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a Danish cohort study

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Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study

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Abstract

Aim We sought to describe the contemporary annual incidence of acute myocardial infarction and cardiogenic shock (AMICS), the proportion of patients developing CS following ST-elevation myocardial infarction (STEMI), and other temporal changes in AMICS in Denmark between 2010 and 2017.

Methods and results Medical records of patients suspected of having AMICS during 2010-2017 were reviewed to identify consecutive patients with AMICS in a cohort corresponding to two-thirds of the Danish population. Due to changes in recruitment area over the study period, population-based incidence could only be calculated from 2012-2017. A total of 1716 patients with AMICS were identified and an increase in the annual incidence was observed, from a nadir 65.3 per million person-years in 2013 to 80.0 per million person-years in 2017 (P for trend < 0.001). This trend corresponded with an increase in patients with non-STEMI and decrease in patients developing CS after STEMI (10.0 to 6.6%, P for trend < 0.001) Also, mean arterial blood pressure at the time of AMICS was lower (63 ± 11 mmHg to 61 ± 13 mmHg, P p for trend=0.001) and the frequency of patients with left ventricular ejection fraction ≤ 30% increased (61.8% to 71.4%, P for trend=0.004). The annual 30-day mortality during the study period remained unchanged at about 50%.

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Conclusion: The incidence rate of AMICS increased in the Danish population between 2012 and 2017. Fewer patients with STEMI developed CS, and the haemodynamic severity of CS increased during the study period; however, the survival rate remained unchanged.

Keywords Cardiogenic shock, Myocardial infarction, Epidemiology, PCI, Mechanical circulatory support

Introduction

Cardiogenic shock (CS) is the leading cause of death in patients with acute myocardial infarction (AMI), reportedly affecting 5 to 10% of cases, with sustained early mortality of approximately 50% for nearly two decades. The exact burden of acute myocardial infarction and cardiogenic shock (AMICS) to public health is unknown as it has never been investigated at the population level. Contemporary data regarding incidence, patient characteristics, management, and the outcome is limited. They are based on registries using diagnosis codes of ST-elevation MI (STEMI) and report conflicting results regarding the incidence, mortality, comorbidity burden, and the use of mechanical circulatory support devices. The temporal trends in the proportion of patients with out of hospital cardiac arrest (OHCA) have not been reported, but likely increased as more patients with OHCA survive to hospital admission in the recent years. Also, the use of mechanical circulatory support devices in AMICS has likely changed since the demonstration of lack of survival benefit with the use of intra-aortic ballon pump (IABP) in a randomised controlled trial in 2012. Thus, the objective of this study was to examine the contemporary trends in the incidence of AMICS at the population level, patient
characteristics, treatment, and outcome in a large consecutive cohort of individually validated patients with AMICS admitted to two tertiary heart centers in Southeastern Denmark from 2010-2017.

Methods

Study setting

Primary percutaneous coronary intervention (PCI) was introduced as a national treatment strategy for STEMI in Denmark in 2003. All patients suspected of having a STEMI or AMICS are transferred immediately to one of the five high-volume centres for evaluation and revascularisation. (12) The number of high-volume centres was reduced to four as of mid-2011. In the present study, patients with AMICS managed at two tertiary University facilities in Denmark (Odense University Hospital and Copenhagen University Hospital Rigshospitalet) from 2010 to 2017 were identified retrospectively. The two centres have a recruitment area of 22,000 km², covering two-thirds of all Danish citizens and 3.9 million citizens in total.

Data sources

Patients with suspected AMICS were identified from the Danish National Patient Registry, where in-hospital activities are linked to a unique Civil Personal Registration (CPR) number and used during every contact with the Danish health care system. (13, 14) Danish hospitals are obligated by law to report every patient contact to the Danish National Patients Registry including one primary diagnosis and optional secondary diagnoses, and these diagnoses are not directly related to reimbursements. Data on invasive interventions were collected from the Western Denmark Heart Registry (WDHR) and Eastern Denmark Heart Registry (PATS). (15) The average annual population size (age ≥18 years) was

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obtained from Statistics Denmark. Pre-hospital management was recorded from emergency medical service records.

