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ORIGINAL RESEARCH

Guideline-Recommended Time Less Than 90 Minutes From ECG to Primary Percutaneous Coronary Intervention for ST-Segment–Elevation Myocardial Infarction Is Associated with Major Survival Benefits, Especially in Octogenarians: A Contemporary Report in 11 226 Patients from NORIC

Alf Inge Larsen, MD, PhD*; Kjetil Halvorsen Løland, MD, PhD*; Siren Hovland, RN, MSc; Øyvind Bleie, MD, PhD; Christian Eek, MD, PhD; Eigil Fossum, MD, PhD; Thor Trovik, MD, PhD; Vibeke Juliebø, MD, PhD; Knut Hegbom, MD, PhD; Rasmus Moer, MD, PhD; Tomas Larsen, MD; Michael Uchto, MD; Svein Rotevatn, MD, PhD

BACKGROUND: Using contemporary data from NORIC (Norwegian Registry of Invasive Cardiology) we investigated the predictive value of patient age and time from ECG diagnosis to sheath insertion (ECG-2-sheath) in primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction (STEMI).

METHODS AND RESULTS: Data from 11 226 patients collected from all centers offering 24/7/365 primary percutaneous coronary intervention service were explored. For patients aged <80 years the mortality rates were 5.6% and 7.6% at 30 days and 1 year, respectively. For octogenarians the corresponding rates were 15.0% and 24.2%. The Cox hazard ratio was 2.02 (1.93–2.11, *P* value <0.0001) per 10 years of patient age. Time from ECG-2-sheath was significantly associated with mortality with a 3.6% increase per 30 minutes of time. Using achievement of time goal <90 minutes in patients aged >80 years and mortality at 30 days, mortality was 10.5% and 17.7% for <90 or ≥90 minutes, respectively. The number needed to prevent 1 death was 39 in the whole population and 14 in the elderly.
Restricted mean survival gains during median 938 days of follow-up in patients with ECG-2-sheath time <90 minutes were 24 and 76 days for patients aged <80 and ≥80 years, respectively.

CONCLUSIONS: Time from ECG-diagnosis to sheath insertion is strongly correlated with mortality. This applies especially to octogenarians who derive the most in terms of absolute mortality reduction.

REGISTRATION: URL: https://helsedata.no/en/forvaltere/norwegian-institute-of-public-health/norwegian-registry-of-invasive-cardiology/.

Key Words: octogenarians ■ primary PCI ■ revascularization ■ STEMI ■ timing

Correspondence to: Alf Inge Larsen, MD, PhD, Department of Cardiology, Stavanger University Hospital, Helse Stavanger HF Postboks 8100 4068 Stavanger, Stavanger 4011, Norway. Email: alf.inge.larsen@sus.no

*A. I. Larson and K. H. Løland are co-first authors.

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CLINICAL PERSPECTIVE

What Is New?

- This study indicates that timely reperfusion with percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction is even more important in octogenarians.

What Are the Clinical Implications?

- These findings further support the new ST-segment–elevation myocardial infarction guidelines' time limits also for octogenarians.

Nonstandard Abbreviations and Acronyms

ECG-2-sheath	ECG diagnosis to sheath insertion
NORIC	Norwegian Registry of Invasive Cardiology
OHCA	out-of-hospital cardiac arrest
pPCI	primary percutaneous coronary intervention

It is recommended that the prehospital management of patients with ST-segment–elevation myocardial infarction (STEMI) is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary percutaneous coronary intervention (pPCI) available to as many patients as possible.[1] Mortality rates have decreased considerably following the implementation of pPCI as the standard of care for urgent revascularization.[2–7] Several factors, including prehospital logistics,[8,9] center volumes[10] and improved cardiac care[11] contribute to this positive development. Key predictors as door-to-balloon time[12] and infarct size[13] serve as indicators of quality.

Limitations of the current reports on prognosis in STEMI are that they are based on selected samples from hospitals voluntary registries,[14] trials[15] and surveys,[16] and thereby lack full population coverage. Furthermore, as noted in the current European Society of Cardiology (ESC) STEMI guidelines, the selection of a 90 through 120 minutes from STEMI diagnosis to percutaneous coronary intervention (PCI)-mediated reperfusion as the cut-off to choose PCI or fibrinolysis is based on relatively old registries and trials with different treatment strategies from those presented in the current guidelines.[1,17,18] In addition to symptom to reperfusion time, patient age also predicts outcome.[19,20] However, contemporary data on timely access to reperfusion therapy and in-hospital outcomes according to the age of older adults presenting with STEMI are limited.

Therefore, we investigated the predictive value of time from ECG diagnosis to sheath insertion (ECG-2-sheath), a mandatory data point in NORIC (Norwegian Registry of Invasive Cardiology), on mortality in patients, including patients aged ≥80 years, undergoing pPCI for STEMI in Norway.

METHODS

Data and methods used in the analysis, and materials used to conduct the research are available for purposes of reproducing the results or replicating the procedure. However, our data permit does not allow for distribution to third-party (explicitly states no data transfer abroad). Access is granted after proper application to the data authorities, in this case the Norwegian Institute of Public Health. After which we would be happy to accommodate the request.

Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Norwegian Institute of Public Health at hkr.oppdrag@fhi.no.

The NCDR (Norwegian Cardiovascular Disease Registry) is a nationwide mandatory, nonconsensual person-identifiable health registry[21] that collects data from all patient contacts with hospitals in Norway for cardiovascular diseases and procedures. NORIC is a national medical quality-registry connected to NCDR which comprises clinical and procedural information from invasive cardiac procedures in the PCI hospitals in Norway. There are 9 centers offering pPCI in Norway, all of them are open 24/7/365.

The registry has collected data from 2013 and had a full national coverage from January 1, 2015. Norwegian PCI centers have provided pPCI 24/7/365 for many years, but the adaption to registration in NORIC was gradual, center-by-center. The coverage for the 5 included PCI centers in 2014 was 99%. Approximately the same applies for 2013. We have no reason to suspect that the achieved results in nonincluded centers from 2013 to 2014 would materially alter the results of the analyses in any direction, as audits from 2015 onwards have shown consistent results between centers.

Information about date of deaths for patients in NORIC is obtained through linkage to the National Population Register using the Norwegian national identity number.

All invasive coronary procedures are registered in a web-based application directly in NORIC by the PCI-operator forthwith including patient, logistical and procedural data.

