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ORIGINAL INVESTIGATIONS

Percutaneous Myocardial Revascularization in Late-Presenting Patients With STEMI

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ABSTRACT

BACKGROUND The optimal management of patients with ST-segment elevation myocardial infarction (STEMI) presenting late—>12 hours following symptom onset—is still under debate.

OBJECTIVES The purpose of this study was to describe characteristics, temporal trends, and impact of revascularization in a large population of latecomer STEMI patients.

METHODS The authors analyzed the data of 3 nationwide observational studies from the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) program, conducted over a 1-month period in 2005, 2010, and 2015. Patients presenting between 12 and 48 hours after symptom onset were classified as latecomers.

RESULTS A total of 6,273 STEMI patients were included in the 3 cohorts, 1,169 (18.6%) of whom were latecomers. After exclusion of patients treated with fibrinolysis and patients deceased within 2 days after admission, 1,077 patients were analyzed, of whom 729 (67.7%) were revascularized within 48 hours after hospital admission. At 30-day follow-up, all-cause death rate was significantly lower among revascularized latecomers (2.1% vs 7.2%; $P < 0.001$). After a median follow-up of 58 months, the rate of all-cause death was 30.4 (95% CI: 25.7-35.9) per 1,000 patient-years in the revascularized latecomers group vs 78.7 (95% CI: 67.2-92.3) per 1,000 patient-years in the nonrevascularized latecomers group ($P < 0.001$). In multivariate analysis, revascularization of latecomer STEMI patients was independently associated with a significant reduction of mortality occurrence during follow-up (HR: 0.65 [95% CI: 0.50-0.84]; $P = 0.001$).

CONCLUSIONS Coronary revascularization of latecomer STEMI patients is associated with better short and long-term clinical outcomes. (J Am Coll Cardiol 2021;78:1291-1305) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

ECG = electrocardiogram

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

A substantial proportion of ST-segment elevation myocardial infarction (STEMI) patients still present late after symptom onset (ie, patient-related delay >12 hours) (1-3), and represents a challenging population. Indeed, late presentation is associated with major adverse clinical outcomes (3-5). The American College of Cardiology Foundation/American Heart Association guidelines state that primary percutaneous coronary intervention (PCI) is reasonable in patients with STEMI if there is clinical and/or electrocardiogram (ECG) evidence of ongoing ischemia between 12 and 24 hours following symptom onset (Class IIa, Level of Evidence: B) (6). Similarly, the European Society of Cardiology guidelines recommend to consider a routine primary PCI strategy in patients presenting late (12-48 hours) after symptom onset (Class IIa, Level of Evidence: B) (7). However, the benefit of late PCI remains controversial, particularly in latecomer STEMI patients presenting between 12 and 48 hours, for whom few data are available (8-13). As a result, there is no real consensus as to whether PCI is also beneficial in patients presenting >12 hours from symptom onset in the absence of clinical and/or electrocardiographic evidence of ongoing ischemia. The aim of the present study was to assess long-term outcomes in latecomer STEMI patients in relation with the use of revascularization in 3 sequential nationwide French surveys conducted between 2005 and 2015.

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METHODS

STUDY POPULATION. Three nationwide French registries were conducted over a 1-month period, 5 years apart, over a 10-year period (2005-2015): FAST-MI (French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction) 2005 (NCT00673036) (14), FAST-MI 2010 (NCT01237418) (15), and FAST-MI 2015 (NCT02566200) (16) (Supplemental Appendix). The methods used to conduct these registries were detailed previously (14-18). Briefly, their primary objectives were to assess the characteristics, management, and outcomes of acute myocardial infarction (AMI) patients, as seen in routine clinical practice, on a countrywide scale.

All 3 registries consecutively included patients with STEMI admitted to intensive cardiovascular care units (ICCUs) within 48 hours of symptom onset, during a specified 1-month period (October to December 2005, 2010, and 2015). AMI was defined by increased levels of cardiac biomarkers (troponins, 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. A total of 13,129 patients were included in the 3 surveys. Diabetic patients included in the FAST-MI 2005 extension phase were excluded (n = 611) and only STEMI patients were kept in the present analysis (n = 6,637). After exclusion of patients for whom the "symptom onset to admission delay" was missing (n = 364), a total of 6,273 STEMI patients were assessed. The analysis focused on the revascularization of latecomers and was performed after exclusion of patients treated with fibrinolysis (n = 59), patients for whom no data about reperfusion was available (n = 1), and patients deceased within 2 days after hospital admission (n = 32) to exclude potential immortal time bias. A detailed flowchart is provided in **Figure 1**.

The study was conducted in accordance with guidelines on good clinical practice and French regulations. The 2005 registry was reviewed and approved by the Committee for the Protection of Human Subjects (CPP) in Biomedical Research of Saint Antoine University Hospital, Paris; the 2010 registry was reviewed and approved by the CPP of Saint Louis University Hospital, Paris; and the protocol of the 2015 registry was reviewed and approved by the CPP of Saint Louis University Hospital, Paris Ile de France IV. Data file collection and storage were approved by the Commission Nationale de l'Informatique et des Libertés. Written consent was obtained for all of these surveys.

DATA COLLECTION. Data on baseline characteristics, including demographics, and medical history, and initial ECG, were collected as previously described (14-18). Patient-related delays, ie, time from

