Acute Myocardial Infarction

Etienne Puymirat, Tabassome Simon, Guillaume Cayla, Yves Cottin, Meyer Elbaz, Pierre Coste, Gilles Lemesle, Pascal Motreff, Batric Popovic, Khalife Khalife, et al.

Acute Myocardial Infarction

Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015

BACKGROUND: ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation myocardial infarction (NSTEMI) management has evolved considerably over the past 2 decades. Little information on mortality trends in the most recent years is available. We assessed trends in characteristics, treatments, and outcomes for acute myocardial infarction in France between 1995 and 2015.

METHODS: We used data from 5 one-month registries, conducted 5 years apart, from 1995 to 2015, including 14423 patients with acute myocardial infarction (59% STEMI) admitted to cardiac intensive care units in metropolitan France.

RESULTS: From 1995 to 2015, mean age decreased from 66±14 to 63±14 years in patients with STEMI; it remained stable (68±14 years) in patients with NSTEMI, whereas diabetes mellitus, obesity, and hypertension increased. At the acute stage, intended primary percutaneous coronary intervention increased from 12% (1995) to 76% (2015) in patients with STEMI. In patients with NSTEMI, percutaneous coronary intervention ≤72 hours from admission increased from 9% (1995) to 60% (2015). Six-month mortality consistently decreased in patients with STEMI from 17.2% in 1995 to 6.9% in 2010 and 5.3% in 2015; it decreased from 17.2% to 6.9% in 2010 and 6.3% in 2015 in patients with NSTEMI. Mortality still decreased after 2010 in patients with STEMI without reperfusion therapy, whereas no further mortality gain was found in patients with STEMI with reperfusion therapy or in patients with NSTEMI, whether or not they were treated with percutaneous coronary intervention.

CONCLUSIONS: Over the past 20 years, 6-month mortality after acute myocardial infarction has decreased considerably for patients with STEMI and NSTEMI. Mortality figures continued to decline in patients with STEMI until 2015, whereas mortality in patients with NSTEMI appears stable since 2010.

Etienne Puymirat, MD, PhD
et al

The full author list is available on page 1917.

Correspondence to: Nicolas Danchin, MD, PhD, Hôpital Européen Georges Pompidou, Department of Cardiology, 20 rue Leblanc, 75015 Paris, France. E-mail nicolasdanchin@yahoo.fr

Sources of Funding, see p 1917

Key Words: coronary artery disease ■ mortality ■ non-ST elevated myocardial infarction ■ percutaneous coronary intervention ■ ST-elevation myocardial infarction

Clinical Perspective

What Is New?

- Previous observational studies have shown a continuous decline in mortality in patients with ST-segment–elevation and non–ST-segment–elevation myocardial infarction, but no studies beyond the early 2010s have analyzed trends in management and mortality.
- We observed major changes in the characteristics and management of both patients with ST-segment–elevation and non–ST-segment–elevation myocardial infarction over the past 20 years.
- Together with these changes, 6-month mortality has consistently declined in patients with ST-segment–elevation myocardial infarction, whereas, in patients with non–ST-segment–elevation myocardial infarction, 6-month mortality reached a plateau after 2010.

What Are the Clinical Implications?

- For patients presenting with ST-segment–elevation or non–ST-segment–elevation myocardial infarction, adoption of recommended strategies, such as promoted by current guidelines, is associated with improved outcomes and should be strongly encouraged.
- Acute-stage mortality has become extremely low in comparison with what was observed 20 years ago, and is not likely to further improve by much.
- The future challenges will be to reduce prehospital mortality (out-of-hospital sudden death) and to improve long-term survival after the acute event, both by increasing the adoption of recommended secondary prevention and by developing new preventative strategies.

The early outcome of patients with acute myocardial infarction (AMI) has improved considerably.[1–6] Among patients with AMI, however, the pathophysiology, management, and outcomes differ between those with ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation myocardial infarction (NSTEMI). Traditionally, patients with NSTEMI have a substantially lower early mortality than those with STEMI, but a higher risk of long-term mortality, likely explained by more frequent risk factors and comorbidities, and a greater burden of coronary artery disease.[7–9]

The improvement in early outcomes up to the early 2010s has been attributed to changes in patient populations, more frequent use of revascularization procedures, and increased use of recommended medications.[5,6,10–12] Since 2010, however, little information is available on early outcomes in real-world settings, although the use of percutaneous coronary interventions (PCIs) has continued to increase and newer antithrombotic agents have become available and are now widely used. Whether these changes in the most recent years have translated into improved early survival, and whether trends in early outcomes differ between patients with STEMI and those with NSTEMI is not known.

The aim of the present study was to assess trends in 6-month mortality in patients with STEMI and NSTEMI, according to their profile and initial management in 5 sequential nationwide French surveys conducted between 1995 and 2015.[13–17]

METHODS

Patient Population

Five nationwide French registries were conducted 5 years apart over a 20-year period (1995–2015): USIK 1995,[13] USIC (Unité de Soins Intensifs Coronaires) 2000,[14] FAST-MI (French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction) 2005 (NCT00673036),[15] FAST-MI 2010 (NCT01237418),[16] and FAST-MI 2015 (NCT02566200)[17] (Methods I in the online-only Data Supplement). The methods used for these registries have been detailed previously[13–17] In brief, their primary objectives were to evaluate the characteristics, management, and outcomes of patients with AMI, as seen in routine clinical practice, on a country-wide scale.

All 5 registries consecutively included patients with STEMI or NSTEMI admitted to cardiac intensive care units within 48 hours of symptom onset, during a specified 1-month period (November 1995 and 2000, October to December 2005, 2010, and 2015). AMI was defined by increased levels of cardiac biomarkers (troponins, creatine kinase [CK], or CK-MB) together with either compatible symptoms or ECG changes. Patients who died soon after admission and for whom cardiac markers were not measured were included if they had signs or symptoms associated with typical ST-segment changes. Exclusion criteria were (1) refusal to participate; (2) iatrogenic myocardial infarctions, defined as occurring within 48 hours of any therapeutic procedure; and (3) AMI diagnosis invalidated in favor of another diagnosis. STEMI was diagnosed when ST-segment elevation ≥1 mm was seen in at least 2 contiguous leads in any location on the index or qualifying ECG, or when presumed new left bundle-branch block or documented new Q waves were observed. In the absence of ST-segment elevation, patients meeting the inclusion criteria were considered to have NSTEMI.

Participation in the study was offered to all institutions, including university teaching hospitals, general and regional hospitals, and private clinics receiving AMI emergencies. Physicians were instructed that the study should not affect clinical care or management. The study was conducted in accordance with the guidelines on good clinical practice and French law. The study protocols for all surveys were reviewed by the relevant Committees for the Protection of Human Subjects. Data file collection and storage were approved by the Commission Nationale Informatique et Liberté. All patients were informed of the nature and the aims of the surveys and could request to be excluded; in addition, written consent was obtained for the 2005, 2010, and 2015 surveys.