**Study population**

We applied the following screening algorithm in the Danish National Patient Registry and identified patients with AMICS treated at two centres from January 1\textsuperscript{st} 2010 to December 31\textsuperscript{st} 2017: patients with a primary or secondary diagnosis of cardiogenic shock (ICD-10, R57.0); patients with a primary or secondary diagnosis of AMI (ICD-10, I21.x) who died during the hospital stay and/or were treated at an intensive care unit and/or with vasoactive drugs and/or a mechanical circulatory assist device; patients with a primary or secondary diagnosis of cardiac arrest (ICD-10, I46.x) who died during the hospital stay and/or were treated at an intensive care unit and/or with vasoactive drugs and/or a mechanical circulatory assist device. The discharge summary of patients in the screening cohort was reviewed by OKMH, JJ, AS, and NLJU to identify patients with AMI. A confirmed diagnosis of AMI was made at the discretion of the treating physician based on the universal definition of myocardial infarction.\textsuperscript{(16, 17)} A full chart review of patients with AMI was performed by OKMH and JJ to identify patients with cardiogenic shock if all of the following criteria were met:

1. Adult patient (age $\geq$18 years)
2. Persistent hypotension with systolic blood pressure $\leq$ 90 mmHg for $>$ 30 minutes or use of vasoactive drugs
3. Signs of impaired organ perfusion (at least one of the following: altered mental status excluding medically induced sedation; cold/clammy skin; oliguria; arterial lactate $\geq$2.5 mmol/L)
4. Documented reduction in left and/or right ventricular function in the absence of hypovolemia, sepsis, anaphylaxis, pulmonary embolism, or primary valve dysfunction.

Patients with AMICS undergoing revascularisation were divided into STEMI and non-STEMI (NSTEMI), based on the information from WDHR and PATS, at the discretion of the interventional cardiologist. If a patient fulfilled the AMICS definition at two distinct hospital admissions, only the first admission was used. Patients treated with acute PCI for STEMI were identified through WDHR and PATS.

Data collection

Individual electronic hospital medical records of patients fulfilling the AMICS definition were reviewed for patient demographics, medical history, and clinical data. Clinical data included interventions performed, location of culprit lesion, use of mechanical circulatory assist device and type, use of mechanical ventilation, and use of vasoactive drugs. Timing of shock was determined relative to arrival at the PCI centre with systolic blood pressure as the key determinant. The pre-hospital shock was defined as a systolic blood pressure measured in the ambulance ≤ 90 mmHg (shock criteria 2) and fulfilling shock criteria 3 and 4 on arrival at the hospital. A minimum of 30-day follow-up was available for all patients. Symptom to revascularisation delay was defined as the time from symptom onset to insertion of PCI-catheter in patients undergoing revascularisation (within 24 hours of symptom onset).

Ethics
This study was approved by The Danish Patient Safety Authority (and the Danish Health and Medicines Authority, formerly handling the applications, case number 3-3013-1133/1) and the Danish Data Protection Agency (file number 16/7381 and 18/23756).

**Statistical Analysis**

The annual incidence rate of AMICS was calculated as the annual number of AMICS cases divided by the average annual population size age $\geq 18$ years, and reported as cases per million person-years. The crude annual incidence rates were adjusted using direct standardisation to the age (10-year intervals) and sex distribution of the population midyear 2014. The changes in the incidence rate were further explored by stratifying patients undergoing revascularisation into those with STEMI/NSTEMI and with/without OHCA. Patients with STEMI and CS may have also been treated at another PCI centre in Copenhagen until 2011. Therefore, the incidence rates at the population level were only calculated for the years from 2012 to 2017. The annual proportion of patients with CS following STEMI were calculated as percentages of patients receiving acute PCI for STEMI. The temporal trend in the rates of STEMI was further explored by classifying patients according to sex and age groups: age $< 60$ years, $60 \leq age \leq 70$ years, and age $>70$ years. Continuous variables with Gaussian distribution are reported as mean $\pm$ SD, non-Gaussian distribution as median (IQR, Q1-Q3), and frequencies are presented as percentages. For time-trend analysis, Poisson regression was used for incidence rate at the population level, variance-weighted least squares test was used for data with normal distribution, and a nonparametric test was used for non-normal distribution. Among patients undergoing revascularisation, the log-rank test was used to evaluate the difference in 30-day survival between patients with STEMI/NSTEMI, those with/without OHCA, and female/male sex. The association of female sex and 30-day mortality was
further explored by logistic regression adjusting for age and symptom to revascularisation delay. All statistical analyses were performed using Stata® software (version 14.2, StataCorp, College Station, Texas, USA).