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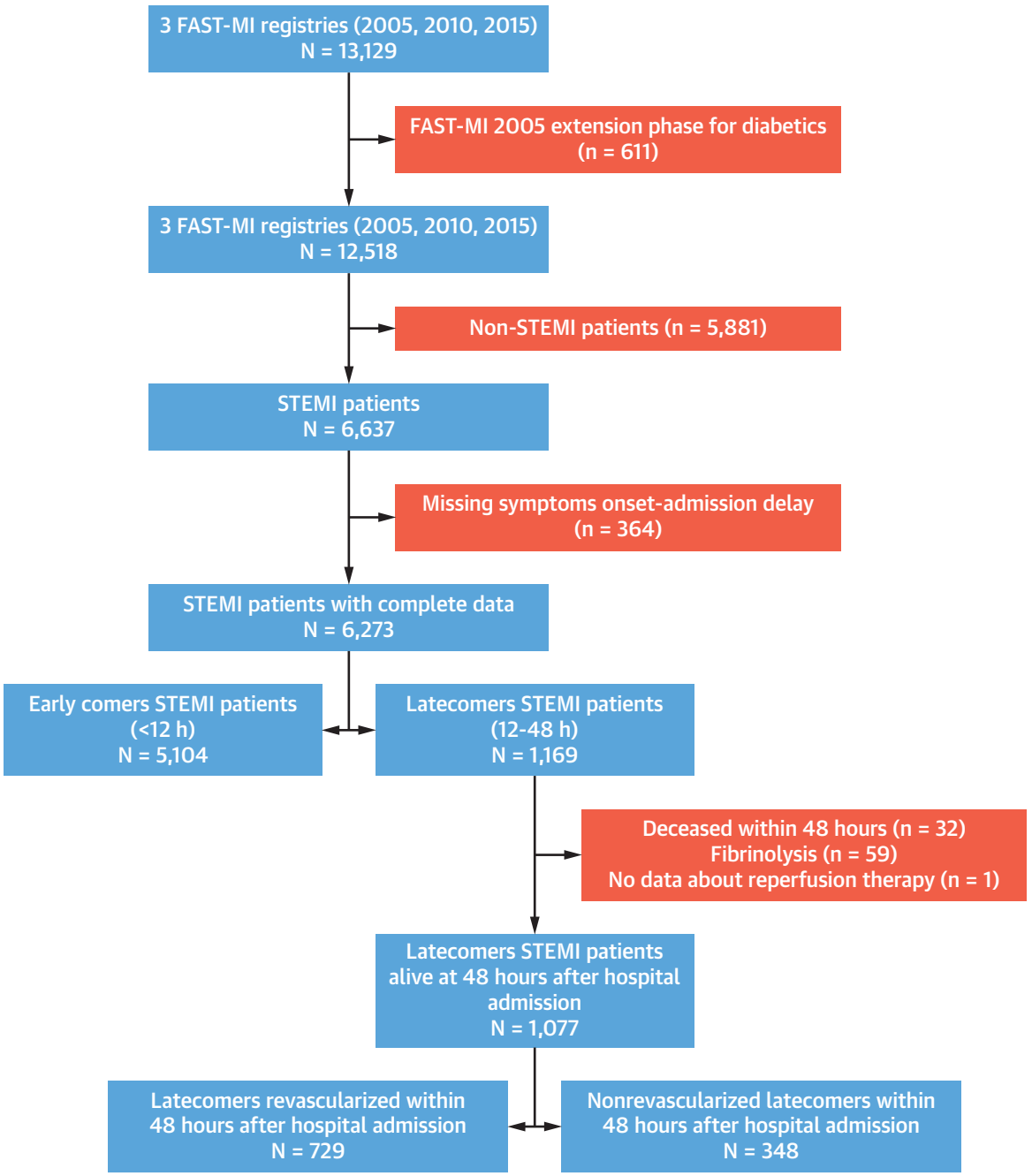
FIGURE 1 Study Flowchart



The study population was derived from 3 French nationwide 1-month registries of myocardial infarction (FAST-MI [French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction] registries) conducted in 2005, 2010, and 2015. PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

symptom onset to first call or medical contact, time from symptom onset to ICCU admission, and first call/medical contact to primary PCI (including either direct admission from outside to catheterization laboratory or indirect transfer in catheterization laboratory), were recorded. Then, STEMI patients were classified as early comers (ie, time from symptom onset to ICCU admission ≤12 hours) or latecomers (ie,

TABLE 1 Comparison of Early and Latecomer Patients Characteristics and Management

	All (N = 6,273)	Early Comers (n = 5,104)	Latecomers (n = 1,169)	*P* Value
Demography				
Age, y	63.1 ± 14.3	62.6 ± 14.1	65.2 ± 14.8	<0.001
Age ≥75 y	1,574 (25.1)	1,203 (23.6)	371 (31.7)	<0.001
Women	1,648 (26.3)	1,288 (25.2)	360 (30.8)	<0.001
Risk factors				
Hypertension	2,967/6,253 (47.5)	2,346/5,086 (46.1)	621/1,167 (53.2)	<0.001
Hypercholesterolemia	2,511/6,244 (40.2)	2,023/5,080 (39.8)	488/1,164 (41.9)	0.187
Diabetes	1,036/6,242 (16.6)	789/5,080 (15.5)	247/1,162 (21.3)	<0.001
Current smoking	2,517/6,120 (41.1)	2,069/4,974 (41.6)	448/1,146 (39.1)	0.120
Family history of CAD	1,570/5,928 (26.5)	1,295/4,822 (26.9)	275/1,106 (24.9)	0.176
Obesity (BMI ≥30 kg/m^2)	1,175/5,860 (20.1)	948/4,781 (19.8)	227/1,079 (21.0)	0.370
Cardiovascular history and comorbidities				
Prior AMI	730/6,221 (11.7)	621/5,061 (12.3)	109/1,160 (9.4)	0.006
Prior PCI	673/6,237 (10.8)	579/5,077 (11.4)	94/1,160 (8.1)	0.001
Prior stroke/TIA	294/6,258 (4.7)	225/5,091 (4.4)	69/1,167 (5.9)	0.030
Peripheral artery disease	321/6,253 (5.1)	248/5,086 (4.9)	73/1,167 (6.3)	0.054
History of heart failure	184/6,254 (2.9)	126/5,087 (2.5)	58/1,167 (5.0)	<0.001
Chronic kidney disease	185/6,254 (3.0)	147/5,087 (2.9)	38/1,167 (3.3)	0.505
Respiratory failure	226/6,243 (3.6)	184/5,077 (3.6)	42/1,166 (3.6)	0.971
History of cancer	491/6,243 (7.9)	383/5,077 (7.5)	108/1,166 (9.3)	0.049
Medication before AMI				
Antiplatelet therapy	1,392 (22.2)	1,131 (22.2)	261 (22.3)	0.901
Statin	1,441 (23.0)	1,168 (22.9)	273 (23.4)	0.731
Beta-blocking agent	1,289 (20.6)	1,042 (20.4)	247 (21.1)	0.586
ACE inhibitor or ARB	1,580 (25.2)	1,245 (24.4)	335 (28.7)	0.002
Clinical presentation				
SBP, mm Hg	132 ± 26 6,068	132 ± 26 4,931	135 ± 26 1,137	<0.001
Heart rate, beats/min	78 ± 18 6,037	77 ± 18 4,910	80 ± 19 1,127	<0.001
LVEF, %	50.1 ± 11.4 4,625	50.4 ± 11.3 3,716	49.0 ± 11.9 1,127	0.002
Anterior MI	2,583/5,865 (44.0)	2,102/4,793 (43.9)	481/1,072 (44.9)	0.546
Typical chest pain	5,335/6,217 (85.8)	4,432/5,066 (87.5)	903/1,151 (78.5)	<0.001
Cardiogenic shock	100/6,008 (1.7)	79/4,889 (1.6)	21/1,119 (1.9)	0.538
GRACE risk score	144 ± 35 5,851	143 ± 34 4,749	147 ± 37 1,102	0.003
Killip class >2	284/6,008 (4.7)	217/4,889 (4.4)	67/1,119 (6.0)	0.028
Out-of-hospital cardiac arrest	151/6,051 (2.5)	138/4,934 (2.8)	13/1,117 (1.2)	0.002
CRP, mg/L	5 (3-13) 4,556	5 (3-10) 3,688	9 (4-30) 868	<0.001
Delays				
Time from onset to first call or contact, h	1.3 (0.5-4.2) 6,229	1.0 (0.5-2.4) 5,076	13.5 (8.0-21.0) 1,153	<0.001
Time from first call or contact to ICU, h	2.2 (1.3-4.0) 6,242	2.0 (1.3-3.2) 5,089	4.8 (2.3-10.2) 1,153	<0.001
Time from onset to ICU admission, h	4.3 (2.5-9.0) 6,273	3.5 (2.3-5.7) 5,104	20.2 (15.4-27.9) 1,169	<0.001
Time from onset to angiography, h	5.6 (3.0-18.9) 5,816	4.4 (2.8-9.1) 4,783	27.5 (18.0-45.8) 1,033	<0.001
Time from onset to balloon, h	5.8 (3.3-18.5) 5,259	4.7 (3.0-9.5) 4,364	26.5 (17.5-45.5) 895	<0.001
Time from door to balloon, h	1.7 (0.7-6.7) 5,227	1.4 (0.6-4.4) 4,346	5.4 (1.9-24.5) 881	<0.001
Time from ICU admission to angiography, h	0.7 (0.3-7.6) 4,988	0.6 (0.3-3.1) 4,106	3.3 (0.7-22.1) 882	<0.001
Time from ICU admission to balloon, h	1.0 (0.5-7.0) 4,561	0.8 (0.5-3.2) 3,806	3.2 (0.9-22.7) 755	<0.001