Data Collection

Data on baseline characteristics, including demographics (age, sex, and body mass index), risk factors (hypertension, diabetes mellitus, current smoking, hypercholesterolemia, and family history of coronary artery disease), and medical history (myocardial infarction, stroke, heart failure, and peripheral artery disease), were collected as previously described.[13–17] Information on the use of cardiac procedures, including the use of PCI, use of medications (anticoagulants, antiplatelet agents, diuretics, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and lipid-lowering agents) in the first 48 hours (or first 5 days, for the 1995 survey) and at-hospital discharge (except for the 1995 survey) was collected. Full appropriate medical therapy was defined as concomitant use of antiplatelet agents, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and β-blockers when appropriate (Methods II in the online-only Data Supplement). Several additional variables were also collected in the most recent surveys.

Information on mortality was obtained directly by the local investigators for the 1995 and 2000 surveys. For the 2005, 2010, and 2015 surveys, follow-up was centralized at the French Society of Cardiology.

Statistical Analysis

Continuous variables are reported as means (SDs) or medians and interquartile ranges, when appropriate. Discrete variables are described as counts and percentages. Groups were compared by analysis of variance for continuous variables and χ^2 or Fisher exact tests for discrete variables. Temporal trends were tested using linear-by-linear association tests for binary and Jonckheere-Terpstra tests for continuous variables. Odds ratios and hazard ratios (HRs) are presented with their 95% confidence intervals (CIs).

To determine independent predictors of the use of procedures (reperfusion therapy in STEMI, PCI ≤72 hours of admission in NSTEMI), binary logistic regression analyses were used, using the same covariables as those listed below.

To account for changes in the baseline characteristics of the populations admitted from 1995 to 2015, we calculated risk scores for the 2015 STEMI and NSTEMI populations, using multiple logistic regression analysis including demographic data, risk factors, medical history, body mass index (using imputed values based on sex and age for the 6% of patients with missing values), and region. This risk score, calculated from the baseline characteristics of the 2015 population (c-statistic, 0.805 for the STEMI and 0.80 for the NSTEMI), was used to standardize the death rates for each of the previous surveys. The standardized death rates therefore represent the rates that would have been expected had the distribution of the baseline characteristics of each of the first 4 surveys been similar to that of the most recent one.

Multivariable analyses of correlates of 6-month mortality were performed using Cox backward stepwise multiple logistic regression, using a threshold of 0.10 for variable elimination. Beside time period, variables included in the final models were selected ad hoc, based on their physiological relevance and potential to be associated with outcomes; they comprised age, sex, risk factors, comorbidity, anterior location of myocardial infarction for STEMI, type of institution, and region. A sensitivity analysis was performed, adding peak CK to the covariates in the main analysis.

To assess the relationship between early management and 6-month survival, further analyses also used in-hospital PCI, type of anticoagulants used, and use of antiplatelet agents, β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during the first 2 days (5 days for the 1995 survey) as covariables, and in 3-day survivors to avoid healthy survivor bias.

Analyses were repeated by using forward stepwise analysis to check the consistency of the results. Collinearity was tested by calculation of variance inflation factors. Statistical analyses were performed by using IBM SPSS 23.0 (IBM SPSS Inc). For all analyses, 2-sided *P* values <0.05 were considered significant.

RESULTS

Study Population

In total, 14423 patients with AMI were enrolled in the 5 surveys. Of all centers managing patients with AMI, 62% (312 centers, 2152 patients) participated in 1995, 83% in 2000 (369 centers, 2317 patients), 60% in 2005 (223 centers, 3059 patients), 76% in 2010 (213 centers, 3079 patients), and 78% in 2015 (204 centers, 3813 patients). Over the 20-year period, the proportion of NSTEMI in the surveys increased: 29% in 1995, 21% in 2000, 47% in 2005, 44% in 2010, and 51% in 2015, corresponding to a change in operational diagnosis of NSTEMI (based on CK up to 2000, troponins in 2005 and 2010, and mostly high-sensitivity troponins in 2015).

In patients with STEMI, mean age decreased from 66.2±14.0 to 63.5±14.6 years, current smoking increased, as did the prevalence of obesity, hypertension, hypercholesterolemia, and diabetes mellitus, whereas history of cardiovascular disease decreased (Table 1).

In patients with NSTEMI, mean age, sex, and current smoking did not vary; hypertension, hypercholesterolemia, obesity, and diabetes mellitus increased. In contrast, history of heart failure and peripheral artery disease decreased (Table 2).

Early Management

In patients with STEMI, median time from symptom onset to hospital admission decreased from 240 (interquartile range, 140–540) minutes to 168 minutes (interquartile range, 100–398); time from onset to first call decreased from 2000 to 2010 and increased between 2010 and 2015, whereas the use of mobile intensive care units increased (Table 1). Reperfusion therapy consistently increased over time, from 49.5% to 82% (adjusted odds ratio 2015 versus 1995, 4.39; 95% CI, 3.73–5.18, *P*<0.001), with more frequent use of primary PCI (12%–76%) and less frequent use of fibrinolysis (37.5%–6%) (Figure I in the online-

Table 1. Baseline Characteristics and Early Hospital Management of Patients With ST-Segment–Elevation Myocardial Infarction From 1995 to 2015

