Twenty-year trends in profile, management and outcomes of patients with ST-segment elevation myocardial infarction according to use of reperfusion therapy: Data from the FAST-MI program 1995-2015

Etienne Puymirat, Guillaume Cayla, Yves Cottin, Meyer Elbaz, Patrick Henry, Édouard Gerbaud, Gilles Lemesle, Batric Popovic, Jean-Noel Labèque, François Roubille, et al.

▶ **To cite this version:**

Etienne Puymirat, Guillaume Cayla, Yves Cottin, Meyer Elbaz, Patrick Henry, et al.. Twenty-year trends in profile, management and outcomes of patients with ST-segment elevation myocardial infarction according to use of reperfusion therapy: Data from the FAST-MI program 1995-2015. American Heart Journal, 2019, 214, pp.97-106. 10.1016/j.ahj.2019.05.007 . hal-02152119

HAL Id: hal-02152119
https://hal.science/hal-02152119

Submitted on 18 Jun 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Twenty-year trends in profile, management and outcomes of patients with ST-segment elevation myocardial infarction according to use of reperfusion therapy: Data from the FAST-MI program 1995-2015

Etienne Puymirat, MD, PhD,[a] Guillaume Cayla, MD, PhD,[b] Yves Cottin, MD, PhD,[c] Meyer Elbaz, MD, PhD,[d] Patrick Henry, MD, PhD,[e] Edouard Gerbaud, MD, PhD,[f] Gilles Lemesle, MD, PhD,[g] Batric Popovic, MD, PhD,[h] Jean-Noel Labèque, MD,[i] François Roubille, MD, PhD,[j] Stéphane Andrieu, MD,[k] Bruno Farah, MD,[l] François Schiele, MD, PhD,[m] Jean Ferrières, MD, PhD,[n] Tabassome Simon, MD, PhD,[o] and Nicolas Danchin, MD, PhD[a], on behalf of the USIC and FAST-MI investigators

Background The increased use of reperfusion therapy in ST-segment-elevation myocardial infarction (STEMI) patients in the past decades is generally considered the main determinant of improved outcomes. The aim was to assess 20-year trends in profile, management, and one-year outcomes in STEMI patients in relation with use or non-use of reperfusion therapy (primary percutaneous coronary intervention (pPCI) or fibrinolysis).

Methods We used data from 5 one-month French nationwide registries, conducted 5 years apart from 2005 to 2015, including 8579 STEMI patients (67% with and 33% without reperfusion therapy) admitted to cardiac intensive care units in France.

Results Use of reperfusion therapy increased from 49% in 1995 to 82% in 2015, with a shift from fibrinolysis (37.5% to 6%) to pPCI (12% to 76%). Early use of evidence-based medications gradually increased over the period in both patients with and without reperfusion therapy, although it remained lower at all times in those without reperfusion therapy. One-year mortality decreased in patients with reperfusion therapy (from 11.9% in 1995 to 5.9% in 2010 and 2015, hazard ratio [HR] adjusted on baseline profile 0.40; 95% CI: 0.29-0.54, $P < .001$) and in those without reperfusion therapy (from 25.0% to 18.2% in 2010 and 8.1% in 2015, HR: 0.33; 95% CI: 0.24-0.47, $P < .001$).

Conclusions In STEMI patients, one-year mortality continues to decline, both related to increased use of reperfusion therapy and progress in overall patient management. In patients with reperfusion therapy, mortality has remained stable since 2010, while it has continued to decline in patients without reperfusion therapy.

From the [a]Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Européen Georges Pompidou, Department of Cardiology, 75015 Paris; Université Paris-Descartes, 75006 Paris, France, [b]Centre Hospitalier Universitaire de Nîmes, 30900 Nîmes, France, [c]Centre Hospitalier Universitaire du Bocage, 21000, Dijon, France, [d]Toulouse University Hospital, Department of Cardiology, 31059 Toulouse, France, [e]Hôpital Lariboisière, Department of Cardiology, 75010, Paris, France, [f]Hôpital Cardiologique Haut Levêque, CHU de Bordeaux, 33600, Pessac, France, [g]Lille Regional University Hospital, Department of Cardiology, 59037 Lille, France, [h]Département de cardiologie, CHU de Nancy, 54511, Vandœuvre-lès-Nancy, France, [i]Centre Hospitalier de la Côte Basque, 64100, Bayonne, France, [j]Montpellier University Hospital, Department of Cardiology, 34090 Montpellier, France, [k]Centre Hospitalier Henri Duffaut, Department of Cardiology, 84902, Avignon, France, [l]Clinique Pasteur, Department of Cardiology, 31059, Toulouse, France, [m]University Hospital Jean Minjoz, Department of Cardiology, 25030 Besançon, France, [n]Toulouse Rangueil University Hospital, Department of Cardiology; UMR1027, INSERM, 31059 Toulouse, France, and [o]AP-HP, Hôpital Saint Antoine, Department of Clinical Pharmacology and Clinical Research Platform of east of Paris (URCEST-CRBH-UEP-CRC-EST), 75012 Paris, France ; Sorbonne-Université (UPMC-Paris 06) ; INSERM U-698, 75012, Paris, France.