Continued on the next page

TABLE 1 Continued

	All (N = 6,273)	Early Comers (n = 5,104)	Latecomers (n = 1,169)	*P* Value
Pre-hospital pathway				
Mobile ICU	4,667/6,247 (74.7)	4,013/5,086 (78.9)	654/1,161 (56.3)	<0.001
Patient's journey includes EMS	3,036/6,247 (48.6)	2,233/5,086 (43.9)	803/1,161 (69.2)	<0.001
Reperfusion therapy				<0.001
None	821 (13.1)	564 (11.1)	257 (22.0)	
Thrombolysis	968 (15.4)	905 (17.7)	63 (5.4)	
No thrombolysis but PCI	4,481 (71.5)	3,634 (71.2)	847 (72.6)	
Procedure during hospitalization				
Coronary angiography	5,993/6,269 (95.6)	4,920/5,101 (96.5)	1,073/1,168 (91.9)	<0.001
PCI	5,307/6,268 (84.7)	4,411/5,101 (86.5)	896/1,167 (76.8)	<0.001
Pre-PCI TIMI flow grade 2 or 3	1,289/5,258 (37.8)	1,671/4,280 (39.0)	318/978 (32.5)	<0.001
Post-PCI TIMI flow grade 2 or 3	4,686/5,384 (87.0)	3,906/4,414 (88.5)	780/970 (80.4)	<0.001
CABG	115/6,272 (1.8)	85/5,104 (1.7)	30/1,168 (2.6)	0.038
Hemodynamic and respiratory support				
IAPB	116/6,119 (1.9)	91/5,071 (1.8)	25/1,164 (2.2)	0.421
Other assistance	27/6,235 (0.4)	23/5,071 (0.5)	4/1,164 (0.3)	0.607
Assisted ventilation	166/6,205 (2.7)	133/5,045 (2.6)	33/1,160 (2.8)	0.691
Medication within first 48 h				
Aspirin	5,779 (88.9)	4,559 (89.3)	1,020 (87.3)	0.042
Clopidogrel	3,665 (58.4)	2,881 (56.5)	784 (67.1)	<0.001
Prasugrel	1,330 (21.2)	1,165 (22.8)	165 (14.1)	<0.001
Ticagrelor	1,304 (20.8)	1,110 (21.8)	194 (16.6)	<0.001
Glycoprotein IIb/IIIa inhibitors	332 (5.3)	249 (4.9)	83 (7.1)	0.002
Unfractionated heparin	2,612 (41.6)	2,117 (41.5)	495 (42.3)	0.588
LMWH	3,458 (55.1)	2,784 (54.6)	674 (57.7)	0.054
Fondaparinux	563 (9.0)	462 (9.1)	101 (8.6)	0.657
Bivalirudin	214 (3.4)	185 (3.6)	29 (2.5)	0.052
ACE inhibitor or ARB	3,824 (61.0)	3,135 (61.4)	689 (58.9)	0.116
Diuretic	1,537 (24.5)	1,202 (23.6)	335 (28.7)	<0.001
Beta-blocker	4,846 (77.3)	3,992 (78.2)	854 (73.1)	<0.001
Statin	5,316 (84.7)	4,357 (85.4)	959 (82.0)	0.004
Medication at discharge				
Aspirin	5,192/6,027 (86.2)	4,280/4,923 (86.9)	912/1,104 (82.6)	<0.001
$P2Y_{12}$ inhibitor (any)	4,566/6,027 (75.8)	3,769/4,923 (76.6)	797/1,104 (72.2)	0.002
ACE inhibitor or ARB	4,386/6,027 (72.8)	3,595/4,923 (73.0)	791/1,104 (73.0)	0.353
Statin	5,137/6,027 (85.2)	4,223/4,923 (85.7)	914/1,104 (82.8)	0.011
Beta-blocker	5,014/6,292 (79.7)	4,088/5,114 (79.9)	926/1,178 (78.6)	0.306
Diuretic	1,246/6,027 (20.7)	978/4,923 (19.9)	268/1,104 (24.3)	0.001
Length of stay, days	7 (5-9)	7 (5-9)	7 (5-10)	0.003
Cardiovascular rehabilitation	641/6,026 (10.6)	524/4,922 (10.7)	117/1,104 (10.6)	0.963

Values are mean ± SD, n (%), n/N (%), n, or median (interquartile range).

ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; ARB = angiotensin 2 receptor blocker; BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; EMS = emergency medical service; IABP = intra-aortic balloon pump; ICU = intensive care unit; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; TIA = transient ischemic attack.

time from symptom onset to ICCU admission >12 hours and ≤48 hours). Information on the use and type of reperfusion therapy (primary PCI or fibrinolysis) in STEMI patients, the use of cardiac procedures (coronary angiography, PCI, intra-aortic balloon pump [IABP] and other cardiac devices), and mechanical ventilation were recorded over the entire hospital stay. Reperfusion therapy was defined as the use of either intravenous fibrinolysis (prehospital or in-hospital) or intended primary PCI, ie, coronary angiography with an intent to perform PCI. Use of medications administered in the prehospital setting, within the first 48 hours and at-hospital discharge were collected. Additional variables such as previous PCI, coronary artery bypass graft surgery (CABG), chronic renal failure, laboratory data (C-reactive protein), or left ventricular ejection fraction were also recorded. Clinical complications at admission or during the initial hospital course, transfer to general intensive care unit (ICU) were also recorded. Patients

were allocated in the "revascularization" group if they benefited from PCI or CABG within 48 hours after hospital admission. Follow-up parameters, including 30-day death rate, recurrent AMI, stroke, all-cause death, all-cause hospitalization, cardiovascular hospitalization, hospitalization for heart failure, and bleeding, were centralized at the French Society of Cardiology.

