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From prediction to treatment in cardiogenic shock - can we do better?

Elma J. Peters



**From prediction to treatment
in cardiogenic shock
Can we do better?**

Elma Joyce Peters

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From prediction to treatment
in cardiogenic shock
Can we do better?

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus

prof. dr. ir. P.P.C.C. Verbeek

ten overstaan van een door het College voor
Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 1 juli 2025, te 16.00 uur

door

Elma Joyce Peters
geboren te Schoorl

PROMOTIECOMMISSIE

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	prof. dr. A.P.J. Vlaar	AMC-UvA
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Faculteit der Geneeskunde

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A

Introduction and thesis outline

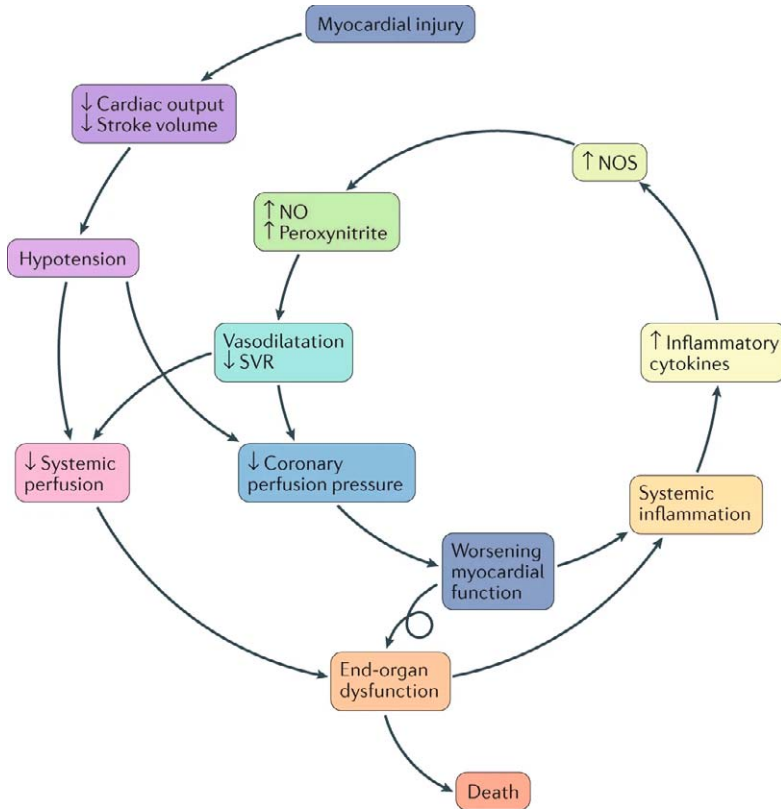
GENERAL INTRODUCTION

Cardiogenic shock (CS) is a clinical state of low cardiac output characterized by hypotension (low blood pressure) and hypoperfusion (inadequate blood flow) of end-organs. This life-threatening condition has many possible causes, of which acute myocardial infarction (AMI) with ventricular failure has historically been the most frequent one (1). And despite only around 5-10% of AMI's being complicated by CS, it remains the leading cause of death in patients hospitalized with AMI (2-5). No major impact in clinical outcome has been achieved over the past decades and much is still unknown, although our knowledge on the complex pathophysiology has evolved and many new treatment strategies have been developed.

PATHOPHYSIOLOGY

A simplified explanation of the pathophysiology of AMI-CS is that this syndrome is initiated with reduced myocardial contractility due to ischemic damage. A downward spiral of reduced cardiac output, hypotension and decreased coronary perfusion is initiated, leading to further reduction of myocardial contractility. In addition, ischemic damage also causes diastolic dysfunction, elevated cardiac filling pressures and subsequent pulmonary edema, contributing to blood and tissue hypoxemia.

Meanwhile however, it is well known that shock is not solely a mechanical problem. Ejection Fractions directly measured after shock diagnosis, were reported to be around 30%; values that also occur in patients without shock symptoms (7). Therefore, it is likely that tissue hypoxia, and subsequent loss of myocardial tissue, leads to more than just a decrease in cardiac output. It triggers a systemic inflammatory response that causes peripheral vasodilation, resulting in an increase of the circulating volume that the heart must supply, usually leading to a further decline in blood pressure. Hence, the cardiogenic shock introduces some form of distributive shock as well. Furthermore, this inflammatory response has a negative inotropic effect and is cardiotoxic through the release of mediators, yielding a further decrease in myocardial function and reducing its mechanisms to compensate for the lower blood pressure (7, 8).

Figure 1. The downward spiral of refractory cardiogenic shock

Nature Reviews | Cardiology

Reyentovich, A., Barghash, M. & Hochman, J. Management of refractory cardiogenic shock. *Nat Rev Cardiol* 13, 481–492 (2016). <https://doi.org/10.1038/nrcardio.2016.96> (6)

PROGNOSIS AND DEFINITION

The mortality rate of AMI-CS hovers around 40-50%, which is over 15 times higher than that of AMI not complicated by CS (9). This rate has hardly dropped over the past decades, despite several efforts to improve outcomes by investigating the optimal treatment approach. The exact mortality rate depends on the definition of the population studied, highlighting a significant challenge in AMI-CS research: the heterogeneous landscape and poor consensus on definition of cardiogenic shock

and of its severity. Generally, CS is reported to be characterized by hypotension and organ hypoperfusion. Herein, hypotension is often defined as a systolic blood pressure < 90 mmHg, a mean arterial pressure < 65 mmHg, or the need for support to maintain a blood pressure above these thresholds. Hypoperfusion can manifest in several ways, including elevated lactate levels, decreased urine output, altered mental status, mottling of the skin, cold extremities, and a high heart rate.

In order to clarify the conversation about CS, different efforts have been undertaken to improve the definition or stratification of this population. In 2019, the Society for Cardiovascular Angiography & Interventions (SCAI) published a consensus document, proposing a categorization for shock severity. It encompasses five stages of increasing severity, depicted by the acronym 'ABCDE' (At risk for CS, Beginning CS, Classic CS, Deteriorating CS and Extremis) (10). This classification was updated in 2022 and the refinement included a more precise characterization of diagnostic features (11). The aim of this standardization of shock severity assessment was "to enhance clinical communication and decision-making (...), to guide further treatment options regarding escalation or de-escalation strategies and to assist in prognosis." In 2023, The Shock Academic Research Consortium (SHARC) introduced a new pragmatic definition for CS, describing the syndrome as: "a cardiac disorder that results in both clinical and biochemical signs of tissue hypoperfusion" (12). Their focus was to develop a pragmatic consensus to enhance the consistency and execution of clinical trials, ultimately supporting regulatory decisions for cardiovascular devices. These tools form a structured framework with the potential to standardize the assessment of patients in shock. While they can improve the understanding and discussion of shock severity, they are not suitable for individualized risk prediction as they lack personalized parameters.

TREATMENT GUIDELINES

The CS treatment guidelines focus on three main topics: revascularization, pharmacologic therapy and mechanical circulatory support (MCS) (13-15). Regarding revascularization, emergency revascularization is superior to initial medical stabilization (16). Additionally, a culprit-only percutaneous coronary intervention (PCI) is preferred over immediate multivessel PCI in patients presenting with multivessel disease (17).

Different vasoactive agents, including inotropes and vasopressors, are available to support compromised circulation and perfusion pressure. However, inotropic agents

are not recommended for routine use in the European heart failure guideline due to safety concerns (Class III) (15). Additionally, this guideline supports considering inotropic agents for patients with a systolic blood pressure (SBP) < 90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, to improve peripheral perfusion and maintain end-organ function (Class IIb). No claims are made on the specific choice of inotrope. Regarding vasopressors, noradrenaline is currently the vasopressor of choice and “may be considered for patients with CS to increase blood pressure and vital organ perfusion” (Class IIb) (15).

Lastly, different MCS devices have increasingly been used over the last decades. Their emergence looked promising but they have, until this moment, shown limited applicability and low if no beneficial effect on mortality while increasing the rate of minor and major complications. At this moment, the use of short-term MCS in patients with ACS and refractory ACS may be considered whereas the routine use of the intra-aortic balloon pump (IABP) is firmly not recommended as it yields no survival benefit (18).

One of the factors hindering therapeutic progress is the ongoing heterogeneity and lack of consensus on the definition of CS. Researchers face challenges in selecting the right patients for trials and identifying which patients would benefit the most from advanced, invasive therapies. A more individualized risk prediction early in the course of disease could also advance the therapeutic field.

THESIS OUTLINE

In this thesis, we touch upon a variety of topics in the spectrum of acute myocardial infarction related cardiogenic shock.

Section B describes the current landscape of cardiogenic shock in the Netherlands using data of the *Netherlands Heart Registration*. In **Chapter 1** the incidence and outcomes of AMI-CS amongst all PCI patients is investigated over a 4-year period. Predictors that predispose CS are identified. In **Chapter 2**, we describe the process of an additional / elaboration on the national registry. Herein, we are able to provide a detailed description of the comorbidities, presenting characteristics, treatment and outcome of the Dutch AMI-CS population.

In section C, we focus on personalized risk prediction; an unmet need in AMI-CS. **Chapter 3** describes the entire process of the development and external validation

of a tool to predict mortality of AMI-CS patients within 30 days. This tool enables a comprehensive risk assessment for clinical settings, and comparison of populations, for example for quality purposes. In **Chapter 4** we investigated the differences between male and female patients with AMI-CS. We identified differences in risk profiles but also in presentation and in-hospital management.

In section D of this thesis therapeutic topics are touched upon. The scarce available evidence states that early revascularization is beneficial in CS, but the optimal route for PCI has not yet been determined. In **Chapter 5** we vouch for a cautious interpretation of the observational data on the optimal vascular approach for PCI in CS. **Chapter 6** tries to contribute to determining the optimal vascular access approach by comparing presentation characteristics and looking at the outcome after propensity score matched analysis. And finally, **Chapter 7** describes the design and rationale of the randomized NORSHOCK trial, that seeks to determine whether treatment with reduced noradrenaline levels leads to better outcomes in patients with AMI-CS.

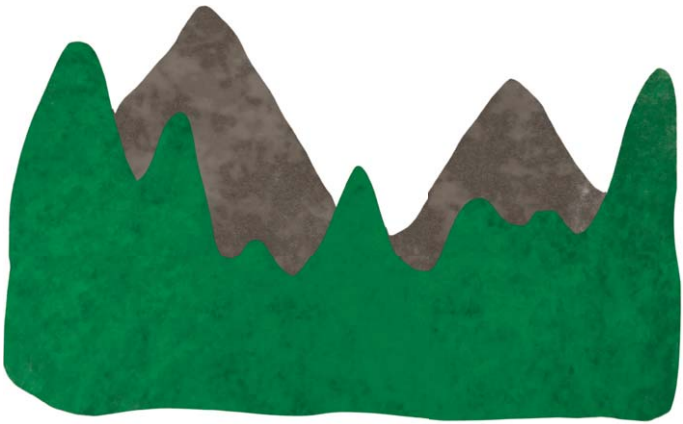
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B

Current national landscape



Chapter 1

Outcome and Predictors for Mortality in Patients with Cardiogenic Shock: A Dutch Nationwide Registry-Based Study of 75,407 Patients with Acute Coronary Syndrome Treated by PCI

Mina Karami, **Elma J. Peters**, Wim K. Lagrand, Saskia Houterman, Corstiaan A. den Uil, Annemarie E. Engström, Luuk C. Otterspoor, Jan-Paul Ottevanger, Irlando A. Ferreira, Jose M. Montero-Cabezas, Krischan D. Sjauw, Jan van Ramshorst, Adriaan O. Kraaijeveld, Niels J.W. Verouden, Erik Lipsic, Alexander P.J. Vlaar, Jose P.S. Henriques and on Behalf of the PCI Registration Committee of The Netherlands Heart Registration

*Adapted from: Journal of Clinical Medicine, 2021;
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ABSTRACT

It is important to gain more insight into the cardiogenic shock (CS) population, as currently, little is known on how to improve outcomes. Therefore, we assessed clinical outcome in acute coronary syndrome (ACS) patients treated by percutaneous coronary intervention (PCI) with and without CS at admission. Furthermore, the incidence of CS and predictors for mortality in CS patients were evaluated. The Netherlands Heart Registration (NHR) is a nationwide registry on all cardiac interventions. We used NHR data of ACS patients treated with PCI between 2015 and 2019. Among 75,407 ACS patients treated with PCI, 3028 patients (4.1%) were identified with CS, respectively 4.3%, 3.9%, 3.5%, and 4.3% per year. Factors associated with mortality in CS were age (HR 1.02, 95%CI 1.02–1.03), eGFR (HR 0.98, 95%CI 0.98–0.99), diabetes mellitus (DM) (HR 1.25, 95%CI 1.08–1.45), multivessel disease (HR 1.22, 95%CI 1.06–1.39), prior myocardial infarction (MI) (HR 1.24, 95%CI 1.06–1.45), and out-of-hospital cardiac arrest (OHCA) (HR 1.71, 95%CI 1.50–1.94). In conclusion, in this Dutch nationwide registry-based study of ACS patients treated by PCI, the incidence of CS was 4.1% over the 4-year study period. Predictors for mortality in CS were higher age, renal insufficiency, presence of DM, multivessel disease, prior MI, and OHCA.

INTRODUCTION

The mortality rate of patients with acute coronary syndrome (ACS) has declined rapidly in recent years due to preventive measures (e.g., cholesterol reduction) and advanced treatment strategies (e.g., revascularization). (1) However, for patients with acute myocardial infarction (MI) who develop cardiogenic shock (CS), mortality remains unacceptably high at around 50%. (2) Based on the demographics of the Dutch population, which resembles the global trend in population aging, an increase in the incidence of acute MI is expected within the next 20 years. (3) As around 5–10% of patients with acute MI develop CS, management of this clinically challenging population will become an even more important health problem worldwide.

It is essential to gain more insight into CS patients, as currently, little is known on the best treatment strategy to improve outcome. Furthermore, if we can determine prognostic characteristics in these patients, we may be able to identify patients that are at greater risk of death and develop preventive measures and patient-specific treatment strategies.

By studying an unselected large and complete real-world cohort of patients treated with percutaneous coronary intervention (PCI) registered prospectively in the nationwide Netherlands Heart Registration (NHR), the aim of this study was to assess the incidence, clinical outcome, and predictors of mortality for CS in ACS patients over a time period of 4 years.

MATERIALS AND METHODS

Study Design

The NHR is a Dutch nationwide registry on all cardiac interventions and surgical procedures, comprising data of 73 centers (PCI or heart center $n = 30$). The NHR main objectives are to maintain and improve quality of care by registering, analyzing, and providing relevant information on treatment of cardiac disease. The NHR registers clinical characteristics and outcome of patients with cardiac disease. Data collection and registration is performed by the participating centers in a secured online environment. A waiver for consent for the NHR data registry was obtained from the Medical Ethics Committee. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. For the purpose of this study, NHR data were extracted on patients treated with PCI from the registry inception in the

year 2015 until 2019. We performed our analysis on patients treated with PCI for the indication ACS.

Definitions

CS was registered in the NHR database if present at admission for PCI. CS was de-fined as the presence of hypotension (systolic blood pressure (SBP) ≤ 90 mmHg during ≥ 30 min, or hemodynamic support required to maintain a SBP ≥ 90 mmHg), together with clinical signs of hypoperfusion (i.e., cold extremities, oliguria < 30 mL/h, and/or a heart rate ≥ 60 beats per minute). ACS was defined as a ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI). MI was defined according to the Third Universal Definition of MI.(4) STEMI was defined as acute chest pain in the presence of ST-segment elevation longer than 20 min. NSTEMI was defined as acute chest pain without the presence of ST-segment elevation, including unstable angina pectoris. There was a universal approach with direct coronary angiography in cases of NSTEMI. Out-of-hospital cardiac arrest (OHCA) was de-fined as a cardiac arrest that involved defibrillation with or without cardiopulmonary resuscitation (CPR), which occurred in the prehospital setting before and in relation to the PCI indication. Multivessel PCI was defined as more than one vessel treated during intervention. The culprit vessel was defined as the vessel that was registered as the primary treated vessel during PCI. Chronic total occlusion (CTO) was defined as the presence of an atherosclerotic occlusion for more than 3 months and Thrombolysis In Myocardial Infarction (TIMI) flow grade of 0 or 1 in one of the treated coronary arteries. Multivessel disease was defined as the presence of a stenosis of $> 70\%$ in luminal diameter in more than two native major coronary arteries or first- order side branches. Dialysis was defined as hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration for renal failure, present at admission for PCI. Serum creatinine level was measured up to 3 months prior to the PCI or on the date of intervention. Estimated glomerular filtration rate (eGFR) in mL/min/1.73 m² was calculated by the following formula: $175 \times ((\text{serum creatinine level}/88.4) - 1.154) \times (\text{age} - 0.203) \times (0.742 \text{ if female})$. Left ventricular ejection fraction (LVEF) was measured up to 6 months prior to the intervention. Descriptive LVEF data were con-verted into a percentage according to: good LVEF 55%, moderate 40%, poor 25%, and severe 20%. Clinical outcome measures were: 30-day and 1-year mortality from PCI date, urgent coronary bypass grafting (CABG) within 24 h after PCI, MI within 30 days after PCI (including STEMI and NSTEMI, excluding periprocedural MI (i.e., type 4; occurring within 48 h after PCI)) and target vessel revascularization (TVR) within 1 year after PCI (defined as revascularization by PCI in the index coronary artery).

Statistical Analysis

The primary outcome of this study was mortality for patients with CS compared to patients without CS. Survival curves were displayed as Kaplan–Meier curves and compared with log-rank test. Furthermore, median follow-up with interquartile ranges (IQR) was calculated for both groups using time (in months) between the date of intervention and last follow-up or death. Secondary outcomes were (1) the incidence of CS, (2) predictors for mortality in patients with CS, and (3) the difference in characteristics and clinical outcome in patients with and without CS. All data were analyzed per patient, not per registered PCI. If a patient had multiple PCIs, we selected the first intervention in which CS was present (shock cohort). In patients without the presence of CS at admission for PCIs, we selected the first intervention that was performed in the patient (no-shock cohort). The incidence of CS per year was calculated as the number of patients with the condition divided by the total number of patients treated with PCI. A Cox proportional-hazard regression analysis was used to identify predictors of mortality in patients with CS. The dependent variable was mortality, and the independent variables were all patient characteristics reported in Table 1 (with less than 20% missing values), including type of treatment center (PCI or heart center) and the year of intervention. A stepwise method (using back-wards elimination) and enter method were compared before selection of variables for the final model. For the enter method, variables with a p-value < 0.10 in univariable analysis were included in the multivariable model. The association between the dependent and independent variables was described as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The non-linearity of variables was tested by categorization into quartiles. A receiver operating characteristic (ROC) curve was used to illustrate the performance of classification according to the multivariable model and an area under the ROC curve (AUC) was calculated. To assess the association between factors and long-term mortality (after 30 days), we also performed a landmark analysis excluding patients who had died before or at 30 days, using univariable and multivariable Cox regression analysis.

In addition, the differences in characteristics and clinical outcome between patients with and without CS before PCI were compared. Normally distributed data were described as mean \pm standard deviation (SD) and compared with the t-test. Non-normally distributed data were described as median with IQR and compared using the Mann–Whitney U test. Categorical data were described as frequencies with percentages and compared using the Fisher's exact or Chi-square test, whichever

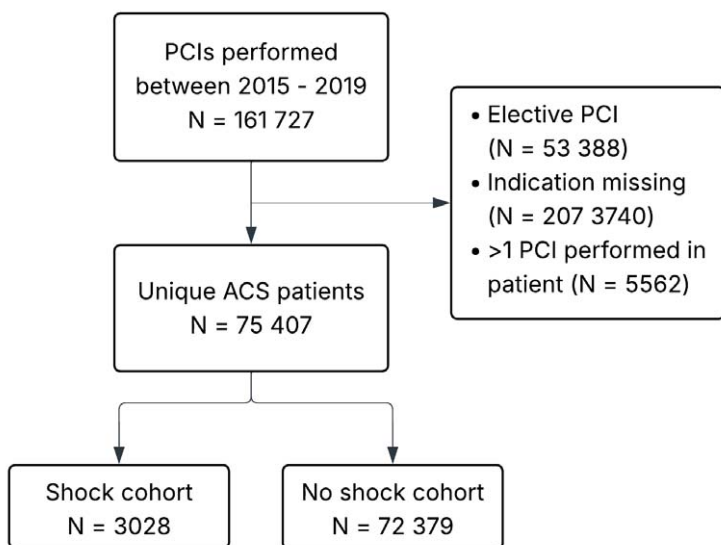
appropriate. A p-value < 0.05 was considered statistically significant for all non-specified analyses. Statistical analyses were performed using IBM SPSS Statistics version 26.0.

RESULTS

Study Population

In the time period 2015 until 2019, 80969 PCIs were performed in the Netherlands for the indication ACS in 75407 patients (see Figure 1). Among ACS patients who were treated with PCI, 3028 patients (4.1%) were identified with CS. The incidences of CS in the 4-year period of this study were respectively 4.3%, 3.9%, 3.5%, and 4.3% per year.

Figure 1. Flowchart of study population: acute coronary syndrome patients treated by percutaneous coronary intervention with ($n = 3028$) and without cardiogenic shock ($n = 72\ 379$)



Baseline Characteristics

Clinical and procedural characteristics are presented in Table 1. Patients with and without CS were similar in percentage of males (71% versus 72%, $p = 0.74$) and presence of diabetes mellitus (DM) (18% versus 19%, $p = 0.41$). Patients with CS were slightly older (66 ± 12 years versus 65 ± 12 years, $p < 0.001$), more frequently had multivessel disease (59% versus 46%, $p < 0.001$), presence of CTO (3% versus 2%, $p < 0.01$), OHCA (45% versus 4%, $p < 0.001$), and worse renal function (eGFR category < 15 ; 2% versus 0.7%, eGFR 15–29; 5% versus 2%, eGFR 30–59; 38% versus 19% and eGFR ≥ 60 ; 56% versus 79%, $p < 0.001$), compared to patients without CS. In addition, CS patients less frequently had prior MI (17% versus 19%, $p = 0.02$) and prior CABG (5% versus 7%, $p < 0.001$). Moreover, patients with CS had worse LVEF ($p < 0.001$), more often dialysis ($p = 0.03$), and less prior PCI ($p < 0.001$), but these findings are limited due to the amount of missing data (42–69%). Of all ACS patients who underwent PCI, 66% was treated in a heart center and 35% in a PCI center. The indication for PCI differed between patients with and without CS ($p < 0.001$). In CS patients, the indication for PCI was STEMI in 89% and NSTEMI in 11%. In patients without CS, the PCI indication was STEMI in 46% and NSTEMI in 54%. The first access method for performing PCI in patients with CS was via the radial artery in 50% and fem-oral artery in 50%. In patients without CS, PCI was performed via the radial artery in 84% and the femoral artery in 15% of the cases.

Table 1. Characteristics and clinical outcome of acute coronary syndrome patients treated by percutaneous coronary intervention with and without cardiogenic shock at admission

	All Patients (n = 75,407)		Missing	Shock (n = 3028)	No Shock (n = 72,379)	p-Value
Clinical characteristics						
Age - years	65 ± 12	0 (-)		66 ± 12	65 ± 12	<0.001
Male	53945 (72)	0 (-)		2158 (71)	51787 (72)	0.74
Diabetes mellitus	13957 (19)	2084 (3)		522 (18)	13435 (19)	0.41
Dialysis	172 (0.5)	42701 (57)		13 (0.9)	159 (0.5)	0.03
Multivessel disease	34781 (46)	523 (0.7)		1770 (59)	33011 (46)	<0.001
Chronic total occlusion	1657 (2)	1245 (2)		90 (3)	1567 (2)	<0.01
Prior MI	13588 (19)	2137 (3)		484 (17)	13104 (19)	0.02
Prior PCI	8352 (19)	31815 (42)		282 (15)	8067 (19)	<0.001
Prior CABG	5136 (7)	1162 (2)		149 (5)	4989 (7)	<0.001
Out of hospital cardiac arrest	4112 (5)	94 (0.1)		1373 (45)	2739 (4)	<0.001
Renal function - (mL/min/1.73 m ²)		8207 (11)				<0.001
eGFR ≥ 60	52257 (78)			1485 (56)	50772 (79)	
eGFR 30 - 60	13243 (20)			1002 (38)	12241 (19)	

eGFR 15 - 29	1205 (2)	51820 (69)	130 (5)	1075 (2)	
eGFR < 15	495 (0.7)		45 (2)	450 (0.7)	
LVEF					<0.001
> 50%	14087 (60)		161 (22)	13926 (61)	
30 - 50%	7562 (32)		319 (44)	7243 (32)	
≤30%	1938 (8)		241 (33)	1697 (7)	
Treatment center		0 (-)			<0.001
Heart center	49396 (66)		2133 (70)	47263 (65)	
PCI center	26011 (35)		895 (30)	25116 (35)	
	Procedure characteristics				
PCI indication		0 (-)			<0.001
STEMI	36288 (48)		2704 (89)	33584 (46)	
NSTEMI	39119 (52)		324 (11)	38795 (54)	
Culprit lesion		37340 (50)			0.02
LAD	15425 (41)		619 (38)	14806 (41)	
Other	22642 (60)		1018 (62)	21624 (60)	
PCI access method (1st)		41448 (55)			<0.001
Radial	28172 (83)		671 (50)	27501 (84)	
Femoral	5704 (17)		681 (50)	5023 (15)	
Brachial	83 (0.2)		4 (0.3)	79 (0.2)	
Culprit lesion PCI	25477 (67)	37327 (50)	1034 (63)	24443 (67)	<0.01
Multivessel PCI	12603 (33)	37327 (50)	603 (37)	12000 (33)	<0.01

Table 1 Continued

	Clinical outcome				
30-day mortality	2722 (4)	462 (0.6)	1080 (36)	1642 (2)	<0.001
1-year mortality *	3346 (6)	228 (0.4)	855 (40)	2491 (5)	<0.001
Urgent CABG within 1 day	206 (0.3)	2002 (3)	38 (1)	168 (0.2)	<0.001
MI within 30 days	393 (0.7)	22,619 (30)	27 (1)	366 (0.7)	<0.01
TVR within 1 year *	2256 (5)	12,099 (22)	71 (5)	2256 (5)	0.16

Data are presented as number (%) or mean (\pm SD). **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **CABG** = coronary bypass grafting; **eGFR** = estimated glomerular filtration rate; **LVEF** = left ventricular ejection fraction; **STEMI** = ST-segment elevation myocardial infarction; **NSTEMI** = non-ST-segment elevation myocardial infarction; **LAD** = left anterior descending coronary artery; **TVR** = target vessel revascularization.

*Only calculated for patients with completed 1-year follow-up (intervention year 2015, 2016, and 2017; n = 54566)

Data were missing in 50% of the cases on culprit lesion location and whether culprit lesion or multivessel PCI was performed.

Clinical Outcome

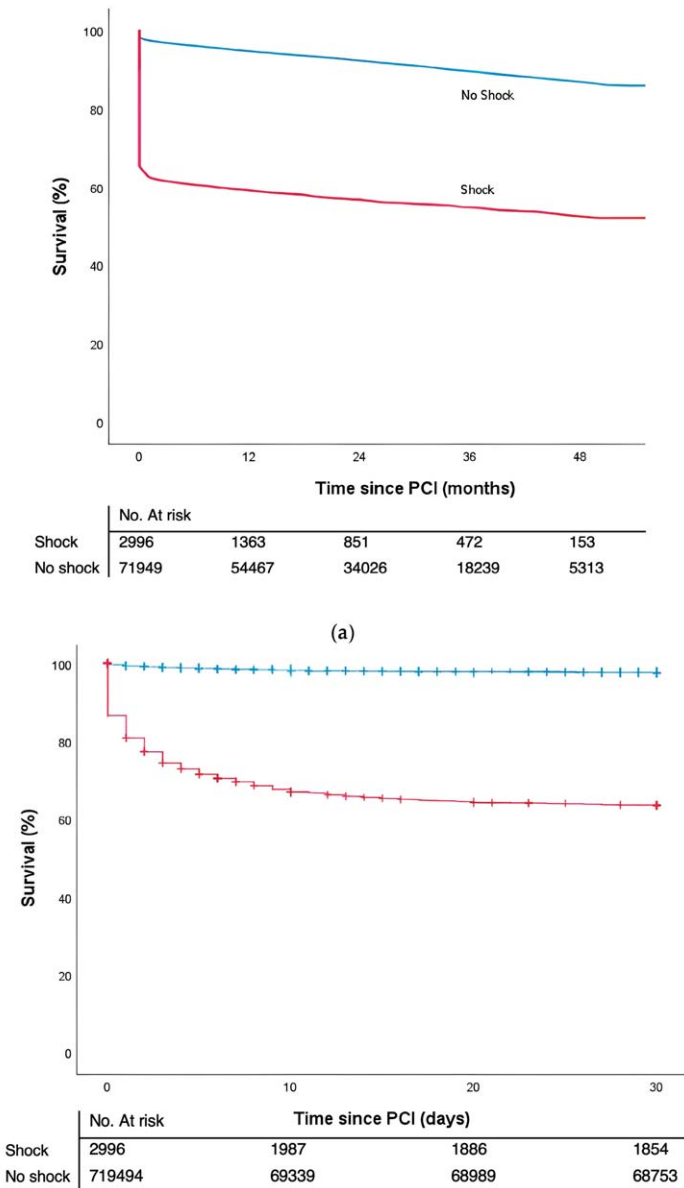
Clinical outcomes are presented in Table 1. Median duration of follow-up was 9 months (0–26) for patients with CS and 22 months (12–36) for patients without CS. Thirty-day mortality was 36% for CS patients versus 2% for patients without CS, $p < 0.001$. One-year mortality was 40% for CS patients versus 5% for patients without CS, $p < 0.001$. Figure 2a,b show the Kaplan–Meier curves for survival over the 4-year study period and within 30-days (both, log-rank $p < 0.001$). Patients with CS more often required an urgent CABG within 1 day (1% versus 0.2%, $p < 0.001$) and more often experienced MI within 30 days after PCI (1% versus 0.7%, $p < 0.01$), compared to patients without CS.