Results

During 2010-2017, 3553 possible candidates were identified from the Danish National Patient Registry of whom 1716 patients fulfilled the criteria for AMICS (Figure 1). During the same period, 11 569 consecutive acute STEMI procedures were identified in the WDHR and PATS registry.

Incidence of AMICS and patient characteristics

From 2012 to 2017, the annual incidence rate of AMICS increased from 75.7 per million person-years to 80.0 per million person-years ($P$ for trend < 0.001), with a steady increase from a nadir of 65.3 per million person-years in 2013 (Figure 2). The increasing incidence of CS was driven by an increase in patients with NSTEMI, with and without OHCA (Figure 3). However, the incidence of CS following STEMI without OHCA decreased (Figure 3). In addition, the annual proportion of CS in patients with STEMI undergoing revascularisation with PCI decreased from 10.0% in 2010 to 6.6% in 2017 ($P$ trend < 0.001) (Figure 4). This trend was specifically observed in males and patients > 60 years of age. The demographics and medical history of patients with AMICS remained unchanged over time with only minor changes such as a decrease in previous ischemic heart disease from 33.3% to 22.5% ($P$ for trend = 0.04) (Table 1). During the recent study years, patients frequently presented with OHCA and fewer patients developed late shock (>12 hours after admission) (Table 1). Also, patients had lower systemic
arterial blood pressure at the time of CS diagnosis and more patients had severely depressed LVEF in recent than earlier years (Table 1).

Revascularisation and mechanical circulatory support

The proportion of patients undergoing revascularisation increased from 83.6% in 2010 to 91.6% in 2017 (P for trend < 0.001) (Table 2). The proportion of STEMI in CS patients undergoing revascularisation decreased from 81.0% in 2010 to 61.2% in 2017 (P for trend < 0.001) (Table 2). The median time delay from symptom onset to revascularisation in the overall AMICS cohort decreased from 264 minutes (IQR 153-411 minutes) in 2010 to 156 minutes (IQR 114-288 minutes) in 2017 (P for trend = 0.01) (Table 2). Likewise, the median time delay from symptom onset to revascularisation for all 11 569 patients with STEMI () decreased from 230 minutes (IQR 150-385 minutes) in 2010 to 172 minutes (IQR 117- 289 minutes) in 2017 (P for trend < 0.001). 13 patients received fibrinolysis of which 11 received additional PCI and 1 received additional CABG. The use of mechanical circulatory support devices nearly halved over the study period with major changes in the type of device utilised. While the use of IABP declined drastically from September 2012 onwards, there was a concomitant increase in the use of other mechanical circulatory support systems (Impella devices and veno-arterial extracorporeal membrane oxygenation (VA-ECMO)) (Table 2).

Thirty-day mortality

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Throughout the study period, 30-day mortality remained constant at approximately 50% for the entire AMICS cohort (Figure 2) and 40% for patients with CS following STEMI (Figure 4). Among patients undergoing immediate revascularisation, mortality was lower in those with STEMI than those with NSTEMI (46.1% vs 57.7%, \( P < 0.001 \)) Also, patients with OHCA had lower mortality than those without OHCA (45.8% vs 51.9%, \( P < 0.001 \)). The overall trend of unchanged 30-day mortality remained even when patients were classified as those with STEMI/NSTEMI and with/without OHCA. Females had higher 30-day mortality compared to males (56.6% vs 46.9%, \( p_{\text{logrank}} < 0.001 \)). Adjusting for age and symptom to revascularisation delay in logistic regression female sex was associated with an odds ratio of 1.20, \( p = 0.18 \).

**Discussion**

In this large cohort of patients with AMI and individual validation of the clinical cardiogenic shock diagnosis, the overall annual incidence of CS increased despite fewer patients with STEMI developing CS. Also, the timing of CS occurrence changed with fewer patients developing AMICS > 12 hours after admission. Finally, during the recent study years, patients with AMICS frequently presented with an OHCA and had severely compromised haemodynamics. Despite the increasing complexity of CS, 30-day mortality remained constant at about 50% over the study years.