Etienne PUYMIRAT, MD, PhD, Hôpital Européen Georges Pompidou—Department of Cardiology, 20 rue Leblanc, 75015, Paris, France.
E-mail: etienne.puymirat@aphp.fr

The early outcome of patients with ST-segment myocardial infarction (STEMI) has considerably improved over the last 20 years.[1-7] This improvement has been attributed to changes in patient populations, more frequent use of reperfusion therapy (primary percutaneous coronary intervention (pPCI) or fibrinolysis), and increased use of evidence-based treatments.[5-10] However, little information is available on trends in STEMI patients treated without reperfusion therapy.

The aim of the present study was to assess 20-year trends in clinical presentation, management, and one-year mortality in STEMI patients in relation with use of reperfusion therapy in 5 sequential nationwide French surveys conducted between 1995 and 2015.[11-15]

Methods

Patient population

Five nationwide French registries were conducted 5 years apart over a 20-year period (1995-2015): USIK 1995, [11] USIC

(Unité de Soins Intensifs Coronaires) 2000,[12] FAST-MI (French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction) 2005 (NCT00673036),[13] FAST-MI 2010 (NCT01237418),[14] and FAST-MI 2015 (NCT02566200)[15] (eMethods 1). The methods used for these registries have been detailed previously.[11-15] Briefly, their primary objectives were to evaluate the characteristics, management, and outcomes of acute myocardial infarction (AMI) patients, as seen in routine clinical practice, on a country-wide scale.

All 5 registries consecutively included patients with STEMI or non-ST-segment myocardial infarction (NSTEMI) admitted to cardiac intensive care units (ICU) within 48 hours of symptom onset, during a specified one-month period (November 1995 and 2000, October-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. Exclusion criteria were (1) refusal to participate; (2) iatrogenic MIs, 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 elevation $\geq$1 mm was seen in at least two 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 that received 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 the 1995 and 2000 registries were reviewed by the Committee for the Protection of Human Subjects (CPP) in Biomedical Research of Nancy University hospital; the 2005 registry was reviewed by the CPP in Biomedical Research of Saint Antoine University Hospital; the 2010 registry was reviewed and approved by the CPP of Saint Louis University Hospital, Paris; and the protocol of 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 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, 2010, and 2015 surveys.

Data collection

Data on baseline characteristics, including demographics (age, sex, body mass index [BMI], risk factors (hypertension, diabetes, current smoking, hypercholesterolemia, family history of coronary artery disease), and medical history (MI, stroke, heart failure, peripheral artery disease (PAD)), were collected as previously described.[11-15] Information on the use of cardiac procedures, including use of PCI, use of medications (anticoagulants, antiplatelet agents, diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), 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. Several additional variables such as previous PCI, coronary artery bypass graft surgery (CABG), or chronic renal failure were also collected in the most recent surveys.

Reperfusion therapy was defined as use of either intravenous fibrinolysis (either pre-hospital or in-hospital), or intended pPCI, i.e. coronary angiography with an intent to perform PCI, within 24 hours of symptom onset, in patients not having received intravenous fibrinolytic therapy.

