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Mortality Trends After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND Observational studies have reported that mortality rates after ST-segment elevation myocardial infarction (STEMI) have been stable since 2006 to 2010.

OBJECTIVES The aim of this study was to evaluate the temporal trends in 1-year, 30-day, and 31- to 365-day mortality after STEMI in Western Denmark where primary percutaneous coronary intervention (PCI) has been the national reperfusion strategy since 2003.

METHODS Using the Western Denmark Heart Registry, the study identified first-time PCI-treated patients undergoing primary PCI (pPCI) for STEMI from 2003 to 2018. Based on the year of pPCI, patients were divided into 4 time-interval groups and followed up for 1 year using the Danish national health registries.

RESULTS A total of 19,613 patients were included. Median age was 64 years, and 74% were male. One-year mortality decreased gradually from 10.8% in 2003-2006, 10.4% in 2007-2010, 9.1% in 2011-2014, to 7.7% in 2015-2018 (2015-2018 vs 2003-2006: adjusted HR [aHR]: 0.71; 95% CI: 0.62-0.82). The largest absolute mortality decline occurred in the 0- to 30-day period with a 2.3% reduction (aHR: 0.69; 95% CI: 0.59-0.82), and to a lesser extent in the 31- to 365-day period (risk reduction: 1.0%; aHR: 0.71; 95% CI: 0.56-0.90).

CONCLUSIONS In a high-income European country with a fully implemented pPCI strategy, 1-year mortality in pPCI-treated patients with STEMI decreased substantially between 2003 and 2018. Approximately three-quarters of the absolute mortality reduction occurred within the first 30 days after pPCI. These results indicate that optimization of early management of pPCI-treated patients with STEMI offers great opportunities for improving overall survival in contemporary clinical practice. (J Am Coll Cardiol 2023;82:999-1010) © 2023 by the American College of Cardiology Foundation.

The last 2 decades have witnessed major changes in the management of ST-segment elevation myocardial infarction (STEMI).[1,2] Some of the most wide-ranging changes are the implementation of primary percutaneous coronary intervention (pPCI) and the introduction of STEMI reperfusion networks as the cornerstones of reperfusion therapy. Although several observational studies have reported reductions in short- and long-term mortality in patients with STEMI,[3-6] the most recent studies showed stagnating mortality rates since 2006 to 2010.[5-10]

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ABBREVIATIONS AND ACRONYMS

aHR = adjusted HR

CABG = coronary artery bypass grafting

DES = drug-eluting stent(s)

FMC = first medical contact

MI = myocardial infarction

PCI = percutaneous coronary intervention

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

WDHR = Western Denmark Heart Registry

In Denmark, pPCI was implemented as a national strategy in 2003 after the DANAMI-2 (Danish Acute Myocardial Infarction 2) trial[11] showed that interhospital transport to pPCI was superior to fibrinolysis at the local hospital with a reduction in short- and long-term major adverse ischemic events.[11,12] Subsequent improvements in the management of STEMI included establishment of a national reperfusion network with direct referral of patients to the catheterization laboratory (ie, bypassing local hospitals and emergency departments),[13,14] a strategy also adopted in many other countries. Further advances include prophylactic medical treatment with high-intensity statins,[15] new potent $P2Y_{12}$ inhibitors,[16] and the introduction of drug-eluting stents (DES).[17] Furthermore, dedicated heart failure clinics and systematic cardiac rehabilitation programs have been established.[18]

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It is not known whether mortality rates after STEMI are still on a decline or have stagnated in Denmark. The present study investigated 1-year, early (0-30 days), and late (31-365 days) mortality and related changes in management and treatment among patients treated with pPCI for STEMI in Western Denmark from 2003 to 2018. Denmark is an ideal case for studying changes in STEMI mortality in a high-income European country with full implementation of a pPCI-based strategy and fast uptake of guideline-recommended therapy.

METHODS

DATA SOURCES. All patients admitted for PCI in the western part of Denmark have continuously been registered in the Western Denmark Heart Registry (WDHR) since 1999. This clinical database contains detailed patient-related, procedural, and lesion-specific data, and it covers a catchment area of approximately 3.5 million inhabitants. Western Denmark is covered by 3 high-volume PCI centers offering 24/7 services. Patients are registered in the database with their unique personal identification number, which all Danish citizens receive at birth or immigration. This allowed us to cross-link the WDHR with national health registries. We obtained information from the Danish Civil Registration System, which contains information on date of birth, sex, and vital status; the Danish National Patient Registry, which contains information on all inpatient and outpatient hospital contacts since 1977; and the Danish National Prescription Registry, which contains information on reimbursed prescriptions redeemed at Danish pharmacies since 1995.

The study was registered at the regional branch of the Danish Data Protection Agency (record number 1-16-02-625-18), and our local institutional ethical board approved data processing without informed consent (record number 1-45-70-118-22).

PATIENT SELECTION AND SETTING. The study included all adult (aged ≥18 years) first-time PCI-treated patients who underwent pPCI for STEMI between January 1, 2003, and October 31, 2018, in Western Denmark. Patients not residing in Denmark at the date of PCI and patients with symptom duration ≥12 hours were excluded. Furthermore, to ensure a first-time pPCI-treated cohort, patients with a history of PCI according to the WDHR or the Danish National Patient Registry were excluded. Patients were divided into 4 groups according to the year of pPCI (2003-2006, 2007-2010, 2011-2014, or 2015-2018). We started patient inclusion in 2003, which is when pPCI was implemented as the national reperfusion strategy for all patients with STEMI.

Furthermore, mortality was compared with individuals without history of MI, PCI, or coronary artery bypass grafting (CABG) sampled from the Western Denmark general population using the Danish Civil Registration System. Patients were matched (1:5 ratio) by age and sex on the day of pPCI.

COMORBIDITY, MEDICATION, AND OUTCOMES. Information on comorbidity at baseline was registered at the time of pPCI in the WDHR; ie, data on body mass index, smoking, hypertension, diabetes, Killip class, and critical preoperative conditions defined as occurrence of ventricular tachycardia, ventricular fibrillation or sudden cardiac death, preoperative resuscitation, ventilation, or use of intravenous inotropes or an intra-aortic balloon pump. These characteristics were supplemented with information on hospital contacts from the Danish National Patient Registry using full look-back of diagnoses since 1977.