Predictors for Mortality in Cardiogenic Shock

The results of the Cox regression analysis are shown in Table 2. Factors that were identified in multivariable analysis as independent predictors for mortality in patients with CS were higher age (HR 1.02, 95%CI 1.02–1.03, $p < 0.001$), lower eGFR (HR 0.98, 95%CI 0.98–0.99, $p < 0.001$), presence of DM (HR 1.25, 95%CI 1.08–1.45, $p < 0.01$), multivessel disease (HR 1.22, 95%CI 1.06–1.39, $p < 0.01$), prior MI (HR 1.24, 95%CI 1.06–1.45, $p < 0.01$), and OHCA (HR 1.71, 95%CI 1.50–1.94, $p < 0.001$). The enter and stepwise method resulted in similar multivariable models.

The ROC curve of classification according to the multivariable model is shown in the Supplementary Materials, Figure S1. At internal validation, the model had an acceptable performance, with an AUC of 0.73. Landmark analysis after exclusion of patients who had died before or at 30 days is presented in the Supplementary Materials Table S1. In the multivariable Cox regression analysis, OHCA was the only factor that was no longer a predictor for mortality. Furthermore, in the Supplementary Materials, Kaplan–Meier survival curves are shown for patients with CS according to different age categories (Figure S2), renal function (Figure S3), and OHCA vs. no OHCA (Figure S4).

Figure 2. Survival curves



Kaplan–Meier curves showing survival of acute coronary syndrome patients treated by percutaneous coronary intervention with and without cardiogenic shock at admission. (a) Over the 4-year study period, (b) within 30-days.

Table 2. Results of univariable Cox regression analysis and multivariable model to predict mortality for patients with cardiogenic shock (n = 3028)

	Univariable			Multivariable		
	HR	95% CI	p-Value	HR	95% CI	p-value
Age (per year)	1.03	1.02–1.03	<0.001	1.02	1.02–1.03	<0.001
Male sex	0.13	0.77–0.97	0.01	0.97	0.84–1.11	0.62
Diabetes mellitus	1.57	1.38–1.80	<0.001	1.25	1.08–1.45	<0.01
Multivessel disease	1.52	1.35–1.71	<0.001	1.22	1.06–1.39	<0.01
CTO	1.29	0.96–1.74	0.09	1.16	0.82–1.64	0.39
Prior MI	1.36	1.18–1.56	<0.001	1.24	1.06–1.45	<0.01
Prior CABG	1.32	1.05–1.65	0.02	0.93	0.72–1.21	0.59
eGFR (mL/min/1.73 m ²)	0.98	0.98–0.98	<0.001	0.98	0.98–0.99	<0.001
OHCA	1.44	1.29–1.60	<0.001	1.71	1.50–1.94	<0.001
STEMI	0.79	0.67–0.93	<0.01	0.88	0.74–1.06	0.18
PCI center	0.95	0.84–1.07	0.41			
Intervention year						
2015	1.14	0.97–1.32	0.11	1.14	0.95–1.35	0.15
2016	1.19	1.02–1.40	0.03	1.08	0.91–1.30	0.38
2017	1.08	0.93–1.26	0.33	1.18	0.99–1.42	0.07

Variables with $p < 0.10$ in the univariable analysis were included in the multivariable model. STEMI vs. NSTEMI; PCI center vs. heart center, reference intervention year was 2018.

CTO = chronic total occlusion; MI = myocardial infarction; CABG = coronary artery bypass grafting; eGFR = estimates glomerular filtration rate; OHCA = out-of-hospital cardiac arrest; STEMI = ST-segment elevated myocardial infarction; PCI = percutaneous coronary intervention.

DISCUSSION

In this large contemporary cohort of ACS patients treated with PCI in the Netherlands, the incidence of CS was 3.5–4.3% per year within a time period of 4 years. CS patients had a poor survival compared to patients without CS, and their survival rate did not significantly improve over the 4-year time period.

The AMIS registry of ACS patients in Switzerland found that the incidence of CS decreased between the years 1997 and 2017, from 8.7% (period 1997–2006) to 7.3% (2007–2017).(5) During this time, the incidence of CS that developed during hospital stay declined from 7.8% to 3.5%, but the incidence of CS on admission increased from 2.5% to 4.6%. The authors speculate that the decline of CS during hospital stay may be due to improvements in the medical treatment, increase of PCIs (causing reduction of the infarct size), and earlier arrival at the hospital. The increase of CS at admission on the other hand may be due to the more frequent and rapid transportation of sicker patients who would otherwise have died before hospital arrival. The 4.6% incidence from the AMIS registry in the time period 2007–2017 corresponds with the 4.1% incidence of CS on admission in our Dutch population during the years 2015–2018. Accordingly, the Swedeheart registry, which collects data on patients who underwent coronary angiography or were treated by PCI in Sweden, found a 4% incidence for CS complicating AMI in the year 2012.(6)

Identifying CS patients who have an increased risk of death is important, since risk stratification can help us select patients for therapies such as mechanical circulatory support. These prognostic characteristics may also be used to reduce treatment selection bias in studies or the comparison of outcomes between different centers. There are several existing risk scores designed to predict outcome in CS patients. For example, the Card-Shock score includes the following risk factors in their calculation: age > 75 years, eGFR, prior MI/CABG, confusion, lactate, CS etiology, and LVEF.(7) The IABP-SHOCK score includes age > 73 years, glucose level >10.6 mmol, creatinine, lactate, and TIMI flow < 3 after PCI.(8) In our study, mortality in CS patients was mainly driven by a higher age, renal insufficiency, and OHCA. This finding emphasizes the importance of including these characteristics in risk stratification. In accordance with characteristics included in current risk scores, we also found an association between increased mortality and prior MI, presence of DM, and multivessel disease. The performance of the multivariable model for predicting mortality in CS patients was acceptable (AUC = 0.73). Sex-related differences were not associated with survival after multivariable adjustment and probably based on the difference in age and comorbidities between males and

females. The mortality of patients with CS is mostly determined in the acute phase. Our results showed that the mortality of CS patients after 30 days was almost identical to patients without CS. Additional mortality after 30 days was 4% in CS and 3% for patients without CS. In the landmark analysis of patients who survived the first 30 days, there was no longer an association between OHCA and mortality. Therefore, OHCA-driven mortality is probably only evident in the acute phase, while other factors are associated with both short-term and longer-term mortality.

The Swedeheart registry reported that STEMI patients more often developed CS, compared to NSTEMI patients ($p < 0.001$).⁽⁶⁾ Similarly, we found that STEMI patients more often presented with CS than NSTEMI patients. Several studies found that although STEMI patients had a higher in-hospital and short-term mortality compared with NSTEMI patients, long-term mortality was similar.^(9, 10) In our study, in patients with CS, STEMI was associated with increased mortality in univariable Cox regression analysis, but this was not significant after multivariable adjustment.

The strength of our study is that it consists of a large nationwide cohort and represents real-world outcomes. The data are contemporary, as they reflect patients who were treated in recent years by PCI. It is the first study to report outcomes specifically for ACS patients treated by PCI with and without CS in the Netherlands. A limitation of our study is that although it represents an unselected cohort, only patients treated with PCI are included in the registry. Patients who died prehospital or before the procedure are not registered, and therefore, the outcomes for CS may be even worse than reported in this study. Furthermore, the NHR is the first nationwide registry on cardiac interventions, which was developed relatively recently in 2015 and it is still being further expanded. A limitation of the registry is that currently, only data are collected on CS that are present at admission, and no data are available on the development of CS after leaving the catheterization laboratory. In addition, the completeness and accuracy of data input is a limitation. A rather large amount of data regarding important variables such as LVEF and culprit lesion location were missing, and not all data that are of clinical and scientific interest are currently collected in the registry (e.g., use of medication, use of mechanical support devices, hemodynamic parameters such as blood pressure, duration of cardiac arrest, laboratory values such as lactate, and success of intervention). This also hampered the calculation of validated risk scores such as IABP- SHOCK II and CardShock). Finally, this study reflects the clinical practice in the Netherlands and may not be representative for other countries. Local differences in the distribution of heart and PCI centers, organization of emergency medical services, and patient management may result in different outcomes.

CONCLUSIONS

In this Dutch nationwide registry-based study on ACS patients treated with PCI, CS had an incidence of 4.1% and was associated with an increased mortality. The survival of CS patients did not improve over the 4-year time period. Factors associated with worse survival in patients with CS were higher age, lower eGFR, presence of DM, multivessel disease, prior MI, and OHCA.

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Chapter 2

Characteristics, Treatment Strategies and Outcome in Cardiogenic Shock Complicating Acute Myocardial Infarction: A Contemporary Dutch Cohort

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ABSTRACT

Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) is associated with high morbidity and mortality. Our study aimed to gain insights into patient characteristics, outcomes and treatment strategies in CS patients. Patients with CS who underwent percutaneous coronary intervention (PCI) between 2017 and 2021 were identified in a nationwide registry. Data on medical history, laboratory values, angiographic features and outcomes were retrospectively assessed. A total of 2328 patients with a mean age of 66 years and of whom 73% were male, were included. Mortality at 30 days was 39% for the entire cohort. Non-survivors presented with a lower mean blood pressure and increased heart rate, blood lactate and blood glucose levels (p-value for all < 0.001). Also, an increased prevalence of diabetes, multivessel coronary artery disease and a prior coronary event were found. Of all patients, 24% received mechanical circulatory support, of which the majority was via intra-aortic balloon pumps (IABPs). Furthermore, 79% of patients were treated with at least one vasoactive agent, and multivessel PCI was performed in 28%. In conclusion, a large set of hemodynamic, biochemical and patient-related characteristics was identified to be associated with mortality. Interestingly, multivessel PCI and IABPs were frequently applied despite a lack of evidence.

INTRODUCTION

Cardiogenic shock (CS) is a clinical syndrome characterized by hypotension and end-organ hypoperfusion. Even though CS complicates only 3–13% of acute myocardial infarctions (AMI), it is the leading cause of death for patients with an acute coronary syndrome. (1-3) While overall 30-day mortality in AMI is around 6% in EU countries, mortality rates for AMI complicated by CS (AMI-CS) are as high as 40–50%. (4-7)

In order to improve outcomes for AMI-CS patients, it is important to gain accurate in-sight into in-depth patient characteristics, current clinical management strategies and out-comes in this specific population. Data regarding these features are limited and often based on clinical trial data or diagnosis codes. In addition, only a few databases have been designed for CS to capture more in-depth CS variables.

The primary aim of this study was to gain insights into contemporary trends in patient characteristics, current treatment strategies and outcome for AMI-CS patients under-going PCI in the Netherlands. Additional aims were to investigate differences in outcome in predefined subgroups and to explore whether the current clinical practice is consistent with available treatment guidelines.

MATERIALS AND METHODS

Patient Selection

Baseline, procedural and outcome data from all patients undergoing PCI in the Netherlands are prospectively registered with the Netherlands Heart Registration (NHR; www.nhr.nl).⁽⁸⁾ Relevant variables and their definitions as collected in the NHR are shown in Appendix A, Table A1. All patients with CS undergoing PCI for STEMI or NSTEMI/AMI between January 2017 and September 2021 were subsequently identified in the NHR database. Cardiogenic shock was defined as the presence of hypotension (systolic blood pressure ≤ 90 mmHg for at least 30 min or the need for supportive measures to maintain systolic blood pressure ≥ 90 mmHg) with signs of hypoperfusion of end-organs (cold extremities and/or oliguria < 30 mL/h and/or heart rate ≥ 60 beats per minute). An additional set of variables was established to be collected in patients with CS. This additional data collection was executed in 14 of 30 PCI centers in the Netherlands. See Appendix B, Table A2 for the participating hospitals.

Variable Selection

A draft version of the set of additional variables to be collected in patients with CS was established in consultation with interventional cardiologists and intensivists from participating hospitals. After pilot testing of this draft version, the updated version was discussed in a multidisciplinary team. A few adjustments were made prior to finalizing the selection and its corresponding data dictionary. (more details of the process and the final set of variables can be found in Appendix C, Figure A1).

Data Collection

Clinical data for all patients were retrieved from the electronic health records. Survival status was retrieved from the governmental Personal Records Database (in Dutch: *Basisregistratie Personen*) in all hospitals with a follow up period of at least one year. Data collection was performed by trained data managers and medical doctors with supervision by an interventional cardiologist or a cardiac intensivist. To ensure quality, several automated quality controls were carried out after data submission according to the quality control system of the NHR as described elsewhere.⁽⁹⁾ The data were pseudonymized and locked after preliminary findings were submitted to the respective hospital with the opportunity for reviewing and complementing.

Statistical Analysis

Statistical analysis was performed using IBM SPSS 28.0 (IBM, SPSS, Inc., Chicago, IL, USA). Normally distributed data were displayed as mean \pm standard deviation (SD) and compared in survivors and non-survivors using the unpaired t-test. Non-normally distributed data were described as median with interquartile range (IQR) and compared with the Mann–Whitney U test. Categorical data were displayed as frequencies and percent-ages and compared using the chi-square test. Temporal trends were analyzed using the Mann–Kendall test. Survival curves were constructed using the Kaplan–Meier method, and comparisons between subgroups were made with the log-rank statistic. Subgroup analyses were performed for sex (male/female), out-of-hospital cardiac arrest (OHCA) (yes/no), indication of PCI (ST-elevation myocardial infarction [STEMI]/non-ST-elevation myocardial infarction [NSTEMI]) and multivessel PCI within multivessel disease (yes/no). A p-value < 0.05 was considered statistically significant for all analyses. Missing data were not imputed for the current analyses. Denominators were notated for categorical variables with missing data.

RESULTS

Patient Characteristics

From January 2017 to September 2021, a total of 2328 patients with AMI complicated by CS and treated with PCI were identified. This was 2.4% of the total PCI population in the selected hospitals ($n = 98.721$). The mean age was 66.4 (± 12.3) years, and 72.9% of patients ($n = 1685$) were male. In this cohort, the prevalence of diabetes was 20.8% ($n = 459$), mostly treated with medication only. A total of 631 patients (29.3%) experienced a prior coronary event, most commonly a prior myocardial infarction ($n = 482$, 21.4%). Patients with CS more often presented with STEMI than with NSTEMI (86.1% vs. 13.9%, $p < 0.001$), and for most patients ($n = 1166$, 58.6%), the onset of symptoms was less than 3 hours before presentation. Of all patients, 934 (40.3%) presented after an OHCA. Details on patient characteristics are displayed in Table 1. Percentages missing can be found in Table A1 and A3 in Appendices A and D for each variable.

Table 1. Patient characteristics for all patients, survivors at 30 days and non-survivors at 30 days

	All Patients (n = 2328)	Alive at 30 Days (n = 1414)	Dead at 30 Days (n = 901)	p-Value
Patient characteristics				
Male	1696 (72.9)	1036 (73.3)	649 (72.0)	0.515
Age—years	66.4 (±12.3)	64.8 (±12.1)	69.0 (±12.1)	<0.001
BMI—kg/cm ²	26.1 (23.9–29.1)	25.9 (23.7–28.8)	26.2 (24.2–29.4)	0.024
Indication of PCI				0.005
STEMI	1941/2254 (86.1)	1193/1359 (87.8)	737/882 (83.6)	
NSTEMI	313/2254 (13.9)	166/1359 (12.2)	145/882 (16.4)	
Out-of-hospital cardiac arrest	934/2317 (40.3)	497/1405 (35.4)	432/899 (48.1)	<0.001
In-hospital cardiac arrest	295/2308 (12.8)	130/1401 (9.3)	165/894 (18.5)	<0.001
Onset of AMI symptoms—hours				<0.001
<3	1166/1991 (58.6)	745/1233 (60.4)	416/746 (55.8)	
3–12	375/1991 (18.8)	245/1233 (19.9)	128/746 (17.2)	
12–24	113/1991 (5.7)	67/1233 (5.4)	44/746 (5.9)	
>24	337/1991 (16.9)	176/1233 (14.3)	158/746 (21.2)	
Intubation pre-PCI	1030/2307 (44.6)	500/1404 (35.6)	524/893 (58.7)	<0.001
Monitoring via PA catheter	118/2119 (5.6)	68/1287 (5.3)	49/832 (5.9)	0.613
Medical history				
Diabetes	463/2219 (20.9)	227/1365 (16.6)	232/841 (27.6)	<0.001
Prior coronary event	631/2153 (29.3)	361/1310 (27.6)	265/831 (31.9)	0.032
Prior MI	482/2253 (21.4)	276/1374 (20.1)	202/867 (23.3)	0.071

	All Patients (n = 2328)	Alive at 30 Days (n = 1414)	Dead at 30 Days (n = 901)	p-Value
<i>Prior PCI</i>	396/2134 (18.6)	239/1299 (18.4)	153/822 (18.6)	0.901
<i>Prior CABG</i>	139/2286 (6.1)	74/1390 (5.3)	65/833 (7.4)	0.048
	Hemodynamics on admission			
Systolic blood pressure—mmHg	100 (80–125)	103 (83–127)	95 (80–118)	<0.001
Diastolic blood pressure—mmHg	61 (50–77)	64 (50–80)	60 (48–75)	<0.001
Mean blood pressure—mmHg	75 (60–93)	77 (63–95)	72 (58–89)	<0.001
Heart rate—bpm	82 (63–101)	80 (60–100)	89 (70–108)	<0.001
Shock index	0.76 (0.58–1.0)	0.72 (0.56–0.95)	0.86 (0.64–1.14)	<0.001
Number of vasoactive agents pre-PCI				<0.001
None	1147/2215 (51.8)	833/1356 (61.4)	309/846 (36.5)	
1	590/2215 (26.6)	320/1356 (23.6)	267/846 (31.6)	
2	376/2215 (17.0)	171/1356 (12.6)	201/846 (23.8)	
≥3	102/2215 (4.6)	32/1356 (2.3)	69/846 (8.1)	
	Laboratory values on admission			
Lactate—mmol/L	5.5 (2.6–9.4)	4.2 (2.1–7.2)	7.8 (3.9–11.4)	<0.001
Creatinine—μmol/L	100 (82–123)	94 (78–113)	110 (91–140)	<0.001
eGFR—mL/min	61 (48–75)	65 (53–80)	54 (40–67)	<0.001
Hemoglobin—mmol/L	8.3 (±1.4)	8.4 (±1.3)	8.1 (±1.5)	<0.001
Glucose—mmol/L	12.2 (8.8–17.1)	10.8 (8.3–14.9)	14.8 (10.4–19.9)	<0.001

Table 1 Continued

	All Patients (n = 2328)	Alive at 30 Days (n = 1414)	Dead at 30 Days (n = 901)	p-Value
Peak hs-troponin-T—ng/L ^a	3534 (828–10000)	3292 (831–10000)	3954 (772–10000)	0.095
Peak CK-MB—U/L ^a	222 (70–510)	203 (67–446)	269 (77–600)	0.013
	Angiographic features			
Multivessel disease	1402/2307 (60.8)	791/1399 (56.5)	603/895 (67.4)	<0.001
Number of treated vessels				<0.001
1	1749/2114 (82.7)	1115/1295 (86.1)	623/806 (77.3)	
≥2	365/2114 (17.3)	180/1295 (13.9)	183/806 (22.7)	
Treated vessel				
Left main	292/2114 (13.8)	142/1295 (11.0)	149/806 (18.5)	<0.001
Left anterior descending	970/2114 (45.9)	576/1295 (44.5)	388/806 (48.1)	0.102
Circumflex artery	479/2114 (22.7)	250/1295 (19.3)	226/806 (28.0)	<0.001
Right coronary artery	794/2114 (37.6)	534/1295 (41.2)	254/806 (31.5)	<0.001
Venous or arterial graft	30/2114 (1.4)	14/1295 (1.1)	16/806 (2.0)	0.103
TIMI flow before PCI				0.721
0/1	1487/1943 (76.5)	905/1189 (76.1)	575/744 (77.3)	
2	208/1943 (10.7)	132/1189 (11.1)	74/744 (9.9)	
3	248/1943 (12.8)	152/1189 (12.8)	95/744 (12.8)	

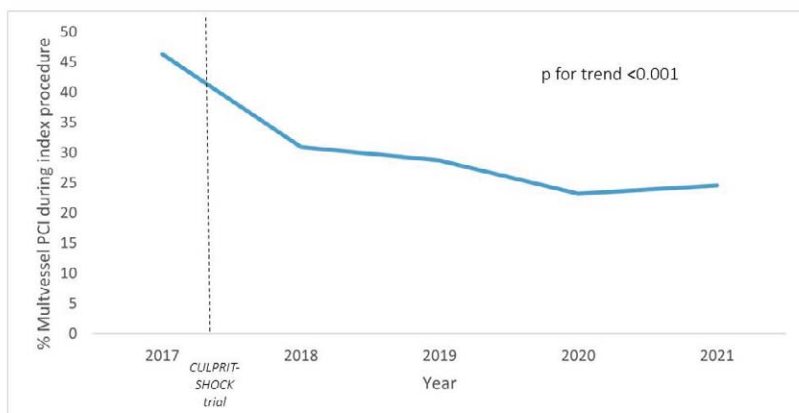
	All Patients (n = 2328)	Alive at 30 Days (n = 1414)	Dead at 30 Days (n = 901)	p-Value
TIMI flow after PCI				<0.001
0/1	182/1999 (9.1)	54/1255 (4.3)	128/735 (17.4)	
2	193/1999 (9.7)	111/1255 (8.8)	81/735 (11.0)	
3	1624/1999 (81.3)	1090/1255 (86.9)	526/735 (71.6)	
Arterial access				<0.001
Radial	1013/2053 (49.3)	718/1242 (57.8)	288/798 (36.1)	
Femoral	1032/2053 (50.3)	521/1242 (41.9)	505/798 (63.3)	
Other	8/2040 (0.3)	3/1242 (0.3)	5/798 (0.7)	
Outcome				
Length of hospital stay—days	5 (1–12)	10 (2–24)	2 (0–6)	<0.001

Values are n (%) or median (25th to 75th percentile). BMI = body mass index; PCI = percutaneous coronary intervention; (N) STEMI = (non-)ST-elevation myocardial infarction; (A)MI = (acute) myocardial infarction; PA catheter = pulmonary artery catheter; CABG = coronary artery bypass grafting; Shock Index was calculated as heart rate/systolic blood pressure; eGFR = estimated glomerular filtration rate; CK-MB = creatine phosphokinase-MB; Vasoactive agents pre-PCI = number of drugs that were administered before PCI (from noradrenaline, adrenaline, dopamine, dobutamine and enoximone/milrinone); TIMI = thrombolysis in myocardial infarction; Length of hospital stay is in days. ^a Peak values within 3 days after PCI.

Angiographic Features

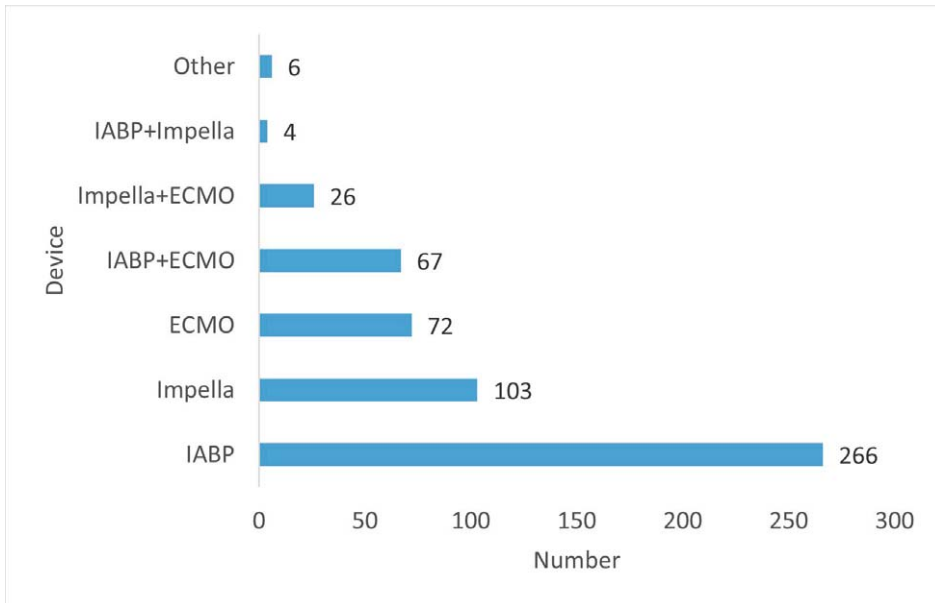
The most frequently treated vessel was the left anterior descending artery ($n = 970$, 45.9%), followed by the right coronary artery ($n = 794$, 37.6%) and the circumflex artery ($n = 479$, 22.7%). Thrombolysis in myocardial infarction (TIMI)-flow < 3 was present in 87.2% ($n = 1695$) of patients before PCI and in 18.8% ($n = 375$) of patients after PCI. Of all patients with multivessel disease, multivessel PCI was performed in 28% ($n = 359$). A decreasing trend over the years was observed in multivessel PCIs performed in patients with multivessel disease (see Figure 1). Vascular access was achieved through the radial artery in 49.3% and the femoral artery in 50.2% of patients. A temporal trend toward less femoral access was seen over the years (60.7%, 55.6%, 52.6%, 47.8% and 48.5% from 2017 to 2021; p -value for trend = 0.019). Overall, unadjusted mortality was significantly higher in the femoral access group (63.3% vs. 36.1%, $p < 0.001$).

Figure 1. Percentage of multivessel PCIs during index procedure within patients with multivessel disease



Mechanical and Pharmacological Support

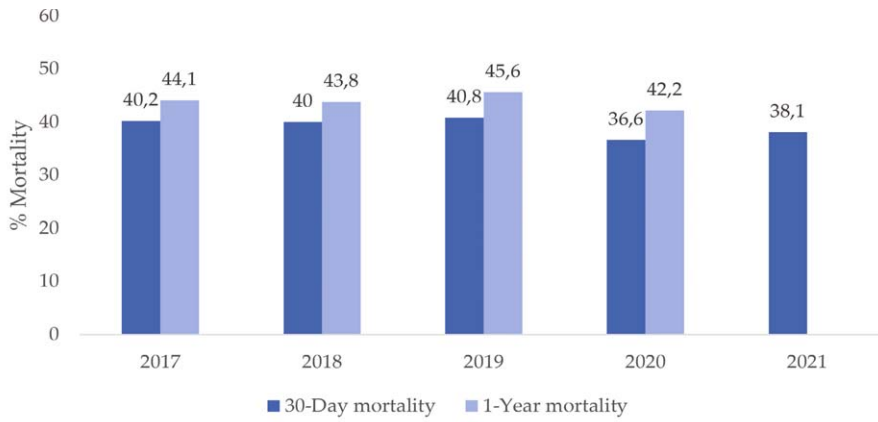
The majority of patients (79.1%, $n = 1842$) received at least one inotropic/vasopressor drug during admission. A total of 710 patients (32.4%) were treated with two vasoactive agents, and ≥ 3 agents were administered to 494 patients (22.5%). Norepinephrine was the drug most frequently used (70.9%, $n = 1613$) either in combination or not with other drugs, followed by dobutamine (30.9%, $n = 699$) and enoximone/milrinone (20.2%, $n = 458$). Mechanical circulatory support was initiated in 544 patients (23.6%). As demonstrated in Figure 2, this amount was mainly driven by intra-aortic balloon pumps (IABPs).

Figure 2. Use of mechanical circulatory support

Survival

The overall 30-day mortality was 38.7% (n = 901), and this percentage was stable over the observation period of four years (details are shown in Figure 3). Survival curves for subgroups are shown in Figure 4. The survival rate was higher in patients presenting with STEMI in comparison to NSTEMI (61.8% vs. 53.4%, $p = 0.005$). On average, those presenting with STEMI were younger (67 vs. 69 years, $p < 0.001$) and had lower rates of diabetes (19.1% vs. 31.2%, $p < 0.001$) and prior coronary events (24.2% vs. 51.5%, $p < 0.001$) than those presenting with NSTEMI. In addition to that, the left ventricular ejection fraction at baseline was lower in NSTEMI patients (35% vs 40%, $p = 0.009$), who also presented with multivessel disease more often (76.5% vs. 57.9%, $p < 0.001$). A higher mortality rate was also seen in patients presenting after an OHCA compared to patients who did not experience an OHCA (48.1% vs. 35.4%, $p < 0.001$). The increase in mortality was even higher for cardiac arrests occurring in-hospital (18.5% vs. 9.3%, $p < 0.001$). Mortality at 30 days was higher when revascularization was unsuccessful (TIMI-flow 0 or 1 post-PCI). In patients with multivessel disease, undergoing multivessel PCI was associated with increased mortality. The overall mortality rate at one year was 44.0% (732/1665) with rates ranging from 42.2% to 45.6% for the individual years of index procedures.