	USIK 1995* (n=1536)	USIC 2000* (n=1844)	FAST-MI 2005 (n=1611)	FAST-MI 2010 (n=1716)	FAST-MI 2015 (n=1872)	*P* Value
Demography						
Age, y	66.2±14.0	64.5±14.6	64.0±14.7	63.3±14.5	63.5±13.8	<0.001
Female, n (%)	431 (28)	499 (27)	458 (28)	423 (25)	469 (25)	0.04
Risk factors, n (%)						
Hypertension	673 (44)	804 (44)	792 (49)	806 (47)	835 (45)	0.006
Hypercholesterolemia	534 (35.5)	719 (39.5)	699 (43)	675 (39)	678 (36)	<0.001
Diabetes mellitus	242 (16)	364 (20)	302 (19)	283 (16.5)	308 (16.5)	0.01
Current smoking	491 (32)	651 (35)	600 (37)	701 (41)	789 (42)	<0.001
Obesity (BMI ≥30)	208 (14)	269 (16)	299 (21)	324 (20)	349 (19.5)	<0.001
Cardiovascular history and comorbidities, n (%)						
Myocardial infarction	225 (15)	276 (15)	180 (11)	187 (11)	231 (12)	<0.001
PCI	–	139 (7.5)	140 (9)	175 (10)	236 (13)	<0.001
CABG	–	50 (3)	34 (2)	96 (6)	32 (2)	<0.001
Stroke or TIA	96 (6)	78 (4)	91 (6)	68 (4)	86 (5)	0.009
Heart failure	98 (6)	84 (5)	56 (3.5)	41 (2)	54 (3)	<0.001
PAD	148 (10)	145 (8)	85 (5)	83 (5)	84 (4.5)	<0.001
CKD	–	66 (4)	50 (3)	42 (2)	61 (3)	0.26
Medications before, n (%)						
Antiplatelet therapy	–	389 (21)	336 (21)	335 (19.5)	490 (26)	<0.001
Statin	–	304 (16.5)	342 (21)	374 (22)	398 (21)	<0.001
β-Blocking agent	–	338 (18)	296 (18)	313 (18)	341 (18)	0.99
ACE-I or ARB	–	349 (19)	395 (24.5)	478 (28)	449 (24)	<0.001
Initial pathway, n (%)						
Mobile ICU	–	427 (23)	666 (41)	837 (49)	953 (51)	<0.001
Time delays,† median [IQR]						
Onset to first call/medical contact	–	120 [40–360] (n=1486)	90 [30–295] (n=1600)	74 [30–240] (n=1674)	90 [30–300] (n=1872)	<0.001
Onset to admission	240 [140–540] (n=1427)	255 [150–540] (n=1706)	200 [120–430] (n=1610)	175 [107–380] (n=1698)	168 [100–398] (n=1843)	<0.001
First call/medical contact to primary PCI						
Direct admission	–	–	165 [110–240] (n=552)	140 [106–196] (n=1039)	131 [99–195] (n=1529)	<0.001
Transfer-in	–	–	230 [150–389] (n=107)	240 [156–379] (n=270)	214 [150–366] (n=358)	0.467
Presentation at admission						
Heart rate, mean±SD, bpm	–	78.2±19.0	78.3±19.7	78.0±20.9	77.3±17.4	0.263
SBP, mean±SD, mm Hg	–	132±27	135±28	141.2±28	134.3±26	0.001
Peak creatine kinase, U/L						
Mean (SD)	919 (928)	774 (781)	554 (805)	487 (779)	425 (673)	<0.001
No. of patients	585	452	1264	1015	876	
Reperfusion therapy, n (%)						
None	777 (51)	870 (47)	495 (31)	331 (19)	339 (18)	<0.001
Lysis	576 (37.5)	545 (30)	463 (29)	238 (14)	116 (6)	
Primary PCI	183 (12)	429 (23)	653 (40.5)	1147 (67)	1417 (76)	

(*Continued*)

Table 1. Continued

	USIK 1995* (n=1536)	USIC 2000* (n=1844)	FAST-MI 2005 (n=1611)	FAST-MI 2010 (n=1716)	FAST-MI 2015 (n=1872)	*P* Value
Procedures during hospitalization, n (%)						
CAG	–	1489 (81)	1449 (90)	1652 (96)	1846 (99)	<0.001
PCI	300 (19.5)	1132 (61)	1221 (76)	1488 (87)	1682 (90)	<0.001
Left ventricular ejection fraction (%)	49±13	52±14	51±13	50±11	50±10	0.228
Medications in first 48 h,‡ n (%)						
Antiplatelet therapy	1419 (92)	1759 (95)	1544 (96)	1672 (97)	1864 (100)	<0.001
Thienopyridine	–	–	1425 (88.5)	1682 (98)	1809 (97)	<0.001
Clopidogrel	–	–	1415 (88)	1459 (85)	509 (27)	<0.001
Prasugrel	–	–	–	571 (33)	457 (24)	<0.001
Ticagrelor	–	–	–	–	1102 (59)	–
GPIIb/IIIa inhibitors	–	351 (19)	614 (38)	732 (43)	441 (24)	<0.001
UFH	1481 (96)	1463 (79)	1074 (67)	768 (45)	1022 (55)	<0.001
LMWH	–	506 (27)	986 (61)	1069 (62)	1146 (61)	<0.001
Fondaparinux	–	–	–	232 (13.5)	352 (19)	<0.001
Bivalirudine	–	–	–	76 (4)	121 (6.5)	0.008
Statin	151 (10)	842 (46)	1262 (78)	1543 (90)	1576 (84)	<0.001
β-Blocking agents	1001 (65)	1348 (73)	1162 (72)	1384 (81)	1421 (75)	<0.001
ACE-I or ARB	733 (48)	764 (41)	853 (53)	1112 (65)	1201 (64)	<0.001
Diuretics	532 (35)	447 (24)	417 (26)	411 (24)	458 (24.5)	<0.001
Appropriate recommended therapy	109 (7)	506 (27)	763 (47)	115 (65)	1145 (62)	<0.001

Data are presented as n (%) or mean±SD. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft surgery; CAG, coronary angiography; CKD, chronic kidney disease; FAST-MI, French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction; GP, glycoprotein; ICU, intensive care unit; IQR, interquartile range; LMWH, low-molecular-weight heparin; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack; UFH, unfractionated heparin; and USIC, Unité de Soins Intensifs Coronaires.

* For 1995 and 2000, blank cells indicate data not available.

†Minutes; median [25th–75th percentiles].

‡ For 1995, medications used at any time during the first 5 days.

only Data Supplement). Coronary angiography during the index admission increased to reach 99% in 2015; in-hospital PCI increased from 19.5% to 90%. Use of evidence-based treatments during the first 48 hours from admission increased gradually; among P2Y12 inhibitors, there was a shift from clopidogrel to prasugrel and ticagrelor in the most recent surveys; unfractionated heparin decreased, and low-molecular-weight heparins or news anticoagulants (bivalirudine, fondaparinux) increased. Overall, the early use of full appropriate therapy increased from 7% in 1995 to 62% in 2015. Cardioverter defibrillators were implanted during the hospital stay in 0% (2005), 0.1% (2010), and 0.6% (2015). At hospital discharge, the proportion of patients receiving recommended medications consistently increased from 2000 to 2010 and remained stable in 2015 (Table I in the online-only Data Supplement).

In patients with NSTEMI, the use of early PCI (≤72 hours from admission) increased from 9% to 60% (adjusted odds ratio 2015 versus 1995, 16.4; 95% CI, 12.0–22.4, *P*<0.001) (Figure I in the online-only Data Supplement), and PCI during the initial hospital stay increased, from 12.5% to 67%, as did the use of coronary angiography at any time during the index admission increased, to reach 95% in 2015. Trends similar to those found in patients with STEMI were observed for evidence-based treatments within 48 hours of admission, as for discharge medications (Table 2, Table I in the online-only Data Supplement).

Outcomes

In-hospital complications decreased, as did 30-day mortality (from 14% to 3% in patients with STEMI and from 11% to 3% in patients with NSTEMI) (Tables II and III in the online-only Data Supplement).