In NORIC the patients with STEMI are categorized in 5 subgroups: 1, STEMI admitted for pPCI within 24 hours of symptoms; 2, STEMI with symptoms

>24 hours; 3, admitted for rescue PCI following failed thrombolysis; 4, Invasive coronary assessment after successful thrombolysis; and 5, out-of-hospital cardiac arrest (OHCA) and STEMI.

Patient Selection

The current analysis includes all patients registered in NORIC from January 1, 2013 until May 27th, 2020, undergoing either successful or attempted pPCI for the indication STEMI with or without OHCA and a valid Norwegian identity number. Patients undergoing only coronary angiography (ie, false cath. laboratory activation, Takotsubo cardiomyopathy, moribund patients, etc), who had received thrombolytic therapy or presented later than 24 hours were excluded.

Ethical Considerations

NORIC[22] is a mandatory, nonconsensual person-identifiable quality health registry organized under the NCDR. The Norwegian Institute of Public Health is the data controller for the registry. Therefore, there are no signed informed consent forms. The regional national ethical committee approves the use of the data for publication # 33912.

Statistical Analysis

We present baseline characteristics of patients with either numbers (%) for categorical or median (interquartile range) for continuous variables. Between group differences were assessed using Fisher exact test for categorical or Kruskal–Wallis test for continuous variables.

All-cause mortality was investigated using the Cox proportional-hazards (PH) model for estimation of hazard ratios (HR) with associated 95% CIs. The independent variables were age as both continuous and categorical variable with and without adjustment for patient sex.

The effect of age on mortality was assessed with Kaplan–Meier plots for different age groups and continuous spline estimates of Cox PH estimated HR.

To assess delays in reperfusion several time intervals were defined from the available time variables; symptom onset, diagnostic ECG (most often prehospital), hospital arrival, sheath-insertion, and target vessel flow reestablished. The interval with good data completeness and deemed most robust was ECG-2-sheath insertion time, which we decided to use as a surrogate for the ESC guidelines time interval ECG-to-wire crossing. Differences in survival between those patients who achieved the recommended <90 minutes as well as 120 minutes time to sheath insertion and those who did not was modeled using Cox PH models as well as restricted mean survival time (difference in average time-to-event/area under the survival curve at a fixed time point) at median follow-up.

To adjust for possible confounders in multivariate Cox PH models variable selection and regularization using least absolute shrinkage and selection operator with penalized maximum likelihood was performed. Input variables were clinically meaningful covariates available before patient admittance to the catheterization laboratory and following treatment: patient age, sex, smoking, diabetes, hypertension, peripheral artery disease, history of prior revascularization, cardiogenic shock, cardiac arrest, contrast use, fluoroscopy time, admittance outside of office hours (1600-0800 hours), use of intracoronary imaging, history of heart failure, number of diseased coronary vessels, use of mechanical circulatory support, arterial access site, ECG-2-sheath time, in-laboratory complications, and complete revascularization at index procedure (n=20). The method needs complete data and because of row-wise deletion the number of patients was reduced to 4919.

For all relevant analyses described above a 2-sided *P* value of 0.05 was selected.

All data handling and analyses were done using R version 4.0.2 (R Core Team [2020]. R Foundation for Statistical Computing, Vienna, Austria) and Rstudio (RStudio Team [2020]. RStudio, Inc., Boston, USA).

RESULTS

Data from January 1, 2013 to May 27, 2020 were explored. During this time period 11 226 patients with valid Norwegian national identity numbers and with symptoms <24 hours undergoing pPCI including incomplete procedures (ie, wiring attempts but not successful revascularization) were included in the analyses. The incidence of pPCI for the years of 2015 through 2019 when the registry had full national coverage was 34, 32, 34, 36, and 35 per 100 000 people per year.

Demographics

Briefly 76% were men and median age was 64 years with a significant age difference between the sexes of 6 years (men 63 years and women 70 years of age, *P* value <0.0001). Cardiogenic shock was present in 5.1%, and 9.1% had OHCA (Table 1). For patients presenting with OHCA, the 30-day and 1-year mortality was 30.0% and 32.2%, respectively, while for cardiogenic shock it was 50.4% and 55.5%, respectively.

Clinical and Procedural Characteristics of the Elderly ≥80 years of Age

The elderly had a more even sex-distribution (54% men). In turns of coronary risk factors more elderly patients