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

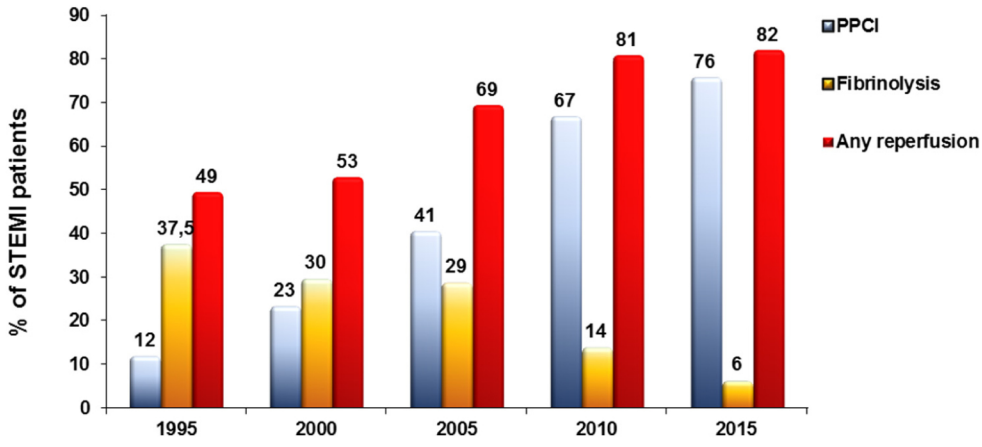
For the present analysis, only patients presenting with STEMI were considered.

Continuous variables are reported as means with standard deviations (SD) or medians and interquartile ranges (IQR), when appropriate. Discrete variables are described as counts and percentages. Groups were compared by analysis of variance for continuous variables and $\chi 2$ 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 (OR) and Hazard ratios (HR) are presented with their 95% CIs.

To determine independent predictors of reperfusion therapy, binary logistic regression analyses were used, using the same covariables as those listed below. Multivariable analyses of correlates of one-year 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, gender, risk factors, comorbidity, anterior location of MI, type of institution, and region.

To assess the relationship between early management and one-year survival, further analyses also used pPCI or fibrinolysis, type of anticoagulants used, and use of antiplatelet agents, beta-blockers, statins and ACE-inhibitors or ARB during the first 2 days (5 days for the 1995 survey) as covariables; sensitivity analyses were

Figure 1



Reperfusion treatment in ST-segment-elevation myocardial infarction (STEMI) patients by year of survey. PPCI, Primary percutaneous coronary intervention.

performed in 3-day survivors to avoid healthy survivor bias. We applied an appropriateness algorithm for treatments, based upon the recent European guidelines (antiplatelet agents and statins for all, beta-blockers and ACE- inhibitors or ARB when indicated; eMethods2).[16]

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 25.0 (IBM SPSS Inc). For all analyses, 2-sided *P* values <.05 were considered significant.

Results

Study population

Among the 8579 STEMI patients enrolled in the 5 surveys, the use of any reperfusion therapy (pPCI or fibrinolysis) increased consistently over the 20-year period ($P < .001$; Figure 1). Patient with reperfusion therapy were younger, and had a lower cardiovascular risk profile, both in terms of risk factors and history of cardiovascular disease (Tables 1, 2). Women received less reperfusion therapy compared to men for each survey ($P < .001$; eTable 1). Finally, current smoking was more frequent in patients with reperfusion therapy.

Initial pathways and early management

In patients with reperfusion therapy, median time from symptom onset to hospital admission decreased from 180 (IQR: 120; 300) minutes to 140 (IQR: 90; 252) minutes, while, in patients without reperfusion therapy, it decreased from 1995 to 2010 and increased between 2010 and 2015. The use of mobile intensive care units was higher in patients with reperfusion therapy but increased in both groups (Tables 3, 4). Use of reperfusion therapy consistently increased over time, from 49% to 82% (adjusted HR 2015 vs 1995: 4.39, 3.73-5.18, $P < .001$), with more frequent use of pPCI (12%-77%) and less frequent use of fibrinolysis (37.5%-6%) (Figure 1). Use of coronary angiography (CAG) at any time during the index admission increased, to reach 100% in 2015 in patients with reperfusion therapy and 92% in those without reperfusion therapy; in-hospital PCI increased from 36% to 94%, and 4% to 73%, respectively ($P < .001$). Use of evidence-based treatments (antiplatelet agents, statins, and when appropriate beta-blockers and ACE-I or ARB) during the first 48 hours from admission increased gradually in all patients; among P2Y12 inhibitors, there was a shift from clopidogrel to prasugrel (available in France since 2009) and ticagrelor (available in France since 2014) in the most recent surveys including in patients without reperfusion therapy; unfractionated heparin (UFH) decreased, and low molecular weight heparins (LMWH) or news anticoagulants (bivalirudin, fondaparinux) increased. Overall, the early use of full evidence-based treatments during the first 48 hours increased from 9% in 1995 to 64% in 2015 in patients with reperfusion therapy and from 5% to 52.0% in those without reperfusion therapy ($P < .001$). At hospital discharge, the proportion of patients receiving evidence-based treatments consistently increased up to 2010 in patients with reperfusion therapy and remained stable thereafter, while in those without reperfusion therapy recommended medications continued to increase in the most recent survey.

