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A nationwide cohort study

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Abstract

Background: Cardiogenic shock remains the leading cause of in-hospital death in acute myocardial infarction (AMI). Due to temporary changes in management of cardiogenic shock with widespread implementation of early revascularization along with increasing attention to the use of mechanical circulatory devices, complete and longitudinal data are important in this subject. The objective of this study was to examine temporal trends of first-time hospitalization, management, and short-term mortality for patients with AMI-related cardiogenic shock (AMICS).

Methods: Using nationwide medical registries, we identified patients hospitalized with first-time AMI and cardiogenic shock from January 1, 2005 through December 31, 2017. We calculated annual incidence proportions of AMICS. Thirty-day mortality was estimated with use of Kaplan-Meier estimator comparing AMICS and AMI-only patients. Multivariable Cox regression models were used to assess mortality rate ratios (MRR).

Results: We included 101,834 AMI patients of whom 7,040 (7%) had AMICS. The median age was 72 (interquartile range (IQR): 62-80) for AMICS and for AMI-only 69 (IQR: 58-79). The gender composition was similar between AMICS and AMI-only (Males: 64% vs. 63%). The annual incidence proportion of AMICS decreased slightly over time (2005: 7.0% vs. 2017: 6.1%, p for trend <0.0001). In AMICS, use of coronary angiography increased between 2005-2017 from 48% to 71%, as did use of left ventricular (LV) assist device (1% vs. 10%) and norepinephrine (30% to 70%). In contrast, use of intra-aortic balloon pump (14% vs. 1%) and dopamine (34% vs. 20%) decreased. Thirty-day mortality for AMICS patients were 60% (95%CI: 59-61) and substantially higher than the 8% (95%CI: 7.8-8.2) for AMI-only (MRR: 11.4, 95% CI: 10.9-11.8). Over time, the mortality decreased after AMICS (2005: 68% to 2017: 57%, p for temporal change in adjusted analysis <0.0001).

Conclusion: We observed a slight decrease in AMICS hospitalization over time with changing practice patterns. Thirty-day mortality was markedly higher for patients with AMICS compared with AMI-only, yet, our results suggest improved 30-day survival over time after AMICS.

Keywords: Cardiogenic shock, myocardial infarction, incidence, short term mortality, epidemiology.

Introduction

Cardiogenic shock remains the leading cause of short-term mortality in acute myocardial infarction (AMI) despite improved therapeutic strategies.[1–3] Driven by change in management, previous studies examined the temporal incidence of AMI-related cardiogenic shock (AMICS).[2,4–11] Most studies observed a decreasing incidence of AMICS,[4–8,10] yet a recent Danish study containing data from two tertiary cardiac centres demonstrated a slight increase in incidence from 2013-2017.[11] The short-term mortality decreased from previous 70-80%[4] to 40-50%,[7,11] and there is general consensus on early revascularization as the most important improvement in therapy.[3]

None of the previous studies consisted of nationwide data, and uncertainty still exists regarding the use of mechanical circulatory support, inotropes and vasopressors in the hemodynamic instable patient. In a large randomized trial, intra-aortic balloon pump (IABP) failed to improve survival and recent observational data raises concern of the effectiveness of left ventricular (LV) assist device to improve outcome.[12,13] Consequently, use of IABP is decreasing[7] compared with increasing use of LV assist device.[11,14,15] Poor evidence exists for the beneficial effects of inotropes and vasopressors with a known risk of enhanced ischemia and arrythmias, but these drugs are often unavoidable in most severely hemodynamic compromised patients with severe hypotension.[16]

To improve patient outcome, it is of high importance to understand the course of AMICS to make prophylactic strategies and to assess the effect of current treatments. We set out to examine the temporal trend in first-time hospitalization and 30-day mortality in an unselected nationwide AMICS cohort, along with the temporal trends in use of revascularization, mechanical circulatory support and inotropes/vasopressors.

Methods

Design and setting

We conducted this population-based cohort study between 2005-2017 using data from registries in Denmark.[17] The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to health care, and partial reimbursement of prescribed medication.[17] The unique 10-digit Danish Civil Personal Register number allows unambiguous linkage of registries at individual level.[18] Since 2003 all patients with ST-segment elevation myocardial infarction (STEMI) or suspected AMICS have been immediately transferred to a tertiary cardiac center for evaluation and early revascularization due to the national revascularization strategy in Denmark.[19]

Study cohorts

We used the Danish National Patient Registry (DNPR) to identify all patients with a first-time hospitalization (as a measure of incidence) of AMICS from 2005 through 2017. The DNPR contains data on all non-psychiatric hospital admissions since 1977 and on all hospital outpatient specialist clinic and emergency room contacts since 1995.[20] Each admission is assigned one primary diagnosis code and one or more secondary diagnosis codes classified according to the International Classification of Diseases (ICD-8) until 1993 and ICD-10 thereafter.[20] Important components of critical care, including treatment with inotropes/vasopressors, have been coded routinely with high validity since 2005, why the year 2005 was chosen as the beginning of the study period.[21]

The study cohort included patients with first-time AMI after 2005, i.e., patients without a previous diagnosis of AMI since 1977 to create a homogenous AMI cohort. We used the ICD-10 code I21 for AMI, and excluded patients with a previous diagnosis code (ICD-10: I21, and ICD-8: 410-411).We used a partially validated definition of cardiogenic shock: death within first admission day, a diagnosis code of cardiogenic shock (ICD-10: R570) and/or by any use of inotropes/vasopressors during the hospitalization.[22] We used validated ICD-10 codes for AMI

(positive predictive value: 97%)[23] and cardiogenic shock (positive predictive value: 94%).[22] Patients treated with inotropes/vasopressors, but without a diagnosis code for cardiogenic shock, were excluded if they had a diagnosis code for septic shock, hypovolemic shock, or shock without further specification during the admission.[22] Moreover, if the use of inotropes/vasopressors were only in relation to a coronary bypass grafting surgery (CABG), and the surgery was not performed on the same date as AMI admission, the patient was classified as AMI-only patient. We classified early AMICS as need of inotropes/vasopressors on the same date as admission, and late AMICS as need of inotropes/vasopressors thereafter. To ensure completeness of AMICS, we included both primary and secondary diagnoses for AMI and cardiogenic shock (*e.g.*, if a patient had a primary code with cardiogenic shock and secondary code with AMI and vice versa). A flowchart is provided in Figure 1. The admission period was defined as the initial hospitalization with AMI, including transfers to other departments and hospitals.

Mortality

We obtained information on all-cause mortality until the end of 2018 from the Danish Civil Registration System.[18] This registry was established in 1968 and contains information on date of birth, residence, immigration, and vital status, with daily updates.[18] The cause of death was obtained from the Danish Registry of Causes of Death.[24]

Covariates

The Danish Civil Registration System was used to obtain data on sex and age.[18] Data on comorbidities were obtained from the DNPR using primary and secondary in- and outpatient diagnoses during a fixed period of 10 years preceding the AMI admission.[20] We included comorbidities that could have a potential impact on mortality: congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, hypertension, atrial

fibrillation/flutter, venous thromboembolism, kidney disease, liver disease, diabetes and cancer. We used the validated definitions of the included comorbidities.[23,25] We obtained data on out of hospital cardiac arrest (OHCA) in relation to AMI admission from the Danish Cardiac Arrest Registry[26] and DNPR. The Danish National Prescription Registry provided information on filled preadmission prescriptions 180 days before the AMI admission for anti-platelets, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, betablockers, statins and anti-diabetics.[27] We defined diabetes mellitus from its diagnosis code or filled prescriptions for anti-diabetic drugs to improve completeness. Coronary angiography (CAG), percutaneous coronary intervention (PCI), CABG, IABP, LV assist device, extra-corporeal membrane oxygenation (ECMO), mechanical ventilation and dialysis during admission were identified from procedure codes in the DNPR. The coding of CABG, PCI and CAG has previously been shown accurate.[28] All codes are provided in eTable 1.