Table 1. Baseline Characteristics

	Complete data (n)	Whole population (n=11 226)	Aged <80 y (n=9826)	Aged ≥80 y (n=1400)	*P* value
Patient characteristics					
Age (y), median (IQR)	11 226	64.00 (56.00, 73.00)	62.00 (54.00, 70.00)	84.00 (81.00, 87.00)	<0.0001
Sex, male n (%)	11 226	8536 (76.04%)	7777 (79.15%)	759 (54.21%)	<0.0001
BMI (kg/m^2), median (IQR)	9224	26.56 (24.22, 29.39)	26.87 (24.49, 29.70)	24.57 (22.41, 26.88)	<0.0001
SBT (mm Hg), median (IQR)	5936	130.00 (110.00, 149.00)	130.00 (110.00, 149.00)	127.50 (110.00, 148.75)	0.25
DBT (mm Hg), median (IQR)	5800	80.00 (69.00, 90.00)	80.00 (70.00, 90.00)	73.00 (60.00, 84.00)	<0.0001
Risk factors					
Diabetes, n (%)	10 720	1467 (13.68%)	1276 (13.57%)	191 (14.50%)	0.37
Hypertension, n (%)	10 409	4075 (39.15%)	3370 (36.85%)	705 (55.82%)	<0.0001
PAD, n (%)	10 063	434 (4.31%)	336 (3.78%)	98 (8.30%)	<0.0001
Current smoker, n (%)	9201	3734 (40.58%)	3575 (43.62%)	159 (15.82%)	<0.0001
Prior MI, n (%)	10 600	1464 (13.81%)	1200 (12.89%)	264 (20.51%)	<0.0001
Prior PCI, n (%)	11 079	1497 (13.51%)	1270 (13.08%)	227 (16.59%)	0.0005
Prior CABG, n (%)	11 161	329 (2.95%)	250 (2.56%)	79 (5.69%)	<0.0001
Prior stroke, n (%)	10 533	454 (4.31%)	343 (3.70%)	111 (8.79%)	<0.0001
Known left ventricular dysfunction (LVEF <50%)	9718	590 (6.01%)	472 (5.49%)	118 (10.57%)	<0.0001
Prehospital care and logistics					
Cardiac arrest, n (%)	11 226	1018 (9.07%)	940 (9.57%)	78 (5.57%)	<0.0001
Admittance between 1600 and 0800, n (%)	11 226	7143 (63.63%)	6307 (64.19%)	836 (59.71%)	0.001
Time from symptoms to ECG (min), median (IQR)	7566	90.00 (163)	90.00 (155)	115 (159)	<0.0001
ECG-2-sheath time (min), median (IQR)	6832	75.00 (52.00, 105.00)	75.00 (52.00, 104.00)	81.00 (56.50, 110.00)	0.0001
Cardiogenic shock on arrival, n (%)	11 226	576 (5.13%)	490 (4.99%)	86 (6.14%)	0.07
Medication at admittance					
ASA, n (%)	5807	1411 (24.30%)	1147 (22.71%)	264 (34.92%)	<0.0001
Statins, n (%)	10 490	2234 (21.30%)	1914 (20.87%)	320 (24.22%)	<0.0001
Angiographic data					
Extent of CAD					<0.0001
Single-vessel CAD, n (%)	11 217	6176 (55.06%)	5571 (56.74%)	605 (43.28%)	
Two-vessel CAD, n (%)	11 217	3049 (27.18%)	2631 (26.79%)	418 (29.90%)	
Three-vessel CAD, n (%)	11 217	1992 (17.76%)	1617 (16.47%)	375 (26.82%)	
Procedural data					
Radial access, n (%)	11 226	9957 (88.70%)	8795 (89.51%)	1162 (83.00%)	<0.0001
Fluoro time (min), median (IQR)	11 150	9.43 (6.00, 15.11)	9.30 (5.98, 14.80)	10.72 (6.72, 17.31)	<0.0001
Contrast volume (mL), median (IQR)	11 220	130.00 (100.00, 180.00)	132.00 (100.00, 180.00)	130.00 (100.00, 180.00)	0.02
Complete revascularization, n (%)	11 086	6785 (61.20%)	6124 (63.06%)	661 (48.07%)	<0.0001
Culprit only, n (%)	11 226	10 058 (89.60%)	8823 (89.79%)	1235 (88.21%)	0.08
No. of stents, mean (SD)	11 197	1.65 (0.93)	1.65 (0.93)	1.70 (0.98)	0.05
MCS, n (%)	11 226	291 (2.59%)	263 (2.68%)	18 (1.29%)	0.001

N=11 226 patients undergoing primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction in Norway from 2013 to May 2020. Continuous variables are presented as median (interquartile range) with the exception of number of stents which is presented as mean (±SD). Categorical variables are presented as number (%) and number/total number in subgroups. *P* value is for Kruskal–Wallis test for continuous variables with the exception for t test for number of stents. *P* value for categorical variables is from Fisher exact test. A 2-sided significance level 0.05 was selected. ASA indicates acetylsalicylic acid; BMI, body-mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DBT, diastolic blood pressure; ECG-2-sheath, ECG diagnosis to sheath insertion; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and SBT, systolic blood pressure.

had hypertension, peripheral artery disease and previous revascularization procedures, but the presence of diabetes was similar with the whole population and the rate of current smoking was lower (16%). Radial access was used in 83% (in contrast to 90% in younger patients, *P* value <0.0001). While fluoroscopic time

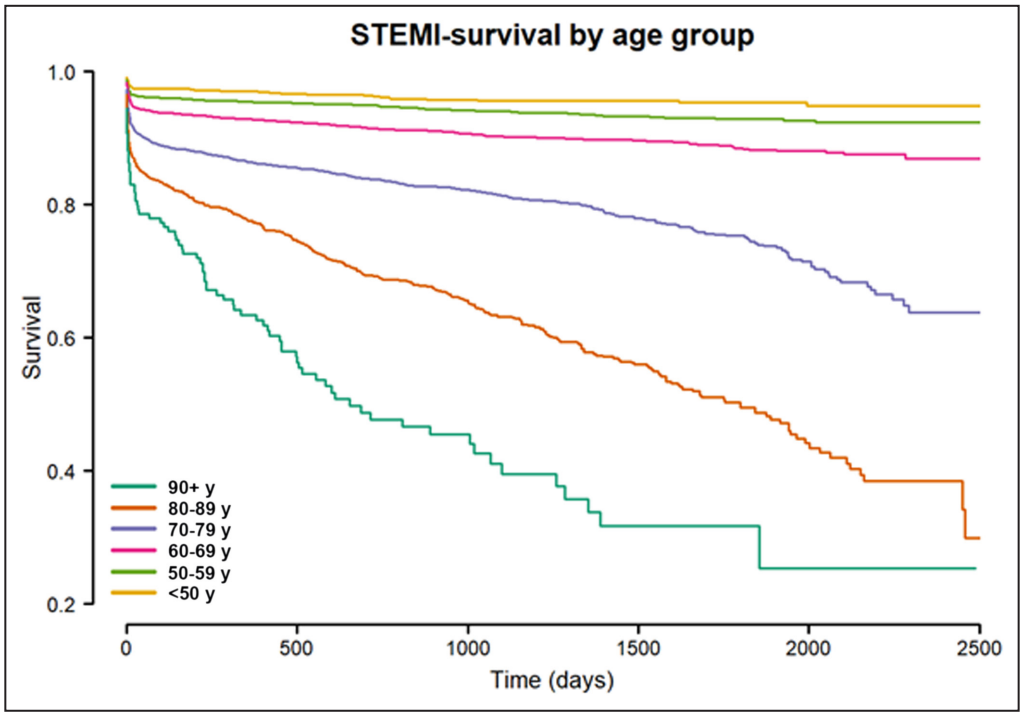

Figure 1. Survival (y-axis) in days (x-axis) following primary percutaneous coronary intervention for STEMI according to different age groups.
Y-axis truncated at 20%. STEMI indicates ST-segment–elevation myocardial infarction.

was increased (median 10 minutes 43 seconds versus 9 minutes 20 seconds, *P* value <0.0001), contrast use was somewhat lower in the elderly compared with the younger patients (median 130 versus 132 mL, *P* value 0.02). Culprit only PCI at index procedure was done in similarly rates (88% versus 90%, *P* value 0.08), but complete revascularization during hospital stay was achieved in only 48% versus 63%, reflecting a greater extent of coronary artery disease with 27% of the elderly presenting with 3-vessel disease in contrast to 16% of patients <80 years of age (Table 1).

Whole Population and Sex-Specific Mortality

Median follow-up was 938 days (interquartile range 379 to 1592 and maximum 2703 days). The total mortality was 14.1% during the entire follow-up.

