ONLINE FIRST

Association of Changes in Clinical Characteristics and Management With Improvement in Survival Among Patients With ST-Elevation Myocardial Infarction

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Context The contemporary decline in mortality reported in patients with ST-segment elevation myocardial infarction (STEMI) has been attributed mainly to improved use of reperfusion therapy.

Objective To determine potential factors—beyond reperfusion therapy—associated with improved survival in patients with STEMI over a 15-year period.

Design, Setting, and Patients Four 1-month French nationwide registries, conducted 5 years apart (between 1995, 2000, 2005, 2010), including a total of 6707 STEMI patients admitted to intensive care or coronary care units.

Main Outcome Measures Changes over time in crude 30-day mortality, and mortality standardized to the 2010 population characteristics.

Results Mean (SD) age decreased from 66.2 (14.0) to 63.3 (14.5) years, with a concomitant decline in history of cardiovascular events and comorbidities. The proportion of younger patients increased, particularly in women younger than 60 years (from 11.8% to 25.5%), in whom prevalence of current smoking (37.3% to 73.1%) and obesity (17.6% to 27.1%) increased. Time from symptom onset to hospital admission decreased, with a shorter time from onset to first call, and broader use of mobile intensive care units. Reperfusion therapy increased from 49.4% to 74.7%, driven by primary percutaneous coronary intervention (11.9% to 60.8%). Early use of recommended medications increased, particularly low-molecular-weight heparins and statins. Crude 30-day mortality decreased from 13.7% (95% CI, 12.0-15.4) to 4.4% (95% CI, 3.5-5.4), whereas standardized mortality decreased from 11.3% (95% CI, 9.5-13.2) to 4.4% (95% CI, 3.5-5.4). Multivariable analysis showed a consistent reduction in mortality from 1995 to 2010 after controlling for clinical characteristics in addition to the initial population risk score and use of reperfusion therapy, with odds mortality ratios of 0.39 (95%, 0.29-0.53, $P<.001$) in 2010 compared with 1995.

Conclusion In France, the overall rate of cardiovascular mortality among patients with STEMI decreased from 1995 to 2010, accompanied by an increase in the proportion of women younger than 60 years with STEMI, changes in other population characteristics, and greater use of reperfusion therapy and recommended medications.

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SEVERAL SOURCES, INCLUDING registries specific to acute myocardial infarction (AMI) and large administrative or billing databases, have shown a decrease in mortality in patients with ST-segment elevation myocardial infarction (STEMI) over the past 10 to 15 years.[1-9] This decline is usually attributed to increased use and improved delivery of reperfusion therapy, in particular primary percutaneous coronary intervention (PCI). We hypothesized that, beyond primary PCI, other factors such as temporal changes in patient population characteristics may account for part of the observed reduction in mortality of patients with STEMI.

The aim of the present study was to assess the association between changes

in early mortality and patient management and risk profile by analyzing data from 4 sequential nationwide French surveys conducted between 1995 and 2010.[10-13]

METHODS

Four nationwide French registries were conducted 5 years apart over a 15-year period (1995 to 2010): USIK 1995,[10] USIC (Unité de Soins Intensifs Coronaires) 2000,[11] FAST-MI (French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction) 2005 (NCT00673036),[12] and FAST-MI 2010 (NCT01237418).[13] All 4 registries included patients with STEMI or non-STEMI admitted alive to a coronary care unit (CCU) or an intensive care unit (ICU) within 48 hours of symptom onset, during a specified 1-month period (November for 1995 and 2000 and between October and mid-November for 2005 and 2010).

The methods used for these cross-sectional registries with longitudinal follow-up have been described previously.[10-14] Briefly, their primary objectives were to evaluate the characteristics, management, and outcomes of patients with AMI admitted to CCUs or ICUs, as seen in routine clinical practice, using a catchment broad enough to provide data representative of the entire country, with strong external validity. Patients were recruited consecutively from CCUs or ICUs during the 1-month periods. Participation in the study was offered to all institutions, including university teaching hospitals, general and regional hospitals, and private clinics with ICUs that received acute coronary syndromes (ACSs) emergencies. Physicians were instructed that the study should not affect clinical care or management.

In each center, a physician was responsible for overseeing the registry and provided a full list of all patients admitted to the unit with suspected MI. Inclusion criteria were (1) adults aged 18 years or older; (2) patients admitted to a CCU or ICU within 48 hours of symptom onset for an AMI characterized by increased troponin, creatine kinase (CK) or CK-MB, associated with at least 1 of the following elements: symptoms compatible with myocardial ischemia, appearance of pathologic Q waves, or ST-T changes compatible with myocardial ischemia (ST-segment elevation or depression, T-wave inversion); and (3) willingness to take part in the study. Patients who died very 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) MI admission more than 48 hours after symptom onset; (3) iatrogenic MIs, defined as occurring within 48 hours of a therapeutic procedure (coronary artery bypass graft surgery, coronary angioplasty, or any other medical or surgical intervention); (4) ACS diagnosis invalidated in favor of another diagnosis; and (5) patients with unstable angina and no increase in cardiac biomarkers.