Early outcomes according to use of reperfusion therapy

In-hospital complications, such as ventricular fibrillation, atrial fibrillation, or new atrio-ventricular block, recurrent MI, stroke, reported major bleeding, were higher in patients without reperfusion therapy, but decreased gradually in both groups (e-Tables 2 and 3).

Table 1. Baseline characteristics of patients with ST-elevation myocardial infarction treated with reperfusion therapy from 1995 to 2015

	USIK 1995a (n = 759)	USIC 2000a (n = 974)	FAST-MI 2005 (n = 1116)	FAST-MI 2010 (n = 1385)	FAST-MI 2015 (n = 1533)	*P for trend*
Demography						
Age	61.6 ± 12.6	60.9 ± 13.7	61.2 ± 13.7	61.9 ± 14.0	62.7 ± 13.7	*.014*
Female, n (%)	142 (19)	217 (22)	277 (25)	318 (23)	361 (23.5)	*.035*
BMI	26.1 ± 3.8 (n = 725)	26.5 ± 4.1 (n = 891)	27.0 ± 4.3 (n = 952)	26.8 ± 4.4 (n = 1267)	26.7 ± 4.4 (n = 1303)	*.002*
Risk factors, n (%)						
Hypertension	289 (38)	365 (37.5)	490 (44)	613 (44)	655 (43)	*.002*
Hypercholesterolemia	284 (38)	396 (41)	493 (44)	536 (39)	565 (37)	*.17*
Diabetes mellitus	110 (15)	162 (17)	180 (16)	206 (15)	230 (15)	*.64*
Current smoking	308 (41)	407 (42)	474 (42.5)	616 (44.5)	664 (43)	*.11*
Obesity (BMI ≥30)	114 (16) (n = 725)	157 (18) (n = 891)	204 (20) (n = 1022)	273 (21) (n = 1318)	280 (19) (n = 1467)	*.031*
Cardiovascular history and comorbidities, n (%)						
Myocardial Infarction	85 (11)	129 (13)	114 (10)	134 (10)	186 (12)	.69
PCI	-	88 (9)	95 (8.5)	136 (10)	191 (12.5)	.001
CABG	-	22 (2)	24 (2)	77 (6)	22 (1)	.90
Stroke or TIA	25 (3)	29 (3)	41 (4)	40 (3)	55 (4)	.23
Heart failure	22 (3)	18 (2)	22 (2)	26 (2)	35 (2)	.60
PAD	55 (7)	49 (5)	48 (4)	58 (4)	62 (4)	.002
CKD	-	16 (2)	23 (2)	21 (1.5)	37 (2)	.28
Medications before, n (%)						
Antiplatelet therapy	-	188 (20)	210 (19)	243 (17.5)	397 (26)	<.001
Statin	-	169 (17)	236 (21)	292 (21)	328 (21)	.032
Beta-blocking agent	-	174 (18)	183 (16)	245 (18)	278 (18)	.59
ACE-I or ARB	-	150 (15)	229 (20.5)	371 (27)	349 (23)	<.001

Data are presented as n (%) or mean ± SD.
ACE-I, Angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *CABG*, coronary artery bypass graft surgery; *CAG*, coronary angiography; *PAD*, peripheral artery disease; *PCI*, percutaneous coronary intervention; *TIA*, transient ischemic attack.

Table 2. Baseline characteristics of patients with ST-elevation myocardial infarction treated without reperfusion therapy from 1995 to 2015