OUTCOMES. Our primary outcome was all-cause mortality. Secondary outcomes were recurrent AMI, stroke, and bleeding (classified according to the TIMI [Thrombolysis In Myocardial Infarction] classification) (19).

Follow-up data were collected yearly by research technicians from the French Society of Cardiology (SFC) using the following sequential procedure:

1. Consulting the registry offices of the patients' birthplaces for death certificates.
2. Contacting the patients' general practitioners and/or cardiologists.
3. Contacting the patients or their relatives. In many instances, written communication was followed by telephone interviews with the patients or their family.
4. Consulting the French national database, which records all deaths occurring in the French population (RNIPP: Répertoire National d'Identification des Personnes Physiques).

For each reported event leading to hospitalization or death, hospital discharge reports were sought and analyzed by at least 1 physician from the research team. All cases of cardiovascular events were centrally reviewed by at least 1 physician. Cases in which the final diagnosis appeared unclear or debatable were reviewed by a 3-member critical events committee.

STATISTICS. Continuous data were expressed as mean ± SD when following a normal distribution, and as median (interquartile range [IQR]) when not. Categorical data were displayed as counts and percentages. Groups were compared using Student's *t*-tests or analysis of variance for continuous variables and chi-square or Fisher exact tests for categorical variables.

Complication incidence rates for occurrence during hospitalization and follow-up were computed. Outcome incidence rates during follow-up are expressed per 1,000 patient-years. Complication occurrences were compared between latecomers and early comers and between revascularized latecomers and nonrevascularized latecomers using a Cox proportional hazards model, after adjustment for age and inclusion year. Survival analyses were conducted using the Kaplan-Meier method. In the latecomers subpopulation, a stepwise backward Cox proportional hazards regression was used to identify factors independently associated with mortality occurrence during follow-up, taking into account variables found related to mortality occurrence with $P < 0.15$ in univariate analyses. Statistical significance was defined by $P < 0.05$ for all tests. A propensity score matching analysis to compare revascularized and nonrevascularized latecomers with similar conditions, was built to determine the impact of revascularization in the latecomer population. Analyses focusing on the impact of myocardial revascularization were performed with a T0 set at 48 hours. All statistics were calculated using Stata statistical software version 14 (StataCorp).

RESULTS

STUDY POPULATION. A total of 6,273 STEMI patients with complete data were included in the 3 pooled FAST-MI registries (1,943 subjects in FAST-MI 2005, 2,274 in FAST-MI 2010, and 2,346 in FAST-MI 2015). Among them, 1,169 (18.6%) presented late (ie, >12 hours after symptom onset) and were classified as *latecomers*. Median time from symptom onset to ICU admission was 3.5 hours (IQR: 2.3-5.7 hours) in the early comers population vs 20.2 hours (IQR: 15.4-27.9 hours) in the latecomers population ($P < 0.001$). Global median follow-up was 59 months (IQR: 40-110 months). From 2005 to 2015, the proportion of latecomer patients among STEMI population decreased from 22.7% to 16.1% ($P < 0.001$) (Supplemental Figure 1).

PATIENT PRESENTATION. Latecomer patients were more frequently women (30.8% vs 25.2%; $P < 0.001$) and significantly older (65.2 ± 14.8 years vs 62.6 ± 14.1 years; $P < 0.001$) than early comers. Diabetes and hypertension were more prevalent in the latecomers population (21.3% vs 15.5% and 53.2% vs 46.1%, respectively; $P < 0.001$ for both). Prior history of heart failure was also more frequent among latecomer patients (5.0% vs 2.5%; $P < 0.001$). In contrast, prior AMI or prior PCI were significantly less frequent in latecomers (9.4% vs 12.3% and 8.1% vs 11.4%, respectively; $P < 0.001$). At admission, chest pain was less frequently typical among latecomers (78.5% vs 87.5%; $P < 0.001$). Latecomers were less likely to be admitted via mobile ICU (56.3% vs 78.9%; $P < 0.001$) and were more often admitted via emergency medical service (69.2% vs 43.9%; $P < 0.001$). A description of patient characteristics

TABLE 2 Comparison of Latecomer Patients According to Their Revascularization Status

	Latecomers[a] (n = 1,077)	Revascularized[b] (n = 729)	Nonrevascularized (n = 348)	*P* Value
Year of admission				<0.001
2005	323 (30.0)	169 (23.2)	154 (44.3)	
2010	390 (36.2)	277 (38.0)	113 (32.5)	
2015	364 (33.8)	283 (38.8)	81 (23.3)	
Demography				
Age, y	65.1 ± 14.7	62.7 ± 14.2	70.2 ± 14.5	<0.001
Age ≥75 y	340 (31.6)	182 (25.0)	158 (45.4)	<0.001
Female	335 (31.1)	204 (28.0)	131 (37.6)	0.001
Risk factors				
Hypertension	579/1,076 (53.8)	354/729 (48.6)	225/347 (64.8)	<0.001
Hypercholesterolemia	449/1,073 (41.9)	299/727 (41.1)	150/346 (43.4)	0.490
Diabetes	227/1,071 (21.2)	142/727 (19.5)	85/344 (24.7)	0.053
Current smoking	415/1,055 (39.3)	323/716 (45.1)	92/339 (27.1)	<0.001
Family history of CAD	256/1,021 (25.1)	193/693 (27.9)	63/328 (19.2)	0.003
Obesity (BMI ≥ 30 kg/m^2)	216/1,012 (21.3)	144/692 (20.8)	72/320 (22.5)	0.542
Cardiovascular history and comorbidities				
Prior AMI	101/1,069 (9.5)	71/725 (8.4)	40/344 (11.6)	0.093
Prior PCI	84/1,070 (7.9)	56/725 (7.7)	28/345 (8.1)	0.824
Prior stroke/TIA	63/1,076 (5.9)	37/729 (5.1)	26/347 (7.5)	0.114
Peripheral artery disease	65/1,076 (6.0)	33/729 (4.5)	32/347 (9.2)	0.003
History of heart failure	53/1,076 (4.9)	23/729 (3.2)	30/347 (8.7)	<0.001
Chronic kidney disease	34/1,076 (3.2)	14/729 (1.9)	20/347 (5.8)	0.001
Respiratory failure	42/1,075 (3.9)	26/729 (3.6)	16/346 (4.6)	0.403
History of cancer	100/1,075 (9.3)	56/729 (7.7)	44/346 (12.7)	0.008
Medication prior AMI				
Antiplatelet therapy	245 (22.8)	145 (19.9)	100 (28.7)	0.001
Statin	250 (23.2)	170 (23.3)	80 (23.0)	0.904
Beta-blocking agent	227 (21.1)	141 (19.3)	86 (24.7)	0.043
ACE inhibitor or ARB	312 (29.0)	197 (27.0)	115 (33.1)	0.042
Initial presentation				
SBP, mm Hg	136 ± 26	135 ± 25	138 ± 27	0.113
Heart rate, beats/min	79.6 ± 18.6	77.4 ± 17.3	83.9 ± 20.2	<0.001
LVEF, %	49.2 ± 11.8	49.7 ± 11.2	48.2 ± 13.1	0.082
Killip class >2	54/1,036 (5.2)	27/697 (3.9)	27/339 (8.0)	0.005
Out-of-hospital cardiac arrest	9/1,031 (0.9)	6/704 (0.9)	3/327 (0.9)	1.000
Anterior MI	444/986 (45.0)	293/691 (42.4)	151/295 (51.2)	0.011
GRACE risk score	146 ± 36	142 ± 34	155 ± 37	<0.001
Medication at discharge (in patients alive at discharge)				
Aspirin	872/1,046 (83.4)	612/715 (85.6)	260/331 (78.6)	0.004
$P2Y_{12}$ inhibitor	759/1,046 (72.6)	554/715 (77.5)	205/331 (61.9)	<0.001
ACE inhibitor or ARB	755/1,046 (72.2)	544/715 (76.1)	211/331 (63.8)	<0.001
Statin	870/1,046 (83.2)	616/715 (86.2)	254/331 (76.7)	<0.001
Beta-blocker	823/1,046 (78.7)	573/715 (80.1)	250/331 (75.5)	0.090
Diuretic	264/1,046 (25.2)	153/715 (21.4)	111/331 (33.5)	<0.001
Length of stay, days	7 (5-10)	6 (5-9]	9 (6-13)	<0.001
Cardiovascular rehabilitation	114/1,046 (10,9)	83/715 (11.6)	31/331 (9.4)	0.279

