 53.6%); the latter findings may be attributed, in part, to selection bias, in which there was under-representation of more-complex patients who developed CS.[16]

Because the use of effective treatments in this study and in previous studies was somewhat suboptimal, more-aggressive and timely use of effective cardiac treatment approaches is encouraged to improve the short-term outcomes of these high-risk patients.

Study Strengths and Limitations

This study has several strengths, including its population-based design that captured the vast majority of cases of AMI that occurred among residents of central Massachusetts. Our data present a more real-world perspective of decade-long trends in the magnitude and outcomes associated with the timing of CS in patients hospitalized with AMI. However, the absolute number of patients with CS remained relatively small compared with data from large national registries or multi-center, randomized trials. Furthermore, because the exact time of onset of AMI was unable to be determined, CS was categorized into 3 distinct groups based on the date of hospital admission, and we were unable to further refine this time interval because of the manner in which this information was collected and recorded. The majority of our study population was white, which may limit the generalizability of the present findings, and we did not have information available about the duration of transport time to each of our central Massachusetts study hospitals. We did not have information available on several patient associated characteristics (eg, socioeconomic status), which may have confounded some of the observed associations, nor did we collect information about the use of invasive hemodynamic monitoring or inotropic or vasopressor agents in this patient population. Finally, we did not collect information about the occurrence of out-of-hospital cardiac arrests in residents of central Massachusetts during the years under study, which may have affected not only the characteristics of our hospitalized patient population, but also the declining death rate we observed in patients with prehospital CS may have been attributed to changes in both the magnitude and characteristics of patients who experienced out-of-hospital cardiac arrest and who survived long enough to be admitted to central Massachusetts hospitals with an AMI.

Conclusions

Despite encouraging declines in the death rates associated with early and late CS in patients hospitalized with AMI, the death rates associated with prehospital CS increased during the years under study. This finding underscores the importance of the greater attention that needs to be directed to patients who develop prehospital CS. More-aggressive use of early coronary revascularization in conjunction with cardiac support therapies should be encouraged in these patients to improve their outcomes. Future studies remain needed to understand the increasing death rates associated with prehospital CS found in our study, and to inform more-optimal treatment strategies for the prevention and management of CS prehospitalization and during hospitalization for AMI.

Patients who developed CS regardless of timing experienced high in-hospital death rates. Effective treatments potentially preventing and treating CS should be encouraged to be used early and more aggressively in high-risk patient groups to ensure the optimal utilization of effective treatment strategies, and to improve patients' outcomes.

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Disclosures

None.

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