	USIK 1995[a] (n = 777)	USIC 2000[a] (n = 870)	FAST-MI 2005 (n = 495)	FAST-MI 2010 (n = 331)	FAST-MI 2015 (n = 339)	*P* for trend
Demography						
Age	70.8 ± 13.8	68.6 ± 14.5	70.3 ± 14.9	69.0 ± 15.3	66.7 ± 15.0	.002
Female, n (%)	289 (37)	282 (32)	181 (37)	105 (32)	108 (32)	.11
BMI	25.7 ± 4.0 (n = 729)	26.0 ± 4.1 (n = 763)	26.8 ± 5.2 (n = 488)	26.4 ± 4.7 (n = 348)	26.8 ± 4.8 (n = 483)	<.001
Risk factors, n (%)						
Hypertension	384 (50)	439 (50.5)	302 (61)	193 (58)	180 (53)	.004
Hypercholesterolemia	250 (33)	323 (38)	206 (42)	139 (42)	113 (33)	.07
Diabetes mellitus	132 (17)	202 (23)	122 (25)	77 (23)	78 (23)	.010
Current smoking	183 (24)	244 (28)	126 (25.5)	85 (26)	125 (37)	.001
Obesity (BMI ≥30)	94 (13)	112 (15)	95 (23)	51 (17)	69 (22)	<.001
Cardiovascular history and comorbidities, n (%)						
Myocardial Infarction	140 (18)	147 (17)	66 (13)	53 (16)	45 (13)	.027
PCI	-	51 (6)	45 (9)	39 (12)	45 (13)	<.001
CABG	-	28 (3)	10 (2)	19 (6)	10 (3)	.48
Stroke or TIA	71 (9)	49 (6)	50 (10)	28 (8.5)	21 (6)	.57
Heart failure	76 (10)	66 (8)	34 (7)	15 (4.5)	19 (6)	.001
PAD	93 (12)	96 (11)	37 (7.5)	25 (8)	22 (6.5)	<.001
CKD	-	50 (6)	27 (5.5)	21 (6)	24 (7)	.37
Medications before, n (%)						
Antiplatelet therapy	-	201 (23)	126 (25.5)	92 (28)	93 (27)	.055
Statin	-	135 (15.5)	106 (21)	82 (25)	70 (21)	.003
Beta-blocking agent	-	164 (19)	113 (23)	68 (20.5)	63 (19)	.92
ACE-I or ARB	-	199 (23)	166 (33.5)	107 (32)	90 (26.5)	.028

Data are presented as n (%) or mean ± SD.
ACE-I, angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *CABG*, coronary artery bypass graft surgery; *CAG*, coronary angiography; *PAD*, peripheral artery disease; *PCI*, percutaneous coronary intervention; *TIA*, transient ischemic attack.

Table 3. Early hospital management of patients with ST-elevation myocardial infarction treated with reperfusion therapy from 1995 to 2015a

	USIK 1995a (n = 759)	USIC 2000a (n = 974)	FAST-MI 2005 (n = 1116)	FAST-MI 2010 (n = 1385)	FAST-MI 2015 (n = 1533)	*P for trend*
Initial pathway and simple risk index, n (%)						
Mobile ICU	-	304 (31)	554 (50)	750 (54)	866 (56.5)	<.001
Simple risk index (SRI)	-	20.9 [13.9; 30.1] (n = 964)	20.3 [14.3; 28.8] (n = 1112)	19.3 [13.4; 28.3] (n = 1370)	21.3 [15.7; 30.0] (n = 1412)	.025
Time delays[b], median [IQR]						
Onset to first call/medical contact	-	75 [30; 166] (n = 833)	60 [30; 172] (n = 1113)	60 [25; 180] (n = 1357)	65 [30; 200] (n = 1533)	.31
Onset to admission	180 [120; 300] (n = 742)	205 [140; 330] (n = 948)	175 [112; 285] (n = 1116)	156 [105;290] (n = 1377)	140 [90;252] (n = 1533)	<.001
Onset to first call/medical contact	-	75 [30; 166] (n = 833)	60 [30; 165] (n = 1035)	60 [28; 180] (n = 1305)	60 [27; 165] (n = 1364)	<.001
Onset to admission	180 [120; 300] (n = 742)	205 [140; 330] (n = 948)	175 [112; 285] (n = 1116)	156 [105;290] (n = 1377)	147 [92;270] (n = 1533)	<.001
Procedures during hospitalization, n (%)						
CAG	-	882 (91)	1100 (99)	1383 (100)	1533 (100)	<.001
PCI	270 (36)	758 (78)	964 (86)	1301 (94)	1436 (94)	<.001
Medications in first 48 hours[c], n (%)						
Antiplatelet therapy	733 (97)	948 (97)	1076 (96)	1356 (98)	1529 (100)	<.001
Clopidogrel	-	-	1025 (92)	1170 (84.5)	383 (25)	<.001
Prasugrel	-	-	-	523 (38)	415 (27)	<.001
Ticagrelor	-	-	-	-	924 (60)	-
P2Y12 inhibitor	-	-	1033 (93)	1370 (99)	1493 (97)	<.001
GPIIb/IIIa inhibitors	0	252 (26)	492 (44)	651 (47)	402 (26)	<.001
Oral anticoagulant	-	2 (0.2)	3 (0.3)	20 (1)	62 (4)	<.001
UFH	736 (97)	831 (85)	802 (72)	630 (45.5)	862 (56)	<.001
LMWH	0	239 (24.5)	679 (61)	863 (62)	950 (62)	<.001
Fondaparinux	0	0	0	182 (13)	284 (18.5)	<.001
Bivalirudin	0	0	0	71 (5)	108 (7)	.031
Statin	96 (13)	502 (51.5)	921 (82.5)	1277 (92)	1317 (86)	<.001
β-Blocking agents	592 (78)	775 (80)	855 (77)	1134 (82)	1183 (77)	.98
ACE-I or ARB	376 (49.5)	403 (41)	599 (54)	913 (66)	1008 (66)	<.001
Diuretics	198 (26)	189 (19)	238 (21)	300 (22)	347 (23)	.59
Appropriate recommended therapy	71 (9)	326 (33.5)	594 (53)	942 (68)	969 (64)	<.001
Medications at discharge, n (%)						
Appropriate recommended therapy	71 (9) (n = 759)	458 (47) (n = 974)	716 (64) (n = 1116)	1084 (78) (n = 1384)	1141 (78) (n = 1470)	<.001