Statistical analysis

We characterized patients according to sex, age, comorbidities, drug therapy, and calendar period of diagnosis. Baseline differences between AMICS and AMI-only patients were tested using χ^2-test for categorical variables and Wilcoxon for continuous variables. For AMICS patients we added information on procedures during admission by calendar periods of diagnosis (CAG, CABG, PCI, IABP, LV assist device, ECMO, mechanical ventilation, dialysis and inotropes/vasopressors). We computed the annual cumulative incidence proportion and the 95% confidence interval using Clopper-Pearson exact methods. We computed probability for trend from 2005 through 2017 using the Cochran-Armitage trend test. Using the Kaplan-Meier estimator we compared absolute 30-day mortality for AMICS vs. AMI-only patients, and we tested unadjusted difference with log-rank test. Cox proportional-hazards models were used to compute crude and adjusted hazard ratios as measure of the 30-day mortality rate ratio (MRR). We adjusted for sex, age groups, comorbidities

and calendar period of diagnosis. The proportional hazards assumption was assessed graphically by plotting log(-log (survival function)) vs. time for all exposure variables and found valid. The potential of effect modification by sex, age groups, and comorbidities were not found present, unless otherwise stated. We characterized cause of 30-day death for AMICS and AMI-only. As a sensitivity analysis, we repeated the analyses in a cohort including patients with previous AMI to add clinically relevant data on AMICS; a condition which may be due to complex vascular disease and prior AMI. A P value less than 0.05 was considered statistically significant. The analyses were performed using SAS version 9.4 and R version 3.5.1.

Ethics approval

Observational register studies do not require ethical permission in Denmark. The use of data for the study was approved by the Danish Data Protection Agency (Approval number: **P-2019-396).**

Results

Patient characteristics

We identified 101,834 patients with first-time hospitalization for AMI between 2005 and 2017, of whom 7,040 (7%) had AMICS (Table 1). AMICS patients were slightly older but had same gender composition compared with AMI-only (median age in years: 72 vs. 69, male gender: 64% vs. 63%) (Table 1). AMICS patients had a larger burden of comorbidities (heart failure: 17% vs. 9%, peripheral vascular disease: 12% vs. 7%, chronic kidney disease: 9% vs. 3%, and diabetes: 19% vs. 15%). More patients with AMICS had OHCA compared with AMI-only (25% vs. 2%). Age, comorbidity burden, and medical therapy remained high over time, and especially the number of patients with diabetes, chronic kidney disease, hypertension, and OHCA increased during the study period (eTable 2).

Trends in cardiogenic shock hospitalization

Overall, the proportion of patients hospitalized with cardiogenic shock among AMI patients decreased slightly over time, as illustrated in Figure 2 (7.0% in 2005 to 6.1% in 2017, p for trend<0.0001). The findings were consistent in the cohort of patients which also included patients with previous AMI (8% in 2005 to 6% in 2017, p for trend <0.0001). Early AMICS increased from 58% in 2005 to 71% in 2017, along with a corresponding decrease in late AMICS from 42% to 29%.

Trends in intensive care and pharmacological management

The annual pharmacological management with inotropes and vasopressors is illustrated in eFigure 1. The use of norepinephrine more than doubled in the study period (from 30% to 70%) (Table 2), whereas use of dopamine was reduced by half (from 34% to 20%). A change in the management of inotropes was present with reduced use of dobutamine and in comparison, use of levosimendan and phosphodiesterase inhibitors went up.

Trends in revascularization and circulatory mechanical support

Among AMICS patients use of CAG increased from 48% to 71% and PCI from 35% to 57%, whereas CABG remained stable around 9% (Table 2 and eFigure 1). The 30% of AMICS patients not treated with CAG were older than CAG patients (median age: non-CAG: 78 vs. CAG: 68 years), were more females, had high comorbidity burden, and high mortality (1-day mortality 55% (95% CI: 53-56), 30-day mortality 82% (95% CI: 81-84)Among AMI-only patients use of CAG and PCI increased in a similar manner (CAG: 65% to 84%, p for trend<0.0001, PCI: 46% to 61%, p for trend<0.0001). The use of IABP declined from a maximum in 2009-2011 of 14% to 1% in 2015-2017, whereas use of LV assist device more than ten-doubled (1% vs 10%) (Table 2, eFigure 1). The use of ECMO was limited.

Thirty-day mortality

The overall cumulative 30-day mortality for patients with AMICS was 60% (95% confidence intervals (CI): 59-61) compared with AMI-only patients with a mortality risk of 8.0% (95% CI: 7.8-8.2) (Figure 3 and eTable 3). The results were similar in the sensitivity analysis including patients with previous AMI. The crude MRR comparing AMICS patients with AMI-only patients was 11.8 (95% CI: 11.3-12.2), and this association was still evident after multivariable adjustments (MRR 11.4, 95% CI: 10.9-11.8) (eTable 3). More patients with AMICS had cardiovascular cause of 30-day death, with AMI accounting for more than 50% of cases, compared with AMI-only patients (cardiovascular: 81% vs. 70%, pulmonary: 5% vs. 9%, cancer: 3% vs. 8%, etc.). Over time survival improved for both AMICS patients and AMI-only patients (Figure 4, eTable 3). For AMICS patients the cumulative mortality decreased from a nadir of 63% to 57%, and for AMI-only patients from 11% to 5% (p for temporal change in adjusted analysis: AMICS p<0.0001, AMI-only p<0.0001) (Figure 4, eTable 3).

Discussion

We observed a slight decrease in first-time hospitalization of AMICS between 2005 and 2017. Secondly, the management changed with increasing use of revascularization in AMICS and AMI-only. Use of IABP changed dramatically with an almost 15-fold decrease, and any use of norepinephrine doubled while dopamine use decreased. Finally, we demonstrated a markedly higher 30-day mortality risk among AMICS patients compared with AMI-only patients, though, survival improved for both AMICS and AMI with time.

Trends in AMICS incidence

Previous studies have examined the temporal incidence with conflicting trends.[2,4–11] The incidence has in most studies decreased with the past three decades with latest incidence of 3-7%,[4–8,10]

whereas two studies observed an increasing trend.[2,11] Few studies contained updated data and no study was based on nationwide data. Hunziker *et al.* based their study on data from the Swiss AMI Plus Registry with a AMICS cohort of 4,090 patients in a period from 1997 through 2017.[7] They discovered a decline in AMICS incidence from 8.7% in 1997 to 7.3% in 2017 (p for trend <0.0001). A recent regional Danish study with 1,716 AMICS patients from two tertiary cardiac centers demonstrated an increase in the annual incidence from a nadir of 65.3 per million person-years in 2013 to 80.0 per million person-years in 2017.[11] Incidence of STEMI-related AMICS decreased, whereas the overall increase was driven by an increase in NSTEMI-AMICS.[11] In line with the findings by Hunziker *et al.*, we discovered an increase in early AMICS and a corresponding decrease in late AMICS. Overall, the incidence has not improved dramatically over the last decades. The stagnation in incidence despite improved management may be explained by the increase in early shock due to improved pre-hospital setting, more OHCA survivors,[26,29] and increasing comorbidity burden on the behalf of reduced late shock caused by early revascularization and improved intensive care.