For the present analysis, only patients presenting with persistent ST-segment elevation or new Q waves were considered. For each of the surveys, the number of patients screened exceeded the number of patients included; the most common reasons for noninclusion in all 4 surveys were onset of chest pain more than 48 hours from admission, admission outside the survey time window, or diagnosis of AMI not retained (eFigure 1 available at http://www.jama.com).

The study was conducted in accordance with the guidelines on good clinical practice and French law. The study protocol for the 1995 and 2000 registries were reviewed by the Committee for the Protection of Human Subjects in Biomedical Research of Nancy University hospital; the 2005 registry was reviewed by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Antoine University Hospital; and the protocol of the 2010 registry was reviewed and approved by the Committee for the Protection of Human Subjects of Saint Louis University Hospital, Paris. Data file collection and storage were approved by the Commission Nationale Informatique et Liberté. All patients were informed of the nature and aims of the surveys and could request to be excluded; in addition, written consent was obtained for the 2005 and 2010 surveys.

Data Collection

Data on baseline characteristics, including demographics (age, sex, body mass index [BMI], calculated as weight in kilograms divided by height in meters squared), risk factors (hypertension, diabetes, current smoking, hypercholesterolemia, family history of coronary artery disease, obesity defined as ≥30 BMI), and medical history (MI, stroke, heart failure, peripheral artery disease), were collected as previously described.[10-14] Information on the use of cardiac procedures, including use and of type of reperfusion therapy (primary PCI or fibrinolysis), use of medications (antiplatelet agents, diuretics, β-blockers, angiotensin-converting enzyme [ACE] inhibitors, and lipid-lowering agents) in the first 48 hours (or first 5 days, for the 1995 survey) and at-hospital discharge was recorded. In 2000, 2005, and 2010, time from symptom onset to first call or medical contact, and time to reperfusion therapy were also recorded. Several additional variables such as previous PCI, coronary artery bypass graft surgery, or chronic renal failure were also collected in the most recent surveys.

Clinical Outcomes

Mortality was assessed at 30 days. Information on this outcome was obtained directly by the physician responsible for overseeing of the study at each center for the 1995 and 2000 surveys. For the 2005 and 2010 surveys, follow-up was centralized at the French Society of Cardiology and dedicated study coordinators contacted both physicians and patients, after checking the patients' vital status in municipal registers.

Statistical Analysis

For quantitative variables, mean (SDs) were calculated, as well as medians and interquartile ranges, when appropriate. Discrete variables are presented as counts and percentages. Comparisons for discrete variables were performed with the χ^2 test or Fisher exact test. Continuous variables were studied by analysis of variance. Temporal trends were tested using linear-by-linear association tests for binary and Jonckheere-Terpstra tests for continuous variables. Odds ratios (ORs) are presented with their 95% confidence intervals.

To account for changes in the baseline characteristics of the populations admitted for STEMI from 1995 to 2010, we calculated a risk score for the 2010 population using multiple logistic regression analysis including demographic data, risk factors, medical history, BMI (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 2010 population (C statistic, 0.75), 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 if the distribution of the baseline characteristics of each of the first 3 surveys had been similar to that of the most recent one. For the 2000 to 2010 surveys, we also used the simple risk index (SRI) and the evaluation of the methods and management of acute coronary events (EMMACE) scores[15] to characterize the changes in risk levels of the populations.

We also examined mortality according to the participation of the centers in each registry; however, because the center codes were not available from the 1995 registry, we compared temporal trends in mortality from 2000 to 2010 in centers having participated in all registries vs the others.

Multivariable analyses of correlates of 30-day mortality were performed using backward stepwise multiple logistic regression analysis, using a threshold of 0.10 for variable elimination. Variables included in the final multivariable models were selected ad hoc, based on their physiological relevance and potential to be associated with outcomes. Thus, we included variables likely to influence outcome negatively (older age, history of heart failure, history of diabetes, history of AMI, history of stroke, history of peripheral artery disease, anterior MI, assessed from the baseline electrocardiogram, when ST-segment elevation was present in at least 2 contiguous leads from V1 to V4) or positively (history of hypertension, current smoking, and use and type of reperfusion therapy) as well as region, type of institution, BMI, sex, and time period (1995, 2000, 2005, 2010). Peak values of total CK were recorded in all surveys, CK-MB was recorded in the 2000 and 2005 surveys, and troponin was recorded in the 2005 and 2010 surveys. A sensitivity analysis was performed, adding peak CK to the covariates in the main analysis.

Analyses were repeated using forward stepwise analysis to check the consistency of the results. Collinearity was tested by calculation of variance inflation factors. Statistical analyses were performed using IBM SPSS 20.0 (IBM SPSS Inc). For all analyses, a 2-sided *P* value $<.05$ was considered to be statistically significant.