In the general population cohort, only data from the Danish National Patient Registry were used. Use of preadmission and postadmission medication was defined as at least 1 redeemed prescription within 6 months before or after pPCI in the Danish National Prescription Database based on Anatomical Therapeutic Chemical codes. A full description of the International Classification of Diseases-10th Revision codes used and the Anatomical Therapeutic Chemical codes is available in Supplemental Table 1. Treatment delays were reported for the 2 most recent time

periods. Total treatment delay was reported as time from symptom onset to wire crossing and included both patient and system reasons for delay. System delay was reported as delay from first medical contact (FMC) to wire crossing. The study outcome was all-cause mortality at 1 year, 0 to 30 days, and 31 to 365 days. Outcome information was obtained from the Danish Civil Registration System.

STATISTICAL ANALYSIS. Patients were followed up from the day of pPCI and until the day of death, emigration, or end of 1-year follow-up. For each time period, 1-year cumulative incidence proportions and incidence rates per 100 person-years were estimated. In addition, we performed a landmark analysis for death from 0 to 30 days and from 31 to 365 days. Cumulative incidence proportion curves were constructed based on the Kaplan-Meier estimator. A Cox proportional hazards model was used to estimate crude and adjusted HRs (aHRs), in which we adjusted for age and sex (model 1) and confounders chosen a priori (model 2). Multiple imputations using chained equations was used in model 2 to account for missing data on smoking in 23% of patients. In the landmark analysis from 31 to 365 days, comorbidities used in adjusted model 2 obtained from national health databases (ie, diabetes, hypertension, peripheral artery disease) were updated up to day 31. The proportional hazards assumption was validated with visual inspection of log-minus-log plots.

For time trend comparisons, the first period (2003-2006) served as the reference. We also compared 1-year mortality in patients with STEMI with an age- and sex-matched general population cohort using the Kaplan-Meier estimator. Three sensitivity analyses were conducted. First, patients with a previous diagnosis of MI and prior CABG were excluded. Second, a complete case analysis was conducted. Third, to account for possible changes in prevalence of patients with a critical preoperative condition, a sensitivity analysis with inclusion of this variable in the multivariable model was conducted. Because this variable was introduced into the database from the second period, mortality changes from the second period and onward were assessed.

Data management and statistical analyses were performed by using STATA version 17.0 (StataCorp LP).

RESULTS

From 2003 to 2018, a total of 19,613 patients with STEMI underwent first-time pPCI in Western Denmark: 5,124 patients were treated from 2003-2006; 5,237 patients from 2007-2010; 4,449 patients from 2011-2014; and 4,803 patients from 2015-2018 (Supplemental Figure 1).

TABLE 1 Baseline Characteristics, Including Comorbidity and Comedication, According to Time Period

	2003-2006 (n = 5,124)	2007-2010 (n = 5,237)	2011-2014 (n = 4,449)	2015-2018 (n = 4,803)
Male	3,711 (72.4)	3,842 (73.4)	3,315 (74.5)	3,572 (74.4)
Age, y	64 (55-74)	64 (55-73)	64 (54-73)	65 (55-74)
Active smoking	2,006 (39.1)	1,741 (33.2)	1,920 (43.2)	1,867 (38.9)
Missing	1,438 (28.1)	1,906 (36.4)	491 (11.0)	593 (12.3)
BMI, kg/m^2	26 (24-29)	26 (24-29)	26 (24-29)	27 (24-30)
Missing	2,815 (54.9)	1,994 (38.1)	433 (9.7)	129 (3.5)
Familial ischemic heart disease	1,377 (26.9)	1,369 (26.1)	1,531 (34.4)	1,391 (29.0)
Missing	1,343 (26.2)	1,770 (33.8)	729 (16.4)	589 (15.8)
Comorbidity				
Diabetes	547 (10.7)	493 (9.4)	472 (10.6)	582 (12.1)
Hypertension	1,748 (34.1)	1,961 (37.4)	1,698 (38.2)	1,578 (42.3)
Prior myocardial infarction	402 (7.8)	266 (5.1)	160 (3.6)	126 (2.6)
Prior CABG	52 (1.0)	43 (0.8)	41 (0.9)	48 (1.0)
Prior ischemic stroke	246 (4.8)	238 (4.5)	154 (3.5)	170 (3.5)
Peripheral artery disease	271 (5.3)	267 (5.1)	193 (4.3)	226 (4.7)
Atrial fibrillation	326 (6.4)	293 (5.6)	256 (5.8)	286 (6.0)
Heart failure	502 (9.8)	375 (7.2)	280 (6.3)	367 (7.6)
Renal disease	123 (2.4)	126 (2.4)	133 (3.0)	148 (3.1)
COPD	306 (6.0)	328 (6.3)	235 (5.3)	282 (5.9)
Comedication				
Aspirin	911 (17.8)	849 (16.2)	592 (13.3)	519 (10.8)
Beta-blocker	817 (15.9)	757 (14.5)	608 (13.7)	583 (12.1)
ACE inhibitor or ATII receptor blocker	1026 (20.0)	1280 (24.4)	1098 (24.7)	1253 (26.0)
Calcium-channel blocker	698 (13.6)	817 (15.6)	741 (16.7)	823 (17.1)
Thiazide	598 (11.7)	628 (12.0)	432 (9.7)	382 (8.0)
Loop diuretics	361 (7.0)	317 (6.1)	229 (5.1)	234 (4.9)
Statin	607 (11.8)	899 (17.2)	769 (17.3)	864 (18.0)
P2Y$_{12}$ inhibitor	44 (0.9)	49 (0.9)	71 (1.6)	138 (2.9)
Oral anticoagulant treatment	108 (2.1)	129 (2.5)	116 (2.6)	177 (3.7)
Vitamin K antagonist	108 (2.1)	126 (2.4)	98 (2.2)	82 (1.7)
DOAC	0 (0.0)	3 (0.1)	21 (0.5)	96 (2.0)
Glucose-lowering drug	358 (7.0)	368 (7.0)	338 (7.6)	443 (9.2)
Insulin	152 (3.0)	148 (2.8)	117 (2.6)	156 (3.2)
Noninsulin glucose-lowering drug	248 (4.8)	264 (5.0)	263 (5.9)	356 (7.4)
Proton pump inhibitor	547 (10.7)	695 (13.3)	677 (15.2)	797 (16.6)

Values are n (%) or median (IQR).