Trends in in-hospital management

Since the SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) revascularization has been a class 1 recommendation for AMICS.[3,30] In our study, use of coronary angiography and PCI increased with time for both AMICS and AMI patients. Still, use of coronary angiography among AMICS patients was not complete (71%) in the end of the study period between 2015 and 2017. Consistent with our finding, previous multicenter studies observed that the use of coronary angiography among AMICS patients was ~80%[2,6–8] whereas it was expectedly higher (92%) in a study from a tertiary cardiac center due to the selection of patients who were immediate candidates for assessment and potentially revascularization .[11]. The lower prevalence of coronary angiography in this study compared to previous studies may reflect the

nationwide setting including patients>75 years with high comorbidity burden, NSTEMI, and potentially late onset cardiogenic shock who were not candidates for transfer to a cardiac center. However, some elderly AMICS patients may benefit from early revascularization,[31] which leaves a challenge for the clinicians to identify older candidates for revascularization.

The use of inotropes and vasopressors is unavoidable in the acute hemodynamic unstable patient despite risk of arrythmias and increased myocardial oxygen consumption.[16,32] Despite vague evidence and recommendations norepinephrine is continuously the most used vasopressor agent.[1,33] Our study confirms the wide use of norepinephrine (70% of AMICS patients) on the behalf of dopamine and epinephrine,[34] and the regime shift was already observed from 2005. The use of levosimendan and phosphodiesterase-inhibitors increased. This increase may be due to the favourable improvement in cardiac contractility and vasodilatation without increased oxygen consumption,[34] still, there are no wide evidence concerning the use of inotropes in patients with AMICS.

An increasing interest has evolved regarding the use of mechanical circulatory devices due to the limitations of vasoactive drugs. Nevertheless, large gaps in evidence exists on the correct timing, indication, and beneficial effect of the different devices. Registry data have indicated that early implementation of mechanical circulatory support may improve survival among AMICS patients.[35] Routine use of IABP was not supported by the findings in the randomized IABP-SHOCK II study. This study comprised 600 AMICS patients in which no improvement in neither 30-day or 6-years mortality were achieved comparing IABP with standard medical therapy.[12] Thus, the use of IABP was downgraded in guidelines, and is currently only recommended for patients with mechanical complications.[33] Consistent with previous studies,[7,11,36–38] we observed an abrupt decrease in use of IABP since the IABP-SHOCK II study. The use of LV assist device increased simultaneously on the behalf of IABP despite no study have proved the superiority of LV assist device vs. IABP or standard medical therapy on 30-day mortality.[13,39] On the positive side, in the

recent meta-analysis including 148 patients from randomized trials comparing active mechanical support, i.e. LV assist device, with IABP, active mechanical support was associated with improved hemodynamic parameters (arterial lactate clearance and middle arterial pressure).[39] However, on the negative side more patients treated with active mechanical support had major bleedings compared with the controls. The regime shift in use of LV assist device was consistent with findings in prior studies,[7,11,36] We expect a minimal impact of the ongoing DanGer Shock randomized trial sinceour results cannot be solely described by the number of included patients in DanGer and the increase in use of LV assist device began before DanGer was initiated (2013) [40] Use of ECMO was very limited in this study. Despite lack of randomized data, previous observational data have associated ECMO with improved survival in AMICS patients.[41] More evidence are needed to choose the correct candidates for treatment with mechanical circulatory devices and to avoid iatrogenic exposure for device-related complications.

Short-term mortality

Through the last decades the short-term mortality has improved substantially,[2,4,5,9,10] however, few updated studies have reported a stagnant mortality in the latest years.[8,11] The overall 30-day mortality in this study was comparable with a previous AMICS cohort comprising both STEMI and NSTEMI patients in multicenter study, as the setting in this study.[6] However, in comparison with previous data restricted to tertiary cardiac centers, the mortality in this study is slightly higher (60% vs. 40-50%).[10,11] Differences in in-hospital mortality may be explained by the higher mortality seen among patients who were never transferred to an invasive cardiology center for evaluation and early revascularization; patients who were not candidates for immediate transfer had 1-day mortality of 50 %, median age 78 years, and high comorbidity burden.

We demonstrated an improved mortality since 2005 for both AMICS and AMI-only patients. Consistent with previous studies the improvements in survival for AMICS faded from

2011 and forward. The mechanisms underlying the observations in this study remain uncertain. The improved mortality in AMICS may be explained by improved pre-hospital setting, immediate transfer to a tertiary cardiac center for early revascularization, and focused intensive cardiac care. However, the stagnation in mortality risk among AMICS recently may be due to increasing comorbidity, and complexity in disease. For AMI-only patients the improved mortality is consistent with previous studies,[42] and may be explained by improved prevention of AMI.

Strengths and limitations

Some considerations must be taken when interpreting our results. The study design with a well-defined nationwide cohort in a country providing tax-financed universal healthcare minimizes the potential of selection bias.[17] The positive predictive value for the diagnosis codes with first-time AMI and cardiogenic shock are >95% in the DNPR,[22,23] and the positive predictive value for the procedure for inotropes/vasopressors as a proxy for shock code is just as high.[22] AMI patients who died within first hours of hospitalization, e.g. during revascularization attempt, were likely not coded with a diagnosis code of shock or procedure code with inotropes/vasopressors since they never reached an intensive care unit. We sought to increase completeness of cardiogenic shock by classifying AMI-only patients who died during first day of hospitalization AMICS patients. We recognize the potential of misclassification for AMI patients who died within first day of admission of other causes than cardiogenic shock as AMICS patients, in addition to the concerns that raises when AMI-only patients are compared with AMICS from date of admission and forward. We cannot exclude the potential of misclassification of OHCA patients on vasopressors, but without manifest cardiogenic shock, as AMICS patients. The completeness of conditions as diabetes and hypertension is sparse since uncomplicated conditions are treated by general practitioners, however, we sought to increase completeness of diabetes by adding information on filled prescriptions for anti-diabetic drugs. The subtypes of MI have high positive predictive value but low completeness in

the Danish National Patient Registry.[23] Furthermore, we do not have data on lactate levels, 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.

Clinical importance

This study adds important information of the temporal nationwide hospitalization and short-term mortality rate among first-time AMICS patients. The grave prognosis and large comorbidity burden among AMICS patients emphasize the need of prophylactic efforts and a significant opportunity for improvement. Future randomized studies are needed to examine the best approach regarding circulatory mechanical support and inotropes/vasopressors to harmonize recommendations, to improve patient outcome and to minimize intensive care unit expenses.

Conclusions

In a large nationwide setting, this study found a slight decrease in first-time hospitalization of AMICS between 2005 and 2017. Management of AMICS changed substantially over time with increased use of revascularization, LV assist device, and norepinephrine, and in contrast an abrupt decrease in use of IABP and a steady decline in the use of dopamine. We demonstrated an improved 30-day survival over time for both patients with AMICS and AMI-only.

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Conflict of Interest:

Dr. Møller reports personal fees from Abiomed, outside the submitted work;

Dr. Hassager reports personal fees from Abiomed, outside the submitted work;

Dr. Torp-Pedersen reports grants from Bayer and Novo Nordisk, outside the submitted work;

Dr. Køber reports personal fees from Novartis, BMS, and AstraZeneca, outside the submitted work;

All other authors have nothing to disclose.

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Figure legends.

Figure 1. Flowchart of patients with first-time acute myocardial infarction-related cardiogenic shock from 2005-2017.

Abbreviations: AMI: Acute myocardial infarction, AMICS: Acute myocardial infarction related cardiogenic shock, ICD-10: International classification of diagnosis codes, 10th revision

Figure 2. Cumulative incidence proportion of acute myocardial infarction-related cardiogenic shock, by calendar year of diagnosis from 2005-2017.

Abbreviations: AMI: Acute myocardial infarction, AMICS: Myocardial infarction-related cardiogenic shock, CI: Confidence interval.