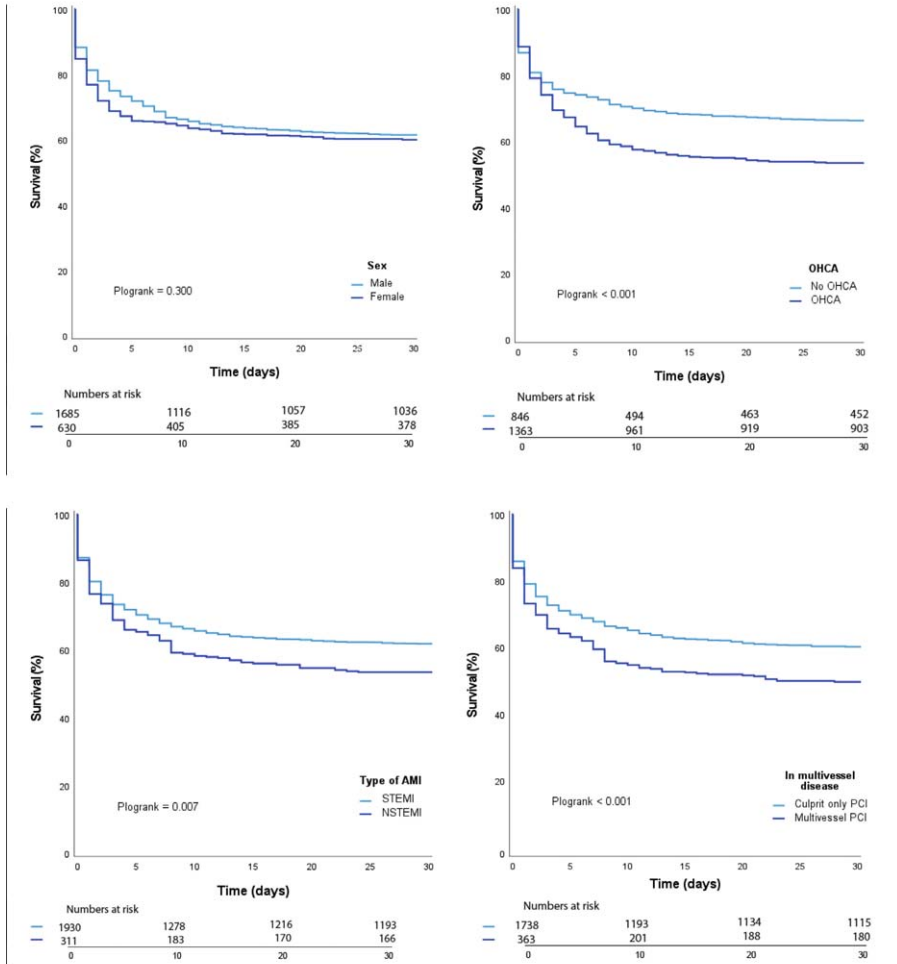
Figure 3. Yearly trend in 30-day and 1-year mortality



■	143/356	161/403	197/483	217/593	183/480
■	157/356	176/403	219/480	180/427	NA ^a
	2017	2018	2019	2020	2021

^a 1-Year follow-up was not completed at the time of submission.

Figure 4. Survival curves for (a) males and females; (b) OHCA yes or no; (c) STEMI and NSTEMI; (d) multivessel and single vessel PCI



2

DISCUSSION

We described a real-time reflection of patients with CS who underwent percutaneous revascularization in the Netherlands with national registry data. A total of 2328 shock patients were identified with a mean age of 66.4 years and of whom 72.9% were male. An overall 30-day mortality rate of 38.7% was found. Mortality was higher in patients presenting with NSTEMI compared to patients with STEMI. Higher mortality rates were also seen in patients presenting after an OHCA and in patients who underwent multivessel PCI. Mortality was similar for male and female patients.

A substantial proportion of the observed results paralleled those reported in previous studies, such as the mean age of almost 70 years and the fact that only a small proportion of patients were female. Mean age and gender distribution were as expected based on the existing literature.(10, 11) Also, the more generally available baseline values for blood pressure and heart rate were very similar to those found in other CS populations, as well as admission levels of lactate and blood glucose. (12, 13) Blood levels of glucose, lactate and hemoglobin have been adopted into several risk-scoring systems for mortality in cardiogenic shock. (14, 15) We also found that higher admission levels of glucose and lactate and lower admission levels of hemoglobin were associated with higher mortality. As infarct size is directly correlated to LV function and mortality, it was not surprising to find higher levels of high-sensitive troponin-T and creatine kinase-MB in non-survivors.

Some remarkable findings were also observed. The reported mortality rate was relatively low compared to general AMI-CS cohorts that reported mortality rates around 50%.(4) This could partly be attributable to the fact that in this NHR CS cohort, per the definition, all patients underwent PCI, whereas in other cohorts, revascularization rates of around 90% were described.(2, 4, 16) In addition to revascularization being the only proven effective therapy for AMI-CS, this could also have led to a more favorable selection of patients who reached the hospital and were in sufficient condition to undergo revascularization.(17)

Another interesting observation was that mortality was higher in patients presenting with NSTEMI than in patients presenting with STEMI. Previous research on this topic is inconclusive, and survival benefit has been described for both NSTEMI and STEMI etiology of shock.(2, 4, 18) In this Dutch cohort, demographic features differed between these groups. In general, NSTEMI patients had more severe clinical risk factors, as they were older and had more comorbidities and worse cardiac function at baseline, which could explain the higher mortality rate.(19, 20)

In our study, we also found that the mortality rate in patients presenting after an OHCA was higher than for non-OHCA patients, which is in line with findings by Ostefeld et al. but in contrast with other results from Denmark.(4, 13) This could again be due to lower revascularization rates in the two latter Danish cohorts than in the current Dutch cohort. As described in the results, in-hospital cardiac arrests (IHCA) affected mortality more than OHCA. This phenomenon is not uncommon, and we hypothesized that a higher rate of comorbidities in IHCA patients causes this difference, as this has been described previously.(21)

Even though the evidence with regard to therapeutic strategies is limited, a few statements have been adopted into the guidelines for the treatment of AMI-CS. In 2017, multivessel PCI for the index procedure was shown to be associated with a worse outcome than single-vessel PCI in patients with multivessel disease.(12) Although the recommendations from the CULPRIT-SHOCK trial were not clearly seen in the first years after publication, it is evident that in the subsequent years, multivessel PCI during the index procedure was performed less and less in patients with multivessel disease. This could be interpreted as a real-world implementation of new evidence in routine clinical practice. The authors hypothesized that despite the results of the CULPRIT-SHOCK trial, physicians may still feel the need to perform immediate multivessel PCI in case of a lack of hemodynamic improvement after initial treatment of the culprit lesion.

In the current cohort, the most frequently used vasoactive agent was norepinephrine, which was administered to 71% of patients. This strategy was consistent with both the American and the European recommendation on medical therapy in CS, as norepinephrine is suggested as the first-choice vasopressor.(20, 22)

Finally, the role of mechanical circulatory support (MCS) in the treatment of AMI-CS patients remains unclear. Even though a survival benefit for patients treated with MCS has yet to be established, almost one quarter of patients in this cohort were supported with at least one MCS device. After the results of the IABP-SHOCK II trial were published in 2012, the routine use of IABP was no longer recommended by the guidelines.(23) Despite these results, 14.6% (n = 337) of patients were treated with an IABP either in combination or not with another device. Randomized evidence from large trials concerning Impella or veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is not readily available, as trials are still recruiting. Treating physicians may at times feel the need to deploy MCS despite the current lack of evidence for their usage. Even though the incidence of MCS use in the Netherlands

seems high, rates of MCS use in other contemporary cohorts are similar, ranging from 19% to 35%.^(24, 25) The distribution between Impella and VA-ECMO, with Impella being used more often, is comparable with other reports.

To the best of our knowledge, this is the largest cohort of patients with CS who underwent PCI with data available on clinical, biochemical and angiographic parameters. It provides a real-world insight covering 49% of all CS patients nationwide in the selected timeframe. Data collection was performed with great care, and high standards of quality control as set by the NHR, were applied. In addition to that, patient survival status was retrieved from the governmental Personal Records Database, guaranteeing reliable documentation. Finally, the amount of variables with high percentages of missing data were limited, especially for those variables that are routinely collected in all patients undergoing PCI.

However, this registry had some limitations as well. Firstly, some selection bias may have been introduced by the partly retrospective aspect of the study. Patients who were initially classified as being in shock but had no source documents confirming the diagnosis of shock other than being labeled as such in the electronic health record, were excluded from the analysis. Nevertheless, this would only strengthen the data on true CS patients. Unfortunately, we did not incorporate the Society for Cardiovascular Angiography and Interventions (SCAI) class definition in our comprehensive CS registry. Regrettably, we did not capture data on bleeding either, which may be of interest, especially in patients treated with mechanical circulatory support.

Furthermore, in some of the additionally collected shock variables, the percentage of missing data exceeded 40%. This was only the case in 5 of these 49 variables, and this was dealt with by providing details on percentages and denominators.

Lastly, despite applying strict criteria and only including AMI-CS patients who underwent PCI, some heterogeneity in the population was inevitable. Only AMI-related CS in patients who underwent PCI was included, but associations between risk factors and out-come could vary for different sub-etiologies; e.g., high lactate on admission might be more indicative of a bad prognosis in non-resuscitated patients than in patients presenting after an OHCA. Nevertheless, we believe that the present variety is in fact a strength because it reflects a real-world population.

CONCLUSIONS

This contemporary Dutch cohort describes characteristics and outcomes of 2328 patients with AMI-CS undergoing PCI. The all-cause mortality at 30 days was 38.7%. Considerable differences were seen in patient, hemodynamic and biochemical characteristics between survivors and non-survivors. Interestingly, multivessel PCI and IABPs were frequently applied despite currently available evidence.

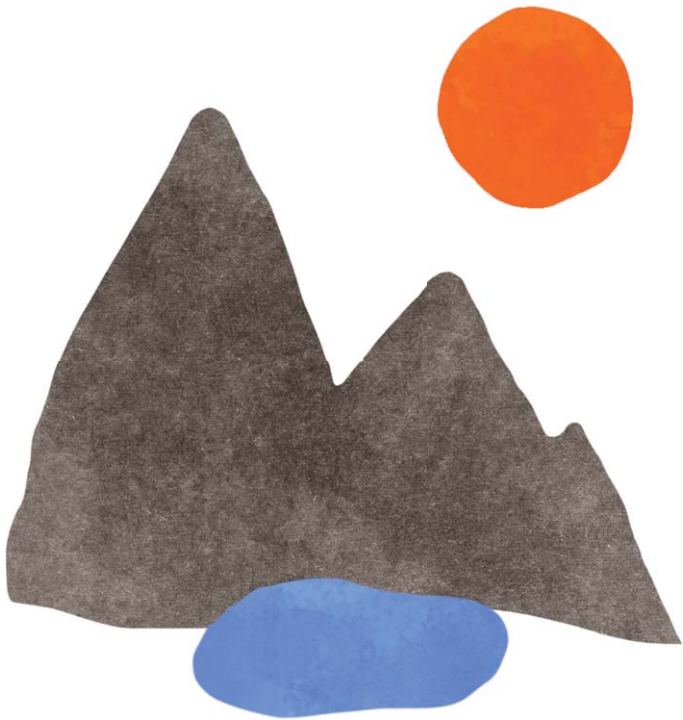
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C

**Individualized risk
assessment**



Chapter 3

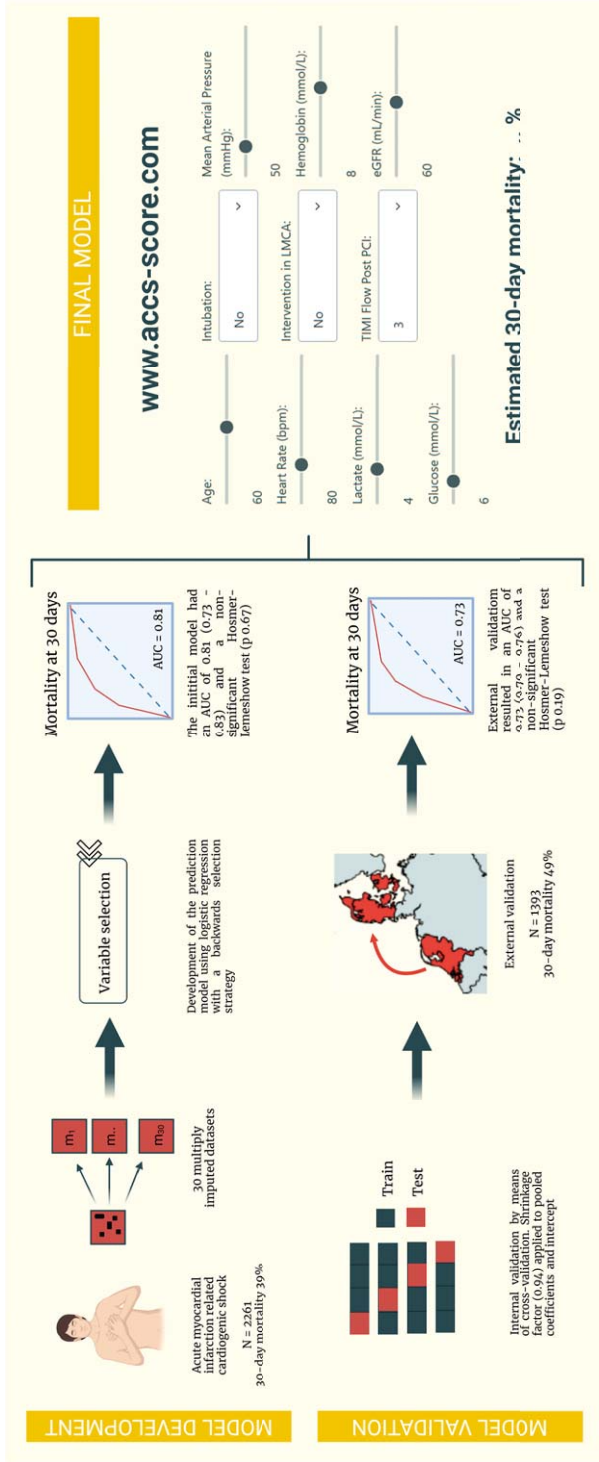
Development and Validation of a Risk Score in Acute Myocardial Infarction related Cardiogenic Shock

The Acute Coronary Syndrome Cardiogenic Shock Score – ACCS Score

Elma J. Peters, Joakim B. Kunkel, Margriet Bogerd, Sanne ten Berg, Marijke J.C. Timmermans, Ole K.L. Helgestad, Hanne B. Ravn, Adriaan O. Kraaijeveld, Luuk C. Otterspoor, Krischan D. Sjauw, Erik Lipšic, Annemarie E. Engström, Alexander P.J. Vlaar, Christian Hassager, Jacob E. Møller, José P.S. Henriques

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Central Illustration



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ABSTRACT

Background

Mortality in patients with acute myocardial infarction-related cardiogenic shock (AMICS) is high, but a widely accepted tool for individual risk assessment is lacking. A reliable prediction model could assist in clinical decision making, patient selection for clinical trials, and comparison of AMICS populations. Therefore, the aim of this study was to develop and externally validate a prediction model for 30-day mortality in AMICS patients.

Methods

This retrospective cohort study included patients from 2017 to 2021 (development cohort) and 2010–2017 (validation cohort). Patients with AMICS undergoing percutaneous coronary intervention in the Netherlands were identified using the Netherlands Heart Registration. International validation was performed in the Danish Retroshock registry. The main outcome was 30-day mortality.

Results

Among 2261 patients, the median age was 67 years (IQR 58–75), and 1649 (73%) were male. The mortality rate at 30 days was 39% (n=886). Significant predictors for mortality were: initial lactate, glucose, renal function, hemoglobin, age, blood pressure, heart rate, intubation prior to PCI, intervention in the left main coronary artery, and successful revascularization. The AUC of the initial model was 0.81 (0.79–0.83). The external validation cohort included 1393 patients with 1050 (75%) male and a median age of 67 years (IQR 59–75). The 30-day mortality rate was 49% (n=680). The model showed good performance on the external validation with an AUC of 0.73 (0.70–0.76).

Conclusions

A prediction model was developed and externally validated using data from two large national registries. The model demonstrated good performance and is suitable for clinical decision-making and quality purposes in AMICS.

INTRODUCTION

Cardiogenic shock (CS) is a clinical syndrome characterized by hypotension and signs of organ hypoperfusion and is frequently caused by acute myocardial infarction (AMI) (1-3). Even though the incidence of AMI related cardiogenic shock (AMICS) only ranges from 3-13%, it is the leading cause of death in AMI worldwide with a 30-day mortality rate of around 40-50% (3-5).

AMICS presents in many phenotypes and individualized assessment of each patient's risk could possibly assist in clinical decision-making for escalation in, e.g., medical therapy or mechanical circulatory support (6). Clinical trials in the acute setting of AMICS greatly suffer from difficulty in selecting patients as they present in a large variety of disease severity (7). Individualized selection could be enhanced by a widely accepted risk stratification tool. It would allow for identification of patients with a low risk of mortality but also of those with advanced shock and minimal chance of survival who would not benefit from more advanced therapy.

Since the 1990's, CS prediction models or severity scoring systems have been proposed for clinical practice (8-18). However, they were often based on mixed CS populations, included only a small number of patients, or were developed in a selected clinical trial population. Additionally, many of these models relied solely on clinical parameters, overlooking the importance of biochemical and angiographic factors (19). This limits the applicability of the existing scores. Hence, a multi-centre observational cohort study was conducted in AMICS patients using real-world data from a Dutch national registry. In this study, clinical, biochemical, angiographic, and therapeutic characteristics were assessed for their prognostic value for mortality in this severe clinical condition (20). The objective of the present study was to develop and externally validate a prediction model to estimate 30-day mortality in AMICS patients.

METHODS

Study population and data collection

Patient data were retrieved from the Netherlands Heart Registration (NHR), a prospective registry in which data on all percutaneous coronary interventions (PCI) in the Netherlands are collected (21). Patients with CS who underwent PCI were identified using this registry. Additional in-depth data was collected from AMICS patients who underwent PCI between January 2017 and September 2021 in 14

participating hospitals in the Netherlands (see: *supplementary table 1*). Details on the establishment and data collection process of this additional shock registry have been described in detail elsewhere (20). No ethical approval was required under the Medical Research Involving Human Subjects Act (WMO) as was confirmed by the Medical research Ethics Committees United (MEC-U). For the validation cohort, patients with AMICS treated by PCI in two centres between January 2010 and December 2017 were identified in the Danish Retroschock cohort (22).

Definitions

Cardiogenic shock was defined as: the presence of hypotension (systolic blood pressure (SBP) ≤ 90 mmHg for ≥ 30 minutes or support to maintain SBP ≥ 90 mmHg) and end-organ hypoperfusion (cold extremities and/or oliguria < 30 mL/hour and/or heart rate ≥ 60 beats per minute). The endpoint *all-cause mortality at 30 days* was defined as whether or not a person was alive on day 30 after PCI. This was reliably obtained from the Personal Records Database (*in Dutch: Basisregistratie Personen*). All other definitions can be found in the data dictionary in *supplementary table 3*. The definition for CS in the validation cohort was previously described by Helgestad *et al*, and was based on ICD-10 codes in combination with treatment in the intensive care unit (ICU) and / or with vasoactive drugs and / or a mechanical assist device (22).

Statistical methods

General

Results are presented as numbers (n) and percentages (%), means and standard deviations (SD), or median and interquartile range (IQR) for variables with a skewed distribution. Comparisons were performed using Student's t-test, Mann-Whitney U-test or chi-squared test, as appropriate. A total of 30 multiple imputed datasets was generated to account for missing data (*see: missing data and sample size*).

Model development

Multivariable logistic regression was performed on the imputed datasets with 30-day mortality as the dependent variable to select significant predictors. Three different models were developed at three different time-settings in patient care. The first model only included variables that were available at hospital admission. The second (and main) model included all variables that were available at the end of the PCI procedure. Lastly, the third model included all details from presentation, procedure and ICU or coronary care unit (CCU) admission. Left ventricular ejection fraction (LVEF) was also considered as a candidate predictor for the third model due to

its deemed importance, despite its percentage missing (14) (see: *missing data and sample size*). Duplicates or different variables expressing the same underlying clinical parameter were removed (e.g. creatinine and dialysis). Continuous variables were checked for linearity and included either as a continuous variable (when appropriate) or as a restricted cubic spline (23). Categorical variables were included as such, with merging of categories where appropriate (based on cell frequencies, clinical relevance and predictive properties). Interaction terms or clinically relevant interactions were included. For the selection of variables, a backward stepwise selection strategy with a significance level value of 0.05 was used. A continued backwards selection was applied to come to a maximum of 10 predictors.

The collaborative consortium deemed the second model to be the most clinically relevant. This model included all variables up to and including the end of the PCI procedure. This model will be referred to as the main model in this paper. It will be presented in various formats, each designed to meet specific needs. Firstly, the regression formula will be provided, allowing users to estimate predicted mortalities for entire cohorts when used with statistical software. This formula could also be integrated into electronic patient records to automatically calculate individual patient risks. Secondly, a nomogram will be offered, giving a quick visual representation of the variables in the models, along with their ranges and relative importance. Lastly, a web-based calculator will be created to accurately compute individual risks in a clinical context.

Model validation

The developed models were internally validated through 5-fold cross-validation with 10 iterations. We calculated the slope value from the cross-validation process to shrink the intercept and coefficients to minimize overfitting (24). The adapted models were then externally validated in Danish Retroschock data (see: *supplementary table 2*). The models' performance was assessed by indices of discrimination and calibration. To assess model discrimination, the C-statistics with corresponding 95% confidence intervals (CI) were calculated from the area under the receiver operating characteristic (ROC) curves (AUC). The model calibration was visually assessed by means of a calibration plot and tested with the Hosmer-Lemeshow goodness-of-fit test (where a non-significant test at the 0.05 level reflects a good model-fit).

Missing data and sample size

Regression analysis was performed after conducting a missing data analysis and applying multiple imputation. All variables with less than 40% missing data were included in the imputation. The outcome variable 30-day mortality was only included as a constraint variable and missing fields were not filled. A total of 30 imputed datasets were generated with the mice package by means of predictive mean matching (mice, van Buuren *et al.*, v. 3.15.0, 2011). The final results were subsequently obtained by pooling using Rubins' Rules (25). A sample size calculation using the criteria proposed by Riley *et al.* was carried out to assess the number of variables that could be included in the model (pmsampsize, Ensor *et al.*, v. 1.1.2, 2022) (26). Based on an expected C-statistic of 0.74 (derived from the IABP- SHOCK II score) and an outcome prevalence of 0.39 (as observed in our own data), the minimum required sample size was 2233 with 19.4 events per variable (10).

All analyses were performed using R 4.2.1. (2022, Vienna, Austria) with the psfmi package (psfmi, Heymans, v. 1.1.0, 2022).

RESULTS

Study population

A total of 2274 consecutive patients were identified that had CS and underwent PCI for AMI. Survival status at 30 days was unknown for 13 patients. Therefore, the final (Dutch) derivation cohort consisted of 2261 patients with an all-cause mortality at 30 days of 39% (n=886) thereby meeting the required sample size. The Danish validation cohort consisted of 1393 patients with an all-cause mortality rate of 49% (n=680). The characteristics of both populations are presented in table 1. The cohorts were comparable in terms of age (median 67), male patient rate (around 74%) and the prevalence of diabetes (around 20%) and a prior coronary event (27%). The levels of lactate, glucose, hemoglobin and eGFR were also comparable at baseline. Some difference was observed in the rate of out-of-hospital cardiac arrest (OHCA), ST-segment elevated myocardial infarction (STEMI) vs. non-STEMI and intubation prior to PCI (41% vs. 58%, 86% vs. 72% and 45% vs. 82% in development and validation data, respectively). The amount of missing data per variable are provided in supplementary figure 1.

Main model development and specification

The predictors resulting from the regression are shown in table 2. The strongest correlations were found for: intubation before PCI, thrombolysis in myocardial infarction (TIMI)-flow post-PCI, age, lactate levels and intervention in the left main coronary artery. Furthermore, lower eGFR, hemoglobin and mean arterial pressure on admission were associated with 30-day mortality. All included variables with corresponding odds ratios are shown in table 2. All details of the additional models can be found in appendices 1+2.

Table 1. Baseline characteristics

	Development cohort				Validation cohort			
	Overall	Survivor	Deceased	Missing fraction	Overall	Survivor	Deceased	Missing fraction
n	2261	1375	886		1393	713	680	
Age (median [IQR])	67 [58, 75]	65 [57, 73]	71 [62, 78]	< 0.001	67 [59, 75]	64 [55, 72]	71 [62, 79]	< 0.001
Male sex (%)	612 (27.1)	367 (26.7)	245 (27.7)	0.65	1050 (75.4)	563 (79.0)	487 (71.6)	0.002
BMI (median [IQR])	26.1	26.0	26.2	0.009	25.6	25.8	25.2	0.024
	[23.9, 29.1]	[23.7, 28.7]	[24.2, 29.6]		[23.5, 28.4]	[23.9, 28.7]	[23.1, 27.8]	
Diabetes (%)	447 (20.8)	217 (16.4)	230 (27.8)	< 0.001	242 (18.3)	95 (13.7)	147 (23.3)	< 0.001
Prior coronary event (%)	549 (26.9)	313 (25.1)	236 (29.6)	0.028	366 (27.2)	189 (27.0)	177 (27.5)	0.878
Multivessel disease (%)	1356 (60.5)	766 (56.3)	590 (67.0)	< 0.001	741 (56.0)	362 (53.0)	379 (59.2)	0.026
LVEF (%)								
Very severely impaired	50 (4.2)	20 (2.8)	30 (6.1)		465 (35.3)	192 (27.5)	273 (44.0)	
Severely impaired	430 (36.0)	199 (28.3)	231 (47.1)	< 0.001	328 (24.9)	198 (28.4)	130 (20.9)	< 0.001
Moderately impaired	157 (13.1)	101 (14.3)	56 (11.4)		284 (21.5)	154 (22.1)	130 (20.9)	
Mildly impaired	407 (34.1)	271 (38.5)	136 (27.8)		224 (17.0)	141 (20.2)	83 (13.4)	
Normal	150 (12.6)	113 (16.1)	37 (7.6)		17 (1.3)	12 (1.7)	5 (0.8)	
STEMI (%)	1930 (86.1)	1193 (87.8)	737 (83.6)	0.006	988 (72.1)	543 (77.5)	445 (66.4)	< 0.001
Chest symptoms (%)								
<3h	1145 (59.0)	733 (60.9)	412 (55.9)		508 (45.2)	293 (50.2)	215 (39.9)	
3-6h	212 (10.9)	147 (12.2)	65 (8.8)		281 (25.0)	141 (24.1)	140 (26.0)	
6-12h	160 (8.2)	97 (8.1)	63 (8.5)	< 0.001	127 (11.3)	52 (8.9)	75 (13.9)	0.005
12-24h	111 (5.7)	67 (5.6)	44 (6.0)		93 (8.3)	45 (7.7)	48 (8.9)	
>24h	312 (16.1)	159 (13.2)	153 (20.8)		114 (10.2)	53 (9.1)	61 (11.3)	
OHCA (%)	927 (41.2)	495 (36.2)	432 (48.9)	< 0.001	797 (57.5)	451 (63.6)	346 (51.2)	< 0.001
IHCA (%)	284 (12.7)	126 (9.3)	158 (18.0)	< 0.001	115 (8.3)	66 (9.3)	49 (7.2)	0.196
MAP (median [IQR])	87 [71, 108]	90 [73, 111]	83 [68, 103]	< 0.001	80 [67, 96]	80 [67, 97]	78 [64, 95]	0.041
Heart rate (median [IQR])	82 [63, 101]	80 [60, 100]	89 [70, 108]	< 0.001	86 [70, 104]	84 [70, 100]	89 [70, 105]	0.026
Intubation pre PCI (%)	1013 (45.2)	494 (36.3)	519 (59.1)	< 0.001	859 (82.0)	462 (83.2)	397 (80.5)	0.289

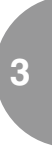


Table 1 Continued

	Development cohort				Validation cohort					
	Overall	Survivor	Deceased	p-value	Missing fraction	Overall	Survivor	Deceased	p-value	Missing fraction
Vasoactive medication pre PCI (%)										
None	1114 (50.9)	810 (60.8)	304 (35.5)	< 0.001	3.2	740 (53.8)	372 (52.5)	368 (55.2)	0.013	1.3
Inotropes	34 (1.6)	22 (1.7)	12 (1.4)	< 0.001		246 (17.9)	144 (20.3)	102 (15.3)		
Vasopressor	826 (37.8)	411 (30.9)	415 (48.5)	< 0.001		177 (12.9)	98 (13.8)	79 (11.8)		
Both	214 (9.8)	89 (6.7)	125 (14.6)	< 0.001		212 (15.4)	94 (13.3)	118 (17.7)		
Lactate (median [IQR])	5.6 [2.7, 9.4]	4.3 [2.1, 7.2]	7.9 [4.0, 11.4]	< 0.001	34.6	5.2 [3.0, 9.2]	4.1 [2.5, 7.2]	6.6 [3.7, 10.7]	< 0.001	17.9
Hemoglobin (median [IQR])	8.4 [7.4, 9.2]	8.5 [7.6, 9.3]	8.2 [7.1, 9.1]	< 0.001	5.5	8.5 [7.5, 9.2]	8.6 [7.8, 9.3]	8.2 [7.3, 9.1]	< 0.001	22
eGFR (median [IQR])	61 [49, 75]	65 [53, 80]	54 [40, 67]	< 0.001	9.5	58 [45, 72]	62 [50, 76]	54 [39, 68]	< 0.001	20.5
Glucose (median [IQR])	12.2 [8.8, 17.1]	10.8 [8.3, 14.8]	14.8 [10.4, 20.0]	< 0.001	11.5	12.5 [9.4, 17.6]	12.4 [9.3, 16.6]	12.6 [9.6, 18.8]	0.084	52.8
Intervention in LCA (%)	1389 (67.9)	802 (63.9)	587 (74.2)	< 0.001	9.5	854 (74.5)	450 (74.8)	404 (74.3)	0.904	17.7
Intervention in RCA (%)	769 (37.6)	520 (41.4)	249 (31.5)	< 0.001	9.5	366 (31.9)	196 (32.6)	170 (31.2)	0.681	17.7
TIMI pre PCI (%)										
0	1277 (67.1)	780 (66.7)	497 (67.8)	0.823	15.9	729 (57.1)	364 (55.3)	365 (59.0)	0.225	8.3
1	182 (9.6)	110 (9.4)	72 (9.8)			107 (8.4)	50 (7.6)	57 (9.2)		
2	205 (10.8)	132 (11.3)	73 (10.0)			149 (11.7)	81 (12.3)	68 (11.0)		
3	238 (12.5)	147 (12.6)	91 (12.4)			292 (22.9)	163 (24.8)	129 (20.8)		
TIMI post PCI (%)										
0	113 (5.8)	33 (2.7)	80 (11.1)	< 0.001	14	48 (3.8)	8 (1.2)	40 (6.5)	< 0.001	8.7
1	66 (3.4)	19 (1.6)	47 (6.5)			35 (2.8)	8 (1.2)	27 (4.4)		
2	188 (9.7)	108 (8.8)	80 (11.1)			117 (9.2)	43 (6.6)	74 (12.0)		
3	1578 (81.1)	1065 (86.9)	513 (71.2)			1072 (84.3)	596 (91.0)	476 (77.1)		

	Development cohort			Validation cohort		
	Overall	Survivor	Deceased	p-value	Missing fraction	Missing fraction
Mechanical circulatory support (%)	523 (23.4)	237 (17.4)	286 (32.5)	< 0.001	1.1	0.1

Baseline characteristics of the two cohorts. **Age** in years; **BMI** = body mass index, in kg/m²; **LVEF** = left ventricular ejection fraction (very severely impaired = LVEF <20%, severely impaired = LVEF 20-30%, moderately impaired = LVEF 30-40%, mildly impaired = LVEF 40-50%, normal = LVEF >50%); **STEMI** = ST-segment elevation myocardial infarction; **Duration of chest symptoms** = amount of time between start symptoms and hospital presentation; **OHCA** = out-of-hospital cardiac arrest; **IHCA** = in-hospital cardiac arrest; **Heart rate** in beats per minute; **MAP** = mean arterial pressure, in mmHg; **Lactate** in mmol/L; **Hemoglobin** in mmol/L; **eGFR** in mL/min; **Glucose** in mmol/L; **LCA** = left coronary artery; **RCA** = right coronary artery; **TIMI** = thrombolysis in myocardial infarction flow

VALIDATION AND PERFORMANCE

The initial model showed a C-statistic of 0.81 (95% confidence interval [CI] 0.79 – 0.83) and demonstrated an adequate fit to the data, as indicated by a non-significant Hosmer- Lemeshow test (p-value 0.67).