ACE = angiotensin-converting enzyme; ATII = angiotensin II; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant.

PATIENT CHARACTERISTICS AND MEDICATION USE. The prevalence of most clinical parameters showed only minor changes during the study period (Table 1). Median age was 64 to 65 years, almost 75% of patients were male, around 40% were active smokers, median body mass index was 26 kg/m^2, and the prevalence of diabetes was 9% to 12%. Over time, more patients with STEMI were diagnosed with hypertension (34% [2003-2006] vs 42% [2015-2018]) and fewer patients had prior MI (7.8% [2003-2006] vs 2.6% [2015-2018]). Around 5% of patients were

TABLE 2 Procedure Characteristics (Patient-Level) and Lesion Characteristics (Lesion-Level) According to Time Period

	2003-2006 (n = 5,124)	2007-2010 (n = 5,237)	2011-2014 (n = 4,449)	2015-2018 (n = 4,803)
Procedure information				
No. of treated vessels				
1	4,690 (91.5)	4,904 (93.6)	4,222 (94.9)	4,434 (92.3)
≥2	429 (8.4)	333 (5.9)	227 (5.1)	369 (7.7)
Missing	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
No. of treated lesions				
1	4,089 (79.8)	4,377 (83.6)	3,843 (86.4)	4,066 (84.7)
2	808 (15.8)	707 (13.5)	493 (11.1)	587 (12.2)
≥3	174 (3.4)	122 (2.3)	97 (2.2)	140 (2.9)
Missing	53 (1.0)	31 (0.6)	16 (0.4)	10 (0.3)
Infarct location				
Anterior	2,162 (42.2)	2,169 (41.4)	1,866 (41.9)	1,972 (41.1)
Inferior	1,802 (35.2)	1,859 (35.5)	1,622 (36.5)	1,942 (40.4)
Posterior	622 (12.1)	718 (13.7)	536 (12.0)	580 (12.1)
Bundle branch block	135 (2.6)	172 (3.3)	115 (2.6)	104 (2.2)
Unable to classify	296 (5.8)	256 (4.9)	300 (6.7)	198 (4.1)
Missing	107 (2.1)	63 (1.2)	10 (0.2)	7 (0.1)
Killip class				
I	4,606 (89.9)	4,651 (88.8)	4,025 (90.5)	4,317 (89.8)
II	245 (4.8)	303 (5.8)	190 (4.3)	274 (5.7)
III	135 (2.6)	126 (2.4)	80 (1.8)	86 (1.8)
IV	138 (2.7)	157 (3.0)	154 (3.5)	126 (2.6)
Critical preoperative condition[a]	-	395 (7.5)	395 (8.9)	340 (7.1)
Emergency medical call to catheterization laboratory	-	349 (6.7)	342 (7.7)	347 (7.2)
Diagnostic visitation				
Prehospital diagnosis, transport to PCI center	-	-	2,439 (54.8)	4,046 (84.2)
Prehospital diagnosis, transport to local hospital	-	-	181 (4.1)	102 (2.2)
Diagnosis at local hospital	-	-	408 (9.2)	458 (9.5)
Diagnosis at PCI center	-	-	153 (3.4)	177 (3.7)
Unknown	-	-	440 (9.9)	14 (0.3)
Missing	-	-	828 (18.6)	0 (0.0)
Stent type (at least 1)				
DES	1,988 (38.8)	3,574 (68.2)	3,675 (82.6)	4,282 (91.2)
Newer-generation DES	7 (0.1)	2,683 (51.2)	3,667 (82.4)	4,281 (89.1)
BRS	0 (0.0)	0 (0.0)	22 (0.5)	32 (0.7)
BMS	2,477 (48.3)	1,127 (21.5)	328 (7.4)	75 (1.6)
Arterial access				
Femoral	4,268 (83.3)	5,016 (95.8)	4,284 (96.3)	2,604 (63.9)
Brachial	34 (0.7)	17 (0.3)	4 (0.1)	16 (0.3)
Radial	195 (3.8)	204 (3.9)	161 (3.6)	1,722 (33.9)
Missing	627 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)
Glycoprotein IIb/IIIa inhibitor use	3,155 (61.6)	3,307 (63.1)	735 (16.5)	404 (8.4)
Missing	341 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Bivalirudin use	10 (0.2)	249 (4.8)	2,453 (55.1)	1,371 (30.1)
Missing	4,196 (81.9)	410 (7.8)	287 (6.5)	221 (5.3)
Cangrelor	-	-	-	898 (18.7)
Heparin only	1,915 (37.4)	1,691 (32.3)	1,325 (29.8)	2,107 (43.9)
Pretreatment with ticagrelor	0 (0)	0 (0)	2,798 (62.9)	4,274 (89.9)
Pretreatment with clopidogrel	4,120 (80.4)	4,769 (91.1)	1,397 (31.4)	290 (6.0)
Pretreatment with aspirin	4,923 (96.1)	5,093 (97.3)	4,349 (97.8)	4,711 (98.1)
Procedure time, min	-	19 (12-30)	18 (12-29)	20 (13-31)
Radiation dose, Gy cm^2	41 (20-85)	32 (16-60)	18 (9-33)	16 (9-30)
Contrast volume, mL	100 (75-160)	90 (60-120)	70 (50-100)	70 (50-100)
Fluoroscopy time, min	6.3 (4-10.4)	5.4 (3.4-9.8)	5.1 (3.1-9)	6.0 (3.5-10)