Data are presented as n (%) or mean ± SD.
ACE-I, Angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CAG*, coronary angiography; *GP*, glycoprotein; *ICU*, intensive care unit; *LMWH*, low molecular weight heparin; *PCI*, percutaneous coronary intervention; *UFH*, unfractionated heparin.
a For 1995 and 2000, blank cells indicate data not available.
b Minutes; median [25th; 75th percentiles].
c For 1995, medications used at any time during the first 5 days.

One-month mortality decreased in patients with reperfusion therapy from 8.3% in 1995 to 3.1% in 2010 and 2015, (HR 2015 vs 1995: 0.47; 95% CI 0.35-0.63, $P < .001$) and in those without reperfusion therapy from 18.9% in 1995 to 4.7% in 2015, HR 0.31, 0.21-0.45, $P < .001$) (Figure 2).

One-year mortality according to use of reperfusion therapy

One-year mortality in patients with reperfusion therapy decreased from 11.9% to 6.2% in 2010 and 5.9% in 2015, with HRs of 0.50 (95% CI 0.37-0.67) and 0.47 (0.35-0.63), respectively (Figure 3). The hazard ratios adjusted on baseline characteristics, time from onset, and location of infarct were 0.42 (0.31-0.56) and 0.40 (0.29-0.54) respectively for 2010 and 2015 versus 1995. After further adjustment on early management during the first 48 hours following admission, the difference was no longer significant with HRs remaining similar for 2010 and 2015: HR 0.95 (0.68-1.34) and 0.96 (0.67-1.36), respectively. The results were essentially unchanged in the sensitivity analysis censoring patients who died during the first 2 days following admission.

Table 4. Early hospital management of patients with ST-elevation myocardial infarction treated without reperfusion therapy from 1995 to 2015

