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Clinical paper

Twenty-year trends in the characteristic, management and outcome of patients with ST-elevation myocardial infarction and out-of-hospital reanimation. Insight from the national AMIS PLUS registry 1997–2017



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Abstract

Background: Few studies describe recent changes in the incidence, treatment and outcome of successfully resuscitated STEMI patients after out-of-hospital cardiac arrest (OHCA) compared with non-OHCA STEMI patients.

Objective: To examine temporal trends in the incidence, therapeutic management, most serious complications, mortality rate and outcome of OHCA patients fulfilling criteria of STEMI compared with a reference group of STEMI patients without OHCA.

Methods: Analysis of registry data (AMIS Plus Registry) among STEMI patients both with and without OHCA between 1997 and 2017.

Results: Among 31,650 patients with STEMI, 6.8% were successfully resuscitated prior to hospital admission. Increasing incidences of hospital-admitted patients following successful out-of-hospital CPR were observed (4.5% in 1999 vs. 8.6% in 2017). OHCA STEMI patients were at higher clinical risk at presentation (36.1% vs. 2.7%; $p < 0.001$ with cardiogenic shock) despite a shorter time span from the onset of symptoms to hospitalization (195 min vs. 107 min; $p < 0.001$) and a lower prevalence of cardiovascular risk factors except smoking. More PCIs were performed in STEMI patients with OHCA (78.9% vs. 74.5% for non-OHCA patients; $p < 0.001$). However, over time PCI became the preferred primary intervention irrespective of the OHCA status of STEMI patients. For STEMI patients without OHCA, there was a significant correlation between PCI and time periods on in-hospital mortality ($p < 0.001$), which was $p = 0.002$ when adjusted for age and gender. For STEMI patients with OHCA, the interaction between PCI and time was unadjusted $p = 0.395$ and $p = 0.438$ when adjusted for age and gender.

Keywords: Out-of hospital resuscitated patients with ST-elevation, Myocardial infarction, Characteristic, Management, Outcome, Cardiogenic shock, Insight from the national AMIS PLUS registry

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Introduction

Cardiac arrest is one of the most life-threatening complications of ST-elevation myocardial infarction (STEMI) and is mainly caused by ventricular fibrillation, pulseless ventricular tachycardia or asystole. Survival rates after out-of-hospital cardiac arrest (OHCA) are poor.^{1,2} The reported survival rate to hospital admission after an OHCA and the reported mortality rates are highly variable, the latter ranging from 40 to 62%.^{3–5} A preliminary analysis over a shorter time period (1997–2011) from the same registry showed a mortality rate of 31.1% for OHCA STEMI patients and a PCI rate of 55.9%. It is interesting to note changes in the incidence rate, the mortality rate and the therapeutic approach over a 20-year period. Recent guidelines recommend that patients with STEMI resuscitated from OHCA should undergo immediate coronary angiography and subsequent percutaneous coronary intervention (PCI).⁷ For the period of observation (1997–2017), recent publications question the mechanical circulatory support of intra-aortic balloon pump (IABP) in patients with AMI-related cardiogenic shock.^{10,11} Based on these results, the 2016 ESC guidelines recommend against the routine use of IABP in the management of CS.¹² Furthermore, given the high incidence of unfavourable cerebral performance of patients who are resuscitated after OHCA as well as the neurologic injuries which have been reported as the cause of death in a majority of patients who died in hospital following cardiac arrest, the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR), among other bodies, recommends considering therapeutic hypothermia for comatose adult patients upon return of spontaneous circulation (ROSC) after OHCA.^{8,9}

Therefore, based on data from the AMIS Plus registry,⁶ a multicentric observational study was carried out to determine the incidence for survival to hospital admission, the most serious complications after OHCA, the mortality rate and the outcome of OHCA patients fulfilling criteria of STEMI compared with a reference group of STEMI patients who were not subject to resuscitation within the period of observation (1997–2017).

Methods

Data collection for the AMIS plus registry (Acute myocardial infarction in Switzerland)

The AMIS Plus project is a nationwide prospective registry of patients with acute coronary syndrome (ACS) admitted to hospitals in Switzerland. The registry was initiated in 1997.⁶ Participating centres, ranging from community care institutions to large tertiary care facilities, provide blinded data for each patient through a standardized electronic or paper-based questionnaire. The registry was approved by the Regional Ethics Committee for Clinical Studies and the Swiss Board for Data Security.