To the best of our knowledge, this is the first study to report incidence of AMICS from a population-based perspective rather than from a diagnosis-based (e.g., AMI/STEMI) perspective. The temporal
increase in the incidence of CS was driven by an increase in the proportion of patients with NSTEMI, with a concomitant decrease in the proportion of patients with STEMI, in line with previous studies reporting similar observations. The increasing proportion of patients with NSTEMI may reflect an increased willingness at tertiary centres to accept these patients for treatment despite poor prognosis. Patients with cardiogenic shock due to NSTEMI are reported to be older, have multiple comorbidities, multivessel coronary artery disease, and poor prognosis compared to those caused by STEMI. Consistent with previous findings, patients with NSTEMI in this study had worse prognosis. Contrary to expectations, increase in the proportion of patients with NSTEMI was not accompanied by increasing age, comorbidity status, or severity of coronary artery disease as these variables were stable throughout the study period. Both the annual incidence of cardiogenic shock following STEMI without OHCA, and the proportion of cardiogenic shock in patients with STEMI decreased from 2010 to 2017. This decrease may partly be explained by the one-hour improvement in the time delay from symptom onset to revascularisation in the overall STEMI cohort. The incidence of cardiogenic shock in patients with STEMI varies in literature as studies show both increasing and declining trends over time, but is typically reported to be between 5-10%. One factor contributing to the varied range in the incidence of CS after STEMI is the prevalence of OHCA, as electrocardiogram (ECG) changes immediately after resuscitation are difficult to interpret for diagnosing STEMI. This study suggests that the prevalence of OHCA in AMICS is increasing and is in agreement with the recent CULPRIT shock trial where > 50% of patients had sustained cardiac arrest before randomisation. We observed that patients with AMICS and OHCA undergoing revascularisation had lower 30-day mortality than patients without OHCA (absolute reduction in mortality of 6%). This topic is poorly studied, and an earlier study from one of the participating centres showed the opposite result,
highlighting the need for further studies. (23) Consistent with previous findings, female sex was associated with worse prognosis in crude analysis, but adjusting for age and symptom to revascularisation delay diminished the trend suggesting that female sex is not an independent risk factor in AMICS. (24) We also observed a change in timing of shock occurrence with only 6.9% of patients developing shock > 12 hours after admission in 2017 compared to 14.8% in 2010. This shift in the onset of CS is consistent with earlier studies, where cardiogenic shock was initially defined as late when occurring > 24 hours after admission with an observed rate of 25-40%, whereas in the more recent studies define cardiogenic shock as late already when occurring after leaving the catheterisation laboratory. (25, 26)

A major shift in the choice of mechanical circulatory support device occurred over the years with an almost complete abandonment of IABP and a concomitant increase in the use of Impella (a transvalvular axial flow pump) and VA-ECMO. Previous studies have also reported a decline in the use of IABP over time but our study demonstrates a near complete elimination of IABP use, and this change coincides with the publication of the results of the IABP-SHOCK II trial. (4, 5, 11, 27) In line with previous studies reporting increased use of VA-ECMO and Impella, we observed increased use of Impella device, reaching a plateau at ~16% in 2016-2017 compared to 3-4% as reported previously. (27) The possible explanations for the higher rates of Impella use include the difference in the study periods of previous studies (2012-2014) and the collateral effect of the ongoing DanShock trial assessing the effect of Impella in patients with cardiogenic shock following STEMI without OHCA (NCT01633502).

Despite an increase in the proportion of patients undergoing revascularization, the 30-day mortality rate remained constant at approximately 50% over the study period. (28) This lack of improvement in
survival may be due to an increase in the frequency of patients with high-risk features associated with early mortality reaching a PCI centre such as patients with NSTEMI, lower arterial blood pressure, severely depressed LVEF along with increasing use of mechanical ventilation. (20, 29)