Time-restricted mortality at 30 days and 1 year was 6.8% and 9.7% for the whole population. For men, 30-days and 1-year mortality was 6.2% and 8.7%—while there was a significant higher 30-days and 1-year mortality for women at 8.7% and 12.8% respectively. Female sex was associated with an increased risk for death following pPCI with a Cox Hazards Ratio (HR) (95% CI) of 1.54 (1.39–1.71, *P* value <0.0001) which was completely attenuated by adjusting for age (HR 0.98 [0.88–1.10], *P* value 0.77). Data not shown in table, only reported in text.

Age at Admission

Mortality was strongly dependent on age (Figures 1 through 3). The Cox HR was 2.02 (1.93–2.11, *P* value <0.0001) per 10 year of patient age. For patients younger than 80 years the mortality rates were 5.6% and 7.6% at 30 days and 1 year, respectively. For patients 80 years of age or older the corresponding rates

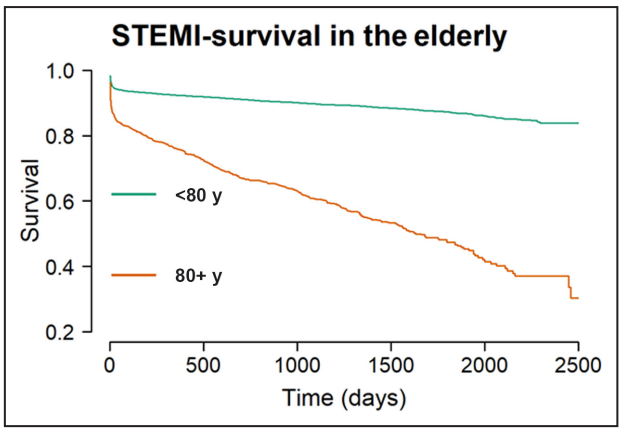

Figure 2. Survival (y-axis) in days (x-axis) following primary percutaneous coronary intervention for STEMI according to patients aged ≥80 or <80 years.
Y-axis truncated at 20%. STEMI indicates ST-segment–elevation myocardial infarction.

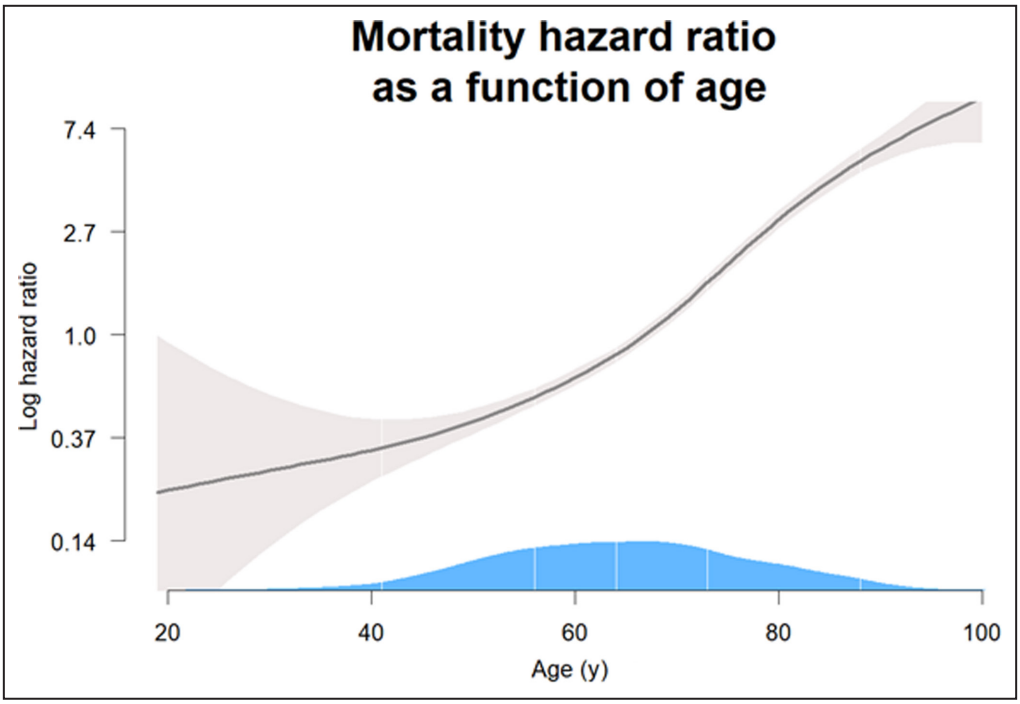

Figure 3. Smoothed spline Cox proportional hazard model for patient age at admission (x-axis) and log-transformed hazard ratio for mortality (y-axis).
Gray shaded area is the 95% CI and the blue shaded area over the x-axis the population density according to age, white lines denote the following percentiles from left to right: 2.5, 25, 50, 75, and 95.

were 15.0% and 24.2%. As presented in Table 2, the HR for the elderly was 4.53, (4.09–5.03, *P* value <0.0001).

Table 2. Cox Proportional Hazards Models

Univariate*	Hazard ratio (95% CI)	*P* value
Age continuous (per 10 y)	2.03 (1.94–2.12)	<0.0001
Age categorical (≥80 y)	4.53 (4.09–5.03)	<0.0001
Sex-adjusted†	**Hazard ratio (95% CI)**	***P* value**
Age continuous (per 10 y)	2.02 (1.93–2.11)	<0.0001
Age categorical (≥80 y)	4.39 (3.94–4.89)	<0.0001
Multivariate model‡	**Hazard ratio (95% CI)**	***P* value**
Age continuous (per 10 y)	2.23 (2.08–2.39)	<0.0001
Sex (men)	0.87 (0.75–1.00)	0.06
Extent of CAD (per vessel)	1.18 (1.08–1.28)	0.0002
Hypertension	1.05 (0.91–1.22)	0.47
Diabetes	1.60 (1.34–1.90)	<0.0001
Current smoker	1.39 (1.19–1.62)	<0.0001
Prior revascularization	1.08 (0.90–1.30)	0.39
Known reduced LVEF	2.15 (1.76–2.63)	<0.0001

Analyses using the Cox proportional hazards model estimating hazard ratio and associated 95% CI. CAD indicates coronary artery disease; and LVEF, left ventricular ejection fraction.
*Univariate model with age as explanatory variable.
†Age as explanatory variable adjusted for patient sex.
‡Multivariate Cox proportional hazards model.