Study population

The present analysis included all patients with a diagnosis of acute STEMI enrolled in the AMIS PLUS registry between 1 January 1997 and 30 June 2017. STEMI is defined according to the universal definitions of acute ST elevation myocardial infarction.⁸ For each

patient enrolled a total of 280 items are collected, including medical history, comorbidities, known cardiovascular risk factors, clinical presentation, out-of-hospital management, early in-hospital management, reperfusion therapy etc.

Information on known risk factors was obtained from the patients' medical history. Dyslipidaemia, arterial hypertension and diabetes were considered if the patient was previously treated for such a condition and/or newly diagnosed. Patients were defined as obese if their body mass index was ≥ 30 kg/m² and as smokers if they were smokers at the time of the cardiovascular event. Patient comorbidities were assessed using the Charlson Index.^{13,14} Immediate drug therapy was defined as that administered within 24 h after admission. Reinfarction was defined as clinical signs or symptoms of ischemia with ECG changes indicative of new ischemia and a re-rise of biomarkers. A cerebrovascular event was defined as any event due to ischemic, thrombotic, haemorrhagic or hypoxic brain damage confirmed by a neurologist or imaging modality.

For the purpose of this study, our STEMI patient population was divided into two groups: those who had experienced OHCA and those who had not. In line with the European Resuscitation Council, OHCA was defined as cardiac arrest requiring resuscitation procedures performed prior to hospital admission. Successful resuscitation was required in order to be included in this study. The reason for OHCA was a composite endpoint of ventricular fibrillation/tachycardia and/or asystole due to an ST-elevation myocardial infarction.

Data set analysis

The patient data set was analysed for differences in patient population characteristics with particular focus on the time from symptoms onset to hospital admission, incidence of cardiogenic shock on admission, single or multi-vessel disease, comorbidities and cardiovascular risk factors. In addition, both groups were compared according to immediate (first 24 h) and late management with regard to the use of PCI, vasopressors, intra-aortic balloon pump, target temperature management and standard STEMI medications, as well as complications during hospital stay. Our outcome parameters were major adverse cardiac and cerebrovascular events (MACCE) and in-hospital mortality.

Statistical analyses

Data are presented as the proportion of valid cases or discrete variables and as means \pm standard deviations and/or medians with interquartile ranges for continuous variables. Differences in baseline characteristics were compared using either the unpaired *t*-test or the Mann-Whitney U test. Statistics for each table are based on all cases with valid data within the specified ranges for all variables in each table. A multivariate logistic regression model of complete cases was used to analyse the independent effect of in-hospital mortality, adjusted for age and gender. In the logistic regression analyses, the odd ratio (OR) for mortality for patients who had CPR prior to admission was, unadjusted, 5.7 (95% confidence interval 5.1–6.3; $p < 0.001$); adjusted for age and gender it was 8.8 (95% confidence interval 7.8–10.0; $p < 0.001$). Results are presented as OR with a 95% confidence interval. A *P*-value of < 0.001 was considered significant. SPSS (version 23; SPSS, Chicago, Ill., USA) was used for all statistical analyses.

Results

Between January 1997 and June 2017, a total of 55,565 patients with a final discharge diagnosis of ACS were enrolled. STEMI was diagnosed for 31,650 patients. Because of incomplete data or missing data on CPR, 376 (1.2%) patients were excluded from the present analysis. Of the remaining 31,274 patients, 2133 patients (6.8%) were resuscitated before being admitted to hospital.

Basic data

Table 1 displays a comparison of baseline characteristics of STEMI patients with and without OHCA prior to admission to hospital. In essence, STEMI patients who had been admitted after an out-of-hospital resuscitation were younger male patients with a lower prevalence of cardiovascular risk except for smoking and hyperten-

sion. Patients with moderate to severe comorbidities (Charlson Index > 1) were equally represented in both groups. In relation to the affected coronary arteries, single vessel disease was more frequent in resuscitated patients. The mean time from the onset of symptoms (pain, dyspnoea, etc.) to hospitalization was significantly shorter (107 min) for the OHCA patients. The incidence of infarction-related cardiogenic shock at admission was significantly higher in OHCA patients.

In-hospital management and outcome

There was a higher incidence of immediate coronary angiography and PCI in STEMI patients with OHCA than in those without OHCA (78.9% versus 74.5% respectively; $p < 0.001$) (Table 2). In STEMI patients with OHCA, CS was more frequent on admission, and it also developed more frequently during the hospital stay (Table 3). Accordingly, the use of catecholamines and IABP was more frequent and the early use of beta

Table 1 – Baseline characteristics of STEMI patients according OHCA status prior admission.