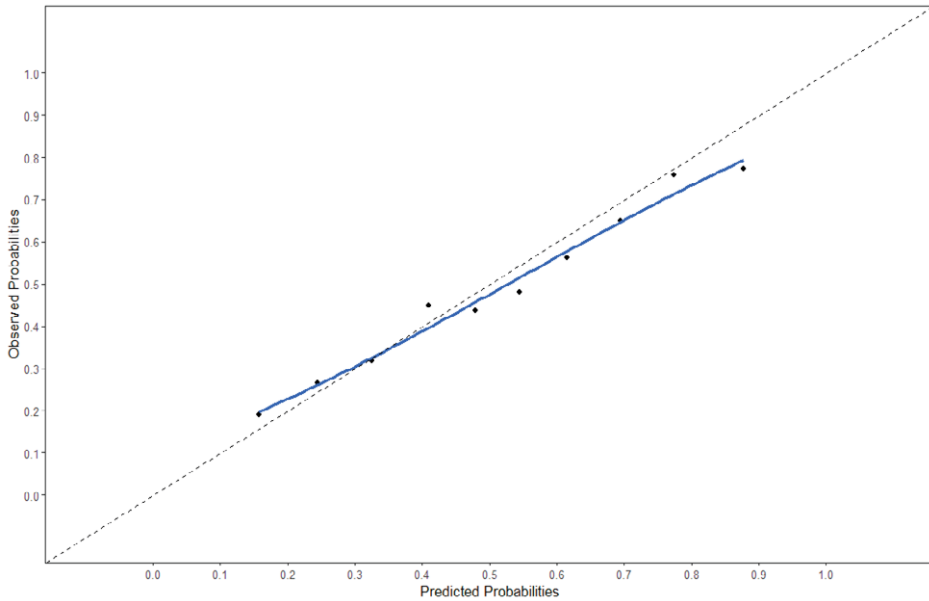
Table 2 Odds ratios main model

Term	Odds ratio	95% Confidence interval		p-value
(Intercept)	0.237	0.047	1.194	0.080
Intubation prior to PCI	2.265	1.825	2.812	< 0.001
Left main intervention	1.554	1.183	2.042	0.005
TIMI flow post PCI (<i>reference 3</i>)				
2	1.731	1.244	2.408	0.001
0/1	4.404	3.099	6.258	< 0.001
Age	1.023	1.007	1.040	0.006
Age' [50-67-82]	1.017	0.998	1.037	0.077
Heart rate	1.014	1.005	1.023	0.003
Heart rate' [45-82-120]	0.995	0.986	1.005	0.308
Lactate	1.212	1.113	1.320	< 0.001
Lactate' [1.3-4.5-12.7]	0.833	0.724	0.958	0.010
Glucose	1.038	0.983	1.096	0.183
Glucose' [7-12-22]	1.021	0.946	1.102	0.591
eGFR	0.969	0.961	0.978	< 0.001
eGFR' [34-61-91]	1.022	1.014	1.029	< 0.001
MAP	0.988	0.979	0.997	0.010
MAP' [58-87-127]	1.005	0.993	1.016	0.435
Hemoglobin	0.857	0.746	0.985	0.030
Hemoglobin' [6.4-8.4-9.9]	1.097	0.942	1.277	0.235

All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

Internal validation was performed by mean of cross-validation with 3 folds and 5 multiple imputation runs. The obtained shrinkage factor (0.89) was applied to the pooled coefficients and the intercept. The improved model was subsequently tested on the external dataset. The model's C-statistic in the external data was 0.73 (95% CI 0.70 – 0.76). The external calibration curve is shown in figure 1.

Figure 1. Calibration curve of the main model



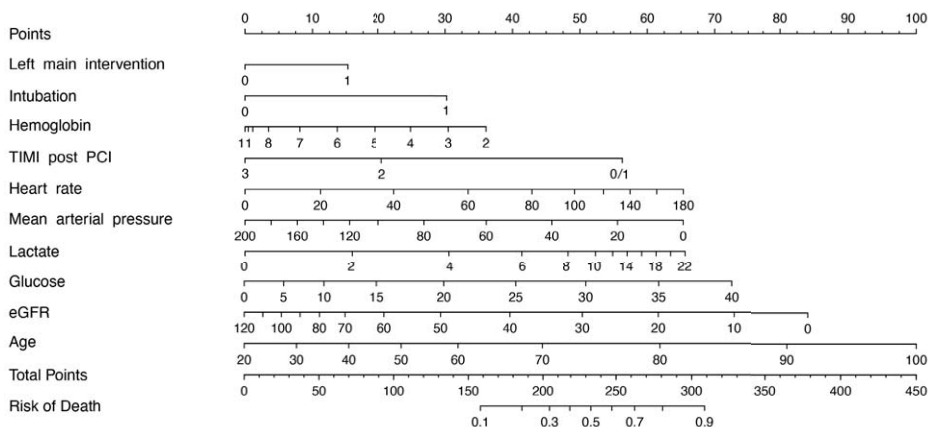
Calibration curve of observed and predicted probabilities in external data of the main model

USAGE IN PRACTICE

We developed three practical applications for clinical usage:

1. The regression formula as shown in appendix 2 and will be added to the digital supplementary files as an R object.
2. A nomogram (figure 2) for a quick impression of an individual's prognosis but moreover to get an impression of the variables in the model including their ranges and weights.
3. A web-based calculator: www.accs-score.com). This is for individual risk assessment in clinical setting.

Figure 2. Nomogram to calculate risk prediction



For each variable, find the corresponding value on its axis. Then, draw a vertical line from that point upward to intersect with the “points scale” at the top of the nomogram to find the number of points assigned based on the patient’s value for that variable. Repeat this process for each variable in the nomogram. Sum all the assigned points to get the total score. Plot the total score on the “total points” axis and draw a vertical line downward to intersect with the “risk of mortality” scale at the bottom. This point represents the estimated risk of mortality for the patient.

DISCUSSION

We developed and externally validated a prediction model for 30-day mortality in AMICS patients treated with PCI using data of two large national registries, yielding an AUC of 0.73 after external validation. The model included 10 predictors commonly collected in clinical practice, including patient-, laboratory- and angiographic parameters.

The excellent performance of the model after internal validation, that was consistent with the initial performance, indicated its reliability and robustness. The external validation in data from a different country adds significant value to the findings. No other shock prediction tool was developed and validated in such large-sized cohorts and the currently developed risk score performs better than other contemporary scoring tools in comparable populations. Of the other scores developed specifically in CS following AMI, the IABP-shock II score is presumably the most widespread and validated score (10). It was developed in 480 patients from a randomized clinical trial and showed an AUC of 0.67 in a recent external validation study in 912 AMICS patients (27). A risk score developed by Klein et al. using registry data from AMI related CS patients only, included 6 variables and showed a C-statistic of 0.76. However, the development cohort of this score consisted of only 483 patients and external validation was omitted (12). An overview of other risk prediction tools including their parameters and discriminative abilities, is provided in supplementary table 4.

Both the Santiago Shock Score and the CardShock risk Score managed to achieve better discriminative performance, with C-statistics of 0.85 in their respective development cohorts (14,17). However, these models were developed in relatively small cohorts (135 and 219 patients, respectively) and included more heterogeneous populations. Given that different shock etiologies have different prognoses, this increased heterogeneity is likely to lead to better discrimination (28). Lastly, the Society for Cardiovascular Angiography and Interventions (SCAI) shock stage classification, has greatly helped the identification of various subgroups of shock severity since its development in 2019 (29). It has been validated and is increasingly being used but is primarily a classification system rather than a prognostic tool for individualized risk assessment due to its broad categorization, limited set of clinical variables to define each stage and absence of quantitative risk estimates (30). It may

serve as a first clinical assessment whereas the currently developed tool may more exactly predict patients' risk for death.

Many variables in our model are established risk factors also found in other scoring systems. However, our study uniquely assesses multiple predictors in a clearly defined, homogeneous group. All measured laboratory values (hemoglobin, lactate, glucose, eGFR) significantly predicted 30-day mortality. Lactate and eGFR, recognized markers of decreased tissue perfusion, are also used in other risk scores (10,11,14,31). Similarly, elevated glucose, or stress hyperglycemia, is known to be associated with mortality in AMICS (32). Although hemoglobin level is not part of other CS risk scores, it is correlated with mortality in various conditions, emphasizing its importance in compromised hemodynamics (33).

OHCA was not independently associated with mortality in our large cohort, nor was it an effect-modifier in the relation between lactate and the outcome or vasoactive medication and the outcome. Literature on this topic is not conclusive but a trend towards higher mortality after OHCA in CS patients is described in most papers addressing this issue (22,34). We hypothesize that intubation before PCI and higher lactate and glucose levels may serve as surrogate markers for both IHCA and OHCA. Interestingly, parameters indicating comorbidities like diabetes, multivessel disease, and prior coronary events were largely insignificant predictors, thereby contrasting recent meta-analysis findings suggesting an increased mortality risk for diabetic patients with AMICS (35). These findings suggest acute disease markers may outweigh premorbid conditions in determining patient outcomes.

The current findings emphasize the role of several available markers in the risk assessment of CS. Decisions for escalation of therapy are often based on a crude clinical assessment including mainly patients' age, whereas we have demonstrated that age is just one of the many factors with prognostic features. More specifically, markers of acute setting play at least an equal role and should be weighed in clinical decision making accordingly.

STRENGTHS AND LIMITATIONS

Most importantly, this model was developed with high methodological accuracy. That is: 1) all candidate predictors could be included in the regression analysis as our cohort included a large number of patients with high outcome incidence; 2) univariable selection was bypassed, and sample size criteria were easily met (37); 3) missing data were properly handled by multiple imputation; 4) U-shaped relationships between mortality and markers were captured using restricted cubic splines (32,38); and 5) external validation was performed on a real-world foreign cohort.

The model's practical applicability is enhanced by the use of objective, clearly defined variables available for almost every patient. This was crucial as we were unable to externally validate any of the existing scores in our current data; despite having over 100 variables present for every patient, all available scores contained unavailable parameters. Moreover, these variables can retrospectively be retrieved from records. By excluding subjective variables (e.g., confusion) and rarely measured biomarkers, this tool is particularly suited for quality of care and population comparisons.

Two real-world cohorts were used, with data manually collected to high standards. Only parameters available directly at the end of the PCI procedure were included in the main analysis, enabling early prediction(39). Finally, the patient cohort is clearly defined and homogeneous while covering several stages of shock, making it easy to determine which patients to apply the model to in practice.

The current study has some limitations as well. The model provides exact estimates when incorporated into electronic patient files or for users of the calculator, but it may be less suitable for mental calculations. Missing data, though handled by multiple imputation, remains a concern. No echocardiographic parameters were included in the main model despite the affirmed association with mortality in CS (14,40). Finally, inclusion periods of both cohorts differed approximately 6 years, but we believe this has minimal influence on the outcomes given the limited progress in terms of treatment or survival over the past years.

CONCLUSION

We developed and externally validated a precise prediction model for 30-day mortality in patients with acute myocardial infarction related cardiogenic shock undergoing percutaneous coronary intervention. The model underscores the importance of several available markers in risk prediction and emphasizes that many factors should be taken into account when it comes to clinical decision making. Besides use in clinical practice, the developed model will facilitate comparisons across different populations and assist in the selection of patients for clinical trials

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APPENDIX INDEX

Appendix 1

- Overview different models

Appendix 2

A. Details model one

1. Odds ratios
2. Regression formula
3. Calibration plot

B. Details model two



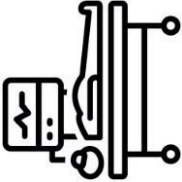
1. Odds ratios
2. Regression formula
3. Calibration plot

C. Details model three

1. Odds ratios
2. Regression formula
3. Calibration plot

APPENDIX 1

Overview different models

	Model 1	Model 2	Model 3
			
Intended use:	Upon hospital arrival	End of cath lab procedure	End of ICU/CCU admission
Variables considered for analysis	Emergency Room Age Sex BMI Diabetes Prior CE Chest symptom duration STEMI/NSTEMI Resuscitated Intubation Heart rate MAP	Interventionalist Age Sex BMI Diabetes Prior CE Chest symptom duration STEMI/NSTEMI Resuscitated Intubation Heart rate MAP	Intensive care doctor Age Sex BMI Diabetes Prior CE Chest symptom duration STEMI/NSTEMI Resuscitated Intubation Heart rate MAP

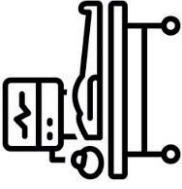
Model 1



Model 2



Model 3



Glucose
eGFR
Hemoglobin
Lactate

Interactions:
Lactate: Resuscitated
Hemoglobin: Sex

Glucose
eGFR
Hemoglobin
Lactate
Inotropic pre type
TIMI flow pre PCI
TIMI flow post PCI
Multivessel disease
Treated vessel

Glucose
eGFR
Hemoglobin
Lactate
TIMI flow pre PCI
TIMI flow post PCI
Multivessel disease
Treated vessel
Number of inotropes during admission
MCS during admission
LVEF

Interactions:
Lactate: Resuscitated
Hemoglobin: Sex
MAP: Inotrope type
Resuscitated: Inotrope type

Interactions:
Lactate: Resuscitated
Hemoglobin: Sex

	MAP: Inotrope type	OHCA: Inotrope type
Variables included	<ol style="list-style-type: none"> Age Heart rate Lactate Glucose eGFR Intubation MAP TIMI post Hemoglobin Left main intervention 	<ol style="list-style-type: none"> Age Lactate Glucose eGFR Intubation TIMI post MAP Inotropes MCS LVEF
Primary performance	AUC 0.80 (0.78 – 0.82) R ² 0.35 Hosmer-Lemeshow p-value 0.44	AUC 0.84 (0.82 – 0.85) R ² 0.42 Hosmer-Lemeshow p-value 0.57
Shrinkage factor	0.94	0.26
After cross-validation	AUC 0.77 (95% CI 0.75 – 0.79) R ² 0.28	AUC 0.80 (95% CI 0.78 – 0.82) R ² 0.39
Performance external	AUC 0.72 (0.69 – 0.75) R ² 0.17	AUC 0.73 (0.71 – 0.76) R ² 0.20



APPENDIX 2

2A Model 1



1. Odds ratios model 1

term	OR	lower.EXP	upper.EXP	p.value
(Intercept)	0.370	0.056	2.438	0.301
STEMI etiology	0.967	0.940	0.996	0.026
Intubation prior to PCI	2.053	1.646	2.561	< 0.001
Chest symptoms (<i>reference < 3 hours</i>)				
3 – 24 hours	1.042	0.812	1.337	0.745
> 24 hours	1.606	1.193	2.162	0.002
Age	1.026	1.009	1.044	0.003
Age' [50-67-82]	1.022	1.002	1.043	0.028
Heart rate	1.015	1.005	1.024	0.002
Heart rate' [45-82-120]	0.995	0.985	1.004	0.279
Lactate	1.264	1.157	1.382	< 0.001
Lactate' [1.3-4.5-12.7]	0.797	0.689	0.922	0.002
Hemoglobin	0.874	0.757	1.010	0.068
Hemoglobin' [6.4-8.4-9.9]	1.115	0.951	1.306	0.180
Glucose	1.040	0.983	1.101	0.170
Glucose' [7-12-22]	1.024	0.947	1.108	0.554
eGFR	0.971	0.962	0.981	< 0.001
eGFR' [34-61-91]	1.021	1.013	1.029	< 0.001
MAP	0.986	0.977	0.996	0.004
MAP' [58-87-127]	1.007	0.995	1.019	0.277

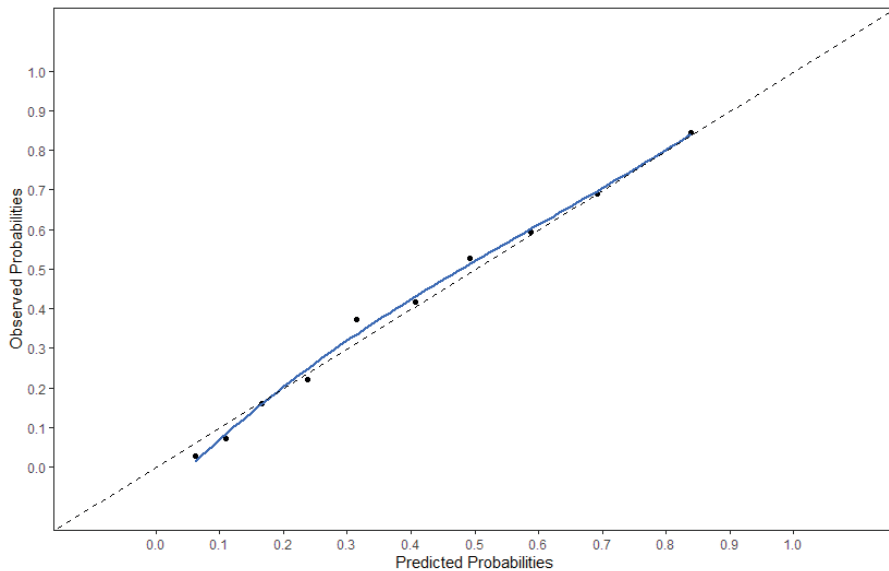
All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

2. Regression formula model 1

$$\begin{aligned}
 \text{LnOdds(30-day mortality)} = & - 0.993 - 0.033 * \text{STEMI} \\
 & + 0.719 * \text{Intubation prior to PCI} \\
 & + 0.041 * \text{Duration of symptoms (3-24 hours)} + 0.474 * \text{Duration of symptoms} \\
 & \quad (> 24 \text{ hours}) \\
 & + 0.026 * \text{Age} + 0.022 * \text{Age}'[50-67-82] \\
 & + 0.015 * \text{Heart rate} - 0.005 * \text{Heart rate}'[45-82-120] \\
 & + 0.234 * \text{Lactate} - 0.227 * \text{Lactate}' [1.3-4.5-12.7] \\
 & - 0.134 * \text{Hemoglobin} + 0.109 * \text{Hemoglobin}' [6.4-8.4-9.9] \\
 & + 0.040 * \text{Glucose} + 0.024 * \text{Glucose}'[7-12-22] \\
 & - 0.029 * \text{eGFR} + 0.020 * \text{eGFR}' [34-61-91] \\
 & - 0.014 * \text{MAP} + 0.007 * \text{MAP}'[59-87-127]
 \end{aligned}$$

Reference for duration of symptoms is < 3 hours. All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

3. Calibration plot model 1



2B Model 2



1. Odds ratios model 2

Term	OR	lower.EXP	upper.EXP	p.value
(Intercept)	0.237	0.047	1.194	0.080
Intubation prior to PCI	2.265	1.825	2.812	< 0.001
Left main intervention	1.554	1.183	2.042	0.005
TIMI flow post PCI (<i>reference 3</i>)				
2	1.731	1.244	2.408	0.001
0/1	4.404	3.099	6.258	< 0.001
Age	1.023	1.007	1.040	0.006
Age' [50-67-82]	1.017	0.998	1.037	0.077
Heart rate	1.014	1.005	1.023	0.003
Heart rate' [45-82-120]	0.995	0.986	1.005	0.308
Lactate	1.212	1.113	1.320	< 0.001
Lactate' [1.3-4.5-12.7]	0.833	0.724	0.958	0.010
Glucose	1.038	0.983	1.096	0.183
Glucose' [7-12-22]	1.021	0.946	1.102	0.591
eGFR	0.969	0.961	0.978	< 0.001
eGFR' [34-61-91]	1.022	1.014	1.029	< 0.001
MAP	0.988	0.979	0.997	0.010
MAP' [58-87-127]	1.005	0.993	1.016	0.435
Hemoglobin	0.857	0.746	0.985	0.030
Hemoglobin' [6.4-8.4-9.9]	1.097	0.942	1.277	0.235

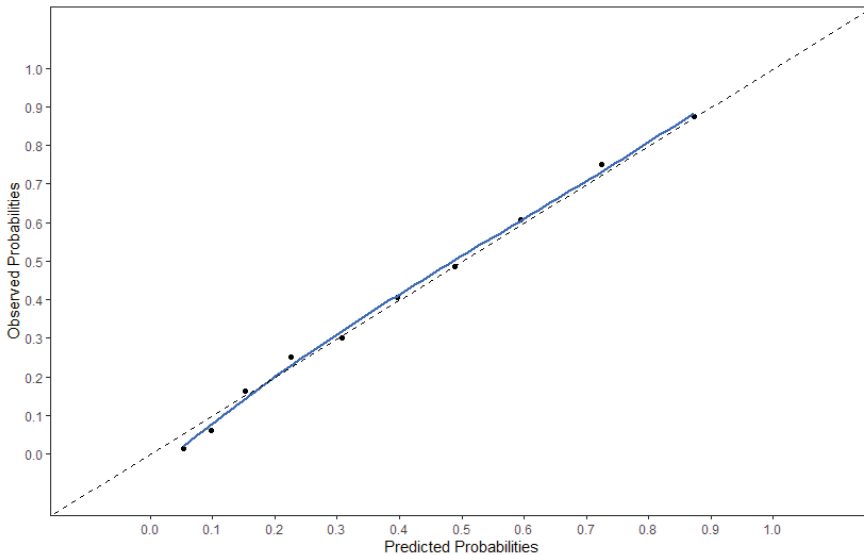
All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

2. Regression formula model 2

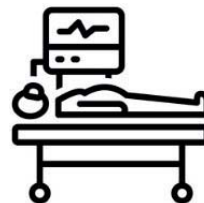
$$\begin{aligned}
 \text{LnOdds(30 day mortality)} = & - 1.438 + 0.818 * \text{Intubation prior to PCI} \\
 & + 0.441 * \text{Left main intervention} \\
 & + 0.549 * \text{TIMI (2)} + 1.482 * \text{TIMI (0/1)} \\
 & + 0.023 * \text{Age} + 0.017 * \text{Age}' [50-67-82] \\
 & + 0.014 * \text{Heart rate} - 0.005 * \text{Heart rate}' [45-82-120] \\
 & + 0.192 * \text{Lactate} - 0.182 * \text{Lactate}' [1.3-4.5-12.7] \\
 & + 0.037 * \text{Glucose} + 0.021 * \text{Glucose}' [7-12-22] \\
 & - 0.031 * \text{eGFR} + 0.022 * \text{eGFR}' [34-61-91] \\
 & - 0.012 * \text{MAP} + 0.005 * \text{MAP}' [58-87-127] \\
 & - 0.154 * \text{Hemoglobin} + 0.092 * \text{Hemoglobin}' [6.4-8.4-9.9]
 \end{aligned}$$

Reference value for TIMI post PCI is 3. All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

Calibration plot model 2



2C Model 3



1. Odds ratios model 3.

term	OR	lower.EXP	upper.EXP	p.value
(Intercept)	0.214	0.051	0.893	0.034
Intubation prior to PCI	2.044	1.625	2.570	< 0.001
Mechanical circulatory support	1.605	1.272	2.025	< 0.001
Left ventricular ejection fraction	0.975	0.964	0.986	< 0.001
TIMI flow post PCI (<i>reference 3</i>)				
2	1.624	1.162	2.270	0.005
0/1	4.734	3.323	6.744	< 0.001
No. Of inotropes (<i>reference 0</i>)				
1	1.609	1.115	2.322	0.011
≥ 2	2.785	1.952	3.973	< 0.001
Age	1.026	1.008	1.043	0.003
Age' [50-67-82]	1.024	1.004	1.044	0.020
Lactate	1.165	1.070	1.268	< 0.001
Lactate' [1.3-4.5-12.7]	0.859	0.746	0.988	0.034
Glucose	1.011	0.957	1.069	0.686
Glucose' [7-12-22]	1.050	0.972	1.135	0.218
eGFR	0.971	0.963	0.980	< 0.001
eGFR' [34-61-91]	1.020	1.013	1.028	< 0.001
MAP	0.991	0.982	1.000	0.048
MAP' [58-87-127]	1.004	0.992	1.015	0.545

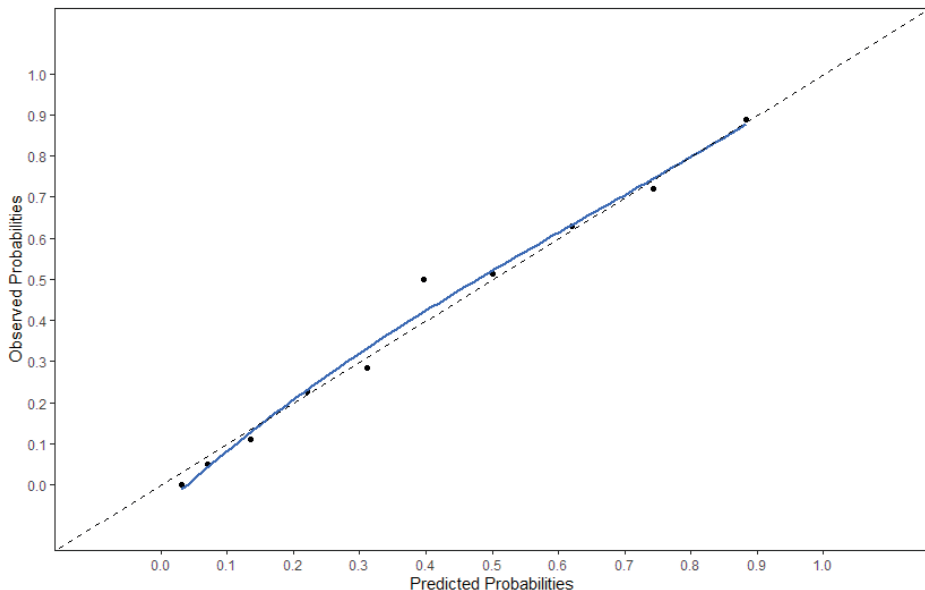
All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

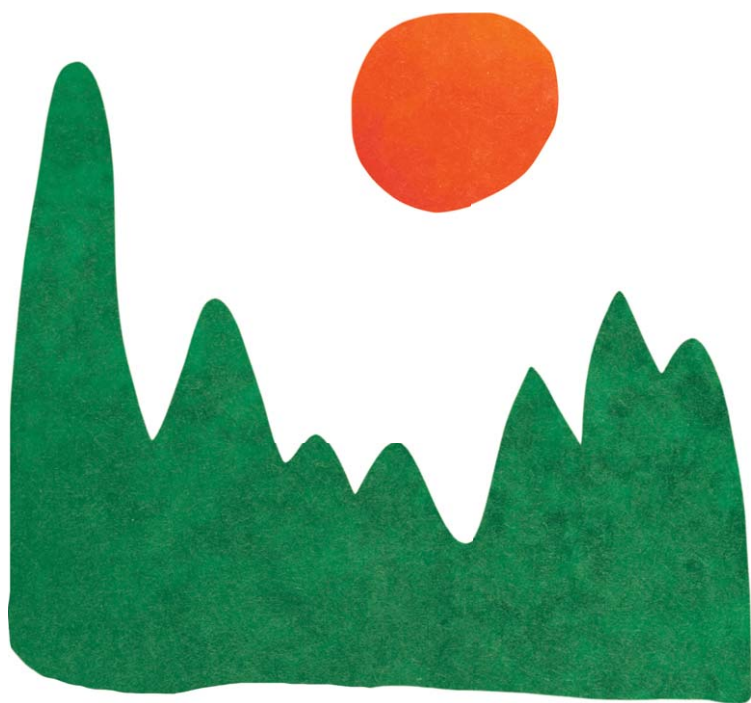
2. Regression formula model 3

$$\begin{aligned}
 \text{LnOdds (30 day mortality)} = & -1.542 + 0.715 * \text{Intubation prior to PCI} \\
 & + 0.473 * \text{MCS} \\
 & - 0.025 * \text{LVEF} \\
 & + 0.485 * \text{TIMI(2)} + 1.555 * \text{TIMI (0/1)} \\
 & + 0.476 * \text{Inotropes during admission (1)} + 1.024 * \text{Inotropes during admission (> 2)} \\
 & + 0.025 * \text{Age} + 0.023 * \text{Age}' [50-67-82] \\
 & + 0.152 * \text{Lactate} - 0.153 * \text{Lactate}' [1.3-4.5-12.7] \\
 & + 0.011 * \text{Glucose} + 0.049 * \text{Glucose}' [7-12-22] \\
 & - 0.029 * \text{eGFR} + 0.020 * \text{eGFR}' [34-61-91] \\
 & - 0.009 * \text{MAP} + 0.004 * \text{MAP}' [58-87-127]
 \end{aligned}$$

Reference value for TIMI post PCI is 3. Reference value for inotropes during admission is zero. All variables denoted with an apostrophe (') represent the restricted cubic spline with 3 knots at 10th, 50th and 90th percentile. Knot locations are displayed between square brackets.