	USIK 1995[a] (n = 777)	USIC 2000[a] (n = 870)	FAST-MI 2005 (n = 495)	FAST-MI 2010 (n = 331)	FAST-MI 2015 (n = 339)	*P* for trend
Initial pathway and simple risk index						
Mobile ICU, n (%)	-	123 (14)	112 (23)	87 (26)	87 (26)	<.001
Simple risk index (SRI)	-	26.8 [18.4; 39.0] (n = 854)	28.7 [19.1; 42.9] (n = 490)	26.3 [18.2; 40.1] (n = 318)	24.7 [16.7; 35.2] (n = 318)	.130
Time delays[b], median [IQR]						
Onset to first call/medical contact	-	270 [68; 745] (n = 653)	266 [60; 1020] (n = 487)	240 [60; 810] (n = 317)	780 [120; 1620] (n = 339)	<.001
Onset to admission	420 [210; 855] (n = 685)	420 [180; 795] (n = 758)	432 [173; 1341] (n = 494)	405 [140; 1115] (n = 321)	835 [174; 1667] (n = 339)	<.001
Procedures						
Coronary angiography	-	607 (70)	349 (70.5)	269 (81)	313 (92)	<.001
PCI during hospital stay	30 (4)	374 (43)	257 (52)	187 (56.5)	246 (73)	<.001
Medications in first 48 hours[c], n (%)						
Antiplatelet therapy	686 (88)	811 (93)	468 (94.5)	316 (95.5)	335 (99)	<.001
Clopidogrel	-	-	390 (79)	289 (87)	127 (37)	<.001
Prasugrel	-	-	-	48 (14.5)	42 (12)	.42
Ticagrelor	-	-	-	-	178 (42.5)	-
P2Y12 inhibitor	-	-	392 (79)	312 (94)	316 (93)	<.001
GPIIb/IIIa inhibitors	0	99 (11)	122 (25)	81 (24.5)	39 (11.5)	<.001
UFH	745 (96)	632 (73)	272 (55)	138 (42)	160 (47)	<.001
LMWH	0	267 (31)	307 (62)	206 (62)	196 (58)	<.001
Fondaparinux	-	-	-	50 (15)	68 (20)	.09
Bivalirudin	-	-	-	5 (1.5)	13 (4)	.06
Statin	55 (7)	340 (39)	341 (69)	266 (80)	259 (76)	<.001
Beta-blocking agents	409 (53)	573 (66)	307 (62)	250 (75.5)	238 (70)	<.001
ACE-I or ARB	357 (46)	361 (41.5)	254 (51)	199 (60)	193 (57)	<.001
Diuretics	334 (43)	258 (30)	179 (36)	111 (33.5)	111 (33)	.006
Appropriate recommended therapy	38 (5)	180 (21)	169 (34)	173 (52)	176 (52)	<.001
Medications at discharge, n (%)						
Appropriate recommended therapy	38 (5) (n = 777)	265 (30.5) (n = 870)	214 (43) (n = 495)	192 (58) (n = 331)	233 (71.5) (n = 326)	<.001

Data are presented as n (%) or mean ± SD.
ACE-I, Angiotensin-converting-enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CAG*, coronary angiography; *GP*, glycoprotein; *ICU*, intensive care unit; *LMWH*, low molecular weight heparin; *PCI*, percutaneous coronary intervention; *UFH*, unfractionated heparin.
a For 1995 and 2000, blank cells indicate data not available.
b Minutes; median [25th; 75th percentiles].
c For 1995, medications used at any time during the first 5 days.

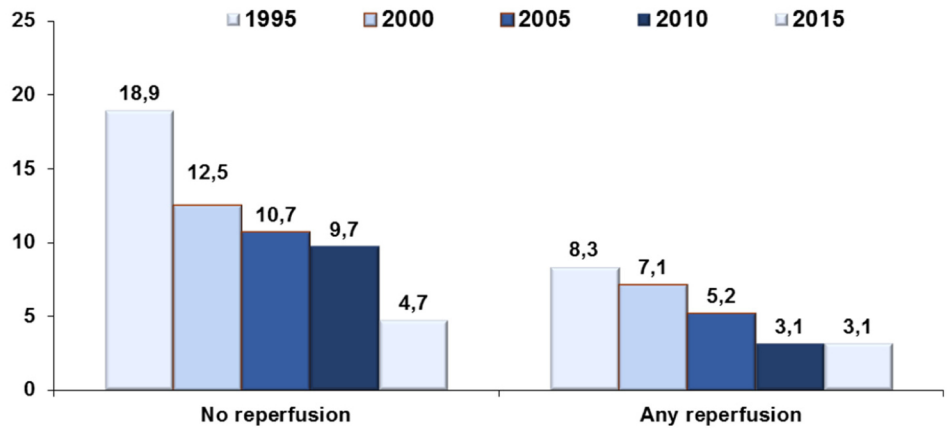
In those without reperfusion therapy, mortality decreased from 25.0% to 18.7% in 2010 and 8.8% in 2015; HRs for one-year death in reference to 1995 consistently decreased over time, to 0.68 (0.51-0.90) in 2010 and 0.33 (0.24-0.47) in 2015 (eTable 4). After adjustment on baseline characteristics, time from onset and location of infarct, the respective HRs for 2010 and 2015 versus 1995 were 0.68 (95% CI 0.52-0.90) and 0.33 (95% CI 0.44-0.92). After further adjustment on early management including use of recommended medications and use of PCI within 2 days of admission, there was no significant difference for one-year mortality in 2010 compared with 1995 (HR 1.24, 95% CI 0.91-1.69), while it was significantly lower in 2015 (HR 0.63, 95% CI 0.44-0.92). In the sensitivity analysis censoring patients who died within 2 days of admission, however, no significant difference between 2015 and 1995 was observed when using the multivariable model including early management (HR 1.16, 95% CI 0.68-1.99).