Figure 3. Cumulative 30-day mortality in acute myocardial infarction patients with and without cardiogenic shock between 2005 and 2017.

Abbreviations: AMI: Acute myocardial infarction, AMICS: Acute myocardial infarction-related cardiogenic shock.

Figure 4. Trends in annual adjusted 30-day mortality rate ratios with 95% CI with year 2005 as reference, in acute myocardial infarction-related cardiogenic shock (A) and acute myocardial infarction without shock (B).

Abbreviations: CI: Confidence interval.

Table 1. Baseline characteristics for patients with first-time acute myocardial infarction from 2005-2017, by cardiogenic shock status.

	AMI-only, n (%)	AMICS, n (%)	P-value
Total	94,794 (100)	7,040 (100)	
Male gender	59,605 (62.9)	4,492 (63.8)	<0.0001
Median age, years [IQR]	69 [58-79]	72 [62-80]	<0.0001
Age, years			
<50	9,673 (10.2)	461 (6.6)	
50-59	16,193 (17.1)	887 (12.6)	
60-69	22,473 (23.7)	1,688(24.0)	
70-79	23,113 (24.4)	2,128 (30.2)	
≥80	23,342 (24.6)	1,876 (26.7)	
Comorbidities			
Heart failure	8,282 (8.7)	1,162 (16.5)	<0.0001
Peripheral vascular disease	6,629 (7.0)	870 (12.4)	<0.0001
Cerebrovascular disease	9,540 (10.1)	981 (13.9)	<0.0001
COPD	6,059 (6.4)	780 (11.1)	<0.0001
Hypertension	21,634 (22.9)	1,974 (28.0)	<0.0001
Atrial fibrillation/flutter	7,465 (7.9)	826 (11.7)	<0.0001
Chronic kidney disease	3,059 (3.2)	621 (8.8)	<0.0001
Venous thromboembolism	2,317 (2.4)	197 (2.8)	0.07
Liver disease	978 (1.0)	158 (2.2)	<0.0001
Diabetes*	13,828 (14.6)	1,347 (19.1)	<0.0001
Cancer	7,791 (8.2)	748 (10.6)	<0.0001
OHCA †	1,244 (1.5)	1,548 (25.2)	
Subtypes of AMI			
STEMI	20,847 (22.0)	1,889 (26.8)	<0.0001
NSTEMI	40,816 (43.1)	1,053 (15.0)	<0.0001
Unspecified	33,131 (35.0)	4,098 (58.2)	<0.0001

Drug therapy before admission ‡			
Anti-platelet §	26,717 (28.2)	2,275 (32.3)	<0.0001
Calcium channel blockers	19,343 (20.4)	1,819 (25.8)	<0.0001
ACE-I/ARBs	30,170 (31.8)	2,605 (37.0)	<0.0001
Betablockers	19,597 (20.7)	1,626 (23.1)	<0.0001
Statins	23,322 (24.6)	1,972 (28.0)	<0.0001
Anti-diabetics	11,816 (12.5)	1,131 (16.1)	<0.0001

Abbreviations: ACE-I: Angiotensin converting enzyme inhibitors, AMI: acute myocardial infarction, AMICS: Acute myocardial infarction-related cardiogenic shock, ARBs: Angiotensin receptor blockers, COPD: Chronic obstructive pulmonary disease, IQR: Inter quartile range, NSTEMI: Non-ST segment elevation myocardial infarction, OHCA: Out of hospital cardiac arrest, STEMI: ST segment elevation myocardial infarction.

* Defined by either an ICD-10 code with diabetes or use of anti-diabetics defines as a redeemed prescription within 180 days before admission.

† Data on OHCA is only available between 2005 and 2015.

‡ Defined as a redeemed prescription within 180 days before admission.

§ Defined as either acetylsalicylic acid or clopidogrel

Table 2. In-hospital procedures in acute myocardial infarction-related cardiogenic shock from 2005-2017, by calendar periods of diagnosis.

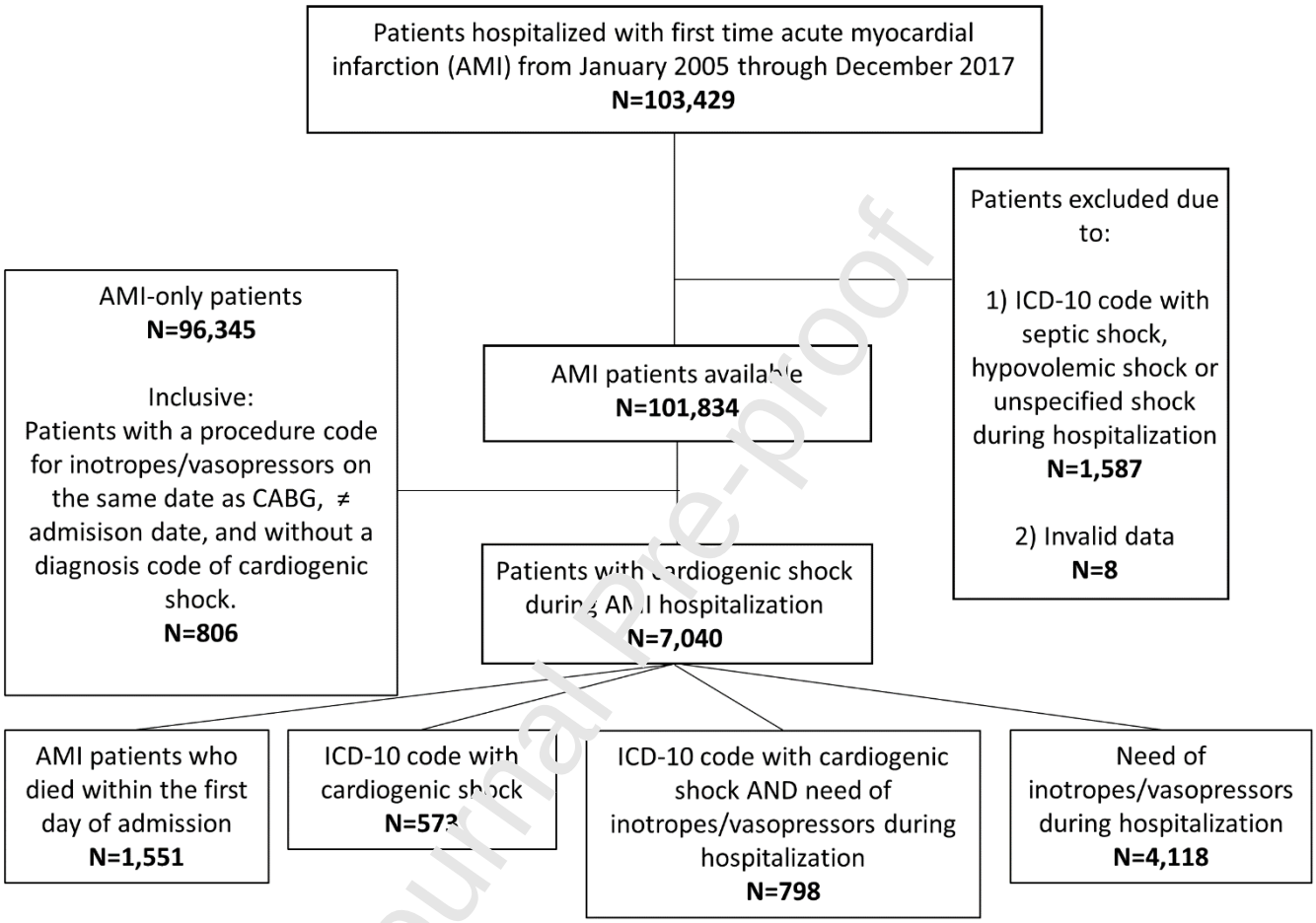
	Calendar period of diagnosis			
	2005-2008* n (%)	2009-2011 n (%)	2012-2014 n (%)	2015-2017 n (%)
Total	2,473 (100)	1,666 (100)	1,505 (100)	1,396 (100)
Admission length, days (median [5th-95th percentile])	2 [0-29]	4 [0-30]	5 [0-30]	5 [1-29]
Cardiac procedures				
Coronary angiography	1,180 (47.7)	921 (55.3)	943 (62.7)	985 (70.6)
PCI	870 (35.2)	697 (41.8)	718 (47.7)	799 (57.2)
CABG	216 (8.7)	153 (9.2)	150 (10.0)	120 (8.6)
Mechanical circulatory support				
IABP	229 (9.3)	230 (13.8)	85 (5.6)	10 (0.7)
LV assist device	16 (0.6)	20 (1.2)	68 (4.5)	135 (9.7)
ECMO	<3 †	<3 †	10 (0.7)	10 (0.7)
Intensive care				
Renal replacement therapy	247 (10.0)	195 (11.7)	215 (14.3)	214 (15.3)
Mechanical ventilation	1,377 (55.7)	1,048 (62.9)	1,066 (70.8)	981 (70.3)
Inotropes/vasopressors				
Dobutamine	626 (25.3)	346 (20.8)	263 (17.5)	162 (11.6)
Dopexamine	22 (0.9)	7 (0.4)	5 (0.3)	-
Levosimendan	35 (1.4)	52 (3.1)	69 (4.6)	121 (8.7)
PDE-inhibitors	195 (7.9)	166 (10.0)	212 (14.1)	200 (14.3)
Epinephrine	368 (14.9)	279 (16.7)	236 (15.7)	234 (16.8)
Norepinephrine	729 (29.5)	768 (46.1)	937 (62.3)	979 (70.1)
Dopamine	837 (33.8)	521 (31.3)	401 (26.6)	276 (19.8)
Combined therapy	429 (17.3)	365 (21.9)	377 (25.0)	438 (31.4)