Six-month mortality decreased from 17.2% to 5.3% in patients with STEMI. Adjusted HR for 6-month death in reference to 1995 consistently decreased over time, to 0.32 (95% CI, 0.26–0.41) in 2015. Standardized death rates decreased continuously from 15.4% in 1995 to 6.8% in 2010, and 5.3% in 2015 (Figure II in the online-only Data Supplement).

Table 2. Baseline Characteristics and Early Hospital Management of Patients With Non–ST-Segment–Elevation Myocardial Infarction From 1995 to 2015

	USIK 1995* (n=616)	USIC 2000* (n=476)	FAST-MI 2005 (n=1448)	FAST-MI 2010 (n=1363)	FAST-MI 2015 (n=1941)	*P* for Trend
Demography						
Age, y, mean±SD	68.5±14.2	68.9±13.5	70.2±13.3	68.6±13.6	68.1±13.5	<0.001
Female, n (%)	188 (30.5)	130 (27)	510 (35)	406 (30)	581 (30)	0.75
Risk factors, n (%)						
Hypertension	303 (50)	272 (57)	962 (66)	847 (62)	1220 (63)	<0.001
Hypercholesterolemia	221 (37)	225 (48)	749 (52)	653 (48)	979 (54)	<0.001
Diabetes mellitus	122 (20)	123 (26)	422 (29)	370 (27)	522 (27)	0.001
Current smoking	157 (26)	103 (22)	322 (22)	334 (24.5)	566 (29)	0.75
Obesity (BMI ≥30)	77 (13)	93 (22.5)	268 (21)	306 (24)	468 (25)	<0.001
Cardiovascular history and comorbidities, n (%)						
Myocardial infarction	169 (27)	135 (28)	345 (24)	311 (23)	469 (24)	0.055
PCI	–	77 (16)	260 (18)	314 (23)	462 (24)	<0.001
CABG	–	48 (10)	132 (9)	116 (8.5)	124 (6)	0.006
Stroke or TIA	44 (7)	33 (7)	141 (10)	71 (5)	143 (7)	<0.001
Heart failure	100 (16)	65 (14)	117 (8)	105 (8)	148 (8)	<0.001
PAD	73 (12)	70 (15)	197 (14)	161 (12)	190 (10)	0.003
CKD	–	42 (9)	113 (8)	87 (6)	136 (7)	0.25
Medications before, n (%)						
Antiplatelet therapy	–	192 (40)	610 (42)	538 (39.5)	828 (43)	0.28
Statin	–	119 (25)	472 (33)	490 (36)	712 (37)	<0.001
β-Blocker	–	132 (28)	437 (30)	425 (31)	646 (33)	0.07
ACE-I or ARB	–	147 (31)	615 (42.5)	552 (40.5)	734 (38)	<0.001
Presentation at admission						
Heart rate, mean±SD, bpm	–	82.9±22.0	81.0±20.9	81.1±19.9	79.0±19.6	<0.001
SBP, mean±SD, mm Hg	–	140±27	143±28.5	148±28	145±27	<0.001
Peak creatine kinase, U/L						<0.001
Mean (SD)	919 (928)	774 (781)	554 (805)	487 (779)	425 (673)	
No. of patients	585	452	1264	1015	876	
Procedures						
Coronary angiography, n (%)	–	338 (71)	1133 (78)	1232 (90)	1852 (95)	<0.001
PCI, n (%)	77 (12.5)	209 (44)	736 (51)	892 (65)	1292 (67)	<0.001
PCI ≤24 h	41 (7)	65 (14)	363 (25)	529 (39)	701 (36)	<0.001
PCI ≤72 h	55 (9)	118 (25)	558 (38.5)	745 (55)	1156 (60)	<0.001
Left ventricular ejection fraction (%)	52±14	54±15	53±14	53±11	53±11	0.775
Medications in first 48 h,† n (%)						
Antiplatelet therapy	546 (89)	445 (93.5)	1365 (94)	1338 (98)	1905 (98)	<0.001
Clopidogrel	–	–	1193 (82)	1223 (90)	790 (41)	<0.001
Prasugrel	–	–	–	183 (13)	98 (5)	<0.001
Ticagrelor	–	–	–	–	1000 (51.5)	–
GPIIb/IIIa inhibitors	–	59 (12)	491 (34)	330 (24)	115 (6)	<0.001
UFH	583 (95)	298 (63)	692 (48)	520 (38)	1062 (55)	<0.001
LMWH	–	194 (41)	959 (66)	818 (60)	965 (50)	<0.001
Bivalirudine	0	0	0	19 (1)	22 (1)	0.51
Fondaparinux	0	0	0	239 (17.5)	667 (34)	<0.001

(*Continued*)

Table 2. Continued

	USIK 1995* (n=616)	USIC 2000* (n=476)	FAST-MI 2005 (n=1448)	FAST-MI 2010 (n=1363)	FAST-MI 2015 (n=1941)	*P* for Trend
Statin	62 (10)	203 (43)	1021 (70.5)	1161 (85)	1521 (78)	<0.001
β-Blocker	372 (60)	306 (64)	955 (66)	1055 (77)	1377 (71)	<0.001
ACE-I or ARB	259 (42)	174 (37)	741 (51)	837 (61)	1100 (57)	<0.001
Diuretics	236 (38)	166 (35)	585 (40)	452 (33)	644 (33)	<0.001
Appropriate recommended therapy	34 (5.5)	118 (25)	611 (42)	853 (63)	1109 (58)	<0.001

Data are presented as n (%) or mean±SD. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; FAST-MI, French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction; GP, glycoprotein; ICU, intensive care unit; LMWH, low-molecular-weight heparin; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; UFH, unfractionated heparin; and USIC, Unité de Soins Intensifs Coronaires.

* For 1995 and 2000, blank cells indicate data not available.

† For 1995, medications used at any time during the first 5 days.

In patients with NSTEMI, mortality decreased from 17.2% to 6.3%, and adjusted HR decreased to 0.40 (95% CI, 0.30–0.54) in 2010, remaining stable at 0.40 (0.30–0.52) in 2015 (Figure 1). Results were similar when peak CK was entered as an additional variable (Table IV in the online-only Data Supplement). Standardized death rates decreased continuously from 15.3% in 1995 to 6.2% in 2010 and were marginally higher at 6.3% in 2015 (Figure II in the online-only Data Supplement).

Outcomes in Relation to Early Revascularization and Early Medications

In the whole STEMI population, mortality decrease remained significant even when both reperfusion therapy and early medications were entered as covariables (Table IV in the online-only Data Supplement). The results were stable after a sensitivity analysis censoring patients who died within 3 days of admission. In patients with reperfusion therapy, 6-month mortality decreased from 10.8% to 4.8%, with little additional gain beyond 2010 (adjusted HR, 0.41; 95% CI, 0.29–0.57 in 2010; 0.36; 95% CI, 0.26–0.50 in 2015), whereas the decrease in mortality persisted in those without early reperfusion, from 23.4% to 7.4% (adjusted HR 0.60; 95% CI, 0.44–0.83 in 2010; 0.32, 95% CI, 0.21–0.49 in 2015) (Figure 2).