3. Calibration plot model 3





Chapter 4

Sex Disparities in Myocardial Infarction related Cardiogenic Shock

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ABSTRACT

Background

Women are underrepresented in cardiovascular disease research, constituting only 30 % of the cardiogenic shock (CS) population. Consequently, guidelines are mainly based on male patients. This study aims to comprehensively examine the sex-specific aspects of acute myocardial infarction (AMI)-related CS, encompassing presentation, treatment and outcomes.

Methods

Patients with CS undergoing percutaneous coronary intervention (PCI) between 2017 and 2021 were identified using the national Netherlands Heart Registration. Mortality was assessed using the Kaplan Meier method, and logistic regression was performed to investigate differences in clinical management between sexes. Furthermore, a sensitivity analysis excluding patients with out-of-hospital cardiac arrest (OHCA) was conducted.

Results

Among 2274 patients, 614 (27 %) were female. Women were older (70 vs. 66 years, $p < 0.001$) and presented with longer symptom duration (> 3 h: 52 % vs. 37 %, $p < 0.001$). Men more often presented with multivessel disease (62 % vs. 56 %, $p < 0.001$), a prior myocardial infarction (23 % vs. 15 %, $p < 0.001$) and after an OHCA (46 % vs. 29 %, $p < 0.001$). A trend towards more usage of mechanical circulatory support in men was observed (adjusted OR 0.86, 95 % CI 0.67–1.09). Mortality, both adjusted and unadjusted, was not statistically different for men and women.

Conclusion

Women with CS present with distinct clinical characteristics, including longer symptom duration, underscoring the importance of symptom recognition. Furthermore, men present at younger age and with more OHCA. Mortality in men and women was similar despite differences in presentation and clinical management.

BACKGROUND

Women are underrepresented in clinical trials across various medical fields, including cardiology (1). Consequently, treatment guidelines are mainly based on data from male patients and sex-specific reactions and effects are not always taken into account. In the case of cardiogenic shock, approximately 30% of patients are female, despite evidence suggesting that women are more susceptible to developing CS as a complication of AMI (2-5).

In addition to differences in prevalence, sex differences also exist in the presentation, treatment, and outcomes of CS. Women typically present at an older age and with more comorbidities, a pattern seen in many cardiovascular disorders (6). Furthermore, less-specific symptom presentation, later recognition and longer time to treatment in women have been described (7-9). Previous research even suggests that women are less likely to undergo revascularization and less invasive therapies such as MCS (10-12). However, the impact of these differences on mortality remains unclear. In addition, female patients tend to participate less in randomized clinical trials and are therefore even more underrepresented. Therefore, this study in a large, real-world cohort aims to comprehensively examine the sex-specific aspects of AMI-related CS, encompassing presentation, treatment strategies and clinical outcomes.

MATERIALS AND METHODS

Data collection

Data of all patients undergoing percutaneous coronary intervention (PCI) in the Netherlands are prospectively collected within The Netherlands Heart Registration (NHR). Details on medical history, procedural characteristics and outcomes are collected by trained data collectors. Additional data were collected from patients with CS undergoing PCI in one of the 14 participating hospitals in an effort to gain more detailed insights into the AMICS population. High quality of the data was assured by the quality system of the NHR that includes a detailed data dictionary, data validation checks and annual independent monitoring visits. Details on this operating procedure and on the additional registry and this cohort have been described published before (3, 13). Furthermore, mortality data were retrieved from the governmental Personal Records Database (in Dutch: *Basisregistratie Personen*).

Study population

All consecutive patients that met the criteria for shock, and underwent PCI between January 2017 and September 2021 in one of the 14 participating hospitals, were included. According to the definition of the NHR, CS was defined as: I) the presence of hypotension (a. systolic blood pressure ≤ 90 mmHg for at least 30 min or b. the need for supportive measures to maintain systolic blood pressure ≥ 90 mmHg); with II) signs of hypoperfusion of end-organs (1. cold extremities and/or 2. oliguria < 30 mL/h and/or 3. heart rate ≥ 60 beats per minute). No ethical approval was required under the Medical Research Involving Human Subjects Act (WMO) as was confirmed by the Medical research Ethics Committee (MEC-U). The outcomes of this study were threefold: to examine differences between men and women in patient characteristics; to assess differences in treatment consisting of vasoactive agents, revascularization strategies and MCS; and to evaluate differences in mortality at 30 days and 1 year.

Statistical analysis

Baseline characteristics were presented as median (25th percentile – 75th percentile) and compared with a Mann-Whitney U test in case of continuous data as all data were non-normally distributed. Discrete data were presented as numbers with percentages and tested with Chi-square / Fisher's exact test. Univariate logistic regression with sex (females vs. males) as the dependent variable was performed to assess differences in presentation characteristics. Mortality at both 30 days and 1 year was analyzed using the Kaplan Meier method with the reporting of log-rank statistics. Multivariate logistic regression analysis with sex as the dependent variable was performed to investigate the effect of sex on treatment, and on 30-day- and 1-year mortality while correcting for the following confounders: age, diabetes, prior coronary event, symptom duration, mean arterial pressure (MAP) and heart rate on admission, OHCA, etiology (ST-segment elevation myocardial infarction [STEMI] vs. NSTEMI), lactate, glucose, estimated glomerular filtration rate (eGFR), treated vessel and thrombolysis in myocardial infarction (TIMI-) flow post PCI. For the sensitivity analysis, the survival analysis were repeated in the sub cohort of patients that did not experience an OHCA. All regression analyses were performed on multiply imputed data to have maximal power. A total of 30 imputed datasets were generated by chained equation using predictive mean matching (mice, van Buuren *et al.*, v3.16.0).

All analyses were performed using R Statistical Software (v4.3.2; R Core Team 2023) and a p-value of 0.05 was considered significant throughout.

RESULTS

Baseline characteristics

Baseline characteristics of all patients with CS that underwent PCI for acute myocardial infarction (n = 2274) are presented in Table 1. The median age of the cohort was 67 (58–75) years and 614 were female (27 %). At presentation, women were older (70 vs. 66 years, $p < 0.001$) and more often had diabetes 24 % vs. 20 %, $p = 0.055$). Men more often presented with multivessel disease (62 % vs. 56 %, $p = 0.009$) and a prior MI (23 % vs. 15 %, $p < 0.001$) and PCI (19 % vs. 13 %, $p = 0.001$).

Presentation

Hemodynamics on baseline did not differ clinically in terms of MAP (87 vs. 86 mmHg, $p = 0.012$) and heart rate (83 vs. 81 beats per minute, $p = 0.232$) in men and women. The duration of symptoms was significantly longer in female patients. Even though the majority of patients in both groups presented with < 3 hours of symptoms, this proportion was larger in men (63% vs. 48%, $p < 0.001$). Most interestingly, men more frequently presented after an out-of-hospital cardiac arrest (OHCA) (46% vs. 29%, $p < 0.001$) and with higher lactate levels (6.0 vs. 5.2 mmol/L, $p = 0.063$). They were also more frequently intubated before undergoing PCI (49% vs. 45%, $p < 0.001$).

In-hospital management

All patients underwent PCI and the rate of success (defined as TIMI-flow 2 or 3 post PCI), was 91% in all patients (92% in men, 89% in women, $p = 0.077$). Men underwent more interventions in the left anterior descending coronary artery (48% vs. 40%, $p = 0.003$), whereas the right coronary artery was more often treated in women (42% vs. 36%, $p = 0.015$). Multivessel PCI was performed less in women than in men, though not statistically significant (adjusted OR 0.78, 95% CI 0.60-1.01) (see Figure 1). Fewer women received any form of vasoactive medication pre PCI (44% vs. 51%, $p = 0.003$). This difference was mainly determined by treatment with a vasopressor only (32% of women, 40% of men, $p < 0.001$). During the entire admission a larger proportion of men received noradrenaline (73% vs. 66%, $p = 0.003$) and adrenaline (41% vs. 33%, $p = 0.001$) but dobutamine, dopamine and phosphodiesterase inhibitors were more frequently administered to women. Mechanical circulatory support was used in 24% (n = 528) of all patients and this was similar in men and women. All types of MCS were less often deployed in women after correcting for relevant confounders, although this difference was only statistically significant for Impella (adjusted OR 0.57, 95% CI 0.36-0.92).

Table 1. Baseline characteristics

	Overall (N = 2274)	Male (N = 1660)	Female (N = 614)	P-value
Age – years	67.0 [58.0, 75.0]	66.0 [57.0, 74.0]	69.5 [61.0, 78.0]	< 0.001
BMI –kg/m ²	26.1 [23.9, 29.1]	26.0 [24.1, 28.8]	26.2 [23.6, 29.7]	0.418
Diabetes	451/2165 (20.8)	311/1573 (19.8)	140/592 (23.6)	0.055
Prior MI	454/2199 (20.6)	365/1603 (22.8)	89/596 (14.9)	< 0.001
Prior PCI	369/2080 (17.7)	297/1530 (19.4)	72/550 (13.1)	0.001
Prior CABG	132/2232 (5.9)	101/1629 (6.2)	31/603 (5.1)	0.4
Multivessel disease	1364/2253 (60.5)	1022/1643 (62.2)	342/610 (56.1)	0.009
Chest symptoms				
<3 hours	1150/1950 (58.9)	905/1438 (62.9)	245/514 (47.7)	< 0.001
3-24 hours	487/1950 (24.9)	315/1438 (21.9)	172/514 (33.5)	< 0.001
>24 hours	315/1950 (16.1)	218/1438 (15.2)	97/514 (18.9)	0.058
ACS etiology				0.762
STEMI	1941/2254 (86.1)	1413/1644 (85.9)	528/610 (86.6)	
NSTEMI	313/2254 (13.9)	231/1644 (14.1)	82/610 (13.4)	
OHCA	932/2263 (41.2)	753/1649 (45.7)	179/614 (29.2)	< 0.001
IHCA	284/2254 (12.6)	218/1645 (13.3)	66/609 (10.8)	0.144
Heart rate – bpm	82.0 [63.0, 101.0]	83.0 [64.0, 101.0]	80.5 [60.0, 100.0]	0.232
MAP – mmHg	86.7 [70.7, 108.0]	87.3 [72.0, 108.8]	85.5 [68.2, 106.1]	0.012
SBP – mmHg	100.0 [80.0, 124.0]	100.0 [80.0, 125.0]	99.0 [78.3, 120.0]	0.049
DBP – mmHg	60.0 [50.0, 77.0]	62.0 [50.0, 78.0]	60.0 [45.0, 73.3]	< 0.001
Hemoglobin – mmol/L	8.40 [7.40, 9.20]	8.70 [7.80, 9.40]	7.70 [6.90, 8.40]	< 0.001
eGFR – mL/min	61.1 [48.5, 75.2]	62.2 [49.8, 76.2]	57.8 [43.7, 70.9]	< 0.001
Lactate – mmol/L	5.6 [2.7, 9.4]	6.0 [2.7, 9.5]	5.2 [2.5, 8.9]	0.063

Glucose – 12.2 [8.8, 17.1] 12.4 [8.9, 17.0] 11.8 [8.8, 17.5] 0.614
mmol/L

Continuous variables are denoted as value (median[IQR]), categorical variables as number/total (%). **BMI** = Body mass index; **MI** = myocardial infarction; **PCI** = Percutaneous coronary intervention; **CABG** = Coronary artery bypass grafting; **ACS** = Acute coronary syndrome; **(N)STEMI** = (Non-)ST-elevated myocardial infarction; **OHCA** = Out-of-hospital cardiac arrest; **IHCA** = In hospital cardiac arrest; **MAP** = mean arterial pressure, **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **eGFR** = estimated glomerular filtration rate

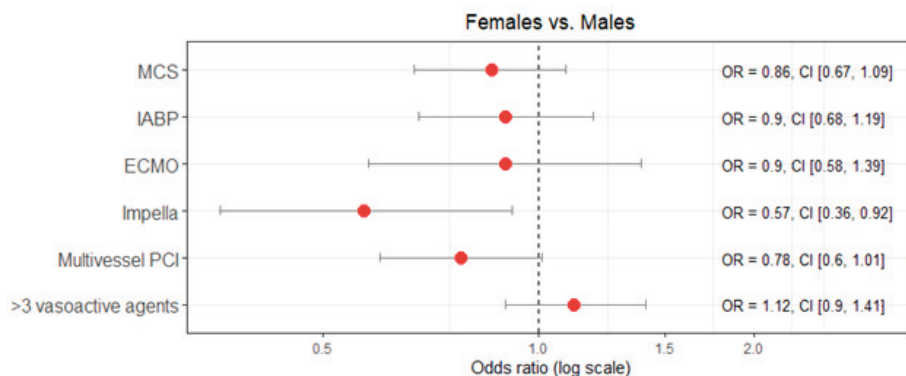
Table 2. In-hospital management

	Overall (N = 2274)	Male (N = 1660)	Female (N = 614)	p-value
Intubated pre PCI	1019/2253 (45.2)	807/1642 (49.1)	212/611 (34.7)	< 0.001
Vasoactive agent pre PCI				0.003
None	1119/2201 (50.8)	783/1603 (48.8)	336/509 (56.2)	< 0.001
Inotrope	35/2201 (1.6)	23/1603 (1.4)	12/509 (2.0)	0.155
Vasopressor	831/2201 (37.8)	642/1603 (40.0)	189/509 (31.6)	< 0.001
Inotrope + vasopressor	216/2201 (9.8)	155/1603 (9.7)	61/509 (10.2)	0.133
PCI access site				
Femoral	1008/2000 (50.4)	709/1478 (48.0)	299/522 (57.3)	<0.001
Radial	984/2000 (49.2)	764/1478 (51.7)	220/522 (42.1)	<0.001
Other	8/2000 (0.4)	5/1478 (0.3)	3/522 (0.6)	0.462
TIMI pre PCI				
0/1	1466/1912 (76.7)	1062/1402 (75.7)	404/510 (79.2)	0.113
2	207/1912 (10.8)	152/1402 (10.8)	55/510 (10.8)	0.975
3	239/1912 (12.5)	188/1402 (13.4)	51/510 (10.0)	0.046
TIMI post PCI				
0/1	179/1954 (9.1)	120/1424 (8.4)	59/530 (11)	0.065
2	189/1954 (9.7)	136/1424 9.6)	53/530 (10.0)	0.766
3	1586/1954 (81.2)	1168/1424 (82.0)	418/530 (78.9)	0.113

Table 2 Continued

	Overall (N = 2274)	Male (N = 1660)	Female (N = 614)	p-value
Treated vessel				
LM	286/2060 (13.9)	209/1518 (13.8)	77/542 (14.2)	0.856
LAD	938/2060 (45.5)	721/1518 (47.5)	217/542 (40.0)	0.003
RCA	775/2060 (37.6)	547/1518 (36.0)	228/542 (42.1)	0.015
RCX	464/2060 (22.5)	350/1518 (23.1)	114/542 (21.0)	0.364
Multivessel PCI	348/1364 (25.5)	270/1022 (26.4)	78/342 (22.8)	0.185
MCS	528/2250 (23.5)	394/1640 (24.0)	134/610 (22.0)	0.333
IABP	332/2250 (14.8)	244/1640 (14.9)	88/610 (14.4)	0.84
ECMO	161/2250 (7.2)	125/1640 (7.6)	36/610 (5.9)	0.188
Impella	125/2250 (5.6)	100/1640 (6.1)	25/610 (4.1)	0.082
Invasive hemodynamic monitoring	150/2086 (7.2)	113/1523 (7.4)	37/563 (6.6)	0.506
No. of inotropes				
0	431/2141 (20.1)	298/1560 (19.1)	133/581 (22.9)	0.052
1	542/2141 (25.3)	406/1560 (26.0)	136/581 (23.4)	0.216
2	694/2141 (32.4)	500/1560 (32.1)	194/581 (33.4)	0.556
≥ 3	474/2141 (22.1)	356/1560 (22.8)	118/581 (20.3)	0.213

All variables as number/total (%). **PCI** = Percutaneous coronary intervention; **TIMI** = Thrombolysis in myocardial infarction flow grade; **LM** = Left main coronary artery; **LAD** = Left anterior descending coronary artery; **RCA** = Right coronary artery; **RCX** = Circumflex coronary artery; **MCS** = Mechanical circulatory support; **IABP** = Intra-aortic balloon pump; **ECMO** = Extracorporeal membrane oxygenation; **No. of inotropes** = Total number of inotropes / vasopressors from presentation to admission (from: noradrenalin, adrenalin, dobutamine, dopamine and milrinone/enoximone).

Figure 1. Adjusted odds ratios for treatment

IABP = Intra-aortic balloon pump; **ECMO** = extra corporeal membrane oxygenation; **PCI** = percutaneous coronary intervention. Odds ratios are adjusted for the following covariables: age, diabetes, prior coronary event, out-of-hospital cardiac arrest, symptom duration, etiology of myocardial infarction, mean arterial pressure, heart rate, lactate, glucose, estimated glomerular filtration rate treated vessel and TIMI flow after PCI.

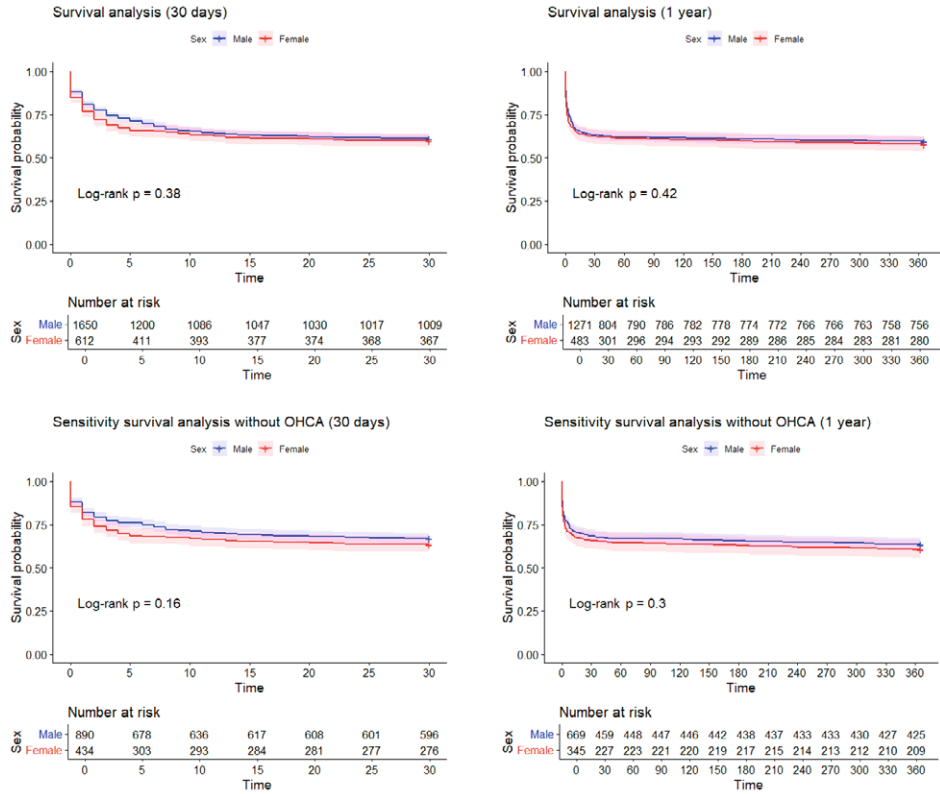
Outcomes

Overall mortality at 30-days was 39% (n = 886) and no association with sex was observed (p = 0.98). These results persisted after one year with a mortality rate of 44% (n = 718, 44% and 46% in men and women respectively, p = 0.98) (see Figure 2). A non-statistically significant lower mortality in women was seen after adjusting for relevant confounding on both 30 days (adjusted OR 0.92, 95% CI 0.73-1.17) and 1 year (adjusted OR 0.91, 95% CI 0.70-1.17) (see Figure 3).

Sensitivity analysis OHCA

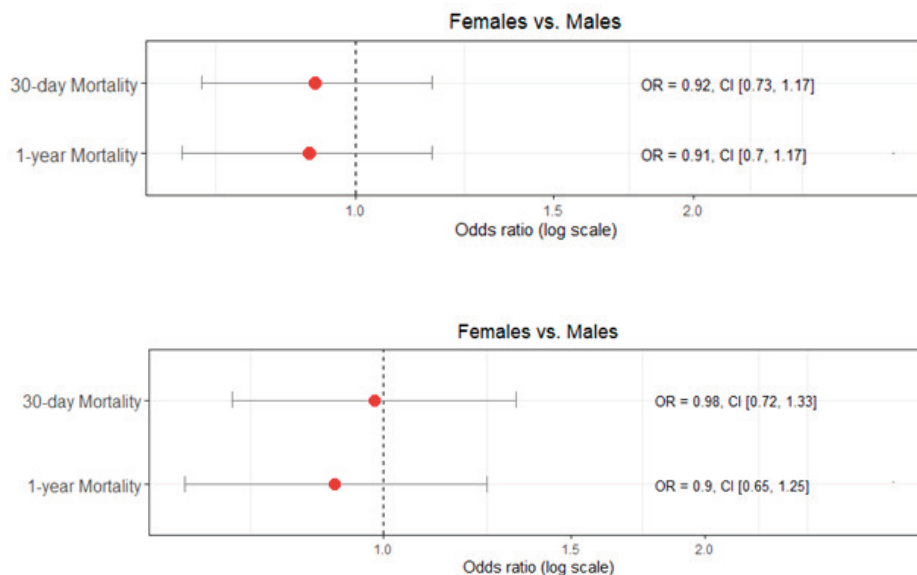
Baseline characteristics for patients that presented without OHCA only were similar to those of the entire cohort. Also here, women were older (71 vs. 69 years, p < 0.001) and the proportion of women with short symptom duration was smaller (42% vs. 51%, p = 0.009). The rate of successful revascularization (TIMI flow 2/3 after PCI) was 90% and this was similar for men and women. Mortality in non-OHCA patients was 34% and 40% at 30 days and 1 year respectively, without a sex-association (see Figure 2C/D). No difference in mortality between sexes was seen after adjustment for relevant confounders (see Figure 3B). All details of the sensitivity analysis can be found in Supplementary Table 1.

Figure 2. Survival curves



For all patients at 30-days (A) and 1 year (B) and for patients without OHCA at 30 days (C) and 1 year (D)

Figure 3. Adjusted odds ratios for mortality for all patients (A) and patients without OHCA (B)



Odds ratios are adjusted for the following covariables: age, diabetes, prior coronary event, out-of-hospital cardiac arrest (panel A only), symptom duration, etiology of myocardial infarction, mean arterial pressure, heart rate, lactate, glucose, estimated glomerular filtration rate treated vessel and TIMI flow after PCI.

DISCUSSION

In this large national contemporary cohort we described sex-specific baseline characteristics, therapeutic strategies and clinical outcomes of an AMI-CS population undergoing PCI. The following important lessons can be learned from the current study: first, women have longer symptom duration prior to PCI. Second, women present at older age and with higher prevalence of renal failure but men have a more extensive history of coronary artery disease. Third, OHCA's are much more frequently observed in male patients. And lastly, both short-term and long-term mortality are similar despite the aforementioned differences in risk profiles and treatment.

Coronary artery disease is often more profound in men compared to women, and men generally develop more efficient collateral circulation (14). This disparity may contribute to the increased susceptibility of women to develop CS as a complication of AMI. Despite this observation, likely resulting in a reduced reserve in women, they constitute only 30% of the overall AMICS population (2-5). Additionally, women are typically older and more frequently present with diabetes at the time of presentation, whereas men have a more extensive history of myocardial infarction and percutaneous coronary interventions (15-17). These differences in demographic and clinical characteristics were also present in our current cohort where the median age at presentation differed 4 years (70 vs. 66), women had diabetes more often (24% vs. 20%) and a prior MI was more prevalent in men (23% vs. 15%). The higher incidence of OHCA in men has previously been described (4). However, the actual difference might be smaller, as women generally have lower chances of being resuscitated following cardiac arrest, which subsequently reduces their likelihood of surviving until PCI (18).

Several differences in treatment strategies have been described in previous research, even though sex-specific recommendations are absent in the current guidelines. For instance, sex differences in the use of vasoactive medication have been reported (4). Additionally, increased use of intra-aortic balloon pumps (IABP), extracorporeal membrane oxygenation (ECMO), and Impella devices was reported by Thangam et al. (10). In our registry, we found an increased use of vasopressors before PCI in men that was largely contributable to the higher rate of OHCA in male patients. With regards to MCS, a trend towards increased use in men was observed for all types of devices. Beneficial anatomy with larger vessels is likely to influence clinical decision making with regards

to MCS placement. Higher rates of revascularization in men have frequently been observed in AMI patients with or without CS (12, 16, 17, 19, 20). Higher reported mortality in women makes sense if they received less PCI, considering primary PCI in still the cornerstone treatment in AMICS (21, 22). By design, this difference was absent in our cohort that only included patients undergoing PCI. We found non-significant differences between sexes to the disadvantage of women in both 30-day and 1-year mortality respectively. However, when adjusted for relevant confounders the odds ratio for women was slightly lower for both 30-day and 1-year mortality in both the complete – and the sensitivity analysis. Thus, for the unadjusted analyses it could be suggested that women perform just as well (or poorly) as men, despite their higher age and different profiles. Additionally, the observed trend towards increased rate of multivessel PCI and MCS suggests that male patients receive slightly more

aggressive therapy. Nonetheless, these observations should be interpreted with caution, as they represent only a trend and are not statistically significant.

Clinical implications

The current results show room for improvement with regards to awareness and recognition in women. The time between symptom onset and revascularization should be minimized in women to align with that of men as immediate revascularization is still the cornerstone treatment for AMICS. Furthermore, men seem more prone to be exposed to non-evidence based therapies, specifically MCS and multivessel PCI. The efficacy of Impella support has only been demonstrated in a very selected AMICS population (23). Similarly, a culprit-only revascularization strategy became the default after the results of the CULPRIT-SHOCK trial in 2017 (24). The observed pattern underscores the importance for clinicians to be aware of sex-based disparities in patient awareness, symptom recognition, and treatment modalities.

Strengths and limitations

This research was done with data from a real-world cohort including a large number of consecutive patients from a national PCI registry. Data were collected with high-quality standards and selection bias could be avoided as no consent from participants was needed due to the registry-based nature of the study. Missing data were handled properly using multiple imputation for the regression analyses. This study deals with all the limitations inherently present in any observational study. The possibility of residual confounding in the regression analyses was mitigated by correcting for confounders but can never be deleted. Furthermore, a more detailed comparison of outcomes including complication could not be provided as these data were not collected.

Conclusion

This study demonstrated differences in clinical presentation, comorbidities and therapeutic strategies between men and women presenting with CS. Importantly, women present after significantly longer duration of symptoms underscoring the importance of symptom recognition in women, who also presented at higher age. Men were more frequently subjected to an out-of-hospital cardiac arrest and had a more extensive history of ischemic heart disease, and received more aggressive treatment. Mortality in men and women was similar despite the aforementioned differences in demographics and clinical management.

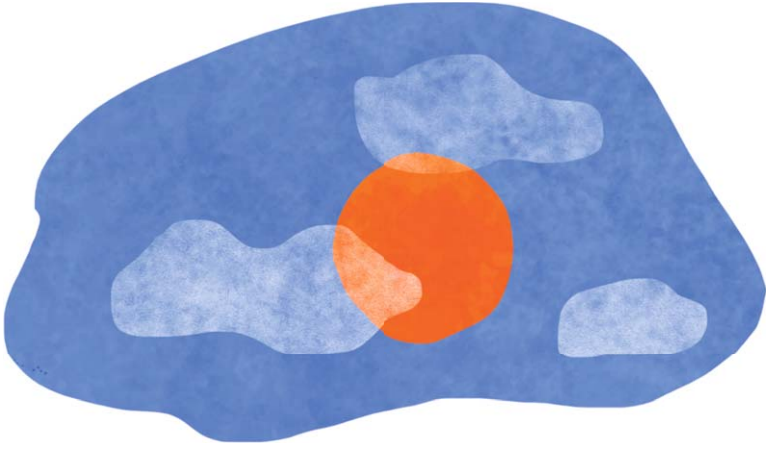
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D

Therapeutic evaluations



Chapter 5

Radial Access for PCI in Acute Myocardial Infarction Related Cardiogenic Shock Underused, Underappreciated?

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The preferred vascular access site for percutaneous coronary intervention (PCI) has been shifting from transfemoral access (TFA) to transradial access (TRA) ever since TRA was first described in 1993.(1) Use of the radial approach has resulted in an impressive reduction of bleeding and vascular complications, which subsequently translates into reductions in acute kidney injury and even mortality. (2) Patients presenting with acute myocardial infarction (AMI) are at the heightened risk for access-site bleeding because of upstream treatment with heparin and dual antiplatelet therapy. Therefore, it is not surprising that the clinical benefits of TRA over TFA appear to be most pronounced in patients with AMI, as shown by a large-scale meta-analysis.(2) Nevertheless, as patients with AMI presenting with cardiogenic shock (CS) have typically been excluded from randomized controlled trials of TRA vs TFA, it remains unknown whether the benefits also apply to this extreme- risk subgroup. Several considerations specific to the symptoms and signs of CS may intuitively favor TFA. Because of the compromised hemodynamic status with which patients with CS present, identification of a very subtle or even an absent radial pulse may be considered too time consuming. Moreover, TFA may facilitate rapid sheath upsizing to large-bore access to insert mechanical circulatory support (MCS) devices. Conversely, these hemodynamically unstable patients (in a precarious condition with a 10-fold higher mortality rate than patients in stable condition) might receive more benefit from the prevention of cardiovascular complications by using TRA. This knowledge gap is reflected in current societal guidelines. Whereas the guidelines clearly favor TRA in acute coronary syndromes without hemodynamic instability, the CS guideline is unclear on this topic and states that “radial arterial access may be challenging in hypotensive patients with CS”, so that approximately only one-half of patients with CS are treated using TRA PCI.(3-5)

In this issue of *JACC: Cardiovascular Interventions*, Mahtta et al present the results of a comprehensive registry- based cohort study that investigated whether characteristics and outcomes differ for TRA vs TFA among patients undergoing PCI for AMI complicated by CS.(6) A total of 35,944 patients with AMI CS undergoing PCI were included. Of these, 9,194 underwent TRA PCI, representing 25.6% of the population. Patients undergoing TRA PCI had a significantly lower frequency of in-hospital major bleeding (OR: 0.71; 95% CI: 0.67-0.76), mortality (OR: 0.73; 95% CI: 0.69-0.78), vascular complications (OR: 0.67; 95% CI: 0.54-0.84), and new dialysis (OR: 0.86; 95% CI: 0.77-0.97). These results were adjusted for a variety of factors, including age, sex, body mass index, preprocedural hemoglobin and thrombolysis In myocardial infarction (TIMI) flow grade, number of diseased vessels, and Society for Cardiovascular Angiography and Interventions (SCAI) lesion class.