	Patients without OHCA prior admission	Patients with OHCA prior admission	P value
Number of patients	29,141	2133	
Sex male (%)	21462/29141 (73.6)	1669/2133 (78.2)	<0.001
Age in years, mean (\pm SD)	65.2 (13.4)	62.6 (12.5)	<0.001
Time to hospital admission in mins. Median (IQR)	195 (105, 480)	107 (66, 190)	<0.001
Killip class IV (%)	640/25035 (2.7)	460/1275 (36.1)	<0.001
Cardiovascular risk factors	11251/26657 (42.2)	879/1695 (51.9)	<0.001
Smoking (%)			
Dyslipidemia (%)	14334/26026 (55.1)	907/1738 (52.2)	0.019
Hypertension (%)	15318/27763 (55.2)	989/1854 (53.3)	0.13
Diabetes (%)	5224/28023 (18.6)	295/1881 (15.7)	0.001
Obesity (%)	4816/24548 (19.6)	274/1616 (17.0)	0.009
Charlson Score >1 (%) (since 2002)	4317/22242 (19.4)	272/1479 (18.4)	0.36
^a Single-vessel disease (%)	7686/17362 (44.3)	672/1397 (48.1)	0.006

^a Data available since 2005, Killip class IV corresponding to Cardiogenic shock at admission.

Table 2 – Immediate therapy in STEMI patients according to OHCA status prior admission.

	Patients without OHCA prior admission	Patients with OHCA prior admission	P value
Number of patients	29141	2133	
Drug therapy			
Aspirin (%)	27863/28966 (96.2)	1968/2105 (93.5)	<0.001
P2Y12 inhibitors (%)	20908/28929 (72.3)	1544/2103 (73.4)	0.27
Heparins (%)	26104/28941 (90.2)	1901/2109 (90.1)	0.91
Beta-blocker (%)	17645/27727 (63.6)	870/1992 (43.7)	<0.001
ACEI/ARB (%)	14798/27628 (53.6)	701/1988 (35.3)	<0.001
Statin (%)	17433/22811 (76.4)	993/1642 (60.5)	<0.001
Interventions			
PCI (%)	21464/28817 (74.5)	1676/2125 (78.9)	<0.001
CPR during hospitalisation (%)	903/27701 (3.3)	273/2009 (13.6)	<0.001
IABP (%)	1053/27489 (3.8)	314/1990 (15.8)	<0.001
Catecholamines	1524/18198 (8.4)	605/1375 (44.0)	<0.001
*Cooling of body temperature (%)	2/2596 (0.1)	61/184 (33.2)	<0.001

P2Y12 inhibitors – clopidogrel, prasugrel or ticagrelor.

Table 3 – Complications and in-hospital outcome.

	Patients without OHCA prior admission	Patients with OHCA prior admission	P value
Number of patients	29141	2133	
Cardiogenic shock ^a (%)	1666/27841 (6.0)	355/2011 (17.7)	<0.001
Re-infarction (%)	507/28896 (1.8)	47/2095 (2.2)	0.10
Cerebrovascular event (%)	225/28849 (0.8)	61/2091 (2.9)	<0.001
In-hospital Mortality (%)	1687/29141 (5.8)	550/2133 (25.8)	<0.001
MACCE (%)	2109/28815 (7.3)	581/2085 (27.9)	<0.001

^a Developing during hospital, MACCE– major adverse cardiac and cerebrovascular event.

blockers and/or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers was less frequent in the group of patients with OHCA. The incidence of cardio-pulmonary resuscitation during hospitalization was more frequent in OHCA patients (Table 2).

Mild therapeutic hypothermia was induced in 61/184 (33.2%) of hospital-resuscitated patients since 2010 (Table 2). Since then, cooling of the body temperature has been recorded by the AMIS Plus registry.

With respect to in-hospital outcomes, the in-hospital mortality rate for STEMI patients with OHCA was several times higher (25.8% vs. 5.8%), whereas there were no differences for the rate of re-infarction, cerebrovascular events and MACCE (Table 3).