Abbreviations: CABG: Coronary artery bypass grafting, ECMO: Extra-corporeal membrane oxygenation, IABP: Intra-aortic balloon pump, PCI: percutaneous coronary intervention, PDE-inhibitors: Phosphodiesterase inhibitors.

* Notice that this column consists of data from a 4-year period compared with 3-year periods in the other columns.

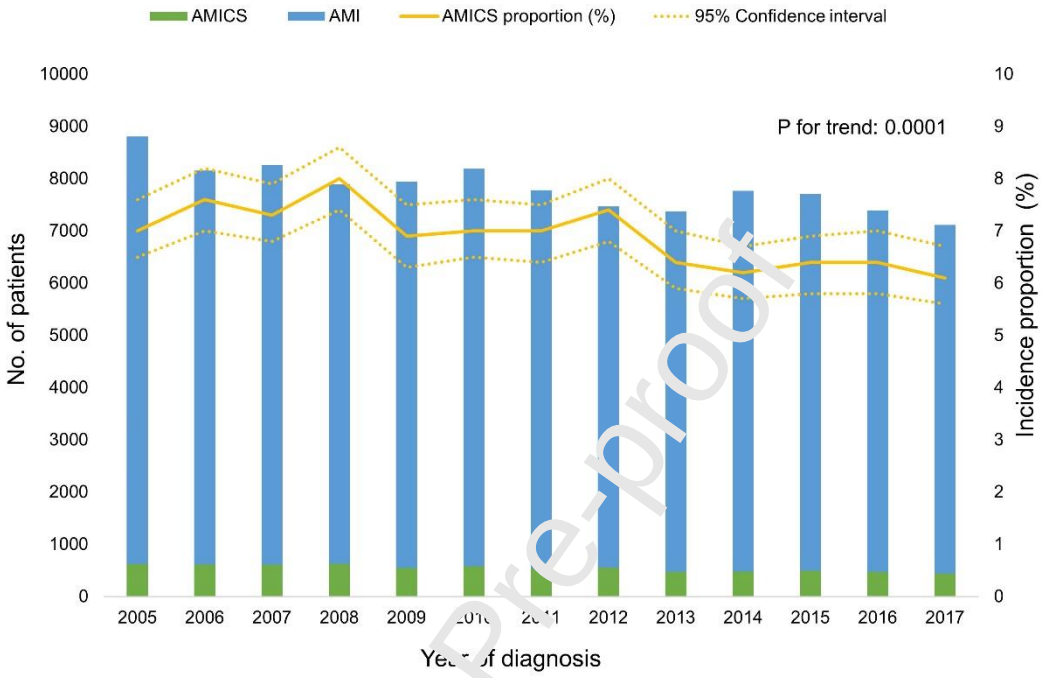
† According to rules of use of data from the Danish National Patient Register, it is not allowed to report less than 3 observations.

Figure 1. Flowchart of patients with first-time acute myocardial infarction-related cardiogenic shock from 2005-2017.



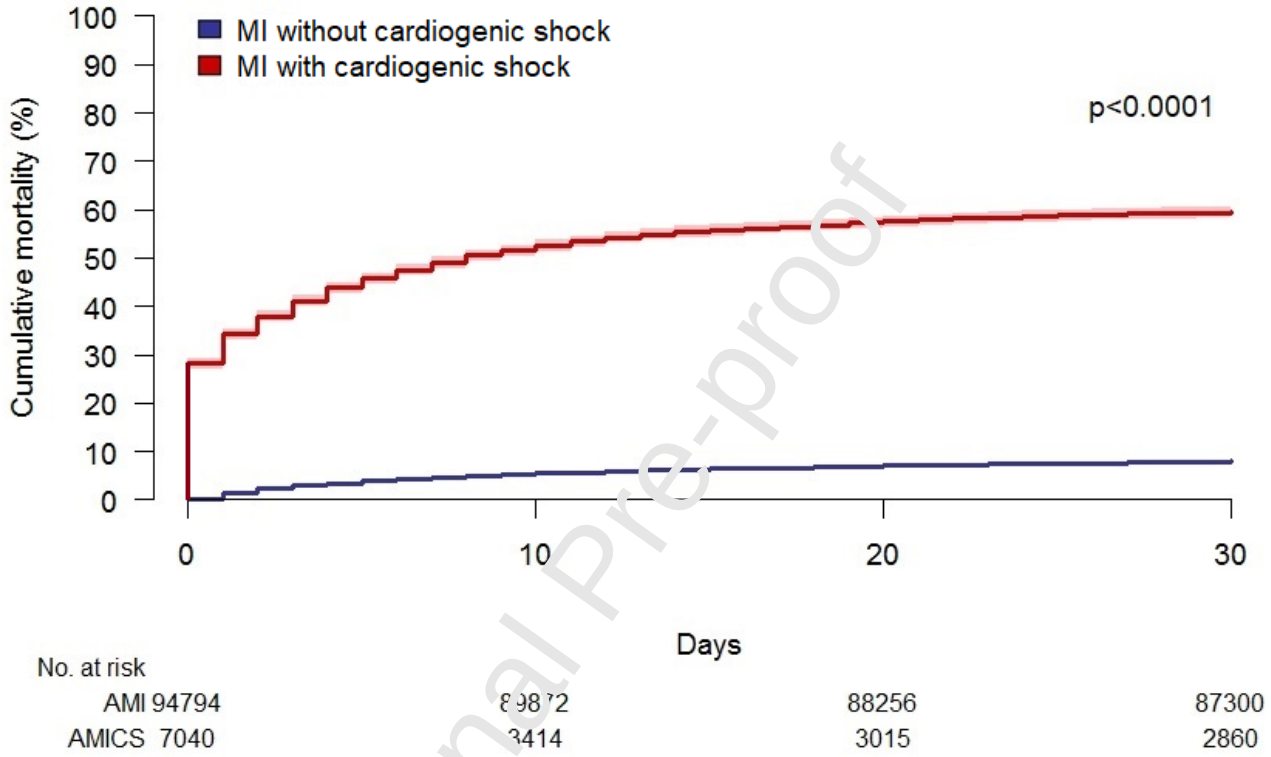
Abbreviations: AMI: Acute myocardial infarction, AMICS: Acute myocardial infarction related cardiogenic shock, ICD-10: International classification of diagnosis codes, 10th revision

Figure 2. Cumulative incidence proportion of acute myocardial infarction-related cardiogenic shock, by calendar year of diagnosis from 2005-2017.