Although the investigators adjusted their results for many clinically significant potential confounders, the lack of comprehensive information on the patients' acute condition appears to be the Achilles' heel of this study. This precludes estimation of the severity of illness and shock stage of patients included. This is of particular importance as the observed mortality in this study is relatively low; in the low 20% range while many other studies report mortality rates of $\geq 50\%$.⁽⁷⁾ Moreover, almost 30% of patients in the study did not receive vasopressors or inotropes. Unfortunately, the authors did not specify the relative proportions of patients receiving vasopressors or inotropes and/or MCS in the TFA and TRA group. This could have provided some insight into the relative "depth" of shock in both groups. The authors did however report that there was no significant interaction between access site and use of MCS for any of the endpoints studied. This is somewhat surprising given that MCS requires femoral access, even in patients in whom the PCI was performed transradially. None of the acute markers of disease are taken into account and even though comorbidities do play a role in CS prognosis, it is clear from common risk stratification tools that acute markers are at least equally, if not more important.⁽⁸⁾ And probably this exact estimation of a patient's acute condition, plays a crucial role in guiding clinical decision-making, including the choice of arterial access site.

Mahtta et al are not the first researchers to demonstrate that using TRA in CS patients is associated with lower rates of vascular complications and mortality. Similar results have been published from other observational cohorts and one meta-analysis that addressed this topic.⁽⁹⁾ This meta-analysis teaches us that, in studies where details on hemodynamics were available, the TFA and TRA populations were not comparable at baseline. In general, TFA patients were older and more often were supported by an intra-aortic balloon pump (IABP), inotropes and mechanical ventilation. This provides more grounds to suspect that an indication bias may be an important confounder for the current study where patients in "deeper" CS may have preferentially been treated transfemorally.

Despite the obvious but inevitable limitations that come with observational research, the current study by Mahtta et al adds further robustness to the available evidence that TRA, when feasible, is safer than TFA, including in the setting of AMI-CS. This contemporary study also shows that a striking institutional variation still exists regarding the arterial access site. However, an encouraging trend towards a larger proportion of TRA was observed during the 3-year study period. Therefore, the current study may serve as a further incentive to the adoption of TRA over TFA across the entire spectrum of indications for PCI.

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Chapter 6

Characteristics and outcome in cardiogenic shock according to vascular access site for percutaneous coronary intervention *Femoral vs. radial access in AMI-CS*

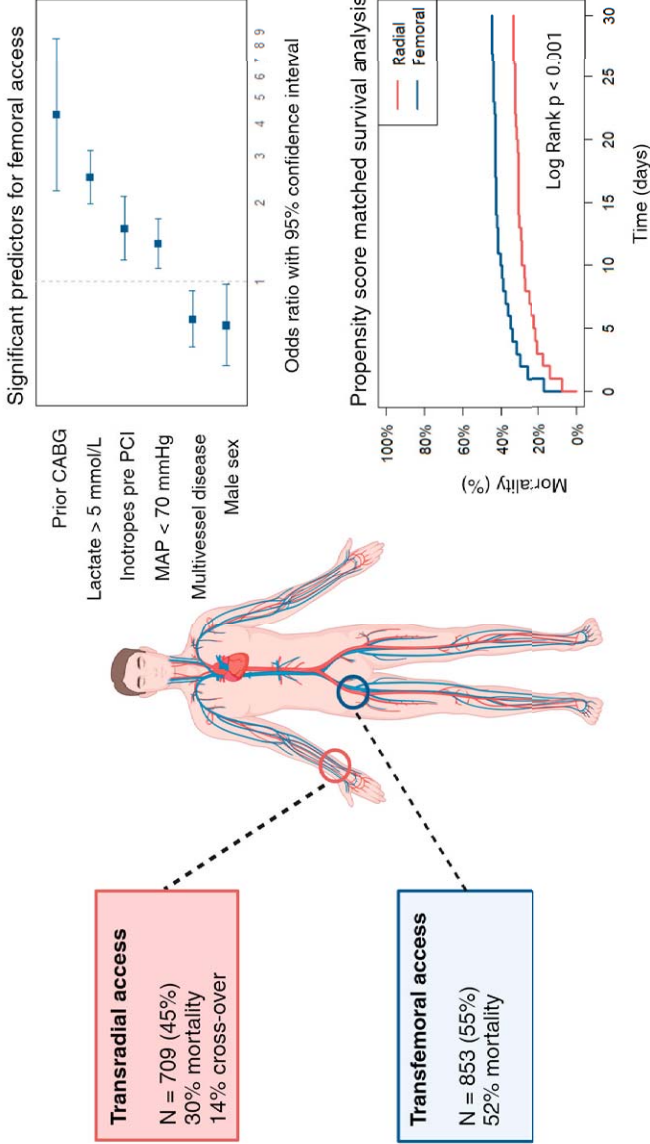
Elma J Peters, Margriet Bogerd, Sanne Ten Berg, Marijke J C Timmermans, Annemarie E Engström, Holger Thiele, Christian Jung, Benedikt Schrage, Krischan D Sjauw, Niels J W Verouden, Koen Teeuwen, Admir Dedic, Martijn Meuwissen, Peter W Danse, Bimmer E P M Claessen, José P S Henriques; Participating Centers of the PCI Registration Committee of the Netherlands Heart Registration

* The last two authors contributed equally to the study

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GRAPHICAL ABSTRACT

Study cohort, predictors for femoral access and propensity score matched survival analysis.



CABG = Coronary artery bypass grafting; **MAP** = Mean arterial pressure. Created with BioRender.com

ABSTRACT

Background

The optimal vascular access site for percutaneous coronary interventions (PCIs) in patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) remains uncertain. While observational data favor transradial access (TRA) due to lower complication rates and mortality, transfemoral access (TFA) PCI offers advantages such as shorter access and procedure times, along with quicker escalation to mechanical circulatory support (MCS). In this study, we aimed to investigate factors associated with a transfemoral approach and compare mortality rates between TRA and TFA in AMI-CS patients undergoing PCI.

Methods and results

Data from a nationwide registry of AMI-CS patients undergoing PCI (2017-2021) were analyzed. We compared patient demographics, procedural details, and outcomes between TRA and TFA groups. Logistic regression identified access site factors and radial-to-femoral crossover predictors. Propensity score-matched (PSM) analysis examined the impact of access site on mortality.

Of the 1562 patients, 45% underwent TRA PCI, with an increasing trend over time. Transfemoral access patients were more often female, had a history of coronary artery bypass grafting, lower blood pressure, higher resuscitation and intubation rates, and elevated lactate levels. After PSM, 30-day mortality was lower in TRA (33% vs. 46%, $P < 0.001$). Predictors for crossover included left coronary artery interventions, multivessel PCI, and MCS initiation.

Conclusion

Significant differences exist between TRA and TFA PCI in AMI-CS. Transfemoral access was more common in patients with worse hemodynamics and was associated with higher 30-day mortality compared with TRA. This mortality difference persisted in the PSM analysis.

INTRODUCTION

Percutaneous coronary intervention (PCI) has traditionally predominantly been performed via the transfemoral access (TFA) route. However, radial access has gained momentum since its description as an alternative technique in 1993(1). Specific anatomical advantages of the radial artery, such as its superficial location which conveniently allows for easy and effective compression, result in significantly fewer vascular complications and access site bleeding compared with the femoral artery. The reduction in access site complications, in turn, manifested as a decrease in acute kidney injury and even mortality compared with TFA (2, 3). Transradial access (TRA) therefore became the preferred and recommended approach for PCI, in particular for patients with acute myocardial infarction (AMI) (4, 5).

Limited randomized evidence is available on the treatment of AMI that is complicated by cardiogenic shock (CS), but since the results of the SHOCK trial have been published in 1999, early revascularization has established its place in all treatment guidelines (6-8). However, there is an ongoing debate on the optimal vascular approach in these critically ill patients. It has been repeatedly suggested that also in CS, TRA is associated with a reduction in complications (9). Unfortunately, all studies aiming to compare outcomes between the two vascular access sites are subject to indication as operators may tend to choose TFA more often in sicker patients. Reasons for this include the possibility for upscaling to large-bore access to facilitate mechanical circulatory support (MCS) insertion and the fact that the femoral artery may be easier to identify than the radial artery, especially in patients with low blood pressures.

To address this issue, we analyzed data from the Netherlands Heart Registration (NHR) where the access site is provided in PCI procedures for CS. We aimed to provide insights into patient characteristics and clinical outcome in CS patients undergoing PCI through either TRA or TFA. Furthermore, we investigated the temporal trend in choice of access site and the factors that are associated with radial-to-femoral crossover during the procedure.

METHODS

Data source, endpoints, and follow-up

The NHR is a nationwide registry in which patient-, procedural- and outcome level data on all PCIs performed in the Netherlands are prospectively registered (10).

Data collection is performed up to high-quality standards (11). In 14 Dutch hospitals, additional data were retrospectively collected in patients with CS undergoing PCI. This process has previously been described in detail elsewhere (12). No ethical approval was required under the Medical Research Involving Human Subjects Act (WMO) as was confirmed by the Medical Research Ethics Committees United (MEC-U). Information on mortality at 30 days and 1 year was collected using the Dutch Personal Records Database (Statistics Netherlands, The Hague, The Netherlands).

Study population

Eligible patients underwent PCI between January 2017 and September 2021 in 1 of the 14 hospitals of the NHR CS registry. Patients were included in the current study if they fulfilled the NHR criteria of CS, where CS is defined as follows: (i) the presence of hypotension (systolic blood pressure [SBP] ≤ 90 mmHg for ≥ 30 min or support to maintain SBP ≥ 90 mmHg) and ii) end-organ hypoperfusion (cold extremities and/or oliguria <30 mL/h and/or tachycardia ≥ 60 b.p.m.). Patients were excluded from the analysis if (i) the arterial access site for PCI was unknown, or other than femoral or radial; or if (ii) shock symptoms developed during or after PCI but not prior to the start of the procedure. All procedural steps, including revascularization strategy, anti-coagulation, and anti-thrombotic therapy, were carried out in accordance with local protocols.

Statistical analysis

The baseline patient- and procedure-level characteristics and mortality rates were compared between TRA and TFA procedures. Categorical data were presented as numbers/total numbers and percentages and compared using the χ^2 test. Numerical data were displayed as medians with interquartile range (IQR) and compared using the Mann-Whitney U test or as means with standard deviation and compared with a *t*-test, depending on normality.

Univariate logistic regression analyses were performed to investigate the association between patient characteristics and choice of vascular access site and crossover. All explanatory variables from Table 1 were considered for the regression analysis but only included in the multivariable model if univariate regression was significant at a P level of 0.10. No multivariable logistic regression was done for the crossover analysis due to the relatively small number of events.

For the crossover analysis, continuous variables were dichotomized using the point closest to the upper left corner of the receiver operating characteristic

(ROC) curve as the cut-off (13). Crossover was defined as the transition from radial to femoral access within the same procedure. To ensure maximal power, all regression analyses were done on multiple imputed data. Five imputed datasets were generated by means of predictive mean matching to account for missing data.

Survival was analyzed at 30 days and 1 year using the Kaplan Meier method and compared between TRA and TFA using the log-rank statistic. A propensity score-matched (PSM) analysis was performed to investigate the impact of access site on 30-day mortality. Propensity scores were calculated using all available patient-level characteristics. Calculations were done in five multiple imputed data sets using the nearest method with a caliper of 0.10. Subsequently, the propensity scores were remerged into the data set with missing data, and TRA patients were matched to TFA patients in a 1:1 ratio. This resulted in 507 matches.

A sensitivity analysis for patients who did not receive any form of MCS before or during their stay in the catheterization laboratory was done for the baseline characteristics. An additional analysis of baseline characteristics was performed including patients who developed CS during or directly after the PCI procedure as these patients may in fact already be in some state of shock.

Furthermore, temporal trends were analyzed using the Mann Kendall test. The year 2017 was excluded from the temporary trend analysis due to incomplete registration of the primary access site in this year. Additionally, the crossover analysis only included patients treated from 2019 onwards since the registration of a second access route was not mandatory in 2017 and 2018.

Baseline and regression analyses were performed with IBM SPSS Statistics version 28.0 (IBM corporation, Armonk, NY, USA). The PSM analysis was performed using R (2022, Vienna, Austria), with packages mice (v3.15; Van Buuren and Groothuis-Oudshoorn; 2011), MatchThem (v1.1; Pihgar *et al.*; 2021) and MatchIt (v4.5.5; Ho *et al.*; 2011). All R packages utilized in this study are detailed in the online supplement.

RESULTS

Baseline

A total of 2328 patients were identified who had CS and underwent PCI between January 2017 and September 2021. Of these, 283 patients were excluded from the analysis because the primary vascular access site was either unknown or other

than radial or femoral. We specifically investigated the differences between TRA and TFA in patients with CS before PCI. For the primary analysis, we therefore excluded patients who developed shock during or after the PCI procedure ($n = 483$). Consequently, this cohort consists of 1562 patients with CS before PCI.

As shown in Table 1, the median age in the entire cohort was 67 (IQR 58 – 75) years, and 1150 patients (74%) were male. The mean arterial pressure upon arrival in the hospital was 71 mmHg with a median systolic pressure of 94 mmHg. Roughly 60% of patients were treated with at least one inotrope or vasopressor. Of all patients, 324 (22%) had a history of diabetes and 916 (59%) had multivessel coronary artery disease. Furthermore, 794 patients (51%) were resuscitated prior to the PCI.

Access site

The primary vascular access site was femoral in 853 of patients (55%) and radial in 709 patients (45%). Whereas TRA was used in 39% of AMICS PCIs in 2018, a significant increase was seen to 47% in 2021 ($P = 0.04$). In 77 patients (14%) with initial radial arterial access, crossover to the femoral artery occurred during the procedure. Patients who underwent TFA PCI differed from the TRA patients in several aspects. In TFA patients, a history of CABG was more prevalent (10% vs. 2%, $P < 0.001$), and the hospital presentation was more often preceded by a cardiac arrest (56% vs. 45%, $P < 0.001$). In general, TFA patients presented with worse hemodynamics: they had a lower blood pressure on presentation and increased levels of markers of organ hypoperfusion such as lactate and creatinine. The rate of vasoactive medication use before the PCI was also significantly higher than in the TRA group (68% vs. 47% received at least one inotrope or vasopressor before PCI, $P < 0.001$). Multivariate logistic regression revealed multiple factors that were significantly associated with the choice for TFA after correction for relevant confounders. These factors included sex, a history of CABG, presence of multivessel disease, a lower MAP, a higher blood lactate level, and the administration of inotropes before PCI (see Table 2). These results persisted when patients that developed shock during or after PCI were added to the analysis (see Supplementary material online, Table S1). The distribution of patient characteristics and comorbidities showed a similar pattern even though the proportion of patients treated by TRA (1013/2045, 50%) was slightly increased in this sensitivity analysis. Patients who underwent TFA PCI had a significantly higher unadjusted mortality rate at 30 days: 47% vs. 26% ($P < 0.001$) in TRA. This difference was also present at 1 year: 55% vs. 36% ($P < 0.001$). The difference in mortality rates was also seen in the PSM analysis: 46% vs. 33% ($P < 0.001$) (see Figure 1 and Table 3).

Table 1. Baseline characteristics of all patients with shock pre PCI

	All N = 1562	Radial access N = 709	Femoral access N = 853	P-value
Baseline and medical history				
Age – years	67 (58-75)	67 (58-74)	67 (58-76)	0.302
Male sex – n (%)	1150 (74)	551 (78)	599 (70)	<0.001
BMI – kg/m ²	26 (24-29)	26 (24-29)	26 (24-29)	0.929
Height – cm	175 (168 – 180)	175 (170 – 180)	175 (167 – 180)	0.023
Medical history – n/N (%)				
<i>Diabetes</i>	324/1480 (22)	136/687 (20)	188/793(24)	0.070
<i>Multivessel disease</i>	916/1554 (59)	435/706 (62)	481/848 (57)	0.051
<i>Prior CABG</i>	96/1536 (6)	17/703 (2)	79/833 (10)	<0.001
<i>Prior MI</i>	324/1510 (21)	134/695 (19)	190/815 (23)	0.057
<i>Prior PCI</i>	267/1514 (18)	114/698 (16)	153/816 (19)	0.219
Current presentation				
MAP – mmHg	71 (58-89)	73 (61-91)	70 (55-87)	<0.001
Heart rate – bpm	83 (61-104)	82 (63-105)	85 (60-103)	0.702
SOFA score	10 (8-12)	10 (7-12)	10 (8-13)	0.054
No. of inotropes – n/N (%)				
0	627/1494 (42)	366/687 (53)	261/807 (32)	<0.001
1	456/1494 (31)	173/687 (25)	283/807 (35)	<0.001
2	325/1494 (22)	115/687 (17)	210/807 (26)	<0.001
>=3	86/1494 (7)	33/687 (5)	53/807(7)	0.145
Etiology – n/N (%)				
<i>STEMI</i>	1314/1550 (85)	587/703 (83)	727/847 (86)	0.203
<i>NSTEMI</i>	208/1550 (13)	102/703 (15)	106/847 (13)	0.251
Symptoms > 24 h – n/N (%)	231/1347 (17)	96/628 (15)	135/719 (19)	0.090
Resuscitated – n/N (%)	794/1556 (51)	315/707 (45)	479/849 (56)	<0.001
Intubated – n/N (%)	786/1557 (51)	287/706 (41)	499/851 (59)	<0.001

	All N = 1562	Radial access N = 709	Femoral access N = 853	P-value
Laboratory values				
Glucose – mmol/L	12.4 (9.2 – 17.4)	11.3 (8.7-15.5)	13.5 (9.8-19.1)	<0.001
Lactate – mmol/L	6.0 (2.8-9.8)	4.4 (2.3-8.0)	6.8 (3.5-11)	<0.001
Hemoglobine mmol/L	8.4 (7.3-9.2)	8.5 (7.5-9.3)	8.2 (7.2-9.1)	0.002
eGFR – mL/min	60 (47-74)	63 (49-78)	58 (45-70)	<0.001
Mechanical circulatory support				
None – n/N (%)	1143/1513 (76)	533/676 (79)	610/837 (73)	0.007
Before PCI – n/N (%)	161/1513 (11)	59/676 (9)	102/837 (12)	0.030
In cath lab, after PCI – n/N (%)	174/1513 (12)	69/676 (10)	105/837 (13)	0.156
Outcome				
30-d mortality – n/N (%)	650/1550 (42)	209/702 (30)	441/848 (52)	<0.001
1-y mortality – n/N (%)	500/1076 (46)	176/487 (36)	324/589 (55)	<0.001

Values are median (interquartile range) unless indicated otherwise. **BMI** = body mass index; **CABG** = coronary artery bypass grafting; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **MAP** = mean arterial pressure; **bpm** = beats per minute; **Inotropes** included the following agents initiated prior to PCI: noradrenaline, adrenaline, dobutamine, dopamine, milrinon / enoximone; **STEMI** = ST-elevation myocardial infarction; **NSTEMI** = non ST-elevation myocardial infarction; **Resuscitated** = either in- or out of hospital cardiac arrest pre PCI

TABLE 2. Univariate and multivariate logistic regression for femoral access in all patients with shock pre-percutaneous coronary intervention

	OR univariate		OR multivariate		P-value	95% CI	P-value	95% CI	P-value
	OR	95% CI	OR	95% CI					
Year (reference 2021)									
2020	0.973	0.736 – 1.287	0.943	0.683 – 1.302	0.848	0.683 – 1.302	0.720		
2019	1.095	0.821 – 1.460	1.120	0.803 – 1.562	0.538	0.803 – 1.562	0.505		
2018	1.384	1.010 – 1.8698	1.321	0.921 – 1.894	0.043	0.921 – 1.894	0.131		
2017	0.736	0.451 – 1.203	0.515	0.263 – 1.008	0.219	0.263 – 1.008	0.053		
Age	1.004	0.996 – 1.012			0.378				
Male sex	0.674	0.536 – 0.848	<u>0.681</u>	<u>0.477 – 0.972</u>	<0.001		<u>0.034</u>		
BMI	1.005	0.991 – 1.020			0.449				
Height	0.984	0.974 – 0.995	0.988	0.971 – 1.004	0.003		0.143		
Diabetes mellitus	1.262	0.982 – 1.623	0.907	0.663 – 1.241	0.069		0.541		
Prior CABG	4.053	2.335 – 7.034	<u>4.227</u>	<u>2.158 – 8.280</u>	<0.001		<u><0.001</u>		
Prior MI	1.277	0.999 – 1.631	1.301	0.957 – 1.769	0.051		0.093		
Prior PCI	1.188	0.911 – 1.550			0.203				
Multivessel disease	0.823	0.671 – 1.010	<u>0.730</u>	<u>0.572 – 0.930</u>	0.062		<u>0.011</u>		
Intubated pre PCI	2.058	1.681 – 2.519	1.330	0.916 – 1.931	<0.001		0.134		
Resuscitated	1.611	1.317 – 1.970	1.033	0.730 – 1.462	<0.001		0.852		
STEMI (vs. NSTEMI)	1.226	0.916 – 1.642			0.170				
MAP	0.993	0.988 – 0.997	<u>0.992</u>	<u>0.987 – 0.997</u>	<0.001		<u>0.003</u>		
Heart rate	0.999	0.995 – 1.003			0.690				

SOFA	1.099	1.040 – 1.161	0.003	1.049	0.972 – 1.132	0.194
Inotropes pre (yes/no)	2.314	1.889 – 2.835	<0.001	<u>1.466</u>	<u>1.098 – 1.958</u>	<u>0.010</u>
Duration of symptoms						
< 3 h	0.946	0.755 – 1.187	0.629			
> 24 h	1.271	0.964 – 1.671	0.089	1.214	0.852 – 1.732	0.282
Lactate	1.128	1.100 – 1.156	<0.001	<u>1.087</u>	<u>1.052 – 1.123</u>	<0.001
Glucose	1.062	1.044 – 1.081	<0.001	1.015	0.991 – 1.040	0.217
Hemoglobin	0.897	0.836 – 0.963	0.003	0.947	0.861 – 1.041	0.259
eGFR	0.991	0.987 – 0.995	<0.001	0.996	0.996 – 1.000	0.073
MCS before PCI	1.439	1.009 – 2.052	0.044	1.062	0.684 – 1.649	0.787

BMI = body mass index, per kg/m²; Height per cm; **CABG** = Coronary artery bypass grafting; **MI** = Myocardial infarction; **PCI** = Percutaneous coronary intervention; **STEMI** = ST-elevation myocardial infarction; **MAP** = Mean arterial pressure, per mmHg; **SOFA** = Sequential organ failure assessment, per point; Lactate per mmol/L; Glucose per mmol/L; Hemoglobin per mmol/L; eGFR per mL/min

Table 3. Characteristics matched cohort

	All N = 1014	Radial access N = 507	Femoral access N = 507	p-value
Baseline and medical history				
Year – n (%)				0.503
2017	47 (5)	22 (4)	25 (5)	
2018	170 (17)	93 (18)	77 (15)	
2019	264 (26)	122 (24)	142 (28)	
2020	304 (30)	155 (31)	149 (29)	
2021	229 (23)	115 (23)	114 (23)	
Age - years	67 (58 – 75)	67 (58 – 75)	67 (59 – 75)	0.989
Male sex – n (%)	761 (75)	380 (75)	381 (75)	1.000
BMI – kg/m ²	26 (24 – 29)	26 (24 – 29)	26 (24 – 29)	0.802
Diabetes – n/N (%)	204/960 (21)	102/489 (21)	102/471 (22)	0.824
Prior coronary event – n/N (%)	256/977 (26)	133/496 (27)	123/481 (26)	0.712
Multivessel disease – n/N (%)	588/1009 (58)	291/505 (58)	297/504 (59)	0.722
Current presentation				
Resuscitated – n/N (%)	513/1009 (51)	254/505 (50)	259/504 (51)	0.776
STEMI – n/N (%)	856/1007 (85)	427/504 (85)	429/503 (85)	0.870
MAP - mmHg	70 (57 – 87)	70 (59 – 87)	70 (54 – 88)	0.312
Heart rate - bpm	84 (60 – 105)	82 (61 – 104)	85 (60 – 105)	0.652
SOFA score	10 (8 – 12)	10 (8 – 12)	9 (8 – 12)	0.489
Symptoms > 24 h – n/N (%)	137/881 (16)	72/447 (16)	65/434 (15)	0.711
Symptoms < 3 h – n/N (%)	524/881 (59)	264/447 (59)	260/434 (60)	0.851
Laboratory values				
Lactate – mmol/L	5.2 (2.6 – 8.6)	5.4 (2.5 – 8.6)	4.9 (2.6 – 8.6)	0.767
Glucose – mmol/L	12.3 (9.3 – 17.0)	12.3 (9.2 – 16.8)	12.3 (9.3 – 17.3)	0.639
Hemoglobin – mmol/L	8.4 (7.4 – 9.3)	8.4 (7.4 – 9.3)	8.4 (7.4 – 9.3)	0.766
eGFR – mL/min	61 (47 – 74)	61 (47 – 75)	62 (48 – 73)	0.890
Hs-troponinT (peak) – ng/L	3539 (778 – 10.000)	3980 (879 – 10.000)	3190 (674 – 10.000)	0.223

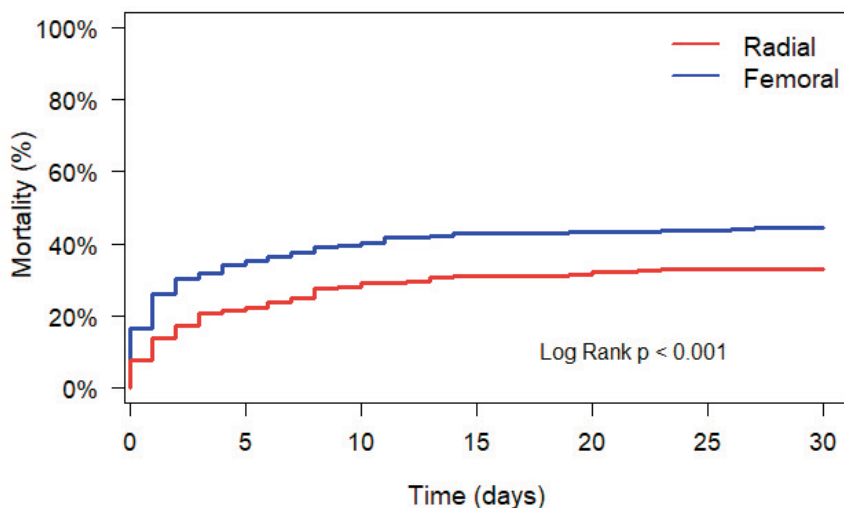
	All N = 1014	Radial access N = 507	Femoral access N = 507	p-value
CKMB (peak) – µg/L	232 (71 – 483)	257 (76 – 483)	198 (58 – 480)	0.130
Procedural details				
TIMI-flow pre PCI – n/N (%)				0.960
0/1	673/879 (76)	341/443 (67)	332/436 (77)	
2	80/879 (9)	39/443 (9)	41/436 (9)	
3	126/879 (14)	63/443 (14)	63/436 (14)	
TIMI-flow post PCI – n/N (%)				0.918
0/1	89/892 (10)	42/446 (10)	47/446 (11)	
2	69/892 (8)	34/446 (8)	35/446 (8)	
3	734/892 (82)	370/446 (83)	364/446 (82)	
Intervention in LCA n/N (%)	648/1000 (65)		325/504 (65)	0.885
Intervention in RCA n/N (%)	413/1000 (41)		211/504 (42)	0.763
Treatment				
Inotropes pre PCI – n/N (%)	561/985 (57)	283/495 (57)	278/490 (57)	0.941
Intubated pre PCI – n/N (%)	481/1009 (48)	240/504 (48)	241/505 (48)	1.000
MCS – n/N(%)	227/1005 (23)	110/502 (22)	117/503 (23)	0.663
Outcome				
30-day Mortality – n/N (%)	391/1007 (39)	166 (33)	225 (45)	<0.001

Values are median (interquartile range) unless indicated otherwise. **BMI** = body mass index; **Coronary event** = myocardial infarction and/or percutaneous coronary intervention and/or coronary artery bypass grafting; **Resuscitated** = either in- or out of hospital cardiac arrest pre PCI; **STEMI** = ST-elevation myocardial infarction; **MAP** = mean arterial pressure; **bpm** = beats per minute; **SOFA** = sequential organ failure assessment; Inotropes included the following agents initiated prior to PCI: noradrenaline, adrenaline, dobutamine, dopamine, milrinone / enoximone; **TIMI** = thrombolysis in myocardial infarction; **LCA** = left coronary artery; **RCA** = right coronary artery; **Hs-troponin T** = high-sensitive troponin T; **CKMB** = creatine kinase myocardial band

Mechanical circulatory support

A total of 335 patients received MCS shortly after hospital admission. In both the TRA and the TFA group, 5% of patients ($n = 31$ and $n = 45$, respectively) were treated with MCS therapy before entering the catheterization laboratory. However, the rate of MCS initiation during the revascularization procedure was 20% in TFA patients and only 6% in TRA patients.