Population-based temporal changes in the recorded incidence, treatment and outcome of OHCA patients over the 20-year observation period

Over the time period, rising trends in the incidence of hospital-admitted patients following successful out-of-hospital CPR were observed. The incidence of patients successfully resuscitated out of hospital increased substantially from 4.5% in 1999 to 8.6% in 2017 (Fig. 1).

With regard to early management, over time PCI became the preferred primary intervention irrespective of the OHCA status of the patient. For STEMI patients without OHCA, there was a significant correlation between PCI and time periods on in-hospital mortality

($p < 0.001$), which was $p = 0.002$ when adjusted for age and gender. For STEMI patients with OHCA, the interaction between PCI and time was unadjusted $p = 0.395$ and $p = 0.438$ when adjusted for age and gender.

With respect to STEMI patients without OHCA, mortality decreased from 10.1% in 1997–2000 to 5.9% in the period 2001–2004; decreased in 2005–2008 to 5.5%; decreased in 2009–2012 to 4.8%; and decreased further to 4.0% in 2013–2016. Mortality for pre-hospital-resuscitated patients remained roughly unchanged (21% in 1997–2000 vs. 24% in 2013–2016 (Fig. 2).

Between 1997 and 2017, the rates of CS on admission increased in both groups, apart from 2013 to 2016 where a declining trend was observed in the OHCA patient group (Fig. 3A). In contrast, the overall rates of cardiogenic shock developing during hospitalization decreased between 1997 and 2017 in both groups: specifically from 12.7% to 8.2% for STEMI patients without OHCA and from 31.6% to 8.2% for pre-hospital-resuscitated STEMI patients (Fig. 3B). However, mortality in CS patients remains high (with a rate between 50 and 60%). Although the mortality in the non-OHCA patients slightly decreased in the last 20 years (58% in 1997–2000 to 51% in 2013–2016), it increased for the group with OHCA (51% in 1997–2000 to 62% in 2013–2017).

Mechanical circulatory support by IABP increased over the course of the earlier years in both groups, but its use has been in decline since 2009. Overall, mechanical circulatory support by IABP was higher in OHCA patients and correlated with a higher rate of CS on admission to

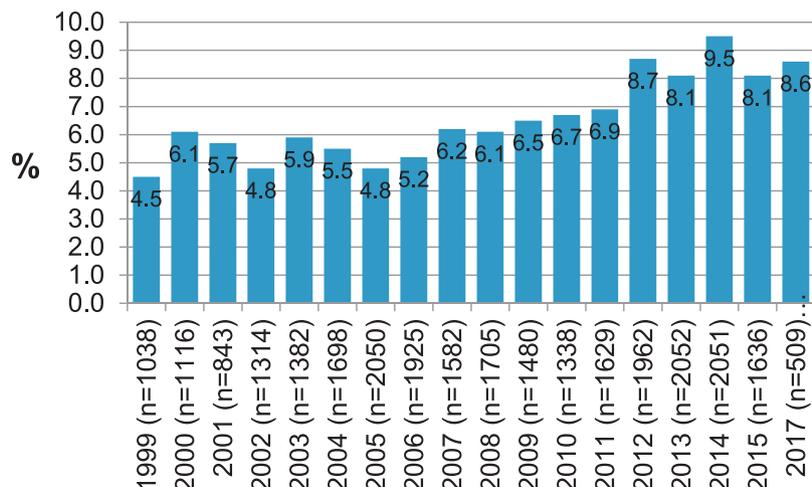


Fig. 1 – Temporal trends from 1999 to 2017 in the incidence of STEMI patients admitted to hospital after successful resuscitation from out-of-hospital cardiac arrest.

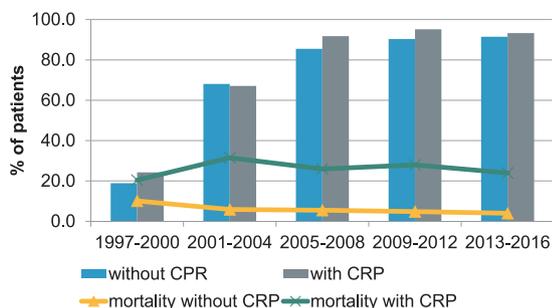


Fig. 2 – Temporal trends from 1999 to 2017 in the frequency of Percutaneous coronary intervention (PCI) and in-hospital mortality according to 4-years periods (%).

hospital and developing during hospitalization. In-hospital mortality for pre-hospital-resuscitated patients supported by IABP increased over the observation period.