RESULTS

Baseline and Presentation Characteristics

A total of 6707 patients with STEMI were enrolled in the 4 nationwide surveys (TABLE 1). The percentage of participating centers compared with all centers providing care for AMI patients in France was 62% in 1995 (312 centers, 1536 patients), 83% in 2000 (369 centers, 1844 patients), 60% in 2005 (223 centers, 1611 patients), and 76% in 2010 (213 centers, 1716 patients).

During this 15-year period, the mean age of patients with STEMI declined from 66.2 (14.0) years to 63.3 (14.5) years, current smoking increased (from 32.0% to 40.9%; percentage change, 8.9 [95% CI, 5.6-12.2]), as did the prevalence of obesity (14.3% to 20.1%; percentage change 5.8 [95% CI, 3.1- 8.4]), hypertension (43.8% to 47.0%; precent change, 3.1 [95% CI, –0.03 to 6.6]) and hypercholesterolemia (34.8% to 39.3%; percentage change 4.6 [95% CI, 1.2-7.9]), whereas history of cardiovascular disease, such as myocardial infarction decreased (14.6% to 10.9%, percentage change, –3.7 [95% CI, –1.5 to –6.1]), heart failure (6.4% to 2.4%, percentage change, –4.0 [95% CI, –2.6 to –5.5]), peripheral artery disease (9.7% to 4.8%, percentage change –4.8 [95% CI, –3.0 to –6.6]), stroke or transient ischemic attack (6.2% to 4.0%, percentage change, –2.3 [95% CI, –0.08 to –3.8]), or any of the above (25.9% to 17.1%) decreased.

Although the overall percentage of women did not vary over time, the proportion of younger women (<60 years) increased from 11.8% to 25.5% within 15 years, consistent with their increased prevalence of current smoking (from 37.3% to 73.1%) and obesity (from 17.6% to 27.1%). The changes in prevalence of risk factors differed markedly according to age and sex (eFigure 2 available at http://www.jama.com). The proportion of younger patients developing STEMI despite not having hypertension, diabetes, or hypercholesterolemia increased markedly, particularly in younger women. This was in parallel with an increase in the proportion of younger patients, particularly women, to present with STEMI having current smoking or obesity as among their only risk factors.

Overall, the baseline risk of death in the entire population decreased consistently over time, as assessed by the specific risk score based on the 2010 population (0.053 in 1995, 0.048 in 2000, 0.048 in 2005, and 0.045 in 2010; –15% from 1995 to 2010 [95% CI, –9.9 to –20.4]; $P=.001$), consistent with the SRI and EMMACE risk scores applied to the 2000-2010 populations (SRI, 27.1 in 2000, 25.9 in 2005, and 24.2 in 2010, –11% from 2000 to 2010 [95% CI, –6.9 to –14.5]; $P<.001$; EMMACE score: 0.188 in 2000, 0.176 in 2005, and 0.156 in 2010; –17% from 2000 to 2010 [95% CI, –10.9 to –23.2]; $P<.001$).

Patient Admission Pathways

Median time from symptom onset to hospital admission decreased from 240 minutes (interquartile range [IQR], 140-540 minutes) to 175 minutes (IQR, 107-380 minutes), as did the median time from onset to first call from 120 minutes (IQR, 41-360 minutes) in 2000 to 74 minutes (IQR, 30-240 minutes) in 2010, whereas the use of mobile intensive care units increased from 23.2% to 48.8% (percentage change, 25.6% [95% CI, 22.5%-28.6%]; TABLE 2). The percentage of admissions to community hospitals decreased from 60.2% to 44.0% (percentage change, –16.2% [95% CI, –12.8% to –19.6%]), together with a decrease in the number of participating institutions, in keeping with the health authorities' recommendation to reduce the number of institutions providing care for STEMI patients from 501 in 1995 to 279 in 2010. Across surveys, the mean (SD) number of patients per center increased from 5.7 (3.6) to 8.7 (8.0).

Table 1. Baseline Characteristics of Patients With ST-Segment Elevation Myocardial Infarction From 1995 to 2010