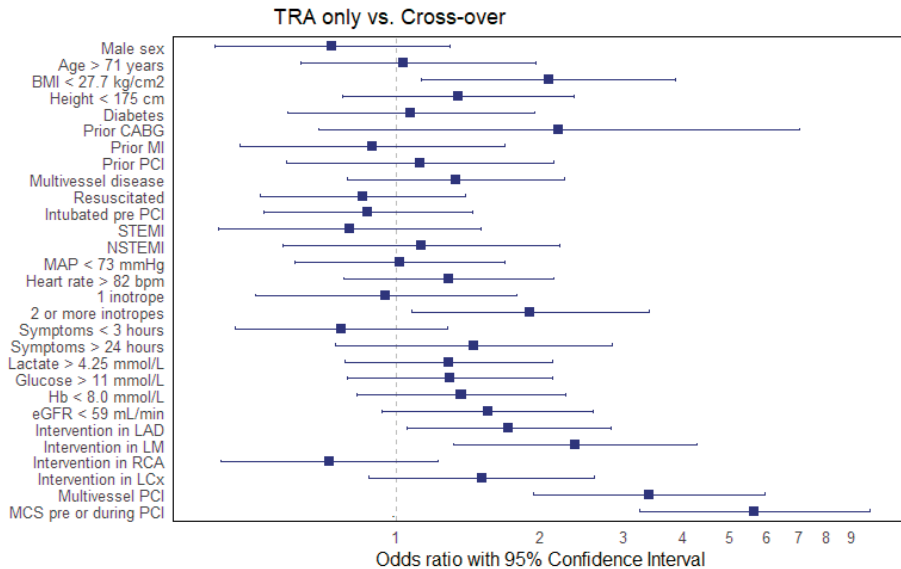
Figure 1. Propensity score matched survival analysis



A sensitivity analysis after removing all patients receiving MCS before or during the PCI showed similar results (see Supplementary material online, Table S3). Again, the distribution between TRA and TFA treatment was approximately equal, and there were no differences in comorbidities compared with the primary analysis. Furthermore, in this sensitivity analysis, TFA patients had worse hemodynamic parameters and increased laboratory measures of hypoperfusion.

Crossover

Of the 553 patients in whom PCI was initiated using TRA, 77 (14%) required vascular crossover from TRA to TFA. Using univariable logistic regression with a P-value of 0.10, 7 factors were identified to be associated with crossover (see Figure 2 and Supplementary material online, Table S4). Factors most strongly predisposing crossover include a body mass index (BMI) ≤ 27.7 kg/m², a history of CABG, ≥ 2 inotropes pre-PCI, an intervention in the left main coronary artery (LM), undergoing a multivessel PCI, and the initiation of MCS before or during the intervention.

Figure 2. Unadjusted Odd's ratios for crossover

*Cut-offs for continuous variables represent the points closest to the upper left corner from the ROC-curve. **BMI** = body mass index; **CABG** = coronary artery bypass grafting; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **(N) STEMI** = (Non) ST-segment elevated myocardial infarction; **MAP** = mean arterial pressure; **Heart rate** in beats per minute; **LAD** = left anterior descending coronary artery; **LM** = left main coronary artery; **RCA** = right coronary artery; **LCx** = left circumflex coronary artery; **MCS** = mechanical circulatory support.*

DISCUSSION

This analysis in 1562 patients with AMI complicated by CS from the Dutch national NHR registry showed relevant differences in baseline characteristics and access site-specific outcomes for TRA- and TFA-treated PCI patients. Important differences in comorbidity, baseline characteristics, and mortality were identified.

Specifically, TFA patients presented with worse hemodynamics, more often had a history of CABG and had a higher rate of mortality after 30 days, even after correction for potential confounders. Furthermore, 14% of patients required radial-to-femoral crossover, and this was mainly driven by the need for MCS insertion.

There are currently no data available from randomized controlled trials to clearly recommend a preferred vascular access site for PCI in AMICS patients. Therefore, the choice of vascular access is influenced by operators' personal preferences depending on perceived advantages and disadvantages of TRA and TFA. By immediately accessing through the femoral artery, operators avoid the risk of having to cross over in exchange for a higher rate of bleedings and other vascular complications associated with TFA. Accessing through the radial artery results in a lower complication rate in AMI PCI in hemodynamically stable patients (3). However, in hemodynamically unstable patients, TRA could result in a longer time to revascularization (and hemodynamic stabilization) due to difficulties puncturing and, moreover, running the risk of having to crossover and use a second access site after all.

Even though this is not the first study to describe an AMI-CS population with regard to the vascular access site, the current manuscript adds substantial knowledge to this topic. By focusing on patient characteristics rather than on outcomes only, we were able to provide detailed insights in the incentives for choosing one or the other access approach. We have demonstrated that in this cohort, TFA patients differed significantly from TRA patients in terms of baseline and hemodynamic characteristics.

Hypotension (and subsequent accompanying measures of organ hypoperfusion) was one of the most important factors associated with choosing TRA over TFA. Mean blood pressures on admission were lower, and both lactate and creatinine levels were higher in TFA patients. In contrast to a recent study, we found that patients' age and BMI were equally distributed in the two groups (14).

Earlier research that focused on identifying risk factors for TRA failure revealed that higher age, female sex, short stature, and a history of CABG were independent predictors of TRA failure in AMI patients without CS (15, 16). Of those, only having a history of CABG showed clinically relevant difference between the two groups in our study. Apparently, the other factors (age, sex, and posture) did not necessarily lead to an immediate femoral approach by operators. Noteworthy, the strongest predictor of TRA failure in regular AMI PCI is the presence of shock (15).

The small number of patients requiring crossover limited our potential to identify factors associated with this phenomenon in a multivariate analysis. Nonetheless, initiation of MCS in the catheterization laboratory was associated with crossover. The increased frequency of requiring a second access site in patients with MCS

can be attributed, in part, to the prior utilization of the alternative access site. We did find unadjusted odds ratios of 1.7 and 2.4 for interventions in the LM and the left anterior descending coronary artery (LAD) respectively. This might indicate difficulty of these specific procedures. Alternatively, significant collinearity may exist between interventions in the LM or LAD and initiation of MCS. We also found an odds ratio of 1.8 for the use of ≥ 2 vasopressors/inotropes before PCI which suggests that TRA may be impeded by excessive vasoconstriction.

We reported a significant temporal trend of an increased use of TRA during the study period. Even though similar trends have previously reported in other national PCI registry, important differences remain in absolute rates of TRA between different countries. Registry data from the USA showed that TRA was used in 29% of AMI-CS PCIs in 2021, which is much lower than the 47% reported in our current data. This observation becomes even more striking when considering that the severity of shock in this American population was probably lower, given the relatively low mortality rate of 20%. It is challenging to put these results in an international perspective as rates of TFA use vary widely over different countries (14, 17, 18).

A sensitivity analysis leaving out all patients receiving any form of MCS was performed, as we suspected that the presence or need for a MCS device will strongly influence the choice for access site. The results of this analysis were similar to the primary analysis. This shows that the factors that determine which approach is chosen, are irrespective of MCS use and thereby add robustness to the results of the primary analysis.

Strengths and limitations

This is the first study to provide a detailed description of the differences in patient characteristics of CS patients undergoing PCI with either TRA or TFA from a large national cohort. The new insights may allow a better interpretation of other studies focusing on vascular access site for PCI in AMI-CS patients. Furthermore, the PSM analysis is the first one in its kind and provides the best available evidence for the association between mortality and access site. Additionally, the current analysis showed that TRA is achievable in a large portion of AMI-CS patients. We have attempted to retain to a homogeneous population by excluding patients who developed shock during or after PCI, even though this hardly influenced the results.

However, the current analysis has some limitations that should be acknowledged. First and foremost, the individual reasons for radial-to-femoral crossover were not known. We assume that difficulty puncturing or experiencing time pressure may have played an important role. However, crossover is perhaps more often due to peripheral vascular conditions and tortuosity than due to failed puncture of radial artery spasm (19). Furthermore, we were not able to differentiate between a radial access revascularization that used femoral for MCS vs. a radial access that was truly transformed into a femoral access revascularization plus MCS (true crossover). And lastly, we were not able to report details on complication rates and outcomes other than mortality as they are not a part of the national registry.

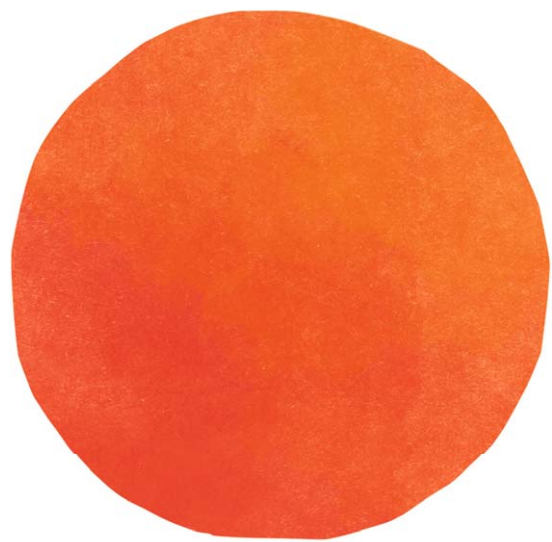
CONCLUSIONS

This study highlights significant differences in patient characteristics between AMI-CS patients undergoing PCI via TRA or TFA. In the current cohort, femoral access was more often deployed in female patients and those with a history of CABG or a preceding cardiac arrest. Operators also deferred to TFA in patients with more pronounced hemodynamic distress or those with a longer duration of symptoms. Nonetheless, the current study underscores the feasibility and major impact on survival of the radial approach for PCI in CS.

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Chapter 7

Clinical Outcome and Cost-effectiveness of Reduced Noradrenaline Mediated Lower Mean Arterial Pressure Target in Patients with Cardiogenic Shock from Acute Myocardial Infarction: Rationale and Design of the NORshock study

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ABSTRACT

Background

Acute myocardial infarction-related cardiogenic shock (AMI-CS) is clinically characterized by low blood pressure. Noradrenaline is the guideline-recommended first-line vasopressor therapy in patients in cardiogenic shock to increase blood pressure. Although no strict criteria exist, noradrenaline is commonly titrated to a mean arterial pressure (MAP) of above 65 mmHg. No evidence however exists that targeting a pharmacologically induced MAP of above 65 mmHg improves clinical outcome. Further, noradrenaline is associated with unwanted effects such as elevated afterload, increased myocardial oxygen demand and arrhythmias. Therefore, we sought to investigate whether treatment with a reduced noradrenaline mediated lower MAP-target regimen in AMI-CS patients leads to improved outcomes.

Methods

In this international, open-label, multicenter, randomized superiority trial, 776 patients will be allocated in a 1:1 ratio to either the index treatment of a reduced noradrenaline mediated lower MAP-target regimen (MAP of 55 mmHg) or a standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg). The NORshock trial tests the hypothesis that a permissive hypotension treatment strategy with reduced use of noradrenaline in patients with AMI-CS is superior to standard care in terms of combined all-cause death and renal replacement therapy within 30 days.

Conclusions

The NORshock-trial is the first randomized trial investigating a strategy with a reduced noradrenaline mediated lower MAP-target regimen (MAP of 55 mmHg) compared with a standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) on clinical outcomes in AMI-CS patients.

INTRODUCTION

Cardiogenic shock (CS) occurs in 3-13% of the total acute myocardial infarction (AMI) population and is associated with 30-day mortality rates of 40-50%. (1-7) This syndrome is characterized by hypotension, inadequate cardiac output and elevated filling pressures, primarily due to cardiac dysfunction. This leads to end-organ hypoperfusion and potentially multi-organ failure and death. (8)

Noradrenaline is the first-line vasopressor in CS to restore hypotension, as recommended by current American and European scientific statements and guidelines. (8, 9) However, this recommendation is based on results of small (sub-)studies with heterogenous study populations. (10, 11) Also, noradrenaline increases afterload, whilst the primary issues in CS are cardiac dysfunction and decreased cardiac output. (12) Therefore, from a physiological perspective, the use of noradrenaline in CS lacks a clear rationale. It is often administered under the assumption that a higher mean arterial pressure (MAP) improves myocardial- and other end-organ perfusion. Although intuitive, no evidence exists that noradrenaline, and the consequently induced elevated blood pressure, leads to improved clinical outcome in CS patients.

In the absence of evidence, the current guidelines refrain from recommending a systolic or MAP target. (8, 9) However, extrapolated from non-CS populations and observational data, targeting a MAP of above 65 mmHg is commonly adopted in clinical practice. (9, 13) Both guidelines, however, address the potentially deleterious impact of high vasoactive medication dosages to achieve high-MAP targets. Notably, noradrenaline is acknowledged for inducing various unwanted physiological and other effects including amongst others arrhythmias, increased afterload and immunomodulation. (12, 14, 15)

The NORshock study is designed to test the hypothesis that a treatment strategy with a lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) in patients with AMI-CS is superior to a standard noradrenaline mediated MAP-target regimen (MAP of at least 65 mmHg) in terms of combined all-cause death and renal replacement therapy (RRT) within 30 days. A piggy-back cost-effectiveness analysis will be performed

METHODS

Trial organization

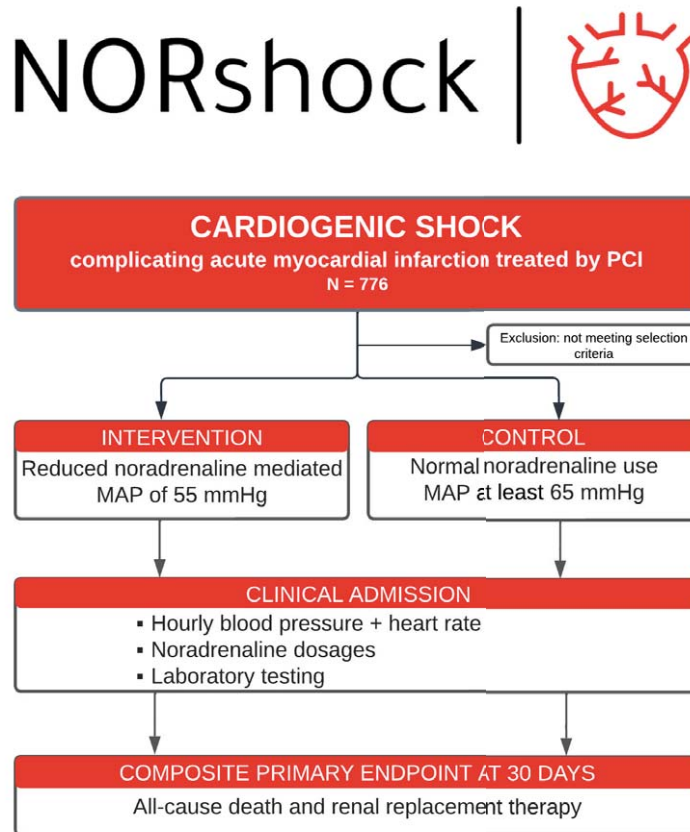
The NORshock study (ClinicalTrials.gov unique identifier NCT05168462) is an open-label, international, multicenter randomized controlled trial (RCT), sponsored and designed by the Amsterdam University Medical Centers. Funding is provided by a research grant from the Rational Pharmacotherapy Programme of ZonMw (grant number: 10140022010005) and the Amsterdam University Medical Center. The steering committee is solely responsible for the study design, trial execution, data-analysis and reporting of results.

The study is designed according to the principles of the Declaration of Helsinki. With permission of the institutional research board, randomized treatment is started without preceding informed consent, because of the imminent need for noradrenaline administration. Legal representatives are approached for consent for continuation of the randomized treatment if and when available. Patients are informed about the randomized treatment after eventual recovery and are asked for informed consent for collection of study data. The informed consent process might differ slightly in the different participating countries and centers, depending on local ethical and legal regulations. Information on the primary endpoint will be collected in all patients, with the exception of those for whom the legal representative(s) or patient has explicitly forbidden to do so.

Objective

The primary objective is to compare clinical outcomes in AMI-CS patients treated with a reduced noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) with patients treated with a standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) (*Figure 1*).

Figure 1. NORshock study flowchart



PATIENT SELECTION

Adult patients presenting with AMI complicated by CS, requiring early revascularization by percutaneous coronary intervention (PCI) are included (Table 1). Myocardial infarction comprises both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). Screening for eligibility takes place at the emergency department, the catheterization laboratory or at the intensive care unit (ICU) / coronary care unit (CCU). Patients can be included before, during or up to 2 hours post PCI.

The exclusion criteria include: resuscitation lasting more than 30 minutes; a mechanical complication of AMI as the cause of CS; shock conditions persisting for over 12 hours at the time of randomization or women under 45 years of age. Additionally, patients are not eligible if there is an imminent clinical need for mechanical circulatory support (MCS) at the moment of randomization.

Table 1. In- and exclusion criteria

Inclusion criteria:	Exclusion criteria:
<ol style="list-style-type: none"> 1. Acute myocardial infarction; STEMI or NSTEMI 2. Early revascularization by PCI 3. Cardiogenic shock, characterized by: <ol style="list-style-type: none"> I. <ol style="list-style-type: none"> a. Systolic blood pressure (SBP) <90 mmHg for > 30 minutes, OR b. Use of drugs to maintain SBP > 90 mmHg at randomization II. Clinical signs of impaired organ perfusion with at least one of the following criteria: <ol style="list-style-type: none"> a. Altered mental status b. Cold, clammy skin and extremities c. Oliguria with urine output < 30 mL / hour d. Serum lactate > 2.0 mmol/L III. Clinical signs of pulmonary congestion 	<ul style="list-style-type: none"> • Resuscitation > 30 minutes • Mechanical cause of cardiogenic shock (e.g. papillary muscle rupture, ventricular septa rupture) • Onset of shock > 12 hours • Imminent need for mechanical circulatory support • Women < 45 year

RANDOMIZATION

When the abovementioned selection criteria are met, patients are randomized in a 1:1 ratio between the index treatment of a lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) and a standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg). A web-based randomization program with stratification per center is used.

TRIAL TREATMENT

In patients randomized to the index regimen, noradrenaline is only initiated when the MAP is below 55 mmHg, preferably measured invasively by an arterial line. The infusion dosage is aimed at a MAP of 55 mmHg for the duration of CS . As soon as the MAP exceeds 55 mmHg, the noradrenaline infusion is reduced or discontinued. Vasodilators are not used to actively lower the MAP. When hemodynamic deterioration is observed, clinical management is lactate-driven. In the event of persistently elevated lactate levels (>2 mmol/L), inotropic treatment may be initiated. If lactate levels fail to decrease despite this new strategy, further medical treatment including abandoning the index MAP-target is at the discretion of the treating physician (*Figure S1*).

In patients randomized to standard of care, noradrenaline is administered to achieve a MAP of at least 65 mmHg, at the discretion of the treating physician.

When the above medical treatment fails, the use of mechanical circulatory support (MCS) is allowed for bail-out. If MCS is initiated, the MAP targets remain as allocated. Other treatments at the CCU or ICU and afterwards are in accordance with local practice and clinical guidelines. (8, 9, 16)

ENDPOINTS

The *primary endpoint* of the study is the composite of all-cause death and RRT within 30 days after randomization. The *ranked secondary endpoints* consist of (1) all-cause death and (2) days alive and out of hospital, both at 30 days. The *key tertiary endpoints* include (1) enzymatic infarct size, (2) lactate clearance, (3) RRT (at 30 days, 1 year), (4) vasoactive inotropic score (VIS) during the first 4 days of ICU/CCU admission, (5) blood pressure and heart rate during the first 24 hours, (6) hemodynamic parameters during ICU / CCU admission, (7) arrhythmias during hospital admission, (8) myocardial re-infarction within 30 days, (9) left ventricular ejection fraction during hospital stay and at 12 months, (10) quality adjusted life-years during 1 year and (11) societal costs during 1 year. A complete list of the tertiary endpoints is provided in the appendix.

DATA COLLECTION AND FOLLOW-UP

All in-hospital data are collected in a dedicated case report form (*Table 2*).

Patients are contacted by telephone at 30 days and at 12 months to collect information about the study endpoints and disability status according to the modified ranking scale score (MRS score).

Patients fill out various questionnaires by e-mail or on paper, including the EQ-5D-5L questionnaire, the institute for Medical Technology Assessment (IMTA) Medical Consumption (iMCQ) and Productivity Costs (iPCQ) questionnaires, and the Short Form Survey (SF-36) at 30 days, 3, 6 and 12 months.

Serious adverse events ((S)AEs) that are part of the natural course of CS are captured in the case report form and do not require special reporting. Other SAEs are reported in accordance with local regulations.

STATISTICAL METHODS

Statistical analysis of primary and ranked secondary endpoints

The trial was primarily designed and powered to assess the superiority of treatment with a lower noradrenaline mediated MAP-target regimen, while also incorporating non-inferiority testing.

The following hypotheses are tested in a hierarchical order, to preserve type I error rate:

Hypothesis 1 - A lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) is non-inferior to the standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) in terms of the primary endpoint of the composite of all-cause death and RRT within 30 days. Non-inferiority is declared if the upper limit of the 95% confidence interval (CI) of the rate difference excludes 10%. This is the equivalent of non-inferiority testing with a one-sided alpha of 0.025 with a non-inferiority limit of 10%.

Hypothesis 2 - A lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) is superior to the standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) in terms of the primary endpoint of the composite of all-

cause death and RRT within 30 days. Superiority is declared if the 95% confidence interval (CI) of the rate difference excludes 0%. This is the equivalent of superiority testing with a 2-sided alpha of 0.05.

Hypothesis 3 - A lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) is superior to the standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) in terms of the first secondary endpoint of all-cause death at 30 days. Superiority is declared if the 95% confidence interval (CI) of the rate difference excludes 0%. This is the equivalent of superiority testing with a 2-sided alpha of 0.05.

Hypothesis 4 - A lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg) is superior to the standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) in terms of the second secondary endpoint of days alive and out of hospital at 30 days. Superiority is declared if the two-sided p-value of the Mann-Whitney-U test applied to days alive and out of hospital at 30 days is lower than 0.05.

All analyses are performed on an intention-to-treat (ITT) basis. The ITT population consists of all patients who have been randomized. Patients are analyzed in accordance with the randomized treatment assignment irrespective of the factual implementation of the assigned treatment regimen. Rates of primary and first secondary endpoint are estimated as the cumulative incidence at 30 days after randomization by the Kaplan-Meier method. Rate differences are defined as the rate in the index group minus the rate in the reference group. The 95%-confidence interval (CI) are estimated according to the Com-Nougue method, with the use of Kaplan-Meier estimates. Tertiary endpoints are analyzed by appropriate statistical methods with a focus on presenting 95%-CIs.

Table 2. Data collection points. T = 0 equals randomization

	Pre		25-48 hours		49-72 hours		73-96 hours		1 year			
	ICU/CCU	T = 0	T = 3	T = 6	T = 12	T = 24 (day 2)	T = 48 (day 3)	T = 72 (day 4)	30 days	3 months	6 months	1 year
Demographics												
Patient characteristics	X											
Clinical risk factors	X											
Angiography and PCI	X											
Laboratory tests												
Lactate	X	X	X	X	X	X	X	X				
Hemoglobin, leukocytes, CRP, urea, ASAT, ALAT	X	X				X	X	X				
Glucose	X											
Creatinin		X				X	X	X				X
HS Troponin T, CK-MB		X		X	X	X	X	X				
NT-proBNP		X				X	X	X				
(Vasoactive) medication												
Highest noradrenaline infusion rate – in µg/kg/min		X				X	X	X				
Noradrenaline dosage – total, in mg		X				X	X	X				
Dosages other vasopressors and inotropes – total, in mg		X				X	X	X				
Sedative medication						X	X	X				
(Cardiac) monitoring												
Hourly blood pressure and heart rate	X	X	X	X	X	X	X	X				

SAMPLE SIZE DETERMINATION

The sample size calculation is based on a superiority test of the primary endpoint. The incidence rate of the primary endpoint in the reference group was estimated from the CULPRIT-SHOCK trial, in which the composite endpoint of death or RRT had occurred in 45.9%. (7) While no other study has directly investigated the same intervention, insights from prior experimental myocardial infarction studies in rats suggest that the administration of noradrenaline is associated with a potential increase in infarct size by up to 22%. (17) Besides that, patients with elevated intrinsic noradrenaline levels post-myocardial infarction have a fourfold higher mortality rate compared to those with normal noradrenaline levels. (18) Therefore, considering the significantly higher death rate and larger infarct size observed in those treated with (higher dosages of) noradrenaline, we hypothesized that the event rate of the primary endpoint in the index MAP-target regimen may be estimated to be 10% lower than in the standard MAP-target regimen, with an expected event rate of 35.9%.

Based hereupon, it was calculated that this trial will need 752 patients to detect an absolute difference of 10% in event rate regarding the primary endpoint with 80% power. To account for an attrition rate of 3%, 776 patients will be randomized.

For non-inferiority testing, we utilized a non-inferiority margin of 10%, equivalent to the inverse of the aforementioned treatment benefit. With 752 evaluable patients, the study has 79% statistical power to show non-inferiority of the lower MAP-target regimen compared to the standard MAP-target regimen, given a non-inferiority margin of 10% and primary endpoint event rates of 45.9% in both treatment regimens.

PRESPECIFIED SUBGROUP ANALYSES

Incidence rates of the primary endpoint of death and RRT within 30 days following randomization will be calculated and exploratory tested in the following subgroups: sex, age (<60, 60-75, >75 years), history of diabetes mellitus, history of hypertension, prior myocardial infarction, prior PCI or coronary artery bypass grafting (CABG), eGFR at baseline (<30, 30-60, >60 ml/min/1.73 m²), lactate level at randomization (<3, 3-6, >6 mmol/L), shock stage at randomization (category C, D, and E, according to Society for Cardiovascular Angiography and Interventions (SCAI)), out-of-hospital cardiac arrest (OHCA) preceding current hospital admission, infarct related artery,

multivessel disease, MAP at randomization (<55 mmHg, 55-65 mmHg, >65 mmHg), mechanical ventilation at randomization, type of acute myocardial infarction (NSTEMI vs STEMI), and randomization before, during or within 2 hours after PCI.

COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS

The economic evaluation of reduced noradrenaline use will be composed of both cost-effectiveness and cost-utility analyses from a societal perspective with a life-time horizon. The health-economic outcome for the cost-effectiveness analysis will be the costs per patient alive without RRT. For the cost-utility analysis the costs per quality adjusted life year (QALY) will be the outcome. Incremental costs per QALY will be evaluated against societal willingness-to-pay values per QALY up to 80,000. A health economic analysis plan (HEAP) will be written prior to database lock.

SAFETY MONITORING

The NORshock trial is overseen by an independent Data Safety Monitoring Board (DSMB) tasked with ensuring the safety of the study participants. The DSMB convenes after enrolment of 25, 60, 100 and every 100 patients. The

DSMB can recommend to continue the study or to discontinue the study in clear evidence of harm of the lower noradrenaline mediated MAP-target regimen (MAP of 55 mmHg). No formal interim analysis for early claims of superiority of the lower MAP-target regimen over the standard MAP-target regimen will be performed.

DISCUSSION

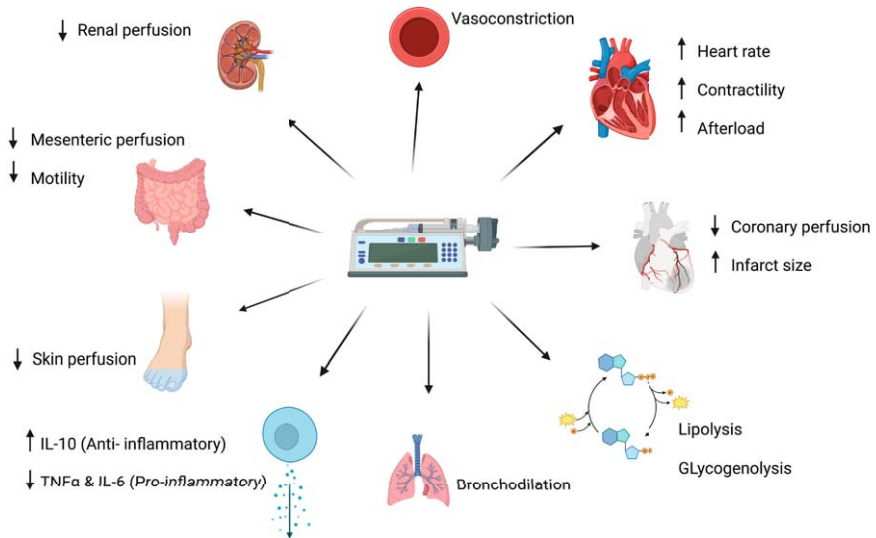
The NORshock trial primarily hypothesizes that reduced use of noradrenaline in patients with AMI-CS will improve outcomes in terms of all-cause death and RRT.

Noradrenaline is commonly used to treat hypotension, that is typically defined as a MAP below 65 mmHg or a systolic blood pressure under 90 mmHg in clinical practice. (1) Noradrenaline is recommended by both the European and American CS guidelines, although both raise serious concerns regarding the limitations of the two RCTs upon which these recommendations are based (*Table S2*). (8-11) In the European guidelines, noradrenaline has a Class IIb recommendation. The American

guidelines mention that noradrenaline may be the vasopressor of choice in many CS patients, but the optimal first-line vasoactive medication remains unclear in the light of major study limitations.

The first trial supporting the recommendation of noradrenaline compared noradrenaline with dopamine in patients with various types of shock. (10) The trial yielded an overall neutral outcome. However, within a small predefined but not appropriately stratified CS subgroup of 280 patients, a trend towards lower 28-day mortality was reported in patients treated with noradrenaline. Notably, only 161 patients had AMI. Another RCT compared noradrenaline with epinephrine in AMI-CS patients and was terminated early after enrolling 57 patients. (11) This was due to a higher incidence of refractory shock, which was reflected, among other markers, by elevated lactate levels in the epinephrine group. However, epinephrine is a strong agonist for β 2-receptors and therefore directly stimulates lactate production. (19) Overall, the results of these two RCTs should therefore be interpreted with caution. Additionally, in a meta-analysis comparing vasopressors and inotropes to a control group not exposed to the vasopressor/inotrope, treatment with noradrenaline was not associated with improved short-term mortality. (20)

Noradrenaline is a strong α 1-receptor agonist known for its various physiological effects, such as an increased afterload, elevated end-systolic volumes, an augmented myocardial oxygen demand with studies reporting contradictory effects on cardiac output. (11, 12, 21, 22) Additionally, there are indications that the use of noradrenaline might actually comprise myocardial blood flow. (23) These effects may potentially result in further ischemia of the myocardium and an increase in infarct size – an important determinant of clinical outcomes. (24, 25) Furthermore, noradrenaline has immunosuppressive effects, contributing to increased susceptibility towards infection. (15, 26) In summary, noradrenaline has an important impact on cellular mechanisms, microcirculation, cardiac and vascular properties and unwanted end-organ effects (*Figure 2*).