A smoothed spline Cox PH model (Figure 3) showed a highly significant (*P* value <0.0001), mostly linear relationship between patient age and increasing risk for log-transformed mortality.

Multivariate Modeling

Multivariate models were designed using clinically relevant variables with few missing data and presented in Table 2. In summary, age, the presence of diabetes and known impaired left ventricular function was strongly associated with mortality. Both the presence of cardiogenic shock and OHCA profoundly affected the multivariate model and were not included as this arguably represents a different clinical entity (data not shown).

Time from Symptom Onset until ECG Diagnosis

Median (IQR) from symptom onset until ECG diagnosis was 90 (163) minutes and differed significantly between those younger than 80 years of age (median 90 minutes) and older (median 115 minutes), *P* value <0.0001. Cox PH modeling showed a linear relationship between symptoms-to-ECG delay in minutes and log-transformed mortality with a HR (95% CI) of 1.10 (1.04–1.17) per quartile, *P* value 0.002. Data were reported in text only.

Table 3. Time to Reperfusion

Cox proportional hazard ratio	Whole population (n=6818)		Aged <80 y (n=5976)		Aged ≥80 y (n=842)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
HR per 10 min increase in ECG-2-sheath time (min)*	1.012 (1.008–1.016)	<0.0001	1.013 (1.008–1.017)	<0.0001	1.010 (1.003–1.017)	0.004
HR for ECG-2-sheath time≥90 min*	1.49 (1.28–1.72)	<0.0001	1.52 (1.26–1.83)	<0.0001	1.31 (1.04–1.66)	0.02
HR for ECG-2-sheath time≥120 min*	1.73 (1.47–2.04)	<0.0001	1.93 (1.5–2.37)	<0.0001	1.32 (1.01–1.74)	0.04
Restricted mean survival time†	**Days lost (95% CI)**	***P* value**	**Days lost (95% CI)**	***P* value**	**Days lost (95% CI)**	***P* value**
ECG-2-sheath time >90 min	35 (23–48)	<0.0001	24 (12–35)	<0.0001	76 (23–128)	0.005
ECG-2-sheath time≥120 min	54 (36–72)	<0.0001	46 (29–63)	<0.0001	71 (5–137)	0.04

ECG-2-sheath indicates ECG diagnosis to sheath insertion; and HR, hazard ratio.
*Sex-adjusted hazard ratio estimates.
†Truncation time was set to median follow-up (938 days) to ensure stability of Kaplan–Meier estimates.

Time from ECG Diagnosis to Sheath Insertion

ECG-2-sheath and the relationship with mortality are presented in Table 3 and Figure 4. ECG-2-sheath time was significantly associated with mortality with HR: 1.012 (1.008–1.016, *P*=0.0001) per 10 minutes which translates into a 3.6% increase in mortality risk *per 30 minutes* of time from ECG to sheath insertion. This relationship was present irrespectively of patient age including the elderly with similar risk estimates. *Per quartile* of ECG-2-sheath time the HR (95% CI) for mortality increased by 1.21 (1.13–1.29, *P*-value <0.0001). For patients younger than 80 years of age HR was 1.24 (1.13–1.34, *P*-value <0.0001) and for the elderly 1.11 (1.00–1.24, *P* value 0.0495), respectively.

Survival in different age groups are presented in Table 3. When time from ECG-diagnosis until sheath insertion was more than 90 and 120 minutes, the HR (95% CI) was 1.49 (1.28–1.72, *P* value <0.0001) and 1.73 (1.47–2.04, *P* value <0.0001), respectively.

The difference in restricted mean survival at the median follow-up of 938 days showed that patients in the <90 minutes group had mean 35 days increased survival (*P* value <0.0001). For patients younger than 80 years, this difference was 24 days (*P* value <0.0001) while it was 76 days in the elderly (*P* value 0.005) (Figure 5). Estimates for sheath insertion more than 120 minutes after ECG diagnosis where 54 days lost (*P* value <0.0001) for the whole population and 46 days (*P* value <0.0001) for patients <80 years of age and 71 days (*P* value 0.04) for patients ≥80 years of age.

Using achievement of time goal (<90 minutes) in the elderly ≥80 years of age and survival at 30 days in a 2×2 table shown in Tables S1 through S4, survival in patients with valid ECG-2-sheath time was 10.7% and 17.9% for <90 or ≥90 minutes, respectively (Chi-square test, *P* value 0.0001). The number of patients, achieving the ECG-2-sheath time goal of less than 90 min, needed to prevent onedeath at 30 days, was 39 in the whole population and 14 in the elderly.

Data adjusted for comorbidities etc. using Cox PH model estimating hazard ratio and associated 95% CI are shown in Table S2.

Additional time points and intervals have been added in Table S3. Secondary analyses using Cox PH modeling of time to mortality according to door-to-flow time shown in Table S4.

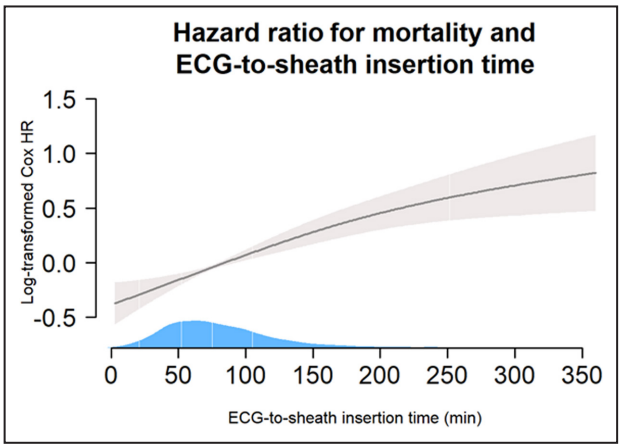

Figure 4. Smoothed spline Cox proportional hazard model of log-transformed hazard ratio for mortality (y-axis) according to time from ECG-2-sheath insertion (x-axis).
Gray shaded area is the 95% CI and the blue shaded area over the x-axis the population density according to age, white lines denote the following percentiles from left to right: 2.5, 25, 50, and 75 (95th percentile not visible). HR indicates hazard ratio.