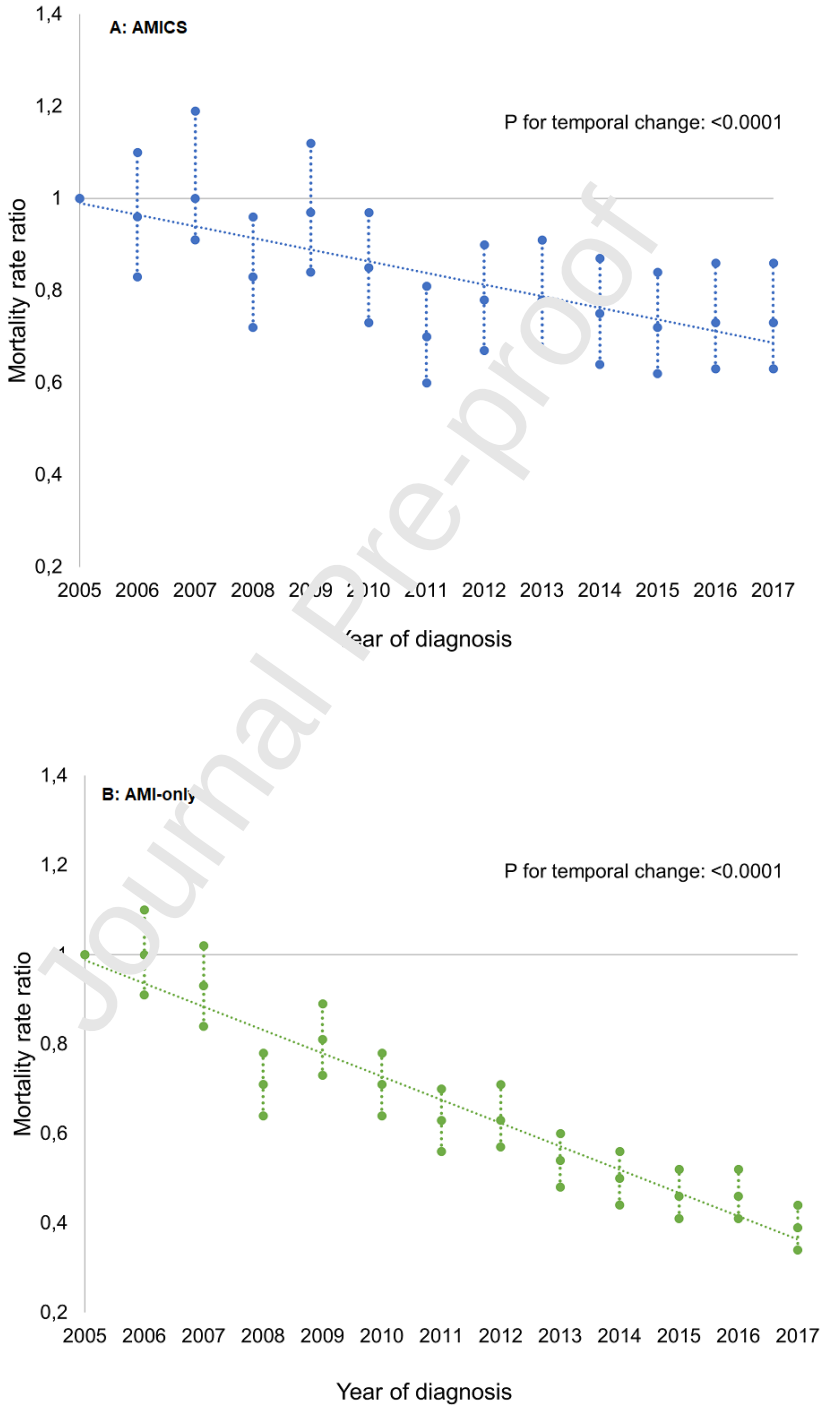
Abbreviations: AMI: Acute myocardial infarction, AMICS: Myocardial infarction-related cardiogenic shock, CI: Confidence interval.

Figure 3. Cumulative 30-day mortality in acute myocardial infarction patients with and without cardiogenic shock between 2005 and 2017.



Abbreviations: AMI: Acute myocardial infarction, AMICS: Acute myocardial infarction-related cardiogenic shock.

Figure 4. Trends in annual adjusted 30-day mortality rate ratios with 95% CI with year 2005 as reference, in acute myocardial infarction-related cardiogenic shock (A) and acute myocardial infarction without shock (B).



Online-only Supplements:

Tables:

Online Table 1.
ICD-10 diagnosis and procedure codes, and ATC-codes of medication.

Online Table 2.
Baseline characteristics for acute myocardial infarction patients with and without cardiogenic shock, by calendar periods of diagnosis.

Online Table 3.
Trends in 30-day mortality rate ratios in acute myocardial infarction-related cardiogenic shock, by year of diagnosis from 2005-2017

Figures:

Online Figure 1.
Trends in any use of inotropes/vasopressors, revascularization and mechanical circulatory support among patients with acute myocardial infarction-related cardiogenic shock, by year of diagnosis.

eTable 1: ICD-10 diagnosis and procedure codes, and ATC-codes of medication.

	ICD-10 codes (primary and secondary in- and out-patient)
Myocardial infarction	I21 (previous MI: ICD-8: 410, 411)
STEMI	I210B, I211A, I212, I213.
NSTEMI	I210A, I211A, I214
Cardiogenic shock	R570
Septic, hypovolemic, or unspecified shock	R571, R572, R578, R579, A419A, R57 (exclusive R570)
Heart failure as endpoint	I50
OHCA	I460
Comorbidities	
Heart failure	I50, I110, I420, I426, I427, I428, I429
Peripheral vascular disease	I70-I74, I77
Cerebrovascular disease	I60-I69, G45, G46
Chronic obstructive lung disease	J42-44, J982, J983
Hypertension	I10-I15
Atrial fibrillation or flutter	I48
Chronic kidney disease	N03-04, N11, N14-19, N26-27, I12-13, Z992, Q611-614, R34
Venous thromboembolism	I801-3, I26
Liver disease	K70-77, B18, I85
Diabetes (defined by a diagnosis code or ATC-code with anti-diabetics)	E10-14 ATC-codes: A10
Cancer	C00-97
Invasive cardiac procedures	
Coronary bypass	KFNA*E, KFNH20
PCI	KFNG, KFNF
CAG	UXAC85
Mechanical circulatory support	
IABP	KFXG, KFXH
Left ventricular assist device	KFXL00
ECMO	KFXE, BGXA2
Implantable cardioverter defibrillator	BFCB0, BFCB6, KFPG
Intensive procedures	
Mechanical ventilation	BGD
Acute dialysis	BJFD0
Inotropes/vasopressors	
Dobutamine	BFHC92B
Dopexamine	BFHC92C
Levomenandion	BFHC92D
PDE-inhibitors	BFHC92E
Epinephrine	BFHC93A
Norepinephrine	BFHC93B
Dopamine	BFHC93C
Combined treatment with vasoactive and heart stimulating drugs	BFHC95
Pharmacotherapy	**ATC-code**
ACE-inhibitors/Angiotensin-II-antagonists	C09
Statins	C10A
Anti-platelets	B01AC04, B01AC06
Beta blockers	C07
Spironolactone	C03D
Calcium antagonists	C08
Anti-diabetics	A10

Abbreviations: ATC: Anatomical therapeutic chemical classification, ACE: Angiotensin-converting enzyme, CABG: Coronary artery bypass graft, CAG: Coronary angiography, ECMO: Extra corporeal membrane oxygenation, IABP: Intra-aortic balloon pump, ICD-10: international Classification of Diseases, 10th revision, OHCA: Out of hospital cardiac arrest, PCI: Percutaneous coronary intervention, PDE-inhibitors: Phosphodiesterase inhibitors.