Continued on the next page

TABLE 2 Continued

	2003-2006 (n = 6,254)	2007-2010 (n = 6,206)	2011-2014 (n = 5,180)	2015-2018 (n = 5,599)
Lesion characteristics				
Lesion length, mm	14 (10-20)	15 (10-20)	15 (11-20)	18 (12-25)
Lesion type of worst lesion				
A	815 (13.0)	762 (12.3)	680 (13.1)	626 (11.1)
B1	2,979 (47.6)	1,531 (24.7)	1,218 (23.5)	1,280 (22.9)
B2	1,089 (17.4)	1,763 (28.4)	1,517 (29.3)	1,584 (28.3)
C	946 (15.1)	1,980 (31.9)	1,751 (33.8)	2,107 (37.6)
Missing	425 (6.8)	170 (2.7)	14 (0.3)	(<1)
Left main coronary artery lesion	99 (1.6)	117 (1.9)	96 (1.9)	160 (2.9)
Stent length, mm	18 (13-23)	18 (14-24)	18 (15-24)	23 (18-31)
Maximum balloon pressure, atm	15 (12-18)	16 (14-18)	16 (12-18)	18 (14-20)
Balloon diameter	3.5 (3.0-3.8)	3.5 (3.0-3.8)	3.4 (3.0-3.7)	3.5 (3.0-4.0)
Minimum lumen diameter before, mm	0.0 (0-0.25)	0.0 (0-0.25)	0.0 (0-0.25)	0.0 (0-0.30)
Minimum lumen diameter post-PCI, mm	3.4 (3.0-3.7)	3.3 (3.0-3.6)	3.2 (2.8-3.6)	3.5 (3.0-3.8)
TIMI flow pre-PCI				
0	3,137 (50.2)	3,089 (49.5)	2,533 (48.9)	2,607 (46.6)
1	338 (5.4)	397 (6.4)	314 (6.1)	306 (5.5)
2	871 (13.9)	807 (13.0)	592 (11.4)	666 (11.9)
3	1,719 (27.5)	1,763 (28.4)	1,727 (33.3)	2,017 (36.0)
Missing	189 (3.0)	170 (2.7)	14 (0.3)	(<1)
TIMI flow post-PCI				
0	165 (2.6)	159 (2.6)	117 (2.3)	121 (2.2)
1	91 (1.5)	72 (1.2)	49 (0.9)	51 (0.9)
2	407 (6.5)	232 (3.7)	162 (3.1)	176 (3.1)
3	5,404 (86.4)	5,572 (89.8)	4,838 (93.4)	5,248 (93.7)
Missing	187 (3.0)	171 (2.8)	14 (0.3)	(<1)
Bifurcation stenting	-	599 (9.7)	482 (9.3)	903 (16.1)
Missing	-	1,175 (18.9)	88 (1.7)	30 (0.5)
Aorta ostial lesions	-	382 (6.2)	148 (2.9)	219 (3.9)
Missing	-	1,178 (19.0)	88 (1.7)	30 (0.5)
Successful procedure	5,789 (92.6)	5,827 (93.9)	5,010 (96.7)	5,439 (97.1)
Missing	181 (2.9)	170 (2.7)	14 (0.3)	(<1%)

Values are N, n (%), or median (IQR). [a]Defined as 1 or more of the following: ventricular tachycardia or ventricular fibrillation or sudden cardiac death, preoperative resuscitation, preoperative ventilation, preoperative intravenous inotropes, or preoperative intra-aortic balloon pump.

BMS = bare-metal stent; BRS = bioresorbable stent; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

categorized as Killip class III or IV over the study period. Moreover, there was a stable prevalence of critical preoperative condition from 2007 to 2010 and onward, where this variable was routinely registered.

When comparing patients with STEMI in 2015-2018 vs patients in 2003-2006, fewer patients in 2015-2018 were treated with aspirin (11% vs 18%), beta-blockers (12% vs 16%), and thiazides (8% vs 12%) before diagnosis; more patients received angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (26% vs 20%), calcium-channel blockers (17% vs 14%), and statins (18% vs 12%). Baseline characteristics of patients with STEMI compared with the age- and sex-matched general population cohort for the entire study period are provided in Supplemental Table 2. Only minor differences in baseline characteristics were observed between patients with STEMI and the matched individuals, except for a higher prevalence of hypertension and diabetes in patients with STEMI.

TIME DELAYS. When comparing the 2 most recent time periods (2011-2014 and 2015-2018), the median time from symptom onset to wire crossing decreased from 180 minutes (IQR: 122-300 minutes) to 171 minutes (IQR: 199-292 minutes). The median time from FMC to wire crossing was 98 minutes (IQR: 76-130 minutes) in 2015-2018, with 70% of patients being treated within the recommended time frame of 120 minutes from FMC to wire crossing. The proportion of patients who were diagnosed in the prehospital setting and transported directly to a PCI center was 84% in the most recent period (2015-2018).

PROCEDURE AND LESION CHARACTERISTICS. Procedure and lesion characteristics are described in

TABLE 3 Temporal Trends in 1-Year Mortality in Patients With STEMI According to Time Period for pPCI

	N	Events	Incidence Rate per 100 Person-Years (95% CI)	1-Year Cumulative Incidence (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
2003-2006	5,124	553	11.86 (10.92-12.90)	10.79 (9.97-11.68)	Reference	Reference
2007-2010	5,237	542	11.35 (10.43-12.35)	10.35 (9.56-11.21)	0.96 (0.85-1.08)	0.92 (0.81-1.05)
2011-2014	4,449	404	9.82 (8.91-10.83)	9.08 (8.27-9.96)	0.83 (0.73-0.95)	0.84 (0.73-0.97)
2015-2018	4,803	368	8.19 (7.39-9.07)	7.66 (6.94-8.45)	0.70 (0.61-0.80)	0.71 (0.62-0.82)

Values are n unless otherwise indicated. [a]Adjusted for age (spline), sex, smoking status, diabetes, hypertension, peripheral artery disease, Killip class, and prior myocardial infarction, with all comorbidities as binary covariates.

pPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Infarct location was similar over time. Most STEMIs were located in the anterior or inferior wall. From 2003-2006 to 2015-2018, the prevalence of pre-PCI TIMI flow grade 3 increased from 27% to 36% and the post-PCI TIMI flow grade 3 increased from 86% to 94% in the culprit vessel.