Figure 2. Effects of noradrenaline

In addition to the absence of a clear recommendation on the choice of vasopressor, target MAPs for CS patients are also lacking in the guidelines as the optimal blood pressure for these patients has not been studied. (8, 9) The main goal of noradrenaline treatment is to maintain adequate perfusion pressures, however, blood pressure is not necessarily a reliable measure of end-organ perfusion. Additionally, it is unclear to what extent hypotension should be treated to ensure the benefits of higher blood pressure outweigh the potential deleterious impact of vasoactive agents. Current targets in clinical practice are extrapolated from non-CS populations, particularly septic shock populations.

The assumption to target a MAP of above 65 mmHg in shock populations is mostly derived from the results of the SEPSISPAM-trial, in which septic shock patients were randomized to a lower versus a higher target MAP (> 65 mmHg vs. 80-85 mmHg) (Table S3). (27) Mortality rates were similar but the incidence of atrial fibrillation was significantly higher in the high MAP group. This was deemed most likely due to higher dosages of vasopressors administered. Consequently, these results led to the notion that targeting a higher MAP is not beneficial across the spectrum of shock etiologies. Additionally, another trial comparing a lower MAP target (60-65 mmHg) to a higher MAP target (>65 mmHg) in elderly patients with vasodilatory hypotension found no difference in 90-day mortality. (28)

Reducing vasopressor dosages through permissive hypotension in AMI-CS patients frequently encounters resistance in the clinical field. This primarily stems from concerns regarding potential hypoperfusion of the brain and kidneys. Four RCTs, comparing a low MAP target (63 mmHg or higher) to a higher MAP target (77 mmHg and above) in patients presenting with an OHCA did not show significant differences regarding neurological outcomes and mortality. (29-32) The same applies to the kidneys, as no evidence exists that targeting a higher MAP is beneficial in preventing acute kidney injury and RRT. Only in a subgroup of sepsis patients with pre-existing chronic hypertension, a lower rate of RRT within seven days of admission was observed. (27) However, this association has not been observed in the OHCA RCTs.

Thus, noradrenaline is commonly used to treat hypotension in AMI-CS patients. The use of noradrenaline is associated with several side effects, raising concerns whether its benefits outweigh its potential deleterious effects. Also, it remains uncertain whether hypotension merely is a marker of critical illness or serves as a modifiable marker affecting outcome. Lastly, the commonly used target MAP of above 65 mmHg is based on study results from diverse shock populations, and may not be applicable to patients with AMI-CS.

CURRENT STATUS

The first patient was randomized October 6th 2022. The first international patient was randomized September 4th 2023 and a total of 230 patients have currently been enrolled. The study needed additional approval via CTIS due to new European regulations for drug trial which was obtained in June 2024. At present, 14 sites have started enrolment. Enrolment and completion of the primary endpoint (30 day follow-up) is expected Q4 2026.

CONCLUSION

The NORshock-trial is the first randomized trial to compare a strategy with a reduced noradrenaline mediated lower MAP-target regimen (MAP of 55 mmHg) with a standard noradrenaline mediated MAP-target regimen (MAP at least 65 mmHg) in terms of clinical outcomes in AMI-CS patients.

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E

Summary (EN)

Samenvatting (NL)

**General discussion and
future perspectives**

Summary (EN)

Chapter 1 forms the base of this thesis by describing cardiogenic shock (CS) and non-CS patients within the Dutch percutaneous coronary intervention (PCI) population. This study identified risk factors for developing shock using data of 75.407 unique acute coronary syndrome patients of whom 3028 (4.1%) developed shock. The risk factors that were identified using multivariable Cox regression analysis, were: higher age, renal dysfunction, diabetes mellitus, multivessel disease, prior myocardial infarction and out-of-hospital cardiac arrest. The study also showed that the 30-day mortality rate was 20 times higher in CS than in non-CS patients.

To gain more in-depth insights in the CS population, a large additional registry was set up, the process of which is described in **Chapter 2**. This study describes more in-depth characteristics of the CS population and adds details on treatment strategies and outcomes of patients with CS. This study identified which factors differed between survivors and non-survivors within the CS group. It showed that non-survivors presented with lower mean arterial pressure, higher heart rate and higher blood lactate and glucose levels. Furthermore, they more often had diabetes, multivessel disease and a prior coronary event. It also gives an impression of the usage of mechanical circulatory support in acute myocardial infarction (AMI) related CS patients in the Netherlands (25%).

The process of developing and externally validating a model to predict 30-day mortality in patients with AMI-CS is described in **Chapter 3**. The following predictors were included: age, heart rate, blood pressure, intervention in the left main coronary artery, successful PCI, lactate, glucose, hemoglobin and renal function. This shows that a lot more than only patients' age should be considered in clinical decision making (e.g. escalation of therapy). Besides use in clinical practice, the developed model will facilitate comparisons across different populations and assist in the selection of patients for clinical trials.

In **Chapter 4**, a critical gap in cardiovascular research was addressed: sex-specific differences in patients with AMI-CS. The study demonstrated that women had longer symptom duration and were older at presentation, whereas men had more multivessel disease and a significantly higher rate of out-of-hospital cardiac arrest. Despite these differences, and the fact that men received more aggressive treatment, mortality was similar in men and women.

In **Chapter 5** we reflect on an American registry-based cohort study comparing outcomes of CS patients treated either through the femoral or through the radial artery. Despite inevitable limitations, this study demonstrates advantages of using the radial approach in CS patients.

Chapter 6 reports that fewer PCI's in shock patients were performed through the radial artery than through the femoral artery in the Netherlands. Transfemoral access patients were generally in "deeper" shock; they had higher resuscitation and intubation rates, higher lactate levels and lower blood pressures on admission. Transfemoral access was associated with higher 30-day mortality, even after propensity score matching on comorbidities and severity of shock.

In **Chapter 7**, the design and rationale of the Norshock trial is described. In this randomized trial, the following hypothesis is tested: treatment of AMI-CS with less noradrenaline, leads to a better outcome in terms of a composite of all-cause mortality and renal-replacement therapy at 30 days. The trial is currently enrolling.

Samenvatting (NL)

Hoofdstuk 1 vormt de basis van dit proefschrift door cardiogene shock (CS) en non-CS patiënten binnen de Nederlandse populatie van percutane coronaire interventies (PCI) te beschrijven. In deze studie zijn risicofactoren voor het ontwikkelen van shock onderzocht aan de hand van gegevens van 75.407 patiënten met een acuut coronair syndroom. Van hen ontwikkelde 3028 (4.1%) shock. De volgende risicofactoren werden gevonden met behulp van multivariate Cox-regressieanalyse: hogere leeftijd, nierfunctiestoornissen, diabetes mellitus, meervatslijden, eerder myocardinfarct en hartstilstand buiten het ziekenhuis. De studie toonde ook aan dat de mortaliteit op 30 dagen 20 keer hoger was in patiënten bij wie het acuut coronair syndroom was gecompliceerd met CS, dan in patiënten bij wie dit niet het geval was.

Om beter inzicht te krijgen in de CS-populatie, werd een grote aanvullende registratie opgezet, waarvan het proces beschreven wordt in **Hoofdstuk 2**. In deze studie zijn kenmerken van de CS-populatie in meer details onderzocht, en is bovendien verder gekeken naar toegepaste behandelingsstrategieën en uitkomsten van CS- patiënten. De studie identificeerde welke factoren verschilden tussen overlevers en niet-overlevers binnen de CS- groep. Het bleek dat niet-overlevers lagere gemiddelde arteriële druk, hogere hartslag en hogere bloedlactaat- en glucosewaarden hadden. Verder hadden zij vaker diabetes, meervatslijden en een voorgeschiedenis met een hartinfarct of dotterprocedure. Ook wordt een indruk gegeven van het gebruik van mechanische circulatoire ondersteuning bij AMI-gerelateerde CS-patiënten in Nederland.

Het proces van het ontwikkelen en extern valideren van een model om 30-dagen mortaliteit te voorspellen bij patiënten met AMI-CS wordt beschreven in **Hoofdstuk 3**. De volgende voorspellers werden meegenomen: leeftijd, hartslag, bloeddruk, interventie in het hoofdstam kransslagvat, succesvolle PCI, lactaat, glucose, hemoglobine en nierfunctie. Dit toont aan dat er veel meer dan alleen de leeftijd van patiënten in overweging moet worden genomen bij klinische besluitvorming (bijv. escalatie van therapie). Naast gebruik in de klinische praktijk zal het ontwikkelde model bijdragen aan vergelijkingen tussen verschillende populaties en het selecteren van patiënten voor klinische studies.

In **Hoofdstuk 4** worden sekseverschillen beschreven bij patiënten met AMI-CS. Hier werd aangetoond dat vrouwen langer symptomen hebben voor zij PCI ondergaan en ouder waren bij presentatie, terwijl mannen vaker meervatslijden hadden en vaker

een reanimatie buiten het ziekenhuis doormaakten. Ondanks deze verschillen, en het feit dat mannen agressiever werden behandeld, was de mortaliteit vergelijkbaar tussen mannen en vrouwen.

In **Hoofdstuk 5** is onze reflectie op een cohortstudie gebaseerd op een Amerikaanse registratie beschreven. Hierin worden de uitkomsten van CS-patiënten vergeleken die behandeld werden via de femorale of via de radiale arterie. Ondanks tekortkomingen van de studie door hoe deze is opgezet, toonde deze de voordelen aan van de radiale benadering bij CS-patiënten.

In **Hoofdstuk 6** werd aangetoond dat er in Nederland minder PCI's in shock-patiënten via de radiale arterie werden uitgevoerd dan via de femorale arterie. Patiënten met transfemorale toegang bevonden zich over het algemeen in een “diepere” shock; zij hadden hogere reanimatie- en intubatiepercentages, hogere lactaatsniveaus en lagere bloeddrukken bij opname. Transfemorale toegang was geassocieerd met hogere 30-dagen mortaliteit, zelfs na het corrigeren voor comorbiditeiten en ernst van shock middels *propensity score matching*.

In **Hoofdstuk 7** wordt het ontwerp en de onderbouwing van de Norshock-studie beschreven. Deze gerandomiseerde studie test de hypothese dat behandeling van AMI-CS met minder noradrenaline leidt tot een betere uitkomst wat betreft de samengestelde primaire eindpunten na 30 dagen: sterfte door alle oorzaken en nierfunctie vervangende therapie. De studie werft momenteel patiënten.

General discussion and future perspectives

The field of cardiogenic shock (CS) remains constrained by limited Class I evidence and a stagnation in prognosis over recent decades, despite growing interest and numerous initiatives aiming to improve the understanding and treatment (1). Nonetheless, the high mortality associated with CS, coupled with an aging population, underscores the urgent need for continued research and innovation (2).

Achieving innovation requires a thorough understanding of the diseased population. However, a detailed mapping of AMI (acute myocardial infarction)-CS patients in the Netherlands was previously lacking. To address this gap, we developed a dedicated registry as an extension of the Netherlands Heart Registration (NHR) (3). While the NHR already collects data on all patients undergoing percutaneous coronary intervention (PCI) in the Netherlands, we introduced a specialized shock section to capture detailed information on patients admitted with shock who underwent PCI (4). This registry proved to be a valuable resource for insights into the characteristics of the AMI-CS-population (5). The data enabled the identification of risk factors, comparison of subgroups, and evaluation of different treatment strategies. The pilot phase of this registry led to the inclusion of around ten shock-related variables in mandatory reporting, ensuring it remains a source of information in the future. Therefore this registry can continuously be used for improvements in several aspects of the domain of AMI-CS.

Prediction

In the field of risk prediction in AMI-CS, efforts are focused on addressing two key questions: I. Which AMI patients are at risk of developing CS?; and II. Which AMI-CS patients are at risk of experiencing worse outcomes?

Identifying which patients are at risk of developing shock, allows for earlier prevention strategies such as timely recognition and early revascularization. Patients at risk could be identified based on having risk factors such as large infarct size, diabetes, previous infarction and multivessel disease (6). Furthermore, it is known that shock is more common after ST-segment elevation myocardial infarction (STEMI) than after non-STEMI, occurs more frequently after anterior myocardial infarction than other infarct location, and female patients appear to be at higher risk than male patients (7-9). Awareness and early recognition are of paramount

importance since early revascularization remains the cornerstone treatment, and infarct size is a major determinant for clinical outcomes (10).

Additionally, within the population of patients in shock, there is a need for individualized risk prediction to better determine who is likely to have poor outcomes. Such personalized risk assessments would not only enhance patient care, but also refine patient selection for clinical trials. Ideally, a score would be based on unselected real- world data, include a wide variety of factors that are easily identifiable and could be applied to a clearly defined population early in the course of disease.

The journey toward identifying risk factors likely began with age, which was recognized early on as a key predictor for both the development of CS and worse outcomes (11). Over time, the understanding of predictive factors has advanced, leading to the proposal of the first multifactorial CS prediction models or severity scoring systems in the 1990s (12). Since then, multiple more sophisticated risk scores have been developed (13-20). Yet, all of them still have significant limitations. Many of them were developed on small cohorts or very heterogeneous populations. Furthermore, they often lacked external validation, included variables that were difficult to collect in clinical practice or simply did not perform well.

When the Society for Cardiovascular Angiography and Interventions (SCAI) shock stage classification was introduced in 2019, it was met with high hopes of resolving ongoing debates (21). With multiple validation studies and broad support within a wide network, it does hold significant potential (6). And the model has proven useful for categorizing patient groups, yet it falls short as a tool for individual risk assessment.

So, no major breakthroughs have been achieved despite numerous attempts and it appears that no risk score fully meets current clinical needs, as none has gained widespread adoption.

The introduction of our Acute Coronary Syndrome Cardiogenic Shock (ACCS) risk score addresses a significant gap in AMI-CS research. This innovative online tool relies solely on easily collectable variables, was developed using a large real-world data cohort, and has been internationally validated on another extensive registry population. It offers detailed risk predictions for patients in AMI-CS undergoing PCI, enabling individualized risk assessments to guide clinical decision-making. Additionally, the ACCS-risk score can enhance the conduction of clinical trials by

improving patient selection through prognostic enrichment. It also proves valuable for retrospective analyses, facilitating comparisons between cohorts. It is currently being implemented in our organization for clinical practice.

Management

A number of changes and improvements in the treatment of AMI-CS have taken place in previous years. For example, a significant shift in revascularization strategies has occurred over time. Since 1999, early revascularization has been the first-in-line treatment for AMICS patients (22). In 2012 a culprit-only strategy was added to the guidelines (23). Up to date, the landscape is still evolving. While transfemoral artery approach was the standard until 1993, the introduction of the transradial approach brought a significant reduction in bleeding and vascular complications (24). Transradial became the preferred approach, especially in patients with uncomplicated myocardial infarction. Although patients in shock could also benefit from these advantages, the femoral artery is still often used in this population. This preference is likely due to a combination of factors including easier identification of the femoral artery in hypotensive patients, the potential need for larger-bore access for MCS, and traditional practices. Despite these challenges, observational data presented in this thesis suggest that also in CS patients radial access is associated with better outcomes. However, these findings are subject to confounding by indication (i.e. the sicker the patient, the higher the chance of the operator preferring the femoral approach) (25-27). Nonetheless, these results should encourage initiatives that promote radial access in shock patients, even if it requires more time or effort. The use of ultrasound in the catheterization lab could further support this approach. Also, outcomes could be improved by identifying risk factors for radial access failure.

Furthermore, the introduction of various mechanical circulatory support devices has brought significant innovation to the therapeutic field. Several devices appeared promising but have not or hardly been proven beneficial in the treatment of CS (28-30). The DanGer Shock trial, which was published in 2024, provided the first positive results for the use of MCS in CS (31). The researchers demonstrated a survival benefit at 180 days with the routine use of a microaxial flow-pump compared to standard care alone, in 360 randomized patients. Despite the promising results, the impact on clinical guidelines remains uncertain as the significance of the results was not robust and the selection criteria stringent and applicable to around 5-10% of all AMI-CS patients. Nonetheless, this trial may have a profound impact on refining criteria for who might benefit most from such advanced therapies.

Finally, attention has traditionally focused on improving tissue perfusion by pharmacologically treating hypotension. This is most commonly done with catecholamines that work through stimulation of the adrenergic and dopamine receptors (32). Despite their clear effectiveness in raising blood pressure, their use has also been linked to unwanted side effects (33). This has raised new questions regarding the optimal dosages and target blood pressure. In the near future, the results of the Norshock trial (*NCT 05168462*), which is currently recruiting participants, are highly anticipated. This trial hypothesizes that treating AMI-CS with a lower dose of noradrenaline, by targeting a lower MAP, will lead to decreased mortality. The findings of this study are estimated to provide valuable guidance for clinicians. Similarly, the DOREMI CAPITAL 2 trial (*NCT 05267886*) has begun enrolling patients (34). This study will evaluate the efficacy of single-agent inotrope therapy compared to placebo in individuals with CS categorized as SCAI class C ('classic') and D ('deteriorating'). Both trials are particularly promising, especially considering the trend in recent times to increase therapeutic interventions, often favoring more medication and aggressive treatments. Reversing this approach by reducing or simplifying treatment is always more challenging than adding new interventions.

So, can we do better? And if so, how?

It is encouraging that new evidence from ongoing clinical trials is on the horizon. At the same time, it remains crucial to follow the currently available evidence as outlined in clinical guidelines, which is not always done optimally (5). This highlights an opportunity to enhance outcomes through systemic changes. One such approach could involve the establishment of dedicated multidisciplinary shock teams and centralized care models, which have shown promise in improving care delivery for CS patients (35). Additionally, clinicians play a crucial role in ensuring the timely recognition of shock, with a particular focus on addressing sex disparities. It is essential that CS is identified as promptly in female patients as it is in male patients. Timely recognition and anticipation could be facilitated by advanced hemodynamic monitoring, the adoption of a universal definition and an integrated risk stratification tool. Ultimately, with the use of artificial intelligence all these findings could be integrated to generate dynamic predictions and tailored treatment advices.

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F

PhD portfolio

Contributing authors

Dankwoord

About the author

PhD PORTFOLIO

Name PhD student	Elma Peters
PhD period	01-02-2021 – 01-09-2024
Names of supervisors	Prof. dr. José P.S. Henriques and prof. dr. Alexander P.J. Vlaar
Names of co-supervisors	Dr. Annemarie E. Engström and dr. Wim K. Lagrand

PhD training		
	Year	ECTS
General courses		
• eBROK	2021	1.0
• Practical biostatistics	2021	1.1
• AMC world of science	2021	0.7
• E-learning courses Medical Literature (PubMed, searching for evidence, Endnote)	2021	0.2
• Research data management	2021	0.8
• Computing in R	2023	0.7
Master Epidemiology		
• Epidemiologic research: basic principles	2021-2023	32
• Principles of epidemiologic data-analysis		
• Regression techniques		
• Clinimetrics: assessing measurement properties of health measurement instruments		
• Advanced epidemiologic research		
• Methodological consulting		
• Missing data: consequences and solutions		
• Clinical prediction models and machine learning		
• Systematic reviews and meta-analyses		
• Multilevel modelling and longitudinal data- analysis		
Seminars, workshops and master classes		
• Impella course	2023	0.5
Presentations		

• EuroELSO - Support for post-PCI cardiogenic shock (lecture)	2021	0.5
• TCT (poster)	2021	0.2
• TCT (moderated poster)	2022	0.2
• NVVC (oral presentation 2x)	2022-2023	0.4
• TCT (oral presentation)	2023	0.2
• NHR (poster)	2024	0.2
• ESC (oral presentation)	2024	0.2
(Inter)national conferences		
• EuroELSO congress (2x)	2021-2022	1.0
• ZonMW congress	2021	0.4
• NVVC congress (5x)	2021-2024	2.5
• Rotterdam ICU symposium	2022	0.4
• International Hypothermia and Temperature Management Symposium	2022	0.4
• ESC congress (3x)	2022-2024	2.6
• TCT congress (3x)	2021-2023	2.4
• Translational ICU symposium (2x)	2022-2023	0.8
• EuroPCR congress	2023	1.0
• NHR congress	2024	0.2

Teaching

	Year	ECTS
Lecturing		
• ECG course for bachelors students	2022	0.4
• Klinische lessen DISCO/Norshock (SEH, CCU, anesthesie, IC)		2.0
Tutoring, Mentoring		
• Kennismaking Wetenschappelijk Onderzoek	2023-2024	1.0

Parameters of Esteem

	Year
Grants	
• ZonMW Rational Pharmacotherapy Programme grant (900k)	2021
Awards and Prizes	
• Best oral presentation, NVVC congress	2023

Publications

Included in this thesis

- Outcome and Predictors for Mortality in Patients with Cardiogenic Shock: A Dutch Nationwide Registry-Based Study of 75,407 Patients with Acute Coronary Syndrome Treated by PCI. *Karami M, Peters EJ, Lagrand WK, Houterman S, den Uil CA, Engström AE, Otterspoor LC, Ottevanger JP, Ferreira IA, Montero-Cabezas JM, Sjauw K, van Ramshorst J, Kraaijeveld AO, Verouden NJW, Lipsic E, Vlaar AP, Henriques JPS, On Behalf Of The PCI Registration Committee Of The Netherlands Heart Registration.* *Journal of Clinical Medicine*, 2021
- Characteristics, Treatment Strategies and Outcome in Cardiogenic Shock Complicating Acute Myocardial Infarction: A Contemporary Dutch Cohort
Elma J. Peters, Sanne ten Berg, Margriet Bogerd, Marijke J.C. Timmermans, Adriaan O. Kraaijeveld, Jeroen J.H. Bunge, Koen Teeuwen, Erik Lipsic, Krischan D. Sjauw, Robert-Jan M.V. Geuns, Admir Dedic, Erik A. Dubois, Martijn Meuwissen, Peter Danse, Niels J.W. Verouden, Gabe Bleeker, José M. Montero-Cabezas, Irlando A. Ferreira, Annemarie E. Engström, Wim K. Lagrand, Luuk C. Otterspoor, Alexander P.J. Vlaar, José P.S. Henriques, On Behalf Of The PCI Registration Committee Of The Netherlands Heart Registration. *Journal of Clinical Medicine*, 2023
- Development and Validation of a Risk Score in Acute Myocardial Infarction related Cardiogenic Shock
Elma J. Peters, Joakim B. Kunkel, Margriet Bogerd, Sanne ten Berg, Marijke J.C. Timmermans, Ole K.L. Helgestad, Hanne B. Ravn, Adriaan O. Kraaijeveld, Luuk C. Otterspoor, Krischan D. Sjauw, Erik Lipšic, Annemarie E. Engström, Alexander P.J. Vlaar, Christian Hassager, Jacob E. Møller, José P.S. Henriques *European Heart Journal Acute Cardiovascular Care*, 2025
- Sex disparities in myocardial infarction related cardiogenic shock
Elma J Peters, Sanne Ten Berg, Margriet Bogerd, Annemarie E Engström, Wim K Lagrand, Marijke J C Timmermans, Luuk C Otterspoor, Krischan D Sjauw, Niels J W Verouden, Alexander P J Vlaar, José P S Henriques, on behalf of the PCI Registration Committee of the Netherlands Heart Registration *International Journal of Cardiology*, 2024

- Radial Access for PCI in Acute Myocardial Infarction Related Cardiogenic Shock: Underused, Underappreciated?

Bimmer EPM Claessen, Elma J Peters

JACC: Cardiovascular Interventions, 2023

- Characteristics and Outcome in Cardiogenic Shock according to Vascular Access Site for Percutaneous Coronary Intervention

Elma J Peters, Margriet Bogerd, Sanne Ten Berg, Marijke J C Timmermans, Annemarie E Engström, Holger Thiele, Christian Jung, Benedikt Schrage, Krischan D Sjauw, Niels J W Verouden, Koen Teeuwen, Admir Dedic, Martijn Meuwissen, Peter W Danse, Bimmer E P M Claessen, José P S Henriques**; Participating Centers of the PCI Registration Committee of the Netherlands Heart Registration

European Heart Journal Acute Cardiovascular Care, 2024

- Clinical Outcome and Cost-effectiveness of Reduced Noradrenaline Mediated Lower Mean Arterial Pressure Target in Patients with Cardiogenic Shock from Acute Myocardial Infarction: Rationale and Design of the NORshock study

E.J. Peters, S. ten Berg*, M. Bogerd, L.C. Otterspoor, A.E. Engström, W. K. Lagrand, M. Karami, C.J.W. Verouden, J.M. Montero-Cabezas, A.O. Kraaijeveld, E. Lipšic, S. Akin, C.A. den Uil, A.D. Cornet, P.S. Monraats, K.D. Sjauw, C. Hassager, M.S. Frydland, C. Jung, T. Balthazar, T. Goslar, J. Fluher, A. Mokhtari, A.S. Triantafyllis, J. Belohlavek, A. Gašceka, A.G. Proudfoot, G.F.T. Svingen, M.G.W. Dijkgraaf, A.P.J. Vlaar, J.P.S. Henriques*
Submitted

Not included in this thesis

- Biomarker Patterns in Patients with Cardiogenic Shock versus Septic Shock

Elma J. Peters, Martin S. Frydland, Christian Hassager, Lieuwe D.J. Bos, Lonneke A. van Vught, Olaf L. Cremer, Jacob E. Møller, Bert-Jan H. van den Born, Alexander P.J. Vlaar, Jose P.S. Henriques, on behalf of the MARS consortium

International Journal of Cardiology Heart & Vasculature, 2024.

DOI: 10.1016/j.ijcha.2024.101424

- Impella and venoarterial extracorporeal membrane oxygenation in cardiogenic shock complicating acute myocardial infarction
Margriet Bogerd, Sanne Ten Berg, Elma J Peters, Alexander PJ Vlaar, Annemarie E Engström, Luuk C Otterspoor, Christian Jung, Westermann D, Pöss J, Thiele H, Schrage B, Henriques JPS
European Journal of Heart Failure, 2023 DOI: 10.1002/ejhf.3025
- Knowledge gaps and research priorities in adult veno-arterial extracorporeal membrane oxygenation: a scoping review
S. Jorinde Raasveld, Carolien Volleman, Alain Combes, Lars M Broman, Fabio S Taccone, Elma J Peters, Sanne Ten Berg, Charissa E van den Brom, Holger Thiele, Roberto Lorusso, José PS Henriques, Alexander PJ Vlaar
Intensive Care Medicine Experimental, 2022.
DOI: 10.1186/s40635-022-00478-z
- Impact of symptom duration and mechanical circulatory support on prognosis in cardiogenic shock complicating acute myocardial infarction
Florien Klein, Caïa Crooijmans, Elma J Peters, Marcel van 't Veer, Marijke J C Timmermans, José P S Henriques, Niels J W Verouden, Adriaan O Kraaijeveld, Jeroen J H Bunge, Erik Lipsic, Krischan D Sjauw, Robert-Jan M van Geuns, Admir Dedic, Eric A Dubois, Martijn Meuwissen, Peter Danse, Gabe Bleeker, José M Montero-Cabezas, Irlando A Ferreira, Jan Brouwer, Koen Teeuwen, Luuk C Otterspoor; PCI registration committee of the Netherlands Heart Registration
Netherlands Heart Journal, 2024. DOI: 10.1007/s12471-024-01881-9
- Resource utilisation associated with extracorporeal membrane oxygenation versus microaxial flow pump for infarct-related cardiogenic shock
Margriet Bogerd, Luc Ten Hoorn 1, Sanne Ten Berg, Elma J. Peters, Annemarie E. Engström, Arjan Malekzadeh, Holger Thiele, Jacob E. Møller, Christian Hassager, Alexander P.J. Vlaar, José P.S. Henriques
European Heart Journal Acute Cardiovascular Care, 2025.
DOI: 10.1093/ehjacc/zuaf024

- Clinical use and impact of mechanical circulatory support for myocardial infarction-related cardiogenic shock in the Netherlands: a registry-based propensity-matched analysis

Margriet Bogerd, Alexander M Griffioen, Jeroen J H Bunge, Elma J Peters, Sanne Ten Berg, Marijke J C Timmermans, Adriaan O Kraaijeveld, Erik Lipsic, Luuk C Otterspoor, Gabe Bleeker, José M Montero-Cabezas, Krischan D Sjauw, Martijn Meuwissen, Eric A Dubois, Robert-Jan M van Geuns, José P S Henriques; PCI Registration Committee of the Netherlands Heart Registration Open Heart, 2025; DOI 10.1136/openhrt-2024-002846

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ABOUT THE AUTHOR

Elma Joyce Peters was born in Schoorl in 1993. She had a carefree time growing up there with her parents Ton and Tineke, and her older sister Mieke. She graduated from the Mummellius Gymnasium, Alkmaar, in 2011. From 2011 to 2014 she obtained her bachelor's degree in medicine at the University of Amsterdam. From 2014 to 2018 she obtained her master's degree with honors while working as a teaching assistant at the department of Anatomy, Embryology and Physiology. Her final internships were intensive care medicine (completed in het Flevoziekenhuis) and global medicine (completed in St. Lukes hospital in Malawi).

After graduating, she got her first job at the Intensive Care Unit in NoordwestZiekenhuis in Alkmaar under supervision of Cynthia Kleppe. This is where her enthusiasm for acute care, vital support and teamwork grew. After this, she worked as a resident not in training in the departments of Cardiology and Pulmonology in the Onze Lieve Vrouwe Gasthuis in Amsterdam under supervision of dr. Jutta Schroeder-Tanka and dr. Bob van de Berg.

She then returned to the place where her medical career took off, when she started working on her doctoral thesis at the department of Cardiology in the Amsterdam University Medical Center, location AMC. Under the direct supervision of prof. José Henriques and prof. Alexander Vlaar she studied the ins and outs of acute myocardial infarction related cardiogenic shock with a special focus on risk prediction and stratification. She stayed in Copenhagen for an international collaboration where she worked in the Rigshospitalet under supervision of prof. Christian Hassager. During her research years she also graduated as epidemiologist after completing the master Epidemiology at the Vrije Universiteit in Amsterdam.

Elma continues her career within the Amsterdam UMC where she started the anesthesiology training in January 2025.