**Strengths and limitations**

This study was carried out in an area with socio-demographic and economic characteristics reflecting those of Denmark, and most industrialised countries except for short transport distances to a tertiary PCI centre. The strengths of this study are the large sample size of individually validated patients with AMICS, population-based design, and complete follow-up. However, there are some limitations as well. Typically, retrospective analysis of patients enrolled in registries introduces the possibility of selection bias. We believe that our screening algorithm including diagnoses appearing as either primary or secondary in the registry has led to the identification of a vast majority of potential candidates. However, we cannot exclude the possibility of missing cases. We identified patients with cardiogenic shock treated at two tertiary cardiac centres performing all acute PCI in the catchment area, but there may have been additional patients admitted to local hospitals developing cardiogenic shock and managed locally without being transferred or dying before referral to tertiary centres. However, we expect the number of patients with AMICS managed at local hospitals to be low given the well-organized Danish national infrastructure with short distance to a PCI centre and centralised revascularisation of all AMIs in select tertiary centres. Further, patients fulfilling shock criteria, but not receiving intensive care treatment and/or vasoactive support besides fluids and surviving to discharge would not have been detected by our screening algorithm. Again, we expect these numbers to be low with minimal effect on the incidence rate of CS. However, the impact of such patients on the survival
rates is difficult to estimate as patients not reaching a PCI centre have a worse outcome than a patient not receiving vasoactive support but surviving to discharge. Other limitations due to the retrospective nature of this study include information bias. The medical history and symptoms at presentation were solely obtained from the medical records as documented by the treating physician or nurse, relying on previous record with the health care system, and information provided by the patient and relatives. Likewise, the definition of myocardial infarction, status of coronary vessel disease, classification of STEMI, location of culprit lesion, and the treatment provided was based on the treating physician’s notes and information available in the medical records and interventional registries. Also, missing data are a limitation when evaluating trend over the years for parameters such as coronary artery disease status of those not revascularised, body mass index, smoking, heart rate, arterial lactate levels, and to a certain extent LVEF. Particularly, missing values severely limit the calculation of disease severity scores thus making it difficult to assess disease severity over the years accurately. Besides, the proportions of patients with CS following STEMI were only calculated among those undergoing revascularisation for STEMI and the proportions are not known for those not undergoing revascularisation. The standard haemodynamic definition of cardiogenic shock, based on systolic blood pressure $\leq 90$ mmHg with cardiac index $<2.0$ and left ventricular end-diastolic pressure $>18$ mmHg, is rarely available in routine practice. Thus, a more pragmatic definition based on hypotension and some degree of end-organ hypoperfusion caused by the decrease in cardiac function are typically utilised. Although most studies on cardiogenic shock use systolic blood pressure $\leq 90$ mmHg as the cut-off level for hypotension, systolic blood pressure $< 80$-$100$ mmHg has also been applied. (1, 2, 22, 28, 30) The degree of end-organ hypoperfusion varies between studies as well, with the signs of congestive heart failure ranging from not included, one of the several possible clinical symptoms to a necessary criterion.
Finally, the cut-off for arterial lactate level varies between studies from 2.0-2.5 mmol/L. These differences between studies underscore the need for a common consensus definition of cardiogenic shock, as variation in inclusion criteria results in different study populations and subsequently makes it difficult to compare studies, especially studies based on analysis of registries using diagnosis code, where the diagnosis of cardiogenic shock is not validated.

**Conclusion**

We found that annual incidence of cardiogenic shock following acute myocardial infarction increased from 2013 to 2017. The proportion of patients developing cardiogenic shock following STEMI decreased, and the 30-day mortality remained constant at ∼50% from 2010 to 2017. The unchanged mortality was likely due to increased complexity of the disease with an increase in the proportion of patients with NSTEMI and severely compromised haemodynamics.

**Acknowledgement**

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corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Conflict of interest

Dr Jacob E. Møller has received research grant and speakers fee from Abiomed. All other authors report no conflict of interest.

References


Legends

Table 1. Temporal trends in patient characteristics in AMICS: MAP: Mean arterial blood pressure. BPM: Beats per minute. LVEF: Left Ventricular Ejection Fraction. OHCA: Out of Hospital Cardiac Arrest. †A more detailed analysis revealed a steady state from 2010 to 2015 (p=0.59) from where the change occurs. ‡p for trend=0.95 in patients without OHCA. ¶p for trend=0.42 in patients with OHCA

Figure 1. Flow-chart of study population. AMICS: Cardiogenic shock following acute myocardial infarction. MI: myocardial infarction. ROSC: Return of spontaneous circulation.

Figure 2. Population based incidence and mortality of AMICS. AMICS: Cardiogenic shock following acute myocardial infarction. Incidence rates were standardised to the age (10-year intervals) and sex distribution of the population midyear 2014. Solid line is crude incidence rates, and dotted lines are standardised incidence rates with error bars indicating 95% confidence intervals.