Clinical Characteristics	1995 (n = 1536)	2000 (n = 1844)	2005 (n = 1611)	2010 (n = 1716)	*P* for Trend	Percentage Change From 1995 to 2010, (95% CI)
Age, mean (SD), y	66.2 (14.0)	64.5 (14.6)	64.0 (14.7)	63.3 (14.5)	<.001	–2.9 (–1.9 to –3.9)
Men						
<60	421 (38.1)	622 (46.3)	585 (50.7)	634 (49.0)		10.9 (7.0 to 14.8)
60-74	457 (41.4)	455 (33.9)	353 (30.6)	420 (32.5)	<.001	–8.9 (–5.0 to –12.8)
≥75	227 (20.5)	267 (19.9)	215 (18.6)	239 (18.5)		–2.1 (1.1 to –5.3)
Women						
<60	51 (11.8)	87 (17.4)	107 (23.4)	108 (25.5)		13.7 (8.5 to 18.8)
60-74	148 (34.3)	166 (33.2)	121 (26.4)	117 (27.7)	<.001	–6.7 (–0.05 to –12.8)
≥75	232 (53.8)	247 (49.4)	230 (50.2)	198 (46.8)		–7.0 (–0.03 to –13.6)
Women, No. (%)	431 (28.1)	500 (27.1)	458 (28.4)	423 (24.7)	.06	–3.4 (–0.4 to –6.4)
BMI, mean (SD)	25.9 (3.9)	26.3 (4.1)	26.9 (4.6)	26.7 (4.4)	<.001	0.8 (0.5 to 1.1)
No. of patients	1454	1654	1440	1615		
Type of institution						
University hospital	380 (25)	518 (28)	609 (38)	634 (37)		12.2 (9.0 to 15.3)
Community/Army hospital	925 (60)	972 (53)	751 (47)	755 (44)	<.001	–16.2 (–12.8 to –19.6)
Private clinic	231 (15)	354 (19)	251 (16)	327 (19)		4.0 (1.4 to 6.6)
Number of patients per center, per mo, mean (SD)	5.1 (3.6)	5.8 (5.6)	7.6 (7.1)	8.7 (8.0)	<.001	3.6 (3.4 to 3.8)
Risk factors, No. (%)						
Hypertension	673 (43.8)	804 (43.6)	792 (49.2)	806 (47.0)	.006	3.1 (–0.03 to 6.6)
Hypercholesterolemia	534 (34.8)	719 (39.0)	699 (43.4)	675 (39.3)	.001	4.6 (1.2 to 7.9)
Diabetes mellitus	242 (15.8)	364 (19.7)	302 (18.7)	283 (16.5)	.92	0.7 (–1.8 to 3.3)
Current smoking	491 (32.0)	651 (35.3)	600 (37.2)	701 (40.9)	<.001	8.9 (5.6 to 12.2)
Obesity	208 (14.3)	269 (16.3)	299 (20.8)	324 (20.1)	<.001	5.8 (3.1 to 8.4)
Cardiovascular history, No. (%)						
Myocardial infarction	225 (14.6)	276 (15.0)	180 (11.2)	187 (10.9)	<.001	–3.7 (–1.5 to –6.1)
Stroke or TIA	96 (6.2)	78 (4.2)	91 (5.6)	68 (4.0)	<.001	–2.3 (–0.08 to –3.8)
Heart failure	98 (6.4)	84 (4.6)	56 (3.5)	41 (2.4)	<.001	–4.0 (–2.6 to –5.5)
Peripheral artery disease	148 (9.7)	145 (7.9)	85 (5.3)	83 (4.8)	<.001	–4.8 (–3.0 to –6.6)
PCI		139 (7.5)	140 (8.7)	175 (10.2)	.005	
CABG surgery		50 (2.7)	34 (2.1)	96 (5.6)	<.001	
Comorbidity						
Chronic kidney disease		66 (3.62)	50 (3.1)	42 (2.1)	.15	
COPD			47 (2.7)	85 (5.0)	.003	
Cancer			100 (6.2)	147 (8.6)	.01	
Medications before, No. (%)						
Antiplatelet therapy		389 (21.1)	336 (20.9)	335 (19.5)	.25	
Statin		304 (16.5)	342 (21.2)	374 (21.8)	<.001	
β–Blocker		338 (18.3)	296 (18.4)	313 (18.2)	.95	
ACE–I or ARB		349 (18.9)	395 (24.5)	478 (27.9)	<.001	

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; blank cells, data not available; BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Hospital Management

The use of reperfusion therapy increased over time, from 49.4% to 74.7% (percentage change, 25.2% [95% CI, 22.0% to 28.4%]) with more frequent use of primary PCI, (11.9% to 60.8%; (percentage change, 48.9% [95% CI, 46.0% to 51.6%]) and less frequent use of fibrinolysis (37.5% to 13.9%; percentage change, –23.6% [95% CI, –20.7% to –26.5%]; Table 2). Use of coronary angiography at any time during the index admission increased, to reach 96.3% in 2010, whereas the rate of hospital PCI, increased from 19.5% to 86.7% (percentage change, 67.2% [95% CI, 64.5% to 69.6%]).