Discussion

In this analysis of a large, population-based registry covering 20 years of observation, increased rates of STEMI patients achieving survival to hospital admission following successful out-of-hospital CPR were reported. Increasing values were documented, starting from the lowest measured values (4.8%) in 1999 up to 8.6% in 2017. This observation is concordant with other studies, including a recent Danish study which also confirmed a significant increase in the proportion of patients achieving survival to hospital admission.^{15–17}

Although our analysis does not allow us to ascertain which factors have contributed most to the improvement of survival to hospital admission after OHCA, the substantial increase in the education of laypersons in bystander CPR, the use of automated external defibrillators, witnessed arrest, shockable initial cardiac rhythm and

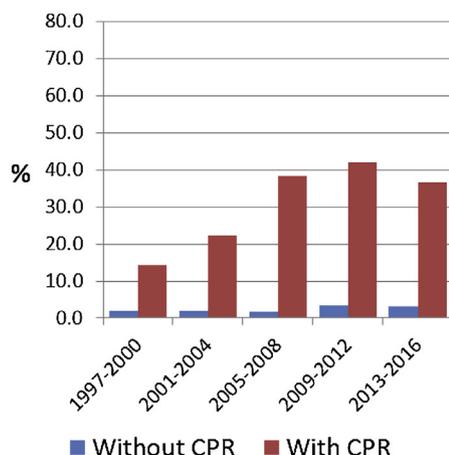
a time to ROSC of < 30 min. have been reported as important factors in other studies.^{18–20}

Previous studies have already evaluated the value of urgent angiography and PCI, and a benefit has indeed been described for this approach.^{21–23} Comparison with an earlier analysis from the same registry over a shorter period (1997–2011) confirms an increasing implementation of guideline-recommended early revascularization for patients with STEMI – in both groups.²⁹ Interestingly, in our cohort PCI was performed more frequently in STEMI patients with OHCA (79%) than in those STEMI patients without OHCA (74%). The higher rate of PCI for patients with OHCA can be attributed to the fact that this group comprises a higher number of patients presenting with CS upon admission (36.1% vs. 2.7%) and that, according to the guidelines, PCI is recommended as the most beneficial immediate therapy strategy for patients in CS.

Increased PCI rates in recent years were associated with lower mortality among STEMI patients without OHCA but not in those patients with OHCA, which indicates that the group of out of hospital resuscitated STEMI patients were in a worse clinical state and were more often in CS. Indirect indications for this in our cohort are the higher incidences for the need for supportive therapies such as IABP and catecholamines as well as the increased rate of repeated resuscitation during hospitalization.

In-hospital mortality for STEMI patients with OHCA was 25.8%. Despite therapy optimization, primarily via an increasing rate of PCI, a significant decline in mortality was not seen in the group of STEMI patients with OHCA over the 20-year observation period. When hypothesising the reason for this, it must be taken into account that during the hospital stay the group of patients with OHCA suffer more complications including CS, cerebrovascular events, multiple organ failure and sepsis. Other studies also show high mortality for STEMI patients with OHCA, with a rate from 50 to 60%.^{3,17,24} Whereas the in-hospital mortality for STEMI patients with OHCA did not change substantially, a significant decline was seen in the in-hospital mortality for STEMI patients without OHCA: from 10.1% in the period 1997–2000 to 4.0% in the period 2013–2016. This could be attributable to the increasing use of PCI as a primary therapy for patients with STEMI. The unadjusted interaction between PCI and time periods on in-

A: Cardiogenic shock at admission



B: Cardiogenic shock in hospital

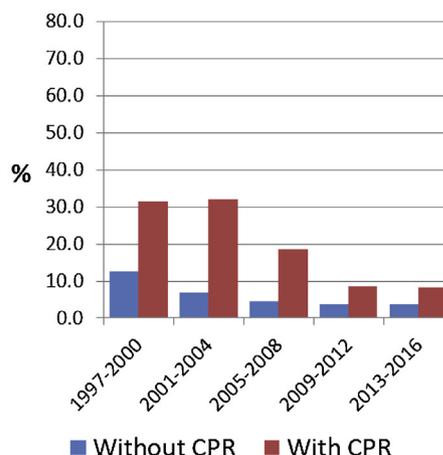


Fig. 3 – A + B: Cardiogenic shock on admission (A) and developing in hospital (B) in STEMI patients with and without resuscitation prior to arrival according to 4-years periods (%).

hospital mortality was significant ($p < 0.001$), and adjusted for age and gender $p = 0.022$.