Values are n (%), mean ± SD, n/N (%), or median (interquartile range). [a]Alive at day 2 and after exclusion of latecomers who received thrombolysis. [b]Within 48 hours after hospital admission.

Abbreviations as in Table 1.

according to their time of presentation is shown in Table 1, and a comparison of latecomers characteristics according to their year of admission is presented in Supplemental Table 1. Characteristics independently related to a late presentation identified by a multivariate analysis were age, diabetes, atypical chest pain, prior heart failure, and admission via emergency medical service before admission

TABLE 3 Early and Long-Term Outcomes of Latecomer Patients According to Their Revascularization Status

	All (N = 1,077)	Revascularized Latecomers (n = 729)[a]	Nonrevascularized Latecomers (n = 348)	*P* Value
Complications at 30 days				
All-cause death	3.7	2.1	7.2	<0.001
Recurrent AMI	0.9	0.6	1.7	0.060
Stroke	1.3	1.2	1.4	0.784
Bleeding (all)	1.6	1.0	2.9	0.018
Major bleeding[b]	0.9	0.4	2.0	0.016
Long-term complications				
All-cause death	44.9 (40.0-50.3)	30.4 (25.7-35.9)	78.7 (67.2-92.3)	<0.001
Recurrent AMI	7.2 (5.2-9.9)	5.4 (3.5-8.5)	11.0 (6.8-17.7)	0.031
Stroke	6.7 (4.8-9.4)	6.0 (3.9-9.1)	8.4 (4.9-14.5)	0.393
Bleeding (all)	9.8 (7.4-13.0)	8.3 (5.8-12.0)	13.1 (8.5-20.3)	0.136
Major bleeding[b]	6.4 (4.5-9.0)	5.1 (3.2-8.2)	9.1 (5.4-15.4)	0.120

Values are % or number of events per 1,000 patient-years (95% CI). [a]Within 48 hours after hospital admission. [b]According to Thrombolysis In Myocardial Infarction classification.

AMI = acute myocardial infarction.

in cardiology; they are presented in Supplemental Table 2.

PATIENT MANAGEMENT. Latecomer patients benefited less frequently from coronary angiographies (91.9% vs 96.5%; $P < 0.001$) and, as a result, these patients underwent less PCI (76.8% vs 86.5%; $P < 0.001$). When PCI was performed in this population, the final angiographic result was not as good as for early comers, with a post-PCI TIMI flow grade 2/3 obtained in 80.4% of latecomers vs 88.5% of early comers ($P < 0.001$). At discharge, aspirin, $P2Y_{12}$ inhibitors, and statins were significantly less prescribed in latecomer patients. No differences were observed regarding angiotensin-converting enzyme (ACE) inhibitors/angiotensin 2 receptor blockers (ARBs) or beta-blockers, whereas diuretic agents were significantly more prescribed in latecomers (24.3% vs 19.9%; $P < 0.001$). The detailed management of patients according to their time of presentation is shown in **Table 1**.

COMPARISON OF REVASCULARIZED VS NONREVASCULARIZED LATECOMER PATIENTS. After exclusion of patients treated by thrombolysis and patients deceased within 2 days after admission, 1,077 latecomers were considered for the analysis of revascularization benefit. Among them, 729 (67.7%) underwent a revascularization within 48 hours following hospital admission: 726 patients were revascularized by PCI and 3 patients benefited from CABG. From 2005 to 2015, the use of coronary angiography in the latecomers population increased from 85.4% to 96.8% ($P < 0.001$), and as a result, revascularization by PCI in this population increased from 66.5% to 82.8% ($P < 0.001$). Over this 10-year period, the rate of utilization of evidence-based post-MI drugs (aspirin, $P2Y_{12}$ inhibitors, beta-blockers, statins, and ACE inhibitors or ARBs) significantly increased in latecomers patients ($P < 0.001$ for all). The detailed management of latecomer patients according to their year of hospitalization is presented in Supplemental Table 1.

Revascularized latecomer patients were younger (62.7 ± 14.2 years vs 70.2 ± 14.5 years; $P < 0.001$) and were less likely to present hypertension (48.6% vs 64.8%; $P = 0.001$), whereas they were more likely to be active smokers (45.1% vs 27.1%; $P < 0.001$) and to present with a family history of coronary artery disease (27.9% vs 19.2%; $P = 0.003$). Revascularized patients also had less comorbidities, such as past medical history of heart failure or chronic kidney disease (3.2% vs 8.7%; $P < 0.001$; and 1.9% vs 5.8%; $P = 0.001$). At discharge, revascularized latecomer patients received significantly more aspirin (85.6% vs 78.6%; $P = 0.004$), $P2Y_{12}$ inhibitors (77.5% vs 61.9%; $P < 0.001$), ACE inhibitors/ARBs (76.1% vs 63.8%; $P < 0.001$) and statin therapy (86.2% vs 76.7%; $P < 0.001$), but less frequently diuretic agents (21.4% vs 33.5%; $P < 0.001$). In the latecomers group, median door-to-balloon time was 5.4 hours (IQR: 1.9-24.5 hours). Although this delay was longer than in the early comers group (1.4 hours [IQR: 0.6-4.4 hours]; $P < 0.001$), it remains relatively short in this context and demonstrates that when revascularization was decided in a latecomer patient, it was achieved promptly in the majority of cases. A comparison between revascularized and nonrevascularized latecomer patients is presented in **Table 2**.