The use of evidence-based treatments during the first 48 hours from admission increased gradually over the 15-year period. Early use of β-blockers increased from 65.2% to 80.7%; (percentage change, 15.5% [95% CI, 12.4% to 18.5%]), ACE inhibitors or angiotensin-receptor blockers from 47.7% to 64.8% (percentage change, 17.1% [95% CI, 13.7% to 20.4%]), and statins from 9.8% to 89.9% (percentage change, 80.1% [95% CI, 77.9% to 82.0%]; all *P* for trend <.001). Likewise, antithrombotic medications used during the first 48 hours of admission changed markedly, with increasing early use of antiplatelet agents from 92.4% to 97.4% (percentage change, 5.0% [95% CI, 3.6% to 6.6%]) intravenous glycoprotein IIb/IIIa inhibitors from 19.0% in 2000 to 42.7% in 2010 (percentage change, 23.6% [95% CI, 20.6% to 26.5%]), and low-molecular-weight heparins from 27.4% in 2000 to 62.3% in 2010 (percentage change, 34.9% [95% CI, 31.7 to 37.9%]), whereas the use of unfractionated heparin decreased from 96.4% to 44.8% (percentage change, –51.7% [95% CI, –49.1% to –54.1%]; all *P* for trend <.001).

The speed of implementation of recommended treatments, reperfusion therapy, or both over the study period was similar across regions and hospital types, although the change in use of primary PCI, was more marked in patients admitted to community hospitals. Proportionally, the use of primary PCI, increased to a greater extent in patients 75 years or older from 5.4% to 54.0% (percentage change, 48.6% [95% CI, 43.1% to 53.6%]) than among patients younger than 60 years, from

Table 2. Early Hospital Management of Patients With ST-Segment Elevation Myocardial Infarction From 1995 to 2010

Clinical Characteristics	1995[a] (n = 1536)	2000 (n = 1844)	2005 (n = 1611)	2010 (n = 1716)	*P* for Trend	Percentage Change From 1995 to 2010, (95% CI)
Initial pathway: mobile ICU, No. (%)		427 (23.2)	666 (41.3)	837 (48.8)	<.001	
Time delay, median (IQR), min						
Symptom onset to first call/medical contact		120 (41 to 360)	90 (30 to 295)	74 (30 to 240)	<.001	
No. of patients		1486	1600	1674		
Symptom onset to admission	240 (140 to 540)	255 (150 to 540)	200 (120 to 430)	175 (107 to 380)	<.001	–62 (–28.7 to –95.3)
No. of patients	1427	1706	1610	1698		
Anterior wall MI	636 (41.4)	746 (40.5)	647 (40.2)	648 (38)	.07	–3.1 (.03 to –6.5)
Peak creatine kinase, U/L						
Mean (SD)	1664 (1671)	1722 (1780)	1654 (1946)	1628 (1881)	.50	–36 (–166 to 94)
Median (IQR)	1200 (608-2112)	1209 (600-2175)	993 (362-2775)	985 (370-2218)		
No. of patients	1527	1832	1437	1366		
Reperfusion therapy, No. (%)						
None	777 (50.6)	870 (47.2)	591 (36.7)	435 (25.3)	<.001	–25.2 (–21.9 to –28.5)
Fibrinolysis	576 (37.5)	545 (29.6)	465 (28.9)	238 (13.9)		–23.6 (–20.7 to –26.5)
Primary PCI	183 (11.9)	429 (23.3)	555 (34.5)	1043 (60.8)		48.9 (46.0 to 51.6)
Procedures during hospitalization, No. (%)						
Coronary angiography		1489 (80.7)	1449 (89.9)	1642 (96.3)	<.001	
PCI	300 (19.5)	1132 (61.4)	1221 (75.8)	1488 (86.7)	<.001	67.2 (64.5 to 69.6)
Medications in first 48 h, No. (%)[b]						
Antiplatelet therapy	1419 (92.4)	1759 (95.4)	1544 (95.8)	1672 (97.4)	<.001	5.0 (3.6 to 6.6)
Thienopyridine			1415 (87.8)	1646 (95.9)	<.001	
Gp IIb/IIIa inhibitor		351 (19.0)	595 (36.9)	732 (42.7)	<.001	
Unfractionated heparin	1481 (96.4)	1463 (79.3)	715 (44.4)	768 (44.8)	<.001	–51.7 (–49.1 to –54.1)
LMWH		506 (27.4)	924 (57.4)	1069 (62.3)	<.001	
Statin	151 (9.8)	842 (45.7)	1262 (78.3)	1543 (89.9)	<.001	80.1 (77.9 to 82.0)
β–Blocker	1001 (65.2)	1348 (73.1)	1162 (72.1)	1384 (80.7)	<.001	15.5 (12.4 to 18.5)
ACE–I or ARB	733 (47.7)	764 (41.4)	853 (52.9)	1112 (64.8)	<.001	17.1 (13.7 to 20.4)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Gp, glycoprotein; ICU, intensive care unit; IQR, interquartile range; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] For 1995, blank cells indicate data not available.

[b] For 1995, medications used at any time during the first 5 days.