CS as the most common complication of STEMI was higher in STEMI patients with OHCA compared with a reference; this also applies for CS developed at admission, as well as for CS developed during hospitalisation. For both groups our analysis of temporal trends revealed a progressive decline in CS developing in hospital, which was also shown in other recent reports from registry data.²⁸ Several factors could have contributed to this observation, one being the aforementioned rise in the rate of PCI and the improved therapeutic management to prevent hemodynamic deterioration.

The in-hospital mortality rate in patients with CS in our study was around 60% and this has not changed over the last 20 years. As in previous studies, the high absolute mortality is likely due to the high-risk presentation in the OHCA group, with a much higher prevalence of CS on admission also reported in a similar manner by Lettieri et al.⁴

Patients admitted to hospital following successful resuscitation after OHCA, compared to those without OHCA, are slightly younger, have more often a single vessel disease and present with a remarkably higher rate of CS, despite a significantly reduced time delay between symptoms onset and hospital admission. These findings are consistent with a previous study by Lettieri et al., who also reported a higher-risk presentation in the OHCA group with a much higher prevalence of CS on admission compared with the group without OHCA. Angiographic (single vessel disease) and procedural features are also similar.⁴ The rate of CS developing during hospitalisation was more than twice that for non-OHCA patients. Accordingly, it is not surprising that the number of CPR events during hospital stay and the need for vasopressors and/or IABP were more frequent in this group of patients. Intervention with IABP was most popular around 2009, did not affect the outcome.

Targeted temperature management (TTM) has been considered effective for a favourable long-term neurological outcome based on several studies, in particular two RCTs published in 2002.^{25–27} Within the last few years, both the 2012 ESC - and the 2013 ACCF/AHA guidelines recommend the use of TTM for STEMI patients who are resuscitated after OHCA but who remain comatose on arrival at hospital. Since 2010, data relating to TTM were recorded in the AMIS plus Registry. Among adult comatose survivors after OHCA, 33% (61/184, $p < 0.001$) were treated with TH. Unfortunately, data on return of spontaneous circulation (ROSC), target temperature, timing and duration for TTH were missing and there is also no information available on cerebral performance category. Therefore, it is not possible to say whether and in what way this neuroprotective measure had an influence on the outcome because of the aforementioned logistical reasons (no separate breakdown and no respective follow-up data were recorded in the AMIS questionnaire). However, a significantly greater number of overall cerebrovascular events were documented in the STEMI patients with OHCA (2.9% vs. 0.8%, $p < 0.001$) which might be at least partially related to hypoxic encephalopathy.

The high mortality rate of patients after OHCA can be attributed to, among other factors, a unique pathophysiological process that involves multiple organs. Initially, prolonged whole-body ischemia causes global tissue and organ injury, and further damage occurs during and after reperfusion. Besides systemic ischemia/reperfusion response, the post-cardiac arrest syndrome includes brain injury, which is a common cause of morbidity and mortality. A study by Laver et al. determined the mode of death in patients admitted to an intensive care unit (ICU) after cardiac arrest who died before hospital discharge. In this study, brain injury was the cause of death in 68% of patients after OHCA and in 23% after in-hospital cardiac arrest.²⁸

Although the data were collected prospectively, these are registry data from hospitals participating voluntarily. Although data collected from hospitals for the registry are representative for the different regions of our country and the spectrum of hospitals among regions, we cannot exclude a selection bias. In addition, we cannot fully exclude the possibility of inaccuracies in the data collection, despite audits performed by the data centre in the participating hospitals. For our study in particular, another limitation is the lack of specific data upon the process of resuscitation of patients with STEMI and OHCA, the in-hospital process of targeted temperature management, and evaluation of the neurologic outcome during hospitalisation. However, our data are unique for the large number of STEMI patients' records and the observation period, allowing the analysis of temporal trends in the treatment of STEMI patients with and without OHCA.

Conclusion

Our study indicates that a minority of patients with STEMI admitted to hospital had an OHCA event. In comparison with STEMI patients without OHCA, those with OHCA had a sicker clinical course and a worse outcome, a situation which did not change over time despite therapy optimization, primarily via an increasing rate of PCI. The major complication in survivors of OHCA is cardiogenic shock, which contributes to further increase in-hospital mortality.

Conflict of interest

The authors declare that there are no conflicts of interest.

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