DISCUSSION

The main findings in this report are that both symptom to ECG and ECG-2-sheath time was significant longer in the elderly (≥80 years) than in the younger patients. Furthermore, time from ECG-diagnosis to procedural start is strongly related to outcomes both in the general

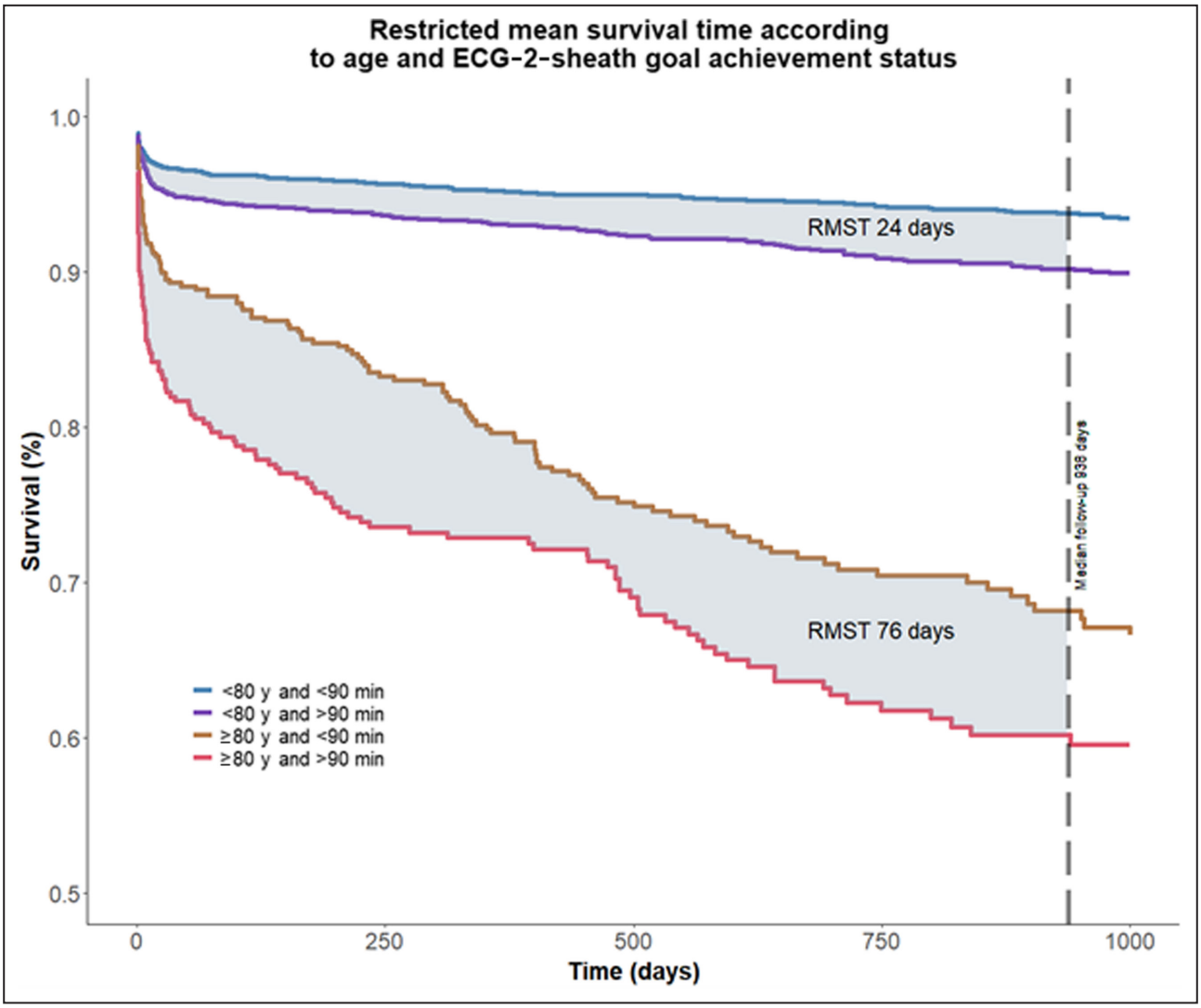

Figure 5. Restricted mean survival gain at the median follow-up time of 938 days according to age and time from ECG to treatment in octogenarians compared with the younger population.
ECG-2-sheath indicates ECG diagnosis to sheath insertion; and RMST, restricted mean survival time.

population, as well as in the elderly >80 years of age. Additionally, ECG-2-sheath time >90 minutes was associated with an even worse prognosis in the elderly aged ≥80 years compared with those <80 years confirming that achievement of guideline recommended time goals <90 minutes is associated with a major survival benefit, especially in the octogenarians.

The clinical characteristics with increased number of risk factors in the elderly ≥80 years of age are natural consequences of the aging process. Additionally, procedural characteristics with fewer patients being fully revascularized is also dependent on a higher relative number of patients with 3-vessel disease.

Although ischemic heart disease develops on average 7 through 10 years later in women compared with men, acute myocardial infarction remains a leading cause of death also in women. Despite improved outcome for both women and men with an invasive strategy in acute coronary syndrome,[23] women with STEMI are less likely to receive invasive management, revascularization, or preventive medication at discharge.[24,25] In line with this, younger age has been associated with higher 30-day mortality rates in women with STEMI even after adjustment for medications, primary PCI, and other coexisting comorbidities. This difference declines after age 60 and is no longer observed in the oldest women.[26] Thus, the results of the current study that show that although women have higher in-hospital mortality than men, female sex itself is not an independent risk factor for in-hospital mortality.[27] This is in accordance with a recent report from the Zwolle Myocardial Infarction Study Group showing that differences in mortality between men

and women with STEMI treated with pPCI are age-dependent.[28]

Despite adjustment for known risk factors, age thus remains as the variable with the strongest risk prediction value in multivariate Cox modeling. In addition to previous ischemic heart disease, diabetes, Killip class, creatinine, hemoglobin, troponin on admission, symptom-to-balloon-time and left ventricular ejection fraction, – *age* - per se has been shown to be a predictor of both 1-year mortality and hospitalization for heart failure.[29] In elderly patients with STEMI and multivessel disease, multivessel PCI is associated with better outcomes especially after staged procedures.[30] However, despite more favorable baseline characteristics, elderly patients with STEMI have worse survival and are at higher risk of stroke compared with patients with non–ST-segment–elevation acute coronary syndromeafter PCI.[31,32] Heart failure on admission and previous coronary artery disease have in addition to age, been shown to be prognostic variables. This is in line with the increased mortality associated with diabetes and reduced left ventricular ejection fraction in the current study.