Figure 3. Population based incidence of AMICS, according to STEMI or NSTEMI with or without out of hospital cardiac arrest. *: Decreasing trend from 2012 to 2014, p<0.001 and increasing trend from 2015 to 2017, p<0.001. STEMI: ST-elevation myocardial infarction. NSTEMI: Non-ST-elevation myocardial infarction. OHCA: Out of hospital cardiac arrest. w: with. w/o: without

Figure 4. Temporal trends of cardiogenic shock following STEMI. AMICS: Cardiogenic shock following acute myocardial infarction. STEMI: ST-elevation myocardial infarction.
Incidence of AMICS

$p$ for trend $< 0.001$

30 day mortality of AMICS

$p$ for trend $= 0.12$
Incidence by STEMI and OHCA

Cases per million person-years

- Not revascularized
- STEMI w/ OHCA
- STEMI w/o OHCA
- NSTEMI w/ OHCA
- NSTEMI w/o OHCA


Statistical significance:
- $p = 0.23$
- $p = 0.17^*$
- $p < 0.001$
- $p < 0.001$
- $p < 0.001$
Proportion of AMICS following STEMI

$\text{p for trend} < 0.001$

Proportion of AMICS following STEMI by sex

- Female, $\text{p for trend} = 0.18$
- Male, $\text{p for trend} < 0.001$

Proportion of AMICS following STEMI by age

- >70 years, $\text{p for trend} = 0.004$
- 60 to 70 years, $\text{p for trend} = 0.002$
- <60 years, $\text{p for trend} = 0.29$

30-day mortality in AMICS following STEMI

$p_{\text{for trend}} = 0.48$
3.553 patients suspected of having AMICS

Excluded due to:
- 743 Cardiac arrest, no MI
- 562 acute MI, no cardiogenic shock
- 138 Cardiac arrest no ROSC
- 62 Angina, no MI
- 70 Chronic heart failure
- 11 Cardiomyopathy
- 42 Aortic Stenosis
- 34 Pulmonary embolism
- 22 Sepsis
- 64 Foreign citizen/u 18 years old
- 89 Other reasons

1.716 Confirmed patients with AMICS
Table 1

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<td>27 (14.8)</td>
<td>22 (11.0)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>Systolic blood pressure at shock, mean (SD), mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>66/1716 missing</td>
<td>85 (15)</td>
<td>84 (13)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>153/1716 missing</td>
<td>52 (11)</td>
<td>55 (11)</td>
</tr>
<tr>
<td>MAP</td>
<td>154/1716 missing</td>
<td>63 (11)</td>
<td>65 (10)</td>
</tr>
<tr>
<td>Heart rate at shock, mean (SD), BPM</td>
<td>234/1716 missing</td>
<td>88 (29)</td>
<td>90 (24)</td>
</tr>
<tr>
<td>LVEF≤30% at shock, No. (%)</td>
<td>100/1716 missing</td>
<td>102 (61.8)</td>
<td>111 (58.7)</td>
</tr>
<tr>
<td>Arterial lactate, median (Q1, Q3), mmol/L</td>
<td>322/1716 missing</td>
<td>6.9 (3.0, 11.4)</td>
<td>4.9 (3.3, 9.1)</td>
</tr>
<tr>
<td>Table 2</td>
<td>Missing data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td>2010</td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>183</td>
<td>201</td>
<td>221</td>
</tr>
</tbody>
</table>

**Vessel disease number, No (%)**

| 1 VD | 52 (35.9) | 66 (40.7) | 89 (47.1) | 70 (39.6) | 69 (39.0) | 72 (38.7) | 92 (43.6) | 92 (41.9) |
| 2 VD | 47 (32.4) | 43 (26.5) | 54 (28.6) | 60 (33.9) | 53 (29.9) | 53 (28.5) | 57 (27.0) | 64 (28.8) |
| 3 VD | 46 (31.7) | 53 (32.7) | 46 (24.3) | 47 (26.6) | 55 (31.1) | 61 (32.8) | 62 (29.4) | 65 (29.3) |

**Attempted revascularised, No (%)**

| 2/1716 missing | 153 (83.6) | 165 (82.5) | 183 (82.8) | 176 (90.7) | 184 (89.8) | 182 (85.9) | 210 (84.3) | 229 (91.6) |

**Symptom to revascularisation delay, minutes, median (Q1; Q3)**

| 11 (2.7) | 247 (1/716 missing) |
| 274 (1/716 missing) |
| 306 (1/716 missing) |
| 348 (1/716 missing) |
| 38 (1/716 missing) |
| 45 (1/716 missing) |
| 77 (1/716 missing) |

**PCI, No (%)**

| 1/1482 missing | 141 (93.4) | 151 (92.1) | 176 (96.2) | 168 (95.5) | 177 (96.2) | 173 (95.1) | 199 (94.8) | 218 (95.2) |