OUTCOMES OF REVASCULARIZED VS NONREVASCULARIZED LATECOMER PATIENTS. At 30-day follow-up, all-cause death rate in the

latecomer population was 3.7%, significantly lower in the revascularized latecomer population than in the nonrevascularized population (2.1% vs 7.2%; $P < 0.001$). Recurrent MI rate was also lower in the revascularized latecomers population, but this was not statistically significant (0.6% vs 1.7%; $P = 0.06$). No differences were observed regarding the rate of stroke (1.2% vs 1.4%; $P = 0.78$); however, severe bleeding (according to TIMI classification) was more frequent among nonrevascularized latecomers (0.4% vs 2.0%; $P = 0.016$)

During follow-up, the all-cause death rate in the latecomer population was 44.9 per 1,000 patient-years (95% CI: 40.0-50.3 per 1,000 patient-years), significantly lower in the revascularized latecomers population than in the nonrevascularized population (30.4 per 1,000 patient-years [95% CI: 25.7-35.9 per 1,000 patient-years] vs 78.7 per 1,000 patient-years [95% CI: 67.2-92.3 per 1,000 patient-years]; $P < 0.001$). Recurrent AMI was also significantly less frequent among revascularized latecomers than in nonrevascularized latecomers (5.4 per 1,000 patient-years [95% CI: 3.5-8.5 per 1,000 patient-years] vs 11.0 per 1,000 patient-years [95% CI: 6.8-17.7 per 1,000 patient-years]; $P = 0.03$) (**Table 3**).

In a multivariate analysis, after adjustment on year of admission, age, smoking status, family history of coronary artery disease, prior AMI or PCI, prior stroke or transient ischemic attack, peripheral artery disease, chronic kidney disease, Killip at admission, and left ventricular ejection fraction at discharge, revascularization remained independently associated with a reduction of the occurrence of mortality (HR: 0.65; 95% CI: 0.50-0.84; $P = 0.001$) during follow-up (**Table 4, Central Illustration**). No interaction was found between the year of inclusion and the benefit of revascularization. Kaplan-Meier curves comparing mortality according to revascularization status for each registry (2005, 2010, and 2015) are shown in Supplemental Figure 2 (log-rank test $P < 0.001$ for all)

In propensity score matching analysis comparing 2 groups of 267 latecomer patients with similar conditions, revascularization was still highly beneficial regarding death occurrence (log-rank test $P = 0.006$) (**Figure 2**).

TABLE 4 Independent Predictors of All-Cause Mortality During Follow-Up in the Latecomer Patient Population

	HR	95% CI	*P* Value
Year			
2005	1.00		
2010	1.11	0.84-1.47	0.470
2015	0.74	0.47-1.16	0.189
Age at entry, y	1.07	1.06-1.09	<0.001
Smoking	1.50	1.07-2.10	0.018
Family history of CAD			
No	1.00		
Yes	0.55	0.37-0.80	0.002
Unknown	1.99	1.09-3.60	0.024
Prior AMI/PCI	2.10	1.57-2.80	<0.001
Prior stroke/TIA	1.61	1.10-2.36	0.015
Peripheral vascular disease	1.62	1.12-2.34	0.010
Chronic kidney disease	1.90	1.16-3.09	0.010
Killip >2 at entry	1.57	1.07-2.30	0.021
Revascularization within 48 h after hospital admission	0.65	0.50-0.84	0.001
LVEF at discharge			
≥40%	1.00		
<40%	2.01	1.44-2.79	<0.001
Unknown	1.25	0.94-1.66	0.123

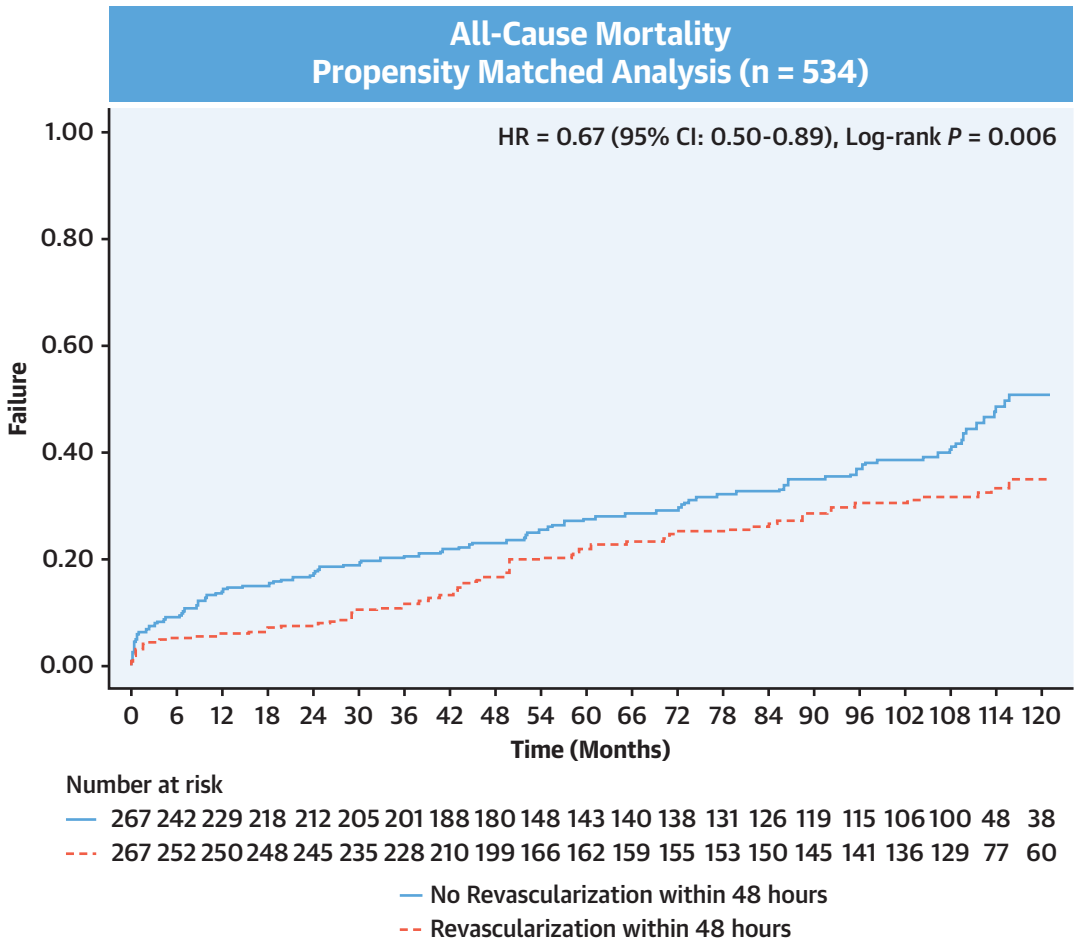
LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