In patients with NSTEMI, mortality decrease over time was no longer significant (adjusted HR 2015 versus 1995, 0.95; 95% CI, 0.66–1.36) when use of early

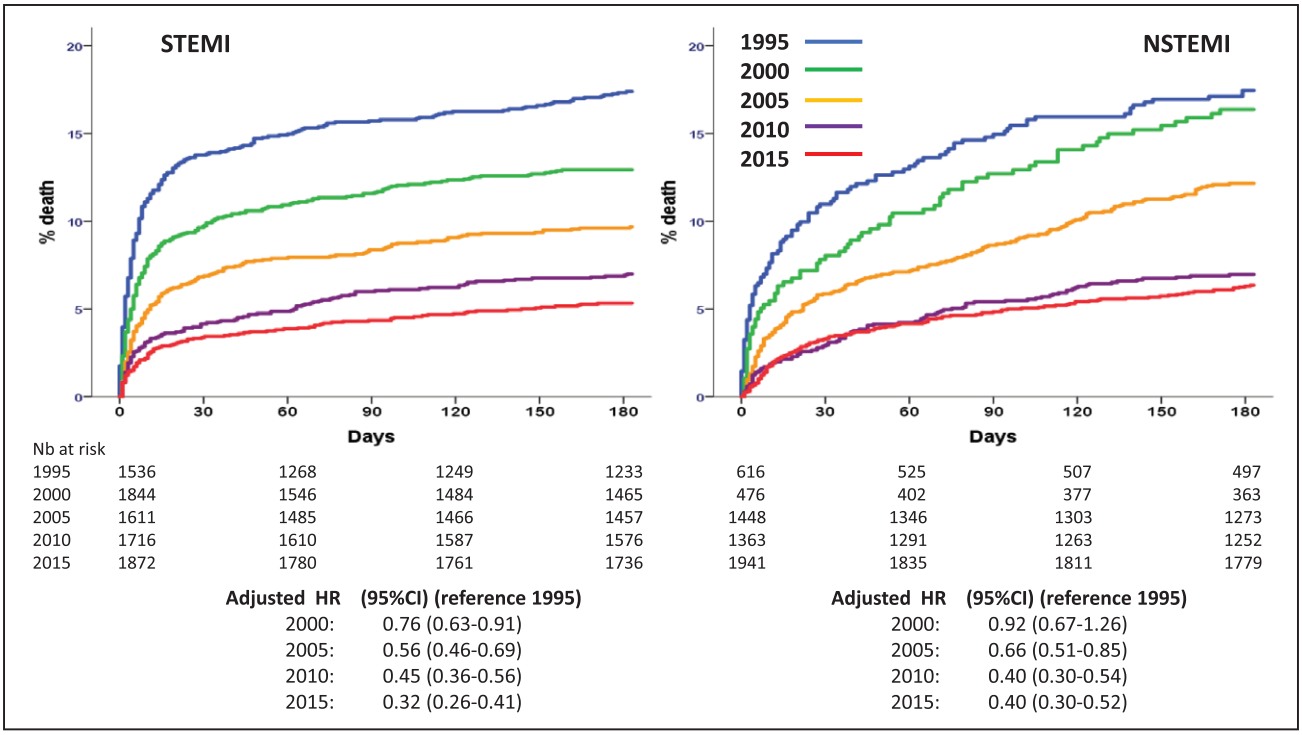

Figure 1. Cumulative 6-month mortality in patients with STEMI and NSTEMI by year of survey.
CI indicates confidence interval; HR, hazard ratio; NSTEMI, non–ST-segment–elevation myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

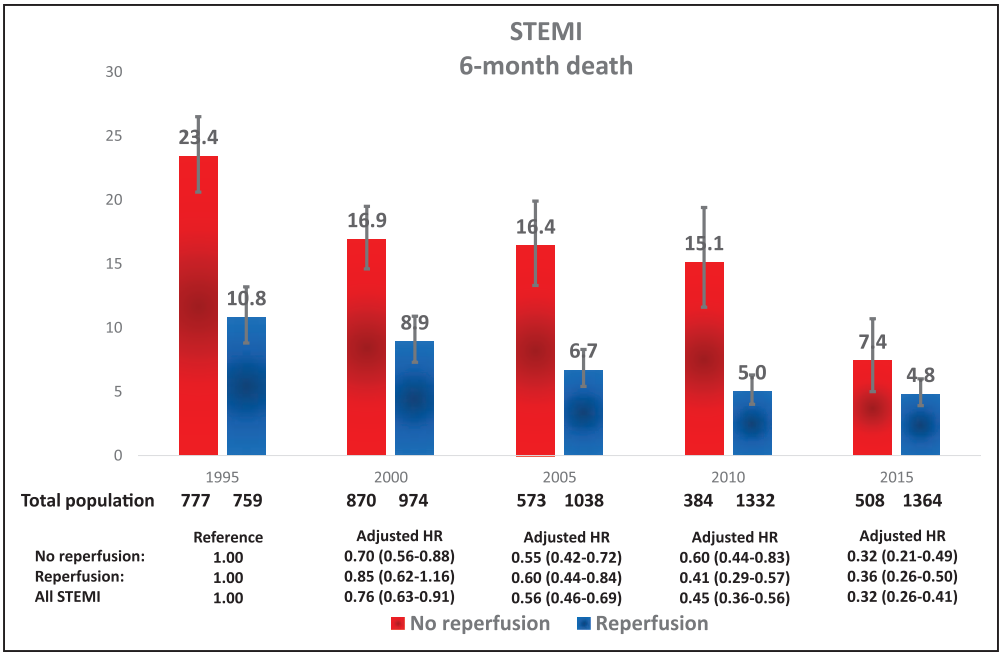

Figure 2. STEMI population.
Trends in 6-month mortality according to use of reperfusion therapy. Adjusted hazard ratios presented with their 95% confidence intervals. HR indicates hazard ratio; and STEMI, ST-segment–elevation myocardial infarction.

PCI and recommended medications were entered as covariables. Early PCI (HR, 0.62; 95% CI, 0.50–0.77), new anticoagulants (HR, 0.68; 95% CI, 0.57–0.82), statins (HR, 0.76; 95% CI, 0.63–0.91), β-blockers (HR, 0.55; 95% CI, 0.46–0.66), and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (HR, 0.69; 95% CI, 0.58–0.82) were all associated with reduced 6-month mortality. In patients without early PCI (≤72 hours from admission), mortality decreased until 2010 (HR, 0.53; 95% CI, 0.38–0.73) and remained stable in 2015 (HR, 0.50; 95% CI, 0.36–0.68); in those with early PCI, mortality also decreased until 2010 (HR, 0.40; 95% CI, 0.30–0.54) and was unchanged in 2015 (HR, 0.40; 95% CI, 0.30–0.52) (Figure 3).