Several changes in the PCI procedure were introduced. In the first period, 48% of patients were treated with bare-metal stents, whereas 91% of patients in the last period received a drug-eluting stent. Newer-generation DES replaced first-generation DES from the second period (2007-2010) and onward. When comparing the first period vs the last period, there was an increased use of the radial approach (4% vs 34%), a decreased use of glycoprotein IIb/IIIa inhibitors (62% vs 8%), and an increased use of cangrelor (0% vs 19%). The use of bivalirudin peaked in 2011-2014 (55%). There was a gradual increase in stenting of type B2/C lesions, which may reflect changes in stenting practice with the implantation of longer DES aiming for "normal-to-normal vessel" stent implantation. Moreover, operators used less radiation and contrast during the procedures.

STUDY OUTCOMES IN PATIENTS WITH STEMI. From 2003 to 2018, 1-year mortality decreased gradually in pPCI-treated patients with STEMI (Table 3, Figure 1). One-year mortality was 10.8% in 2003-2006, 10.4% in 2007-2010, 9.1% in 2011-2014, and 7.7% in 2015-2018. After adjustment for baseline confounders, this corresponded to a relative risk reduction of 29% (aHR: 0.71; 95% CI: 0.62-0.82) from the first to the last time period. The crude analysis showed very consistent results with both of the adjusted analyses (model 1 and model 2) (Supplemental Table 3). The largest absolute mortality reduction occurred from 0 to 30 days after PCI, where mortality was reduced from 7.4% in 2003-2006 to 5.1% in 2015-2018 (aHR: 0.69; 95% CI: 0.59-0.82). Among 30-day survivors, mortality was reduced from 3.7% to 2.7% the following 31 to 365 days (aHR: 0.71; 95% CI: 0.56-0.90) (Table 4, Central Illustration). Thus, based on the absolute reductions, approximately three-quarters of the 1-year mortality decline occurred from 0 to 30 days after STEMI. The multivariable model showed that apart from the reduced 1-year mortality by time period, diabetes (aHR: 1.51; 95% CI: 1.33-1.71), previous MI (aHR: 1.52; 95% CI: 1.31-1.75), and Killip class (Killip class II aHR: 2.41 [95% CI: 2.08-2.80]; Killip class III aHR: 9.70 [95% CI: 4.18-5.78]; Killip class IV aHR: 9.70 [95% CI: 8.53-11.02]) were independently associated with increasing mortality (Supplemental Table 4). In a sensitivity analysis excluding patients with prior MI or CABG showed results similar to the main analysis (Supplemental Table 5). Moreover, results were robust in the complete case analysis and with inclusion of critical preoperative condition in the multivariable model (Supplemental Tables 6 and 7).

PATIENTS WITH STEMI VS INDIVIDUALS FROM THE GENERAL POPULATION. When comparing 1-year mortality trends in patients with STEMI vs an age- and sex-matched general population, the absolute difference in 1-year mortality decreased from 7.6% in 2003-2006 to 5.2% in 2015-2018 (Table 5). Although mortality was reduced by 0.7% in the matched general population (decreasing from 3.2% in 2003-2006 to 2.5% in 2015-2018), the absolute mortality decline observed in patients with STEMI was approximately 4.5-fold as large (absolute reduction: 3.1%).

POSTDISCHARGE MEDICATION. Changes in postdischarge medication are presented in Supplemental Table 8. From 2003-2006 to 2015-2018, there was a major increase, from 3% to 87%, in postdischarge use of high-intensity statin treatment. Furthermore, antiplatelet therapy after pPCI switched from clopidogrel (90% in 2003-2006) to ticagrelor (80% in 2015-2018).

DISCUSSION

The present investigation assessed temporal trends in mortality and related changes in management,

medication, and interventional devices in consecutive patients with first-time pPCI-treated STEMI from 2003 to 2018 in Western Denmark. The study was undertaken in a high-income European country where pPCI was fully implemented in 2003 and with rapid uptake of guideline-directed treatments.

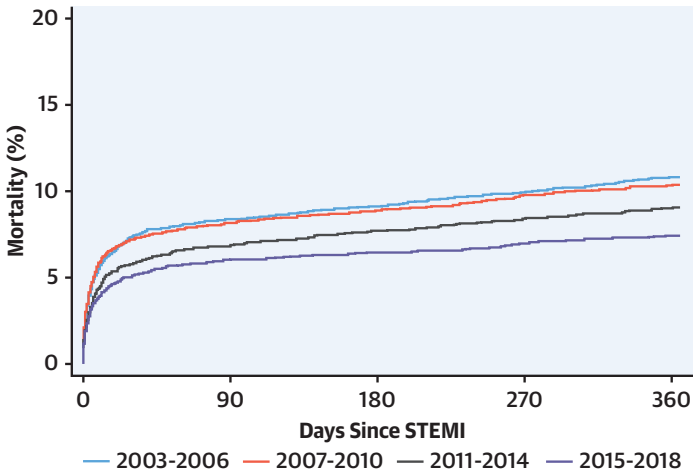
We report 4 main findings. First, from 2003-2006 to 2015-2018, the 1-year mortality gradually declined without showing signs of a plateau phase. The absolute risk reduction within the study period was 3.1%, corresponding to nearly 30% adjusted relative risk reduction. Second, the largest absolute decline in mortality was observed from 0 to 30 days after pPCI, with an absolute mortality reduction of 2.3%, whereas an absolute mortality reduction of 1.0% was observed in the 31- to 365-day period. Third, the gradual improvement in cardiovascular prognosis coincided with optimization of prehospital triage, increased use of secondary preventative treatments, and changes in the PCI procedure, including implantation of newer-generation DES. In the last time period, approximately 5 of 6 patients were diagnosed in the prehospital setting and directly transported to a PCI center, and the median delay from symptom onset to wire crossing was reduced to 171 minutes. For comparison, in DANAMI-2 (1997-2001), this delay was 224 minutes for patients randomized to undergo pPCI at referral hospitals and 188 minutes for those randomized to treatment at invasive centers.[11] Fourth, the observed absolute mortality reduction in patients with STEMI was approximately 4.5-fold as large as that observed in a matched general population, which indicates that the observed reduction in STEMI mortality should be explained by more than general improvements in public health.