	First-time myocardial infarction							
	No cardiogenic shock				Cardiogenic shock			
	2005-2008,[a] n (%)	2009-2011, n (%)	2012-2014, n (%)	2015-2017, n (%)	2005-2008,[a] n (%)	2009-2011, n (%)	2012-2014, n (%)	2015-2017, n (%)
Total	30,637[4] (100)	22,240 (100)	21,102 (100)	20,815 (100)	2,473 (100)	1,666 (100)	1,505 (100)	1,396 (100)
Male gender	11,721 (38.3)	8,450 (38.0)	7,814 (37.0)	7,204 (34.6)	1510(61.1)	1034(62.1)	1008(67.0)	940(67.3)
Median age [IQR]	71 [60- 81]	70 [59-81]	69 [58-79]	69 [58-78]	73 [63-81]	73 [63-81]	72 [63-80]	71 [62-80]
Age, years								
<50	2,934 (9.6)	2,299 (10.3)	2,297 (10.9)	2,143 (10.3)	142 (5.7)	101 (6.1)	103 (6.8)	115 (8.2)
50-59	4,997 (16.3)	3,560 (16.0)	3,669 (17.4)	3,967 (19.1)	292 (11.8)	225 (13.5)	194 (12.9)	176 (12.6)
60-69	6,929 (22.6)	5,365 (24.1)	5,195 (24.6)	4,984 (23.9)	577 (23.3)	404 (24.3)	365 (24.3)	324 (24.5)
70-79	7,455 (24.3)	5,232 (23.5)	5,050 (23.9)	5,376 (25.8)	755 (30.5)	493 (29.6)	454 (30.1)	426 (30.5)
≥80	8,322 (27.2)	5,784 (26.0)	4,891 (23.2)	4,345 (20.9)	707 (28.6)	443 (26.6)	389 (25.9)	337 (24.1)
Comorbidities								
Heart failure	2,823 (9.2)	2,049 (9.2)	1,751 (8.3)	1,659 (8.0)	458 (18.5)	258 (15.5)	228 (15.1)	218 (15.6)
Peripheral vascular disease	1,944 (6.3)	1,629 (7.3)	1,513 (7.2)	1,543 (7.4)	292 (11.8)	196 (11.8)	189 (12.6)	193 (13.8)
Cerebrovascular disease	2,885 (9.4)	2,320 (10.4)	2,181 (10.3)	2,154 (10.3)	345 (14.0)	239 (14.3)	216 (14.4)	181 (13.0)
COPD	1,781 (5.8)	1,532 (6.9)	1,357 (6.4)	1,389 (6.7)	264 (10.7)	179 (10.7)	181 (12.0)	156 (11.2)
Hypertension	5,492 (17.9)	5,152 (23.2)	5,408 (25.6)	5,642 (27.1)	558 (22.6)	468 (28.1)	502 (33.4)	446 (31.9)
Atrial fibrillation/flutter	2,211 (7.2)	1,796 (8.1)	1,694 (8.0)	1,764 (8.5)	285 (11.5)	201 (12.1)	191 (12.7)	149 (10.7)
Chronic kidney disease	795 (2.6)	715 (3.2)	707 (3.4)	842 (4.0)	183 (7.4)	143 (8.6)	143 (9.5)	152 (10.9)
Venous thromboembolism	600 (2.0)	529 (2.4)	536 (2.8)	602 (2.9)	48 (1.9)	49 (2.9)	50 (3.3)	50 (3.6)
Liver disease	256 (0.8)	223 (1.0)	227 (1.1)	272 (1.3)	57 (2.3)	31 (1.9)	37 (2.5)	33 (2.4)
Diabetes[b]	3,990 (13.0)	3,271 (14.7)	3,265 (15.5)	3,302 (15.9)	411 (16.6)	327 (19.6)	324 (21.5)	285 (20.4)
Cancer	1,999 (6.5)	1,744 (7.8)	1,906 (9.0)	2,142 (10.3)	228 (9.2)	185 (11.1)	159 (10.6)	176 (12.6)
OHCA[c]	394 (1.3)	349 (1.6)	390 (1.9)	112[2] (1.6)	439 (17.8)	464 (27.9)	494 (32.8)	151[2] (30.9)
Drug therapy[d]								
Antiplatelet[e]	8,902 (29.1)	6,802 (30.6)	5,937 (28.1)	5,076 (24.4)	1,633 (66.0)	1,095 (65.7)	1,025 (68.1)	1,012 (72.5)
Calcium channel blockers	5,905 (19.3)	4,621 (20.8)	4,592 (21.8)	4,225 (20.3)	1,877 (75.9)	1,229 (73.8)	1,074 (71.4)	1,041 (74.6)
ACE-I/ARBs	8,536 (27.9)	7,385 (33.2)	7,162 (33.9)	7,087 (34.0)	801 (32.4)	642 (38.5)	623 (41.4)	539 (38.6)
Betablockers	6,200 (20.2)	4,753 (21.4)	4,495 (21.3)	4,149 (19.9)	551 (22.3)	392 (23.5)	367 (24.4)	316 (22.6)
Statins	6,044 (19.7)	5,873 (26.4)	5,787 (27.4)	5,618 (27.0)	559 (22.6)	487 (29.2)	490 (32.6)	436 (31.2)
Anti-diabetics	3,410 (11.1)	2,772 (12.5)	2,825 (13.4)	2,809 (13.5)	335 (13.5)	276 (16.6)	287 (19.1)	233 (16.7)

eTable 2. Baseline characteristics for acute myocardial infarction patients with and without cardiogenic shock, by calendar periods of diagnosis.

Abbr

Chronic obstructive pulmonary disease, IQR: Inter quartile range, NSTEMI: Non-ST segment elevation myocardial infarction, OHCA: Out of hospital cardiac arrest, STEMI: ST-elevation myocardial infarction.

[a] Notice that this column consists of data from a 4-year period compared with 3-year periods in the other columns.

[b] Defined by either an ICD-10 code with diabetes or use of anti-diabetics defines as a redeemed prescription within 180 days before admission.

[c] Data on OHCA is only available between 2005 and 2015.

[d] Defined as a redeemed prescription within 180 days before admission.