Finally, we assessed the association between the use of reperfusion therapy (STEMI) or early PCI (NSTEMI) and early use of newer parenteral anticoagulants and recommended medications, with 6-month mortality, not taking into account the survey period (Table V in the online-only Data Supplement). In patients with STEMI, the use of primary PCI, fibrinolysis, anticoagulants other than unfractionated heparin, and the appropriate use of recommended medications were all strongly associated with lower mortality. Similar associations were found in patients with NSTEMI.

DISCUSSION

The present study documents the major changes in the characteristics and management of both patients with STEMI and NSTEMI over the past 20 years. Together with these changes, 6-month mortality has declined: in patients with STEMI, 6-month mortality has continued to decrease with a further 22% reduction in standardized mortality from 2010 to 2015; in contrast, in patients with NSTEMI, 6-month mortality reached a plateau after 2010 (3% increase in standardized mortality from 2010 to 2015). Furthermore, in patients with STEMI, mortality gain over time persists even after accounting for reperfusion therapy, seeming partly related to improved overall organization of care in the most recent period (improved patient information to reduce onset-to-call times, reduced number of centers taking care of patients with STEMI, direct admission to PCI-capable centers, etc), whereas in patients with NSTEMI, mortality gain seems essentially related to early management with PCI and recommended medications.

To the best of our knowledge, there are no published data reporting on trends in mortality of patients with AMI beyond the early 2010s. Before that, most reports showed increased use of primary PCI and recommended medications, with a concomitant decrease in early mortality,[5,6,10–12] including in specific populations such as the elderly.[18] The only major exception to this general finding is the China's PEACE registry (Patient-centered Evaluative Assessment of Cardiac Events Retrospective Study of Acute Myocardial Infarction): despite increased use of primary PCI from 11% to 28% from 2001 to 2011, only a nonsignificant 18% reduction in mortality was observed over this time period.[19]

In terms of patient characteristics, it is noteworthy that the age of patients with STEMI declined, and that

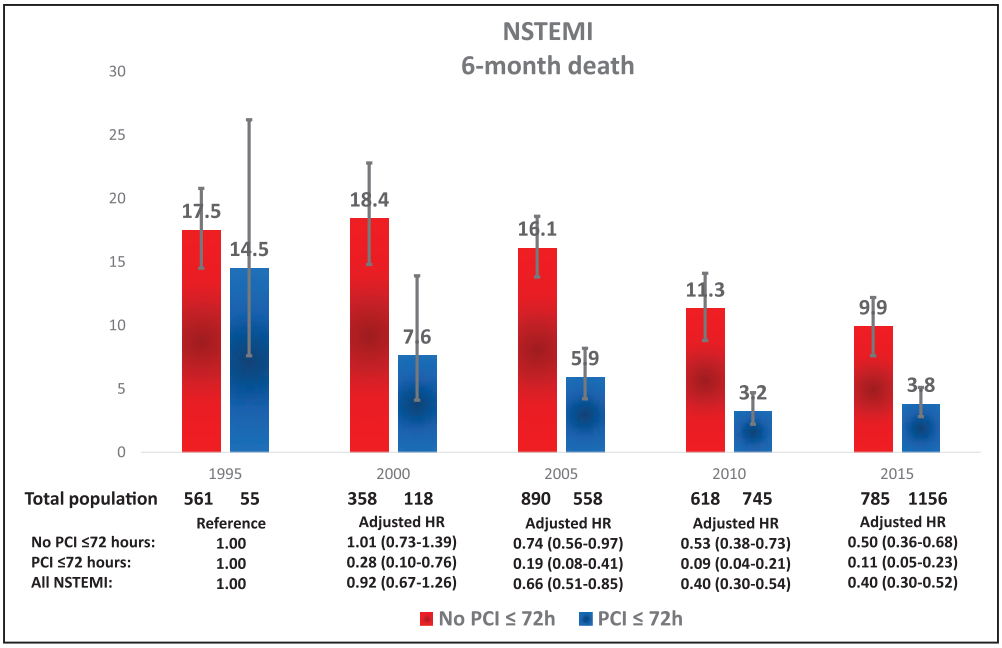

Figure 3. NSTEMI population.
Trends in 6-month mortality according to the use of PCI within 72 hours of admission. Adjusted hazard ratios presented with their 95% confidence intervals. HR indicates hazard ratio; NSTEMI, non–ST-segment–elevation myocardial infarction; PCR, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

peak CK also decreased with time, indicating that infarct size may currently be smaller than 20 years ago, possibly because of better primary prevention or earlier management.

It is impressive that invasive strategies have standardized, both for patients with STEMI and with NSTEMI, to the point that admission for AMI has now become nearly synonymous with the use of coronary angiography. The figures observed in the 2015 survey are higher than those usually reported (eg, 54% in the 2009–2010 period in the MINAP registry [Myocardial Ischaemia National Audit Project]),[11] although very high rates (93%) were already reported in 2007 for patients with STEMI in the Swedish registry,[10] or, for men in Lombardia, 92% in 2010 in comparison with 72% only in women[20]; likewise, in patients with NSTEMI, PCI was generally less used in other countries, typically 19% in the United Kingdom and 35% in Sweden.[21] The impact of invasive strategies may differ according to type of AMI: in patients with STEMI, mortality gain over time appears mediated both by the increased use of reperfusion therapy and recommended medications, and also by the organization of care aimed at shortening total ischemic time and referring patients to centers with a larger experience in STEMI care in the most recent period, whereas in patients with NSTEMI, early management with PCI and recommended medications appears to explain the near-totality of mortality gain.

One of the remarkable findings of this study is that, although there was very little change in the characteristics of the patients in the 2 most recent surveys (2010 and 2015), both for patients with STEMI and NSTEMI, 6-month mortality continued to decrease in patients with STEMI, whereas it remained stable in patients with NSTEMI.

In patients with STEMI, although the percentage of patients getting reperfusion therapy remained stable between 2010 and 2015, primary PCI was used more often, there was a switch from clopidogrel or prasugrel to ticagrelor; fondaparinux and bivalirudine were used more often, although often concomitantly with unfractionated heparin; finally, appropriate use of recommended medications at the acute stage and at discharge remained stable. Most of the improvement in 6-month outcome was related to improved survival in patients who had not received early reperfusion therapy, possibly related to the lower age of these patients in the most recent surveys (average age 66 years in 2015 versus 71 years in 1995) and to higher use of recommended medications, and subsequent use of PCI during the hospital stay, as well (4% in 1995, 43% in 2000, 45% in 2005, 49% in 2010, and 65% in 2015). Consequently, the mortality gain in the overall STEMI population seems to have resulted from both an increase in primary PCI (which had an intrinsically lower mortality) and from improved survival in the remaining patients not having received reperfusion therapy at the acute stage.