TREATMENT DELAY. The present study showed a stepwise reduction in 1-year, 0- to 30-day, and 31- to 365-day mortality from the first period to the last period in a cohort of first-time pPCI-treated patients with STEMI. Importantly, the largest absolute mortality reduction occurred within 0 to 30 days, with 1 additional death prevented within 30 days for every 43 patients with STEMI undergoing pPCI in 2015-2018 compared with patients in 2003-2006. In comparison, from 31 to 365 days, 1 death per 105 patients with STEMI was prevented in those alive at 30 days. This indicates a large mortality benefit derived from changes in management and treatment in the early phase of STEMI (ie, in the prehospital and in-hospital phases).

Coinciding with the DANAMI-2 trial, the first steps toward prehospital electrocardiography transmission from the ambulance to a pPCI-capable hospital were taken in Western Denmark.[19] After the DANAMI-2 trial was published in 2003, the prehospital triage in Denmark was reorganized to reduce treatment delay and, hereby, total ischemic time.[11,13] By 2006, all ambulances had equipment for prehospital transmission of the electrocardiography data to the pPCI center, and the combination of prehospital diagnosis plus field triage enabled direct referral of patients with STEMI to pPCI centers with 24/7 service.[13] The delay from symptom onset to wire crossing in DANAMI-2 was 188 minutes for patients admitted at invasive centers and 224 minutes for patients admitted in local hospitals.[11] In a 2002-2008 series of real-world patients with STEMI from Western Denmark, these delays were 172 minutes for patients field-triaged directly to pPCI vs 240 minutes for patients admitted at local hospitals and transferred for pPCI.[13] In the present study, 84% of the patients were diagnosed and referred directly to one of the PCI centers, and the median treatment delay was reduced to 171 minutes in all patients (both referred and transferred patients). Thus, the median treatment delay observed in 2015-2018 was substantially reduced compared to both the reported delays in the DANAMI-2 trial[11] and our previous 2002-2008 report.[13]

The concept of "time is muscle" in STEMI is well accepted, and it has been estimated that every 60 minutes of treatment delay is associated with a

FIGURE 1 1-Year Mortality in Patients With STEMI According to pPCI Treatment Period



The figure illustrates the cumulative incidence curves of mortality up to 1 year after primary percutaneous coronary intervention (pPCI) according to treatment period. The mortality was gradually reduced after ST-segment elevation myocardial infarction (STEMI) from the first period to the last period.

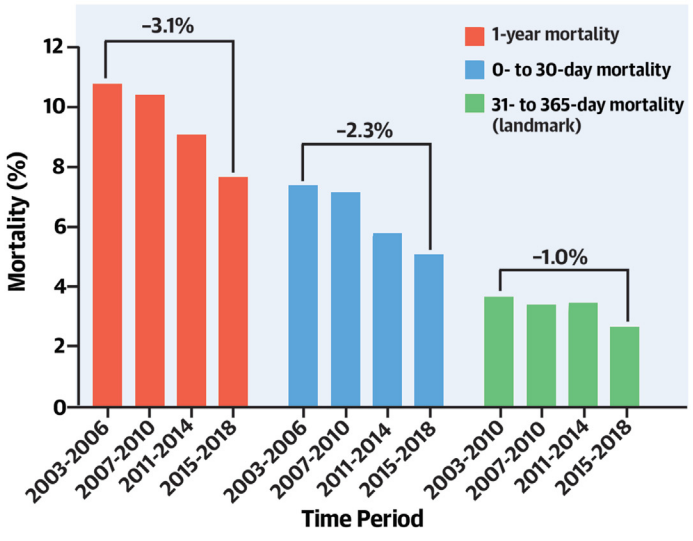
TABLE 4 Landmark Analyses of 0- to 30-Day and 31- to 365-Day Mortality in Patients With STEMI According to Treatment Period for pPCI

	N	Events	Cumulative Incidence (95% CI)	Absolute Risk Difference (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
0- to 30-day mortality						
2003-2006	5,124	380	7.42 (6.73 to 8.17)	Reference	Reference	Reference
2007-2010	5,237	377	7.20 (6.53 to 7.93)	0.22 (-0.79 to 1.23)	0.97 (0.84 to 1.12)	0.96 (0.83 to 1.10)
2011-2014	4,449	259	5.82 (5.17 to 6.55)	1.60 (0.60 to 2.60)	0.78 (0.67 to 0.91)	0.77 (0.66 to 0.90)
2015-2018	4,803	245	5.10 (4.51 to 5.76)	2.32 (1.36 to 3.28)	0.68 (0.58 to 0.80)	0.69 (0.59 to 0.82)
31- to 365-day mortality						
2003-2006	4,744	173	3.65 (3.15 to 4.22)	Reference	Reference	Reference
2007-2010	4,858	165	3.40 (2.92 to 3.95)	0.25 (-0.48 to 0.98)	0.93 (0.75 to 1.15)	0.93 (0.75 to 1.16)
2011-2014	4,190	145	3.46 (2.95 to 4.06)	0.19 (-0.57 to 0.95)	0.95 (0.76 to 1.18)	0.94 (0.75 to 1.18)
2015-2018	4,558	123	2.70 (2.27 to 3.21)	0.95 (0.24 to 1.66)	0.73 (0.59 to 0.93)	0.71 (0.56 to 0.90)