DISCUSSION

The present study investigated the characteristics, prevalence, management, and outcomes of latecomer STEMI patients (ie, admitted >12 hours after symptom onset) over a period of 10 years (2005-2015) in metropolitan France based on 3 registries conducted in a 1-month period (2005, 2010, and 2015 FAST-MI registries). We observed a reduction of the latecomer patient proportion from 22.7% in 2005 to 16.1% in 2015, and an increase of the use of invasive strategy and evidence-based medications in this population. Moreover, we noticed that revascularization within 48 hours after hospital admission was independently and significantly associated with an improvement of short- and long-term clinical outcomes in these patients. To the best of our knowledge, this report is the first documenting long-term clinical outcomes of latecomers according to their revascularization status in a large nationwide registry.

LATECOMERS PROFILE AND PREVALENCE. In our population, diabetes, age, prior heart failure, and atypical chest pain are independent predictors of late arrival. These parameters were identified as predictors of late arrival in previous reports (5,20,21); our data are thus consistent with the published data. On the contrary, a prior history of AMI was, in our study, independently related to a 35% reduction in the probability of late arrival, probably caused by the patients' awareness of AMI symptoms—this phenomenon has already been described in the GRACE registry (21). Interestingly, female sex was not related to late arrival in our cohort, whereas it was suggested in previous works (21). This difference we observed with older studies might be caused by an increasing awareness among physicians and the population of

FIGURE 2 Mortality in the Latecomer Population in a Propensity-Matched Analysis



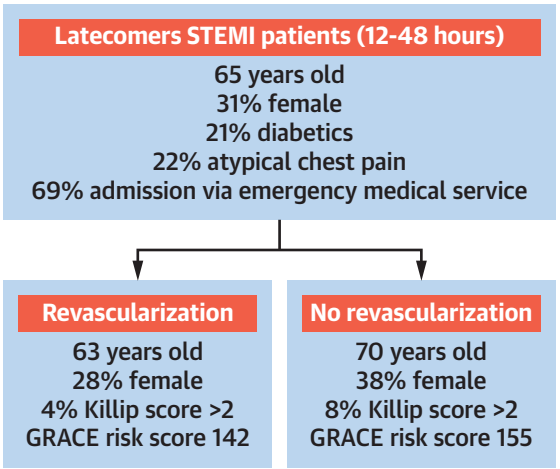
In this propensity-matched analysis, which included 2 groups of 267 matched latecomer patients, revascularization within 48 hours after hospital admission was associated with a significant reduction of mortality rate during follow-up (log-rank test $P = 0.006$; HR: 0.67; 95% CI: 0.50-0.89).

AMI symptoms in female patients, because these are more likely to be atypical.

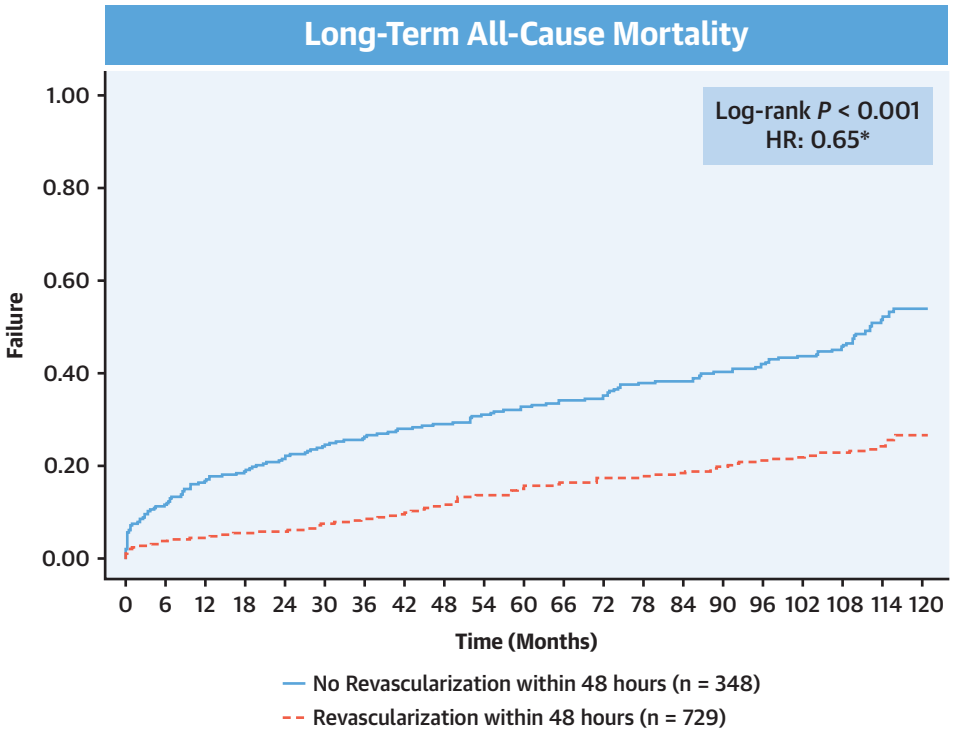
Our data describe a substantial reduction of latecomer prevalence, from 23.6% in 2005 to 16.1% in 2015. A recent study from Roberto et al. (1) describing temporal trends in latecomers in Switzerland between 1997 and 2017 reports a reduction in the latecomers prevalence among STEMI patients in similar proportions (1). Indeed, because the benefit of revascularization is known to be time-dependent (8,22), significant efforts in public health politics have been conducted to reduce patient-related delays of hospitalization according to STEMI guidelines (7) that recommend timely reperfusion therapies. These efforts consisted in raising public awareness of cardiovascular symptoms through information campaigns and developing networks between pre-hospital medical units and interventional cardiologic centers. As a consequence, between 1995 and 2015 the median delay from onset to admission reduced from 240 to 168 minutes (23) in metropolitan France.

BENEFIT OF REVASCULARIZATION OF LATECOMER STEMI PATIENTS: PATHOPHYSIOLOGY AND CLINICAL TRIALS. The benefit of the revascularization of the infarct artery beyond 12 hours remains debated. European guidelines on STEMI recommend the realization of PCI for patients presenting between 12 and 48 hours after symptom onset (7) (Class IIa, Level of Evidence: B), whereas current American guidelines support the realization of PCI in STEMI patients—without cardiogenic shock—beyond 12

CENTRAL ILLUSTRATION **Mortality Comparison in the Latecomer Population According to Revascularization Status**



30-day mortality (%)	2.1%	7.2%	$P < 0.001$
Long-term mortality (for 1,000 patient-years)	30.4	78.7	$P < 0.001$



Bouisset, F. et al. J Am Coll Cardiol. 2021;78(13):1291–1305.