In patients with NSTEMI, in contrast, despite a further increase in the use of invasive strategies and PCI within 3 days of admission, and the replacement of clopidogrel with newer P2Y12 inhibitors, as well, and

increased use of newer parenteral anticoagulants, 6-month mortality did not decrease beyond 2010. The reasons for lack of further mortality gain in the most recent survey remain speculative. In particular, following the results of the Trial to Assess Improvement in TRITON (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) and PLATO (Platelet Inhibition and Patient Outcomes) trials, and subsequent guidelines, a shift from the use of clopidogrel to the use of prasugrel and, more recently, ticagrelor, was found and an impact on outcomes would have been expected; it must be pointed out, however, that we studied all-cause mortality and not a composite end point similar to the one of the randomized trials, although ticagrelor was associated with reduced all-cause mortality, as well, in PLATO.[22,23] Because of the low mortality rates observed, it may also be needed to have longer periods of follow-up to document further improvement in survival.

Limitations and Strengths

Beyond the usual limitations intrinsic to any observational cohort, and, in particular, the fact that association between patient characteristics and management (eg, type of anticoagulant used) do not imply a causal relationship because some of the variables may be fraught with uncorrected confounding, the FAST-MI program has specific limitations that must be emphasized. None of the registries was population based, and the total number of sites taking care of patients with AMI changed over the study period, as a consequence of deliberate health policy planning to avoid referral of patients with AMI to small nonspecialized centers. Also, the operational definition of NSTEMI changed with the generalized use of troponin measurements and then of high-sensitivity troponins, instead of CK, which was the marker of myocardial injury used in the first 2 surveys. Consequently, a large proportion of patients (those with increased troponins but no elevated CK) in the 3 latter surveys would not have been included in the 1995 and 2000 surveys, because they would have been considered to present with unstable angina; we did, however, use CK values in the multivariable analyses to adjust for these differences in initial patient profiles. The 1:1 ratio of NSTEMI and STEMI in the most recent surveys may appear intriguing; it must be noted that, in contrast with several other registries, we did not include patients with unstable angina (who are usually included among non–ST-segment–elevation acute coronary syndromes); in addition, in the most recent surveys, some patients with NSTEMI type 2 may not have been included, because they may have been hospitalized in regular wards instead of intensive cardiac care units. In addition, because the population was recruited from cardiac intensive care units, 2 types of populations are likely to be underrepresented: first, patients with out-of-hospital cardiac arrest, admitted to general intensive care units instead of intensive cardiac care units, because of severely compromised conditions after resuscitation; second, very elderly individuals with AMI, who may have been admitted to geriatric units or general wards. Finally, for the present analysis, because we wanted to include the most recent survey performed at the end of 2015, only 6-month follow-up was available. Conversely, all surveys can be considered highly representative of the management and outcomes of patients hospitalized for AMI in France, with a high overall participation rate, with all major institutions actually participating in the surveys, and with the totality of the metropolitan French territory covered. The size of each cohort is sufficient to allow statistically reliable comparisons with a good degree of precision, and the snapshot nature of the different registries allows comprehensive data collection and monitoring, without exhausting the investigators. To our knowledge, this approach, on a country scale, and setup as early as 1995 remains unique.

CONCLUSIONS

From 1995 to 2015, 6-month mortality of both patients with STEMI and NSTEMI decreased considerably, together with major increases in the use of recommended medications and procedures over time. In patients with STEMI, mortality has continued to decrease since 2010, to reach an all-time low in 2015. In patients with NSTEMI, despite recent changes in antithrombotic medications at the acute stage, mortality has remained similar in 2015 in comparison with 2010. Prolonged follow-up will determine whether improvement in survival will persist or materialize in both types of patients.

ACKNOWLEDGMENTS

The authors are deeply indebted to all physicians who have taken care of the patients at the participating institutions.

SOURCES OF FUNDING

The French Society of Cardiology received grants for supporting the FAST-MI program from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, MSD, Pfizer, and Sanofi.

DISCLOSURES

None.

AUTHORS

Etienne Puymirat, MD, PhD; Tabassome Simon, MD, PhD; Guillaume Cayla, MD, PhD; Yves Cottin, MD, PhD; Meyer

Elbaz, MD, PhD; Pierre Coste, MD, PhD; Gilles Lemesle, MD, PhD; Pascal Motreff, MD, PhD; Batric Popovic, MD, PhD; Khalife Khalife, MD; Jean-Noel Labèque, MD; Thibaut Perret, MD; Christophe Le Ray, MD; Laurent Orion, MD; Bernard Jouve, MD; Didier Blanchard, MD; Patrick Peycher; Johanne Silvain, MD, PhD; Philippe Gabriel Steg, MD; Patrick Goldstein, MD; Pascal Guéret, MD, PhD; Loic Belle, MD; Nadia Aissaoui, MD, PhD; Jean Ferrières, MD, PhD; François Schiele, MD, PhD; Nicolas Danchin, MD, PhD; for the USIK, USIC 2000, and FAST-MI investigators

AFFILIATIONS

Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Européen Georges Pompidou, Department of Cardiology; Université Paris-Descartes, Paris, France; INSERM U-970, France (E.P., N.A., N.D.). AP-HP, Hôpital Saint Antoine, Department of Clinical Pharmacology and Unité de Recherche Clinique (URCEST), Paris, France; Université Pierre et Marie Curie (UPMC-Paris 06); INSERM U-698, France (T.S.). Centre Hospitalier Universitaire de Nîmes, France (G.C.). Centre Hospitalier Universitaire du Bocage, Dijon, France (Y.C.). Toulouse University Hospital, Department of Cardiology, France (M.E.). Hôpital Cardiologique Haut Levêque, CHU de Bordeaux, Pessac, France (P.C.). Lille Regional University Hospital, Department of Cardiology, France (G.L.). Department of Cardiology, University Hospital of Clermont-Ferrand, UMR 6284 Auvergne University, France (P.M.). Département de cardiologie, CHU de Nancy, Vandœuvre-lès-Nancy, France (B.P.). Centre Hospitalier Régional de Metz-Thionville, Mets, France (K.K.). Centre Hospitalier de la Côte Basque, Bayonne, France (J.-N.L.). Department of cardiology, Centre Hospitalier St Joseph et St Luc, Lyon, France (T.P.). Centre Hospitalier Bretagne Atlantique, Vannes, France (C.L.R.). Department of Cardiology, Centre Hospitalier de Vendée, La Roche-sur-Yon, France (L.O.). Hospital of Aix en Provence, Department of Cardiology, France (B.J.). Clinique St Gatien, Tours, France (D.B.). Clinique Axium Aix en Provence, France (P.P.); Institut de Cardiologie, Centre Hospitalier Pitié-Salpêtrière, Paris, France (J.S.). AP-HP, Hôpital Bichat, Paris, France; Université Paris-Diderot, Sorbonne Paris-Cité, France; INSERM U-698, 75018 Paris, France (P.G.S.). Lille Regional University Hospital, Emergency Department, France (P. Goldstein). University Hospital Henri Mondor, Department of Cardiology, Créteil, France (P. Guéret). Department of Cardiology, Centre hospitalier Annecy Genevois, Epagny Metz-Tessy, France (L.B.). Toulouse Rangueil University Hospital, Department of Cardiology; UMR1027, INSERM, France (J.F.). University Hospital Jean Minjoz, Department of Cardiology, Besançon, France (F.S.).