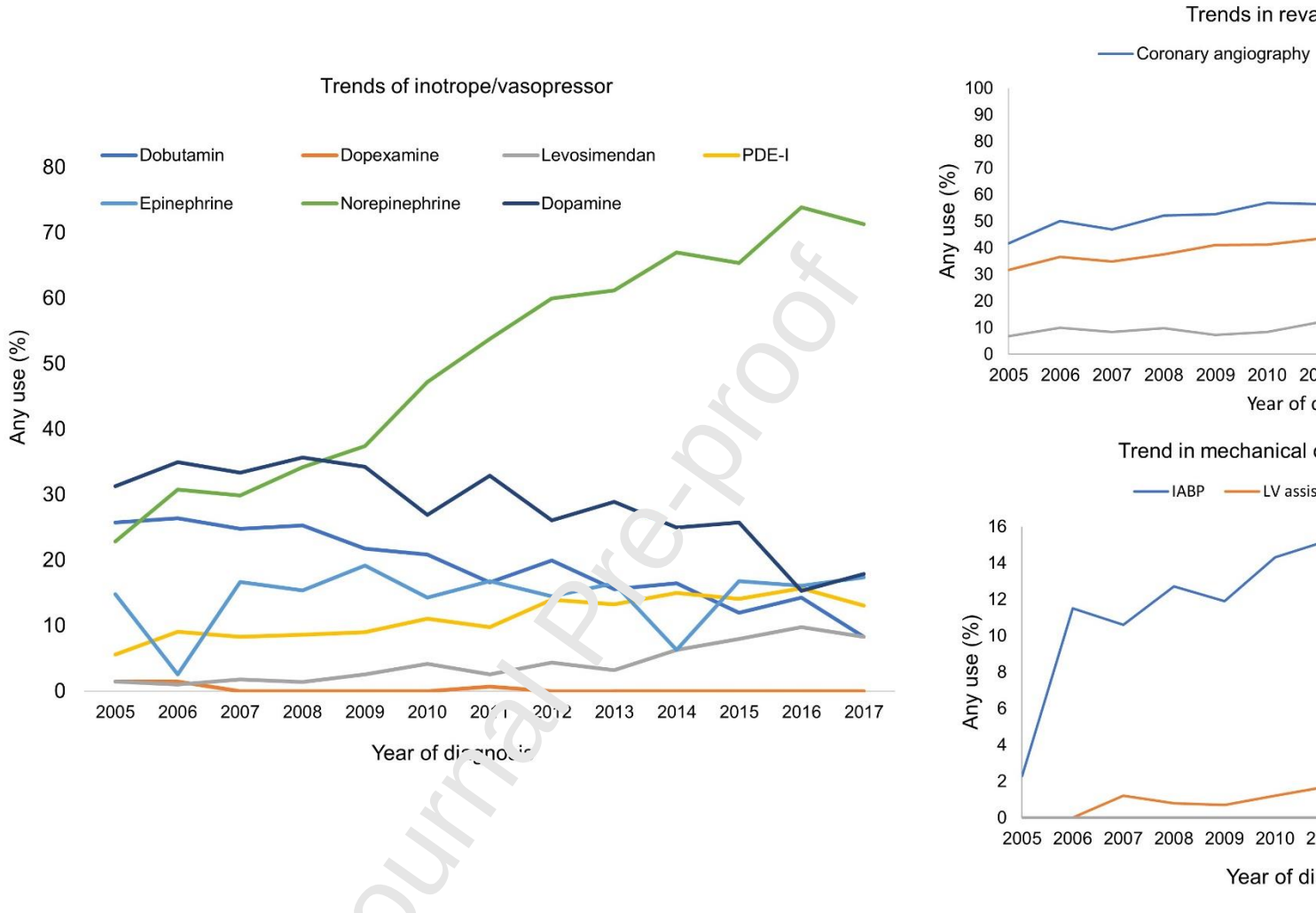
[e] Defined as either acetylsalicylic acid or clopidogrel.

eTable 3. Trends in 30-day mortality rate ratios in acute myocardial infarction-related cardiogenic shock, by year of diagnosis from 2005-2017.

	MI	MI-CS, n (%)	30-day mortality risk, % (95%CI)		MRR (95%CI)			
					No CS		MI-CS	
					Crude	Adjusted[a]	Crude	Adjusted[a]
Total	94,794	7,040 (6.9)	8.0 (7.8-8.2)	59.6 (58.5-60.8)	1 (ref)	1 (ref)	11.8 (11.3-12.2)	11.4 (10.9-11.8)
Year of diagnosis								
2005	8,189	620 (7.0)	11.2 (10.6-11.9)	67.7 (64.1-71.4)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2006	7,535	617 (7.6)	11.0 (10.3-11.7)	62.4 (58.6-66.2)	0.97 (0.88-1.04)	1.00 (0.91-1.10)	0.87 (0.76-1.00)	0.96 (0.83-1.10)
2007	7,656	605 (7.3)	10.4 (9.7-11.1)	67.9 (62.2-71.7)	0.92 (0.84-1.01)	0.93 (0.84-1.02)	0.99 (0.87-1.14)	1.04 (0.91-1.19)
2008	7,257	631 (6.1)	8.6 (8.0-9.3)	58.6 (54.8-62.5)	0.77 (0.71-0.85)	0.71 (0.64-0.78)	0.79 (0.69-0.91)	0.83 (0.72-0.96)
2009	7,394	546 (6.9)	9.8 (9.1-10.5)	64.7 (60.6-68.7)	0.87 (0.79-0.96)	0.81 (0.73-0.89)	0.90 (0.78-1.04)	0.97 (0.84-1.12)
2010	7,609	579 (7.1)	8.5 (7.9-9.1)	61.3 (57.3-65.3)	0.73 (0.67-0.80)	0.71 (0.64-0.78)	0.82 (0.71-0.94)	0.85 (0.73-0.97)
2011	7,237	541 (7.0)	7.6 (7.0-8.2)	52.3 (48.1-56.5)	0.66 (0.60-0.74)	0.63 (0.57-0.70)	0.65 (0.56-0.76)	0.70 (0.60-0.81)
2012	6,919	551 (7.4)	7.6 (6.9-8.2)	56.4 (52.3-60.6)	0.66 (0.60-0.72)	0.63 (0.57-0.71)	0.73 (0.63-0.85)	0.78 (0.67-0.91)
2013	6,899	474 (6.4)	6.4 (5.8-7.0)	59.1 (54.6-63.5)	0.56 (0.50-0.62)	0.54 (0.48-0.60)	0.76 (0.66-0.89)	0.78 (0.67-0.91)
2014	7,284	480 (6.2)	5.9 (5.3-6.4)	56.0 (51.6-60.3)	0.51 (0.45-0.56)	0.50 (0.44-0.56)	0.71 (0.61-0.83)	0.75 (0.64-0.87)
2015	7,213	489 (6.4)	5.4 (4.8-5.9)	53.2 (48.7-57.6)	0.46 (0.41-0.52)	0.46 (0.41-0.56)	0.68 (0.58-0.80)	0.72 (0.62-0.84)
2016	6,921	471 (6.4)	5.4 (4.9-6.0)	53.9 (49.4-58.4)	0.47 (0.42-0.52)	0.46 (0.41-0.56)	0.67 (0.57-0.79)	0.73 (0.63-0.86)
2017	6,681	436 (6.1)	4.9 (4.4-5.5)	56.7 (52.0-61.3)	0.42 (0.37-0.48)	0.39 (0.34-0.44)	0.72 (0.62-0.85)	0.73 (0.63-0.86)

Abbreviations: MI: Acute myocardial infarction, MI-CS: Myocardial infarction-related cardiogenic shock, CI: Confidence intervals, MRR: Mortality rate ratios.
[a] Multi-variate adjusted for sex, age groups, year of diagnosis and comorbidities.

eFigure 1. Trends in any use of inotropes/vasopressors, revascularization and mechanical circulatory support among patients with acute myocardial infarction-related cardiogenic shock, by year of diagnosis.



Abbreviations: CABG: Coronary artery bypass graft, ECMO: Extra-corporeal membrane oxygenation, IABP: Intra-aortic balloon pump, PCI: Percutaneous coronary intervention