Table 3. Observed and Risk Score-Standardized 30-Day Mortality Rates

Year	No. of Events	No. of Patients	30–Day Mortality, % (95% CI)		Multivariable Logistic Regression Analyses, OR (95% CI)[a]	*P* Value
			Observed	Standardized		
1995	210	1536	13.7 (12.0-15.4)	11.3 (9.5-13.2)	1 [Reference]	
2000	160	1844	8.7 (7.4-10.0)	7.6 (5.7-9.5)	0.64 (0.51-0.81)	.001
2005	111	1611	6.9 (5.7-8.2)	6.4 (5.1-7.7)	0.52 (0.40-0.68)	.001
2010	75	1716	4.4 (3.5-5.4)	4.4 (3.5-5.4)	0.39 (0.29-0.53)	.001

[a] Adjusted for patient risk profile, infarct location, region, type of institution, and reperfusion therapy.

15.9% to 64.0% (percentage change, 48.1% [95% CI, 43.0% to 52.8%]), with little difference according to sex.

Outcomes

Thirty-day mortality decreased from 13.7% in 1995 to 4.4% in 2010 (TABLE 3) In multivariable logistic regression analyses, compared with 1995, the risk of death was lower in 2000 (OR, 0.64 [95% CI, 0.51-0.81]; $P<.001$) than in 2005 (OR, 0.52 [95% CI, 040-0.68] $P<.001$) and in 2010 (OR, 0.39 [95% CI, 0.29-0.53]; $P<.001$). Mortality decreased irrespective of use and type of reperfusion therapy, including among patients who did not receive any reperfusion therapy: no reperfusion (18.9% to 8.7%; adjusted OR. 0.47 [95% CI, 0.32-0.70), fibrinolysis (8.2% to 2.1%; adjusted OR, 0.29 [95% CI, 0.11-0.76]), primary PCI, (8.7% to 3.2%; adjusted OR, 0.29 [95% CI, 0.15-0.58]; FIGURE).

Likewise, mortality decreased consistently regardless of age, sex, or patient risk level (eFigure 3). In particular comparing 1995 to 2010, mortality decreased from 9.8% to 2.6% in men (adjusted OR, 0.30 [95% CI, 0.20-0.46]) and from 23.7% to 9.8% in women (adjusted OR, 0.48 [95% CI, 0.32-0.74]). Likewise, the decrease in mortality was consistent in the centers participating in all surveys (8.3% in 2000, 6.6% in 2005, and 4.6% in 2010; $P<.001$), and in those who had not participated in all surveys (9.1% in 2000, 7.6% in 2005, and 4.1% in 2010, $P=.001$).

Mortality from 1995 to 2010 declined in both academic centers (9.2% in 1995 to 4.7% in 2010) or community hospitals (15.5% to 5.5%), and type of institution was not an independent correlate of 30-day mortality in multivariate analyses. In addition, examination of early vs later deaths revealed consistent findings. Deaths within 48 hours were 4.0% in 1995, 3.7% in 2000, 2.0% in 2005, and 1.5% in 2010 (P for trend $<.001$), whereas deaths from 48 hours to 30 days were 10.1% in 1995, 5.2% in 2000, 5.0% in 2005, and 3.0% in 2010 (P for trend $<.001$).

When death rates were standardized for the 2010 risk score (representing the expected rates, standardized on the risk distribution profile of 2010), mortality decreased gradually over time: 11.3% in 1995, 7.6% in 2000, 6.4% in 2005, and 4.4% in 2010. Adding total CK as a covariate in the model yielded similar results when comparing ORs against 1995: 0.62 (95% CI, 0.49-0.80) in 2000; 0.55 (95% CI, 0.41-0.72) in 2005; and 0.37 (95% CI, 0.26-0.53) in 2010.

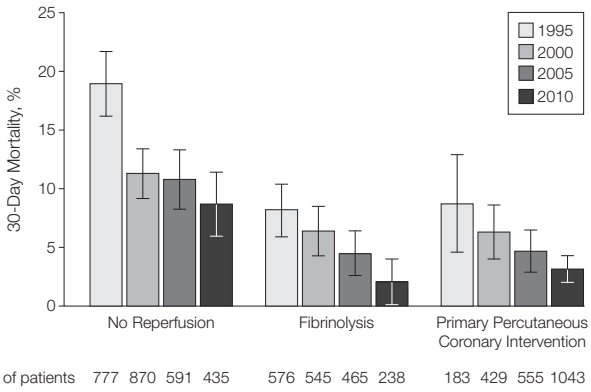
Consistent with the decrease in mortality, all major hospital complications of STEMI also decreased over time: cardiogenic shock, 7.4% to 4.7% (adjusted OR, 0.66 [95% CI, 0.48-0.92]); recurrent myocardial infarction, 2.6% in 2000 to 1.0% (adjusted OR, 0.51 [95% CI, 0.29-0.90]); ventricular fibrillation or cardiac arrest, 4.2% to 2.7% (adjusted OR, 0.68 [95% CI, 0.46-1.01]); atrial fibrillation, 12.5% to 5.6% (adjusted OR, 0.46 [95% CI, 0.36-0.60]); and atrioventricular block, 7.8% to 2.6% (adjusted OR, 0.32 [95% CI, 0.22-0.45]). Bleeding complications were recorded from 2005; investigator-reported major bleeding decreased from 1.9% in 2005 to 0.8% in 2010; transfusion rates, however, remained unchanged.