FOOTNOTES

Received July 28, 2017; accepted August 14, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.030798/-/DC1.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Rosamond WD, Chambless LE, Heiss G, Mosley TH, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom AR. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. *Circulation*. 2012;125:1848–1857. doi: 10.1161/CIRCULATIONAHA.111.047480.
2. Rogers WJ, Frederick PD, Stoehr E, Canto JG, Ornato JP, Gibson CM, Pollack CV, Gore JM, Chandra-Strobos N, Peterson ED, French WJ. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156:1026–1034.
3. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610.
4. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA Jr, Granger CB, Flather MD, Budaj A, Quill A, Gore JM; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. 2007;297:1892–1900. doi: 10.1001/jama.297.17.1892.
5. Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, Khalife K, Goldstein P, Cattan S, Vaur L, Cambou JP, Ferrières J, Danchin N; USIK USIC 2000 Investigators; FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308:998–1006. doi: 10.1001/2012.jama.11348.
6. Puymirat E, Schiele F, Steg PG, Blanchard D, Isorni MA, Silvain J, Goldstein P, Guéret P, Mulak G, Berard L, Bataille V, Cattan S, Ferrières J, Simon T, Danchin N; FAST-MI investigators. Determinants of improved one-year survival in non-ST-segment elevation myocardial infarction patients: insights from the French FAST-MI program over 15 years. *Int J Cardiol*. 2014;177:281–286. doi: 10.1016/j.ijcard.2014.09.023.
7. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, Califf RM, Kong DF, Roe MT. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation* 2009;119:3110–3117.
8. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, Sadiq I, Kasper R, Rushton-Mellor SK, Anderson FA; GRACE Investigators. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90:358–363.
9. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J*. 2002;23:1190–1201.
10. Jernberg T, Johanson P, Held C, Svennblad B, Lindbäck J, Wallentin L; SWEDEHEART/RIKS-HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA*. 2011;305:1677–1684. doi: 10.1001/jama.2011.522.
11. Gale CP, Allan V, Cattle BA, Hall AS, West RM, Timmis A, Gray HH, Deanfield J, Fox KA, Feltbower R. Trends in hospital treatments, including revascularisation, following acute myocardial infarction, 2003-2010: a multilevel and relative survival analysis for the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2014;100:582–589. doi: 10.1136/heartjnl-2013-304517.
12. Stolt Steiger V, Goy JJ, Stauffer JC, Radovanovic D, Duvoisin N, Urban P, Bertel O, Erne P; AMIS Plus Investigators. Significant decrease in in-hospital mortality and major adverse cardiac events in Swiss STEMI patients between 2000 and December 2007. *Swiss Med Wkly*. 2009;139:453–457. doi: smw-12607.
13. Danchin N, Vaur L, Genès N, Renault M, Ferrières J, Etienne S, Cambou JP. Management of acute myocardial infarction in intensive care units in 1995: a nationwide French survey of practice and early hospital results. *J Am Coll Cardiol*. 1997;30:1598–1605.
14. Hanania G, Cambou JP, Guéret P, Vaur L, Blanchard D, Lablanche JM, Boutalbi Y, Humbert R, Clerson P, Genès N, Danchin N; USIC 2000 Investigators. Management and in-hospital outcome of patients with acute myocardial infarction admitted to intensive care units at the turn of the century: results from the French nationwide USIC 2000 registry. *Heart*. 2004;90:1404–1410. doi: 10.1136/hrt.2003.025460.
15. Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-

MI): study design and baseline characteristics. *Arch Mal Coeur Vaiss*. 2007;100:524–534.
16. Hanssen M, Cottin Y, Khalife K, Hammer L, Goldstein P, Puymirat E, Mulak G, Drouet E, Pace B, Schultz E, Bataille V, Ferrières J, Simon T, Danchin N; FAST-MI 2010 Investigators. French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010. FAST-MI 2010. *Heart*. 2012;98:699–705. doi: 10.1136/heartjnl-2012-301700.
17. Belle L, Cayla G, Cottin Y, Coste P, Khalife K, Labèque JN, Farah B, Perret T, Goldstein P, Gueugniaud PY, Braun F, Gauthier J, Gilard M, Le Heuzey JY, Naccache N, Drouet E, Bataille V, Ferrières J, Puymirat E, Schiele F, Simon T, Danchin N; FAST-MI 2015 investigators. French Registry on Acute ST-elevation and non-ST-elevation Myocardial Infarction 2015 (FAST-MI 2015). Design and baseline data. *Arch Cardiovasc Dis*. 2017;110:366–378. doi: 10.1016/j.acvd.2017.05.001.
18. Schoenenberger AW, Radovanovic D, Windecker S, Iglesias JF, Pedrazzini G, Stuck AE, Erne P; AMIS Plus Investigators. Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome. *Eur Heart J*. 2016;37:1304–1311. doi: 10.1093/eurheartj/ehv698.
19. Li J, Li X, Wang Q, Hu S, Wang Y, Masoudi FA, Spertus JA, Krumholz HM, Jiang L; China PEACE Collaborative Group. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. *Lancet*. 2015;385:441–451. doi: 10.1016/S0140-6736(14)60921-1.
20. Corrada E, Ferrante G, Mazzali C, Barbieri P, Merlino L, Merlini P, Presbitero P. Eleven-year trends in gender differences of treatments and mortality in ST-elevation acute myocardial infarction in northern Italy, 2000 to 2010. *Am J Cardiol*. 2014;114:336–341. doi: 10.1016/j.amjcard.2014.05.007.
21. Chung SC, Sundström J, Gale CP, James S, Deanfield J, Wallentin L, Timmis A, Jernberg T, Hemingway H; Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies/Register of Information and Knowledge about Swedish Heart Intensive care Admissions; National Institute for Cardiovascular Outcomes Research/Myocardial Ischaemia National Audit Project; Cardiovascular Disease Research Using Linked Bespoke Studies and Electronic Health Records. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. *BMJ*. 2015;351:h3913.
22. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. doi: 10.1056/NEJMoa0706482.
23. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsén M; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327.