Time from Symptom Onset until ECG-Diagnosis

Median time from symptom onset until ECG diagnosis differed significantly between those <80 years of age with additional 25 minutes in the elderly (shown in text in Results section). This in accordance with a recent published study in elderly patients treated with reperfusion therapy for STEMI.[33] Since patient-delay is also related to mortality—albeit weaker than for door-to-balloon delay, some of the difference in mortality could be attributable to delayed time from symptoms to ECG. This delay might be explained by atypical presentation,[34] cognitive status,[35] or earlier time to death among older adults.[36] However, using other forms of first medical contact than the organized emergency medical service is also associated increased time delay to diagnosis is verified.[37] Intense measures must therefore be taken to educate the public about the prognostic importance of an early and correct first action with an exclusive use of the emergency medical service when suspecting a myocardial infarction. Any effort must thus be made to keep the respective time intervals between the onset of symptoms and the beginning of reperfusion therapy as short as possible. On the other hand, there have been some unintended consequences of trying to reduce door-to-balloon time, as many as one third of activations of STEMI teams are now false alarms.[38]

Time to Reperfusion

The goal of reperfusion therapy is to restore blood flow to ischemic, but still viable, myocardium and reduce infarct size in a timely fashion, reducing the time to treatment and maximizing myocardial salvage—in keeping with the mantra that "time is muscle". Contemporary guidelines explicitly list maximal tolerated transfer delays to be shorter than 120 minutes, or even 60 minutes in cases where the patient first presents directly to a PCI-capable hospital or when presenting within 2 hours after symptom onset.[1] Maximum time from first medical contact to ECG diagnosis should be <10 minutes. If reperfusion with PCI can be performed within 120 minutes pPCI is the choice of strategy. In patients admitted directly to PCI hospitals this should be <60 minutes, and in transferred patients <90 minutes.

The ESC guideline recommended time limit of 120 minutes from ECG diagnoses until wire-crossing, was not logged in NORIC until recently. Time of ECG is defined as the time of recording. However, ECG-2-sheath insertion time is a good surrogate for time to wire crossing in well-established centers with experienced operators where sheath-to-wire crossing time is low and comparable with the time from ECG recording to established STEMI diagnosis.

In the current report 80% of the patients received pPCI within 115 minutes, with the longest delays in north of rural Norway. This is a quality indicator of a well-functioning pPCI network.[34]

In a recent study with 2823 patients admitted for pPCI for STEMI, a longer symptom-to-balloon time ≥180 minutes was the only component associated with higher in-hospital major adverse cardiovascular and cerebrovascular events in the present study.[39] Previously, the issue of interest was the door-to-balloon time. However, although door-to-balloon times have improved significantly for patients undergoing primary PCI for STEMI, in-hospital mortality has remained virtually unchanged.[40] This underlines that the whole chain of treatment from symptoms to reperfusion should be in focus, justifying a time from prehospital ECG to wire crossing of <90 minutes as the most important prognostic factor, as demonstrated in the current study, also in the elderly (aged ≥ 80 years) where it is associated with an average survival benefit of 76 days at 2.5 years of follow-up.

Strength and Limitations

Our study has several limitations including a selected population of patients with STEMI, who survived until hospital admission. We excluded both false scrambling of catheterization laboratory as well as patients who were dead at admission from the analyses. Only patients with a valid Norwegian national identity number were subject to this analysis, ie, excluding tourists and patients not entered correctly in the system. While NORIC has >99% coverage nationally, not all variables are complete.

On the other hand, a >99% national coverage of all pPCI procedures and use of the National Population Register, which includes all deaths should reassure robust data with generalizability. Data are entered into NORIC by the actual PCI-operator (usually) the same day. The technical aspects and variables of the procedure and time delays are thus more likely to be correct than if data were entered by nonphysician personnel using the electronic patient record system at a later time point.

Data are not externally monitored. However, data are continuously validated using automatic internal logical algorithms. In studies using general registries and medical records coverage might be low, but this is not the case in NORIC.

The use of "ECG-2-sheath insertion" is not a standard time metric for studies evaluating primary PCI. However, we used this time metric and not the other time intervals because this is the most robust representation of the true pre- and intrahospital logistical chain. The time of first balloon inflation is not logged in NORIC. Total ischemic time depends on both accurate time dating of symptom onset, which is subject to several challenges including, but not limited to recollection bias, patient sedation and agitation, crescendo or stuttering chest pain onset etc. as well as established flow. In cases with thrombolysis in myocardial infarction 3 flow at angiography, this time variable is set to "missing" by default. A minor part of the patients admitted with STEMI was not treated with PCI.

Most patients have thrombolysis in myocardial infarction (TIMI) flow 0, but some patients had TIMI 1-2 as usual in STEMI registries and studies. In addition, many patients continue to experience chest pain and ST-segment elevation after reestablished thrombolysis in myocardial infarction 3 flow, eg, due to microvascular obstruction, intramyocardial hemorrhage etc. When considering these points we concluded that time to flow was not robust. In addition, the degree of flow is subject to inter-observer variation in scoring.

The time point for insertion of the vascular sheath is more objective, happens in all patients, noted by the nurses on in-laboratory case forms and presumably has more at-random distribution of missing data. Also, considering that all ECGs are automatically time-stamped on recording we would argue that ECG-2-sheath insertion is more robust and more accurately describes the logistical chain. The degree of missing data is not materially different between the different time intervals (Table S3). In addition, median time from sheath insertion to flow is 11 minutes, arguably close to the speculated time from ECG-recording to STEMI-diagnosis by hospital physician after electronic transfer which in essence equates this interval with the ESC guideline recommended ECG-diagnosis-to-wire crossing.

CONCLUSIONS

Patient age at admission, but not sex adjusted for age, was a strong predictor for mortality in patients undergoing pPCI for STEMI. Time from ECG-diagnosis to sheath insertion was strongly correlated with mortality. Achievement of guideline recommended time goals <90 minutes for time from ECG to pPCI was associated with a major survival benefit, especially in the octogenarians.

ARTICLE INFORMATION

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Affiliations

Department of Cardiology, Stavanger University Hospital, Stavanger, Norway (A.I.L.); Institute of Clinical Sciences, University of Bergen, Bergen, Norway (A.I.L.); Norwegian Registry of Invasive Cardiology (NORIC) (K.H.L., S.H., S.R.) and Department of Heart Disease (K.H.L., Ø.B.), Haukeland University Hospital, Bergen, Norway; Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway (C.E.); Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway (E.F.); Department of Cardiology, University Hospital of North Norway, Tromsø, Norway (T.T.); Department of Cardiology, Akershus University Hospital, Lørenskog, Norway (V.J.); Clinic for Heart Disease, St. Olav's University Hospital, Trondheim, Norway (K.H.); LHL Hospital, Gardermoen, Norway (R.M.); Hospital of Southern Norway, Arendal, Norway (T.L.); and Division of Internal Medicine, Nordlandssykehuset, Bodø, Norway (M.U.).