COMMENT

The main findings of this study are that 30-day STEMI mortality decreased by approximately 9%, a decrease of 68% in 15 years, and although this reduction parallels improvements in care, such as greater use of primary PCI, and adjunctive therapies, it was also associated with a substantial change in the patient risk profile. Specifically, the absolute 30-day mortality decreased from 9.3% (observed) to 6.9% (standardized), attesting a 26% reduction related to the changes in patient risk profile. Within the STEMI population targeted by these sequential registries, the relative proportion of older patients has decreased, while the proportion of younger men and the proportion and numbers of younger women have increased. These observations suggest that future reductions in the incidence and mortality related to AMI will need specific targeting of preventive measures toward younger women and possibly younger men.

The progressive decline in early mortality over time observed in the present nationwide surveys is consistent with many other sources in the United States[1,3-5] and Europe.[2,6,7,16] This change is explained largely by major improvements in the delivery of care for AMI, including the more frequent implementation of reperfusion therapy, the more frequent use of primary PCI, as a reperfusion method, and use of potent adjunctive evidence-based therapies (including antithrombotic agents, statins, β-blockers, and ACE inhibitors or angiotensin-receptor blockers). It may also be related to changes in patient behavior, such as faster calls for medical assistance after symptom onset and more

Figure. Changes in 30-Day Mortality According to Use and Type of Reperfusion Therapy



The adjusted odds ratios comparing 1995 with 2010 are 0.47 (95% CI, 0.32-0.70) for those who received no perfusion, 0.29 (95% CI, 0.11-0.76) for those who received fibrinolysis treatment, and 0.29 (95% CI, 0.15-0.58) for those who received percutaneous coronary intervention. Error bars indicate 95% CIs.

frequent use of the prehospital mobile intensive care system, as well as changes in the general organization of care for STEMI patients, with the concentration of care provision in a smaller number of institutions, treating larger numbers of patients. In this regard, it must be noted that French health authorities have launched several media campaigns in the past 10 years to increase public awareness of the initial symptoms of heart attacks and to encourage the use of the national emergency telephone number. Attesting that the changes in early mortality went well beyond the broader use of primary PCI and reperfusion therapy, we observed that the risk of death within the groups receiving reperfusion by primary PCI or by fibrinolysis also decreased considerably.

Associated with these changes in patient behavior and physician management, during this 15-year period profound changes in the characteristics of the AMI population occurred, with presentation at a younger age, particularly in women. As expected, the lower age was associated with a reduction in the prevalence of comorbidities and history of cardiovascular disease. The increased proportion of younger patients was mainly at the expense of a reduction in the proportion of patients aged 60 to 74 years—from 39.3% to 31.3%, whereas the proportion of 75 years or older of age was less affected—from 30.0% to 25.5%.

Overall, while the catchment area of the sequential registries may have varied somewhat, which may account for some changes in patient age and sex, the absolute numbers of patients 65 years or older has substantially decreased. This decrease was all the more striking considering that the French population got older from 1995 to 2010. In fact, the decrease in the number of older patients with STEMI in the subsequent years of the registry is consistent with population-based epidemiological data showing a progressive decrease in the average age of patients hospitalized with AMI, both in France[17] and in other countries.[2]

As the relationship of prevention strategies with cardiovascular events and death rates has been conclusively demonstrated,[18] the age decrease in STEMI patients can be hypothesized to result from the efficacy of primary prevention in patients with recognized, treatable risk factors such as hypercholesterolemia, hypertension, or diabetes and may result from the decrease in smoking among older individuals in France.

Concordant with our results, the incidence of hospitalized AMI cases has been decreasing by about 2.5% per year in recent years, both in France (Christine De Peretti, MD, Institut National de Veille Sanitaire, written communication, August 2, 2012), in the United States,[8] and in other countries.[7] In a nationwide population-based study in France, the decrease in the incidence of AMI was most evident in both men and women who were older than 65 years, while it was less marked in younger men, and the reverse trend (ie, increased incidence) was observed for younger women (De Peretti, written communication). Likewise, in our registries, even though STEMI in women mostly affected older patients, the relative proportion of women younger than 50 years hospitalized for STEMI has increased considerably from 3.7% to 11.1%). These observations are consistent with the increase in current smoking among younger women during the past 30 years in France.[19]

The greater proportional increase in primary PCI, in elderly patients was somewhat unexpected; it might be related to the fact that younger patients may have less obstructive disease and more thrombosis.

The greater magnitude of mortality decrease in community hospitals, compared with academic institutions, might be explained by a shift of more severe patients, formerly treated in community hospitals and now preferentially referred to academic centers, and by the closure or regrouping of smaller hospitals, with less experience in treating STEMI patients.