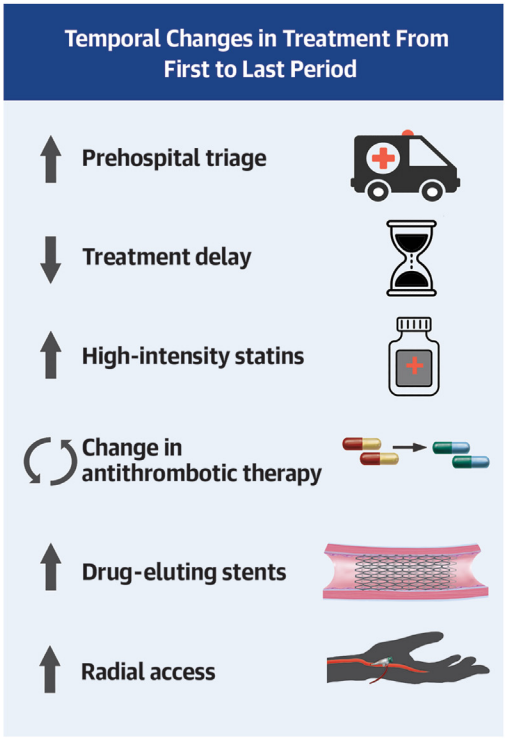
Values are n unless otherwise indicated. [a]Adjusted for age (spline), sex, smoking status, diabetes, hypertension, peripheral artery disease, Killip class, and prior myocardial infarction, with all comorbidities as binary covariates.

Abbreviations as in Table 3.

CENTRAL ILLUSTRATION 1-Year, 0- to 30-Day, and 31- to 365-Day Mortality Trends in Primary Percutaneous Coronary Intervention-Treated Patients With ST-Segment Elevation Myocardial Infarction



From 2003 and 2018:
Continuous reduction in 1-year mortality in pPCI-treated STEMI patients; three-quarters of this reduction was observed within the first 30 days.



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The figure illustrates a gradually decreasing 1-year mortality after primary percutaneous coronary intervention (pPCI)-treated ST-segment elevation myocardial infarction (STEMI) from the first period to the last period. The largest absolute mortality reduction was observed in the initial 30 days after STEMI. The mortality reduction coincided with changes in prehospital management and pharmacologic and interventional treatments.

TABLE 5 Temporal Trends in 1-Year Mortality in Patients With STEMI and a Matched General Population

			Matched General Population		Patients With STEMI		Absolute Difference in 1-Year Mortality After STEMI vs Matched General Population (%)[a]
	Events	N	1-Year Cumulative Incidence (95% CI)	Crude HR	1-Year Cumulative Incidence (95% CI)	Crude HR	
2003-2006	809	25,620	3.16 (2.95-3.38)	Reference	10.79 (9.97-11.68)	Reference	7.63 (6.76-8.50)
2007-2010	763	26,185	2.92 (2.72-3.13)	0.92 (0.83-1.01)	10.35 (9.56-11.21)	0.96 (0.85-1.08)	7.43 (6.56-8.30)
2011-2014	555	22,245	2.50 (2.30-2.71)	0.79 (0.70-0.88)	9.08 (8.27-9.96)	0.83 (0.73-0.95)	6.58 (5.71-7.45)
2015-2018	601	24,013	2.50 (2.31-2.71)	0.79 (0.71-0.88)	7.66 (6.94-8.45)	0.70 (0.61-0.80)	5.16 (4.29-6.02)

Values are n unless otherwise indicated. [a]Matched general population in the same calendar period was used as reference.
STEMI = ST-segment elevation myocardial infarction.

10% increase of death.[13] In addition to reducing time to pPCI treatment, prehospital diagnosis holds the advantage of early administration of unfractionated heparin and aspirin in the ambulance. Moreover, during this study period, our management protocol advised giving $P2Y_{12}$ inhibitor treatment as a bolus in the ambulance. From 2003 to late 2011, clopidogrel was used; from late 2011 to 2018, clopidogrel was replaced by ticagrelor. This switch from clopidogrel to ticagrelor was temporally associated with increased TIMI flow grade 3 pre-PCI and post-PCI. Thus, early diagnosis, field triage directly to a PCI center, early initiation of antithrombotic therapy, and change in prehospital antiplatelet regimen are possible explanations for the observed increase in pre-PCI TIMI flow grade 3 and the improved survival.

STATINS, ANTIPLATELET DRUGS, AND DES. From 2003 to 2018, there has been an increased focus on reducing the risk of subsequent ischemic events after STEMI and targeting the overall atherosclerotic burden with the introduction of long-term secondary preventive treatments.[1,2] Accordingly, we observed a rapid increase in the use of high-intensity statins around 2012,[15] and the antiplatelet regimen switched almost instantly from clopidogrel to ticagrelor after PLATO (Study of Platelet Inhibition and Patient Outcomes) was published in 2009.[16] These changes may be important for the reduction in 1-year mortality with a main effect on long-term mortality.[16,20]

In the present study, a gradual transition from bare-metal stents to first-generation DES[17] followed by increased use of newer-generation DES (89% in 2015-2018) was observed. These changes may have contributed to the reduction in late mortality from 31 to 365 days through a reduction of in-stent restenosis with first-generation DES and stent thrombosis with newer-generation DES.[21-23] Other important changes in pPCI technique include the switch from femoral to radial access and the decreased, and more selective, use of glycoprotein IIb/IIIa inhibitors; both of these changes may have reduced the risk of major bleeding events and led to reduced early mortality.[24,25]

IMPROVED SURVIVAL AFTER STEMI. Our findings support that the accumulated changes in management and treatment coincide with significant reductions in 1-year mortality in patients with STEMI. Importantly, the substantial 30-day mortality reduction indicate a large benefit derived from changes in prehospital and in-hospital management. Indeed, other factors, such as changes in the STEMI population or general improvements in societal health, could contribute to the observed mortality decline. However, changes in the STEMI population is considered to be limited as STEMI is a clinical diagnosis depending on only 2 factors, electrocardiography findings and symptoms, and this definition of STEMI has not changed over the years. Moreover, it is important to emphasize that pPCI has been the only accepted reperfusion strategy in Denmark since 2003 with no upper age limit for this treatment. Finally, the baseline clinical characteristics exhibited only minor changes over time.

To capture the changes in public health with increased life expectancy in the general population, we compared mortality trends vs those of an age- and sex-matched general population and found that the absolute reduction in STEMI 1-year mortality over time was around 4.5 times as large as that observed in the matched general population. Based on these findings, the observed reduced mortality from 2003 to 2018 should be explained by more than societal improvements.