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Supplemental Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. 30 day mortality according to ECG2sheath time over/under 90 minutes and age group.

Whole group

ECG2Sheath time	*Alive*	*Dead*	*Total*	*Percentage*
<90 min	4017	173	4190	4.1 %
90 min+	2351	170	2521	6.7 %
Total	6368	343		

Age <80yo

ECG2Sheath time	*Alive*	*Dead*	*Total*	
<90 min	2057	30	2087	1.4 %
90 min+	3598	123	3721	3.3 %
Total	5655	153		

Age >80yo

ECG2Sheath time	*Alive*	*Dead*	*Total*	
<90 min	294	64	358	17.9 %
90 min+	419	50	469	10.7 %
Total	713	114		

2x2 table showing survival at 30 days for all patients, and divided by age over/under 80 years according to ECG2sheath insertion time over/under 90 minutes.

Table S2. Regularized Cox PH model using LASSO for variable selection (n = 4 919 patients).

Model 1 including ECG2Sheath time* (AIC 5844.77)	**Hazard ratio (95% CI)**	**p-value**
Age continuous (per 10 years)	2.16 (1.96 - 2.38)	<0.0001
Sex (male)	0.81 (0.65 - 1.00)	0.05
Diabetes mellitus	1.53 (1.17 - 1.98)	0.002
Peripheral artery disease	1.65 (1.19 - 2.28)	0.003
Cardiogenic shock at admittance	3.88 (2.79 - 5.38)	<0.0001
Cardiac arrest	2.72 (1.87 - 3.96)	<0.0001
No history of reduced LVEF	0.56 (0.42 - 0.76)	0.0001
Fluro time (per minute)	1.002 (0.993 - 1.011)	0.64
MCS use (any device)	1.73 (1.09 - 2.73)	0.02
Radial access	0.55 (0.43 - 0.71)	<0.0001
In-lab complications (any)	2.78 (1.83 - 4.23)	<0.0001
Complete revascularization at index procedure	0.91 (0.74 - 1.12)	0.36
Ecg2sheath time (per 10 min)	1.007 (1.001 - 1.013)	0.03
Model 2 excluding ECG2Sheath time † (AIC 5846.474 ‡)		
Age continuous (per 10 years)	2.16 (1.95 - 2.38)	<0.0001
Sex (male)	0.80 (0.65 - 1.00)	0.05
Diabetes mellitus	1.53 (1.18 - 1.99)	0.001
Peripheral artery disease	1.69 (1.22 - 2.33)	0.002
Cardiogenic shock at admittance	3.97 (2.86 - 5.50)	<0.0001
Cardiac arrest	2.69 (1.85 - 3.92)	<0.0001
No history of reduced LVEF	0.56 (0.42 - 0.75)	<0.0001
Fluoro time (per minute)	1.002 (0.993 - 1.011)	0.64
MCS use (any device)	1.71 (1.09 - 2.70)	0.02
Radial access	0.56 (0.43 - 0.72)	<0.0001
In-lab complications (any)	2.77 (1.82 - 4.21)	<0.0001
Complete revascularization at index procedure	0.90 (0.73 - 1.11)	0.35

Analyses using the Cox Proportional Hazards model estimating hazard ratio and associated 95% confidence interval. Variable selection and regularization using LASSO with penalized maximum likelihood. Input variables was patient age, sex, smoking, diabetes, hypertension, peripheral artery disease, history of prior revascularization, cardiogenic shock, cardiac arrest, contrast use, fluoro time, admittance outside of office hours (1600-0800h), use of intracoronary imaging, history of heart failure, no. of disease coronary vessels, use of mechanical circulatory support, arterial access site, ECG2sheath time, in-lab complications and complete revascularization at index procedure (n = 20). The method needs complete data and due to row vise deletion, the number of patients was reduced to 4919. LASSO, least absolute shrinkage and selection operator; ECG, electrocardiogram; AIC, Akaike information criterion; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support.

*Model using all 20 variables as input.

†Model using all variables except ECG2sheath time.

‡AIC of model 2 is higher indicating poorer model fit.

Table S3. Missing observations according to variables (total n = 11 226).

Time points	Median (IQR)	Present - no. (%)	Missing - no. (%)
Onset of symptoms	NA	9730 (86.7)	1496 (13.3)
ECG	NA	8320 (74.1)	2906 (25.9)
Admittance	NA	10567 (94.1)	659 (5.9)
Sheath insertion	NA	8842 (78.8)	2384 (21.2)
Flow	NA	7401 (65.9)	3825 (34.1)
Time intervals			
Symptoms2ECG	90 (149) minutes	7413 (66.0)	3813 (34.0)
Symptoms2flow	187 (179) minutes	6348 (56.5)	4878 (43.5)
ECG2sheath	75 (53) minutes	6832 (60.9)	4394 (39.1)
ECG2flow	87 (55) minutes	5527 (49.2)	5699 (50.8)
Door2flow	27 (23) minutes	6746 (60.1)	4480 (39.9)
Sheath2flow	11 (8) minutes	5231 (46.6)	5995 (53.4)

Data completeness regarding logistical time points and subsequently derived intervals as well as median and interquartile range values for the latter. NA, not applicable; ECG, electrocardiogram.

Table S4. Door-to-flow time and mortality.

Cox Proportional Hazard Ratio	**Whole population (n = 6,737)**	
	Hazard ratio (95% CI)	*p-value*
HR per 10 min increase in door2flow time (min)*	1.034 (1.017 - 1.052)	<0.0001
HR per quartile of door2flow time (min)*	1.22 (1.15 - 1.29)	<0.0001
	<80 y.o. age (n = 6.015)	
	Hazard ratio (95% CI)	*p-value*
HR per 10 min increase in door2flow time (min)*	1.039 (1.018 - 1.061)	<0.0001
HR per quartile of door2flow time (min)*	1.22 (1.13 - 1.31)	<0.0001
	Age ≥ 80 y.o. age (n = 722)	
	Hazard ratio (95% CI)	*p-value*
HR per 10 min increase in door2flow time (min)*	1.002 (0.971 - 1.033)	0.92
HR per quartile of door2flow time (min)*	1.08 (0.97 - 1.20)	0.16

*Sex-adjusted hazard ratio estimates.