Revascularization of latecomer STEMI patients is associated with a significant reduction of mortality rate during follow-up (log-rank test $P < 0.001$; adjusted HR: 0.65; 95% CI: 0.50-0.84; $P < 0.001$). This comparison is done on latecomer STEMI patients alive at 48 hours, revascularized within 48 hours following hospital admission, and after exclusion of patients who received thrombolysis. *Immortal time bias avoided in the design and adjustment for confounders in the analysis. STEMI = ST-segment elevation myocardial infarction.

hours but no later than 24 hours after symptom onset and in the concomitant presence of symptoms of ongoing ischemia (6) (Class IIA, Level of Evidence: B).

Ischemia duration was identified as a major determinant of infarct size in the late 1970s with the description of "the wave front phenomenon" by Reimer et al (24) based on animals' experimental studies. This phenomenon corresponds to the progressive necrosis of myocardium from endocardium to epicardium, proportionately to the duration of coronary artery occlusion. Canine models suggested that myocardium remained viable only within the first 6 hours after coronary occlusion, whereas clinical observations suggested a benefit of revascularization beyond this short delay. Indeed, large trials focusing on thrombolytic therapy demonstrated a mortality benefit up to 12 hours after symptom onset (25-29), which is precisely the origin of the 12-hour limit generally accepted to classify patients as latecomers. To reconcile these contradictory results between experimental and clinical studies, Eugene Braunwald developed the "open artery hypothesis" (30,31) and suggested that the benefit of revascularization beyond the first 6 hours might be caused by a limitation of the remodeling process or the reduction of rhythmic complications. There are, in fact, significant differences between animal models and clinical myocardial infarction that explain this difference. In clinical myocardial infarction, up to one-half of patients present with an incomplete coronary occlusion and the preservation of a minimal blood flow (12,32). Preservation of antegrade blood flow in the infarct-related artery was found to be associated with reduction of infarct size (33,34) and better clinical outcomes (35). Moreover, collateral circulation development, induced by chronic myocardial ischemia that frequently precedes the AMI, permits retrograde coronary perfusion (36,37). These mechanisms can thus preserve antegrade or retrograde coronary flow, whereas in animal models, myocardial infarction was provoked by complete and fixed ligation of the coronary artery, which implies no possible residual anterograde blood flow. Finally, repetitive myocardial ischemia in patients presenting with intermittent occlusion and recanalization before AMI allow myocardial preconditioning, increasing the resistance of myocardium to ischemia (38,39). As a result, in humans, some mechanisms can maintain a substantial myocardial viability far beyond the limit of 6 hours experimentally determined by Reimer et al (24). This explains the potential benefit of late coronary revascularization in AMI.

Various clinical studies investigated the interest of PCI in latecomer STEMI patients with conflicting results. In the 1990s and early 2000s, some reports suggested a potential benefit of revascularization over optimal medical treatment alone on left ventricular ejection fraction (10), quality of life (40), and long-term major adverse cardiac events (11,41) in latecomer STEMI patients. In 2005, the BRAVE 2 trial (Beyond 12 Hours Reperfusion Alternative Evaluation 2) included 365 latecomer STEMI patients who were randomized between a conservative therapy and an invasive strategy with PCI and showed that infarct size—assessed by single-photon emission computerized tomography—was significantly reduced in the PCI arm of the study (12). At 4-year follow-up, a significant reduction of all-cause death by 45% ($P = 0.04$) (13) was observed, suggesting a benefit of invasive strategy on mortality in latecomers. The same year, however, the DECOPI (DEsobstruction COronaire en Post-Infarctus) randomized trial, which included 212 latecomer STEMI patients, reported no benefit of revascularization at 1 year on a composite primary endpoint that included cardiac death, nonfatal MI, or ventricular tachyarrhythmia (42). In 2006, the large OAT (Occluded Artery Trial), which included 2,166 stable latecomer STEMI patients randomized between a conservative therapy and PCI, failed to demonstrate any benefit of revascularization on combined criteria (death, reinfarction, and heart failure) after 4 years of follow-up (HR: 1.16 [95% CI: 0.92-1.42]; $P = 0.20$) (43). The apparently conflicting results of the previously mentioned trials can probably be explained by a significant difference among their population. Indeed, in the DECOPI and OAT trials—which both reported negative results—patients were randomized with a median delay from symptom onset of 5 and 8 days, respectively, whereas in the positive BRAVE 2 trials, patients presented much earlier, between 12 and 48 hours after symptom onset. This suggests that revascularization of latecomers STEMI patients is relevant only in the relatively early period following symptom onset. More recent studies confirm this observation, demonstrating that the myocardial salvage, assessed by single-photon emission computerized tomography (8) or cardiac magnetic resonance imaging (9), remains substantial in a large proportion of latecomers provided that it was performed within 72 hours following symptom onset. The favorable results of revascularization on clinical outcomes during follow-up observed in our cohort of latecomer STEMI patients are thus fully in line with these previous studies and confirm, for the first time on a large nationwide registry, the interest of revascularization of STEMI patients presenting 12 to 48 hours following symptom onset; these results also provide an adequate

comparison of revascularized and nonrevascularized latecomers, which was missing to date in the published data (44). Although late STEMI presentation is becoming rare in recent registries, it still represents 10% to 15% of STEMI patients (1,3). Moreover, these results are particularly relevant in the actual context of the coronavirus disease 2019 pandemic. Indeed, longer duration of ischemia has been reported in this context (45,46), leading clinicians to face more latecomer STEMI patients.

STUDY LIMITATIONS. The main limitation of this study is its observational design, which cannot confirm causality but only describes statistically significant and independent associations between observed clinical outcomes and patient management. Indeed, after having avoided immortal time bias in the design and performed a multivariate analysis, potential confounding factors that were not considered in the study cannot be fully excluded.

CONCLUSIONS

Although the relative proportion of latecomer STEMI patients decreased over the 10-year period of this study, they still constitute a significant proportion of STEMI patients who are more likely to present comorbidities and atypical presentation. Coronary revascularization of the infarct artery of latecomer STEMI patients admitted before 48 hours after symptom onset is associated with better long-term clinical outcomes on hard endpoints. Our results strengthen the current European guidelines that recommend performing a PCI on STEMI patients up to 48 hours after symptom onset.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PCI in patients presenting between 12 and 48 hours after onset of STEMI is associated with improved short- and long-term clinical outcomes.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify subgroups of patients presenting even later after onset of STEMI who benefit from PCI.

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APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.