PCI TREATMENT AND MORTALITY TRENDS IN OTHER COUNTRIES. Most recent studies assessing temporal trends in patients with STEMI in this century report that mortality first declined and then plateaued from around 2006 to 2010.[5-10] Based on these results, it has been suggested that the ceiling of treatment has been reached and that further lowering of mortality will be

difficult to achieve.[5,6] In studies from France[6] and Sweden,[5] approximately 75% were treated with pPCI in the most recent time period (from 2013-2015), whereas a recent U.S. registry study[26] (2018-2021) reported that 85% of patients with STEMI were treated with pPCI. Furthermore, in a study from New Zealand, 62% received PCI in 2016, but it was not clear if this included PCI after fibrinolysis in the early time periods, which may explain the lack of mortality improvement over time in this study (2006-2016).[10] In contrast, the studies from France and Sweden described a gradual transition from fibrinolysis to pPCI, coinciding with reduced mortality rates in the first decade of this century in these countries.[5,6]

These important studies differ in several ways from the present study. First, it is compulsory to register each patient with STEMI in the WDHR as this is part of a national surveillance program. Moreover, time delays are entered by the PCI operator at the time of arrival at the catheterization laboratory (ie, consecutive patients with STEMI treated with pPCI are reported in our study). In comparison, the U.S. "Get With The Guidelines-Coronary Artery Disease" program has a different primary aim as it is a voluntary quality improvement project with the objective of assisting participating hospitals in improving their processes of care. As adequately acknowledged by the authors, it is unlikely that consecutive patients with STEMI were entered into the U.S. registry.[26] In addition, time delays were obtained retrospectively by chart reviews. Second, complete implementation of pPCI is not possible in many countries as distance to a PCI-capable hospital and other factors preclude timely reperfusion by pPCI, and fibrinolysis was the chosen reperfusion modality in approximately 5% in most of these prior studies, even in the most recent time period.[5,6,26] In contrast, fibrinolysis has not been an acceptable treatment option in Denmark since 2003. Third, up to 20% of patients did not receive any reperfusion treatment in the aforementioned studies,[5,6,10,26] and in some of these,[5,10] it is unclear whether other causes of ST-segment elevation may have been included. One of the advantages of acute angiography as the default STEMI strategy is to confirm the diagnosis of an acute coronary occlusion; that is, acute angiography secures a high positive predictive value of the STEMI diagnosis, and the risk associated with unnecessary fibrinolysis is avoided.[27] We have previously shown that 80% of patients referred for acute angiography had an identifiable culprit lesion leading to pPCI.[27] In line with this finding, we could confirm that the proportion of first-time pPCI-treated patients with STEMI constituted 82% of patients undergoing first-time coronary angiography with an indication of STEMI in Western Denmark in the same period.

Besides these differences in study design, large geographic variations in clinical practice and management of patients with STEMI exist.[26,28] In a recent analysis of 32 mainly European countries, large variations in time delay to pPCI between countries were found, while the study reported smaller differences in use of guideline-recommended therapy.[28] In particular, system goals for time delay were not met in patients transferred from another hospital to PCI, which may represent both geographical challenges and lack of systems for prehospital triage. This finding was also observed in a recent U.S. registry study on time delays in patients with STEMI.[26] Notably, the U.S. registry study also reported a large number of walk-in/self-transporting patients (28%) who had longer patient delay (symptom onset to FMC). This is in contrast to Denmark, where patients are almost exclusively admitted via the general practitioner (who arranges emergency medical transport) or emergency medical telephone call.

Although the present study provides important new data showing that mortality in pPCI-treated patients with STEMI was continuously reduced from 2003 to 2018, there may be room for further optimization of the prehospital and in-hospital management of patients with STEMI. The delay from FMC to wire crossing has been reduced by up to 1 hour since the DANAMI-2 trial in 1999-2001. However, 30% of patients still had a delay beyond the 120-minute time frame in the most recent time period (2015-2018). Transportation by helicopter rather than ambulance may be a way to further reduce time delays. Other opportunities for improving STEMI care are increased use of radial approach[24] and optimizations in antithrombotic, lipid-lowering, or anti-inflammatory therapy.[29]

STUDY STRENGTHS AND LIMITATIONS. A default strategy of treating patients with STEMI with pPCI was introduced in Western Denmark immediately after the DANAMI-2 trial was published in 2003. This makes Western Denmark an ideal case for studying changes in treatment and mortality in pPCI-treated patients with STEMI. Moreover, a strength of our study is accurate individual-level record linkage of data sources in a taxpayer-funded health care system with equal access for all residents, which reduces selection bias. Limitations include the observational temporal design that precludes conclusions on causal relationships. Second, our data on prehospital delays

were limited to the data registered in the WDHR at the specific time point and thus only available for the last part of the study period. Moreover, left ventricular function was not routinely registered. Third, out-of-hospital cardiac arrest was not explicitly registered in our database but included as a composite measure of "critical preoperative condition"; however, this variable did display an overall stable trend.

CONCLUSIONS

In a high-income European country where pPCI has been the strategy for all patients with STEMI since 2003, 1-year mortality was reduced by approximately 30% from 2003-2006 to 2015-2018, with three-quarters of this mortality reduction observed within the first 30 days. These results indicate that optimization in the early management of patients with STEMI, including reductions in time delays and uptake of new guideline-initiated pharmacologic and interventional treatments, offers great opportunities for improving overall survival in contemporary clinical practice.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Mortality after STEMI in Denmark declined from 2003 to 2018, with the greatest reduction occurring in the initial 30 days. Improved outcomes coincided with prehospital diagnosis, field triage with transport to a PCI center, and advances in interventional techniques and in medical therapy for secondary prophylaxis.

TRANSLATIONAL OUTLOOK: Further efforts are needed to reduce treatment delay, optimize periprocedural treatment, and understand national and regional differences in outcomes based on demographic characteristics and systems of care.

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KEY WORDS myocardial infarction, prognosis, registry, reperfusion, time trends

APPENDIX For supplemental tables and a figure, please see the online version of this paper.