Limitations

As in any observational study, there are limitations to our analysis. None of the registries considered was population-based, and their catchment areas may have changed slightly over time, although every effort was made in each survey to capture the greatest possible proportion of centers participating in the care of STEMI patients in the entire country. The total number of such sites did change over 15 years, as a consequence of deliberate health policy planning that tried to avoid referral of STEMI patients to small nonspecialized centers.

Patients were included during the months of October or November, so we therefore have no means to detect possible temporal trends in seasonal variations. Also, we did not record specific contraindications to any medication; this may have influenced the rate of use of certain medications, and may have been an unrecognized confounder, but we would not expect the prevalence of contraindications to specific therapies, particularly antithrombotic therapies to change markedly. If anything, the modest decrease in age would be expected to be associated with a modest reduction in contraindications.

Because the criterion for enrollment was admission to a CCU or ICU, changes over time in admission policy and changes in risk of prehospital sudden death may also have affected the type and number of patients eligible for enrollment. Also, we cannot exclude that a very small number of patients might have died of other conditions such as aortic dissection, with ST-elevation on their electrocardiographs, before any imaging technique could be performed. Owing to the lack of certain variables in the first registries, we could not use well-validated scores such as the Global Registry on Acute Coronary Events (GRACE) or Thrombolysis In Myocardial Infarction (TIMI) scores to compare the baseline risks of the populations. We therefore used an internally derived multivariable model to predict death and categorize patient risk, which yielded adequate discriminating power (C statistic, 0.75); also, sensitivity analyses performed using 2 well-validated risk scores yielded identical results.

Although we hypothesize that the reduction in the proportion of older patients with STEMI was related to the efficacy of prevention, we cannot within the scope of this study document such an effect, but our findings are consistent with observations suggesting that the reduction in cardiovascular mortality observed in recent years in North America and Western Europe is a consequence of successful prevention efforts at least as much as a consequence of improved curative treatments.[20,21]

CONCLUSIONS

In France, the overall rate of cardiovascular events and mortality in patients hospitalized with STEMI has decreased from 1995 to 2010. This was accompanied by an increase in the proportion of younger women and changes in population characteristics, a reduction in the number of institutions providing care for STEMI patients together with an increased use of recommended therapeutic measures, and changes in patients' behavior when confronted with symptoms of infarction.

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REFERENCES

1. Rosamond WD, Chambless LE, Heiss G, et al. 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(15):1848-1857.

2. 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(16):1677-1684.

3. Kostis WJ, Deng Y, Pantazopoulos JS, Moreyra AE, Kostis JB; Myocardial Infarction Data Acquisition System (MIDAS14) Study Group. Trends in mortality of acute myocardial infarction after discharge from the hospital. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):581-589.

4. Movahed MR, John J, Hashemzadeh M, Jamal MM,

Hashemzadeh M. Trends in the age adjusted mortality from acute ST segment elevation myocardial infarction in the United States (1988-2004) based on race, gender, infarct location and comorbidities. *Am J Cardiol*. 2009;104(8):1030-1034.
5. Rogers WJ, Frederick PD, Stoehr E, et al. 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(6):1026-1034.
6. Stolt Steiger V, Goy JJ, Stauffer JC, et al; 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(31-32):453-457.
7. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? evidence from a prospective population-based study. *Circulation*. 2008;117(5):598-604.
8. 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(23):2155-2165.
9. Fox KA, Steg PG, Eagle KA, et al; GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. 2007;297(17):1892-1900.
10. Danchin N, Vaur L, Genès N, et al. 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(7):1598-1605.
11. Hanania G, Cambou JP, Guéret P, et al; 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(12):1404-1410.
12. 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(6-7):524-534.
13. Hanssen M, Cottin Y, Khalife K, et al; FAST-MI 2010 Investigators. French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010: FAST-MI 2010. *Heart*. 2012;98(9):699-705.
14. Danchin N, Vaur L, Genès N, et al. Treatment of acute myocardial infarction by primary coronary angioplasty or intravenous thrombolysis in the "real world": one-year results from a nationwide French survey. *Circulation*. 1999;99(20):2639-2644.
15. Gale CP, Manda SO, Weston CF, Birkhead JS, Batin PD, Hall AS. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart*. 2009;95(3):221-227.
16. Schiele F, Hochadel M, Tubaro M, et al. Reperfusion strategy in Europe: temporal trends in performance measures for reperfusion therapy in ST-elevation myocardial infarction. *Eur Heart J*. 2010; 31(21):2614-2624.
17. Wagner A, Ruidavets J, Montave M, et al. Trends in coronary heart disease in France from 2000 to 2007. *BEH*. 2011;40-41:414-419.
18. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366(4): 321-329.
19. Beck F, Guignard R, Richard J, Wilquin J, Perreti-Watel P. Increasing trends in smoking in France: main results of the French Health Barometer, France 2010. *BEH*. 2011;20-21:230-233.
20. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. *Circulation*. 2012;125(8):987-995.
21. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356(23):2388-2398.