**Multivessel PCI in MVD, No (%)**

| 38/740 missing | 18 (25.7) | 23 (33.3) | 21 (26.6) | 19 (21.3) | 25 (27.5) | 33 (34.4) | 31 (33.3) | 29 (26.6) |

**CABG, No (%)**

| 10/1 missing | 11 (7.3) | 20 (12.1) | 9 (4.9) | 10 (5.7) | 11 (6.0) | 16 (8.8) | 13 (6.2) | 11 (4.8) |

**STEMI, No (%)**

| 45/1482 missing | 115 (81.0) | 128 (83.7) | 151 (83.0) | 136 (79.1) | 122 (67.3) | 106 (59.6) | 119 (59.2) | 139 (61.2) |

**Culprit, No (%)**

| 16/1482 missing | 25 (16.6) | 18 (11.1) | 19 (10.4) | 17 (9.7) | 25 (13.6) | 23 (12.8) | 38 (18.5) | 29 (12.9) |

**Troponins**

| 77/1716 missing | 25 (16.6) | 18 (11.1) | 19 (10.4) | 17 (9.7) | 25 (13.6) | 23 (12.8) | 38 (18.5) | 29 (12.9) |

**First TNI, ng/L median (Q1; Q3), n= 708**

| 3890 (910; 28710) | 2740 (491; 13830) | 4120 (1150; 22700) | 1962 (283; 25591) | 1693 (218; 9888) | 2204 (303; 10581) | 973 (231; 11213) | 1562 (253; 10927) |

**Maximum TNI, ng/L median (Q1; Q3)**

| 49725 (9100; 50000) | 48240 (8595; 50000) | 36800 (8989; 50000) | 31344 (6640; 50000) | 40357 (9092; 50000) | 40704 (6242; 50000) | 32979 (9189; 50000) | 29522 (9948; 50000) |

**First TNT, ng/L median (Q1; Q3), n= 1116**

| 641 (127; 2965) | 405 (100; 1380) | 379 (131; 1930) | 634 (202; 2760) | 455 (109; 2070) | 501 (177; 1740) | 335 (98; 1340) | 326 (138; 1600) |

**Maximum TNT, ng/L median (Q1; Q3)**

| 5380 (2640; 9485) | 5150 (1445; 10000) | 3660 (942; 10000) | 5140 (1250; 10000) | 4510 (943; 10000) | 4389 (1055; 10000) | 3930 (883; 9720) | 3713 (1170; 10000) |

**Mechanical circulatory support, No (%)**

| 69 (37.7) | 79 (37.8) | 63 (28.5) | 34 (17.5) | 34 (16.5) | 37 (17.5) | 53 (21.3) | 49 (19.6) |

**IABP, No (%)**

| 64 (35.0) | 70 (34.8) | 38 (17.2) | 4 (2.0) | 9 (4.4) | 1 (0.5) | 2 (1.0) | 7 (3.3) |

**Impella, No (%)**

| 5 (2.7) | 10 (5.0) | 26 (11.8) | 29 (15.0) | 24 (11.7) | 32 (15.2) | 42 (16.9) | 41 (16.4) |

**VA-ECMO, No (%)**

| 5 (2.7) | 0 (2.0) | 5 (2.3) | 2 (1.0) | 6 (2.9) | 9 (4.3) | 18 (7.2) | 16 (6.4) |

**Vasoactive drug infusion, No (%)**

| 20/1716 missing | 152 (85.9) | 163 (81.9) | 183 (82.8) | 171 (88.1) | 183 (88.8) | 171 (86.5) | 211 (97.7) | 213 (87.3) |

**Mechanical ventilation, No (%)**

| 5/1716 missing | 135 (74.6) | 155 (77.1) | 170 (77.3) | 152 (78.4) | 161 (78.2) | 152 (77.1) | 206 (83.4) | 213 (85.2) |

**Renal replacement therapy for AKI, No (%)**

| 3/1716 missing | 33 (18.2) | 34 (16.9) | 40 (18.1) | 46 (23.7) | 37 (18.0) | 45 (21.1) | 62 (24.9) | 48 (19.3) |

**Use of temporary pacemaker, No (%)**

| 17/1716 missing | 26 (14.6) | 31 (15.4) | 38 (17.3) | 37 (19.2) | 37 (18.0) | 43 (20.4) | 53 (21.5) | 34 (13.9) |

**P value for trend**

| <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

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