An additional analysis was performed in patients receiving all recommended medications within 48 hours from admission: there was no significant association between one-year mortality and survey year, both for patients with (HR 2015 vs 1995: 1.10, 95% CI 0.14-8.84) and those without reperfusion therapy (HR 1.50; 95% CI 0.35-6.28).

Trends in early versus late mortality

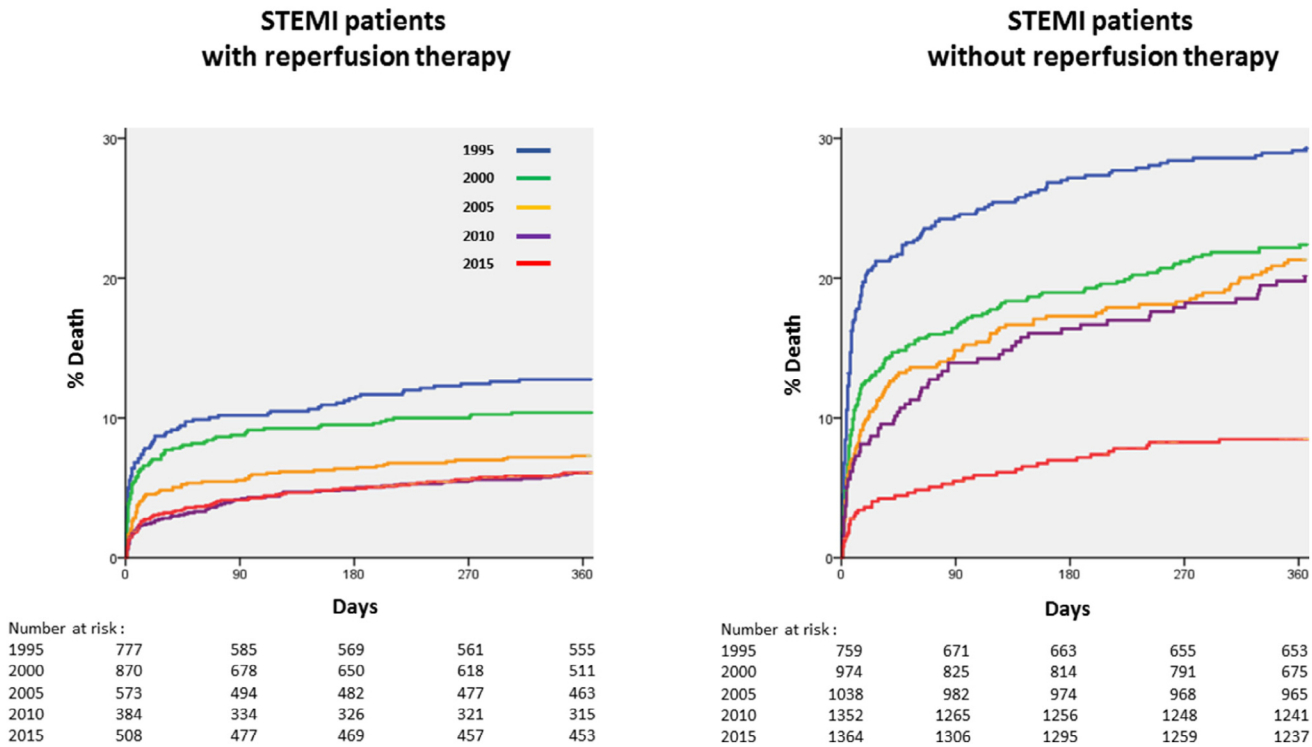
In patients with reperfusion therapy, using a time-dependent analysis, most of the improvement in mortality from 1995 to 2015 was observed at 30 days (HR 0.35, 95% CI 0.24-0.52), compared to the period from 1 month to 1 year (HR 0.75, 95% CI 0.46-1.21). After

Figure 2



Thirty-day mortality according to use of reperfusion therapy.

Figure 3



Number at risk:

1995	777	585	569	561	555
2000	870	678	650	618	511
2005	573	494	482	477	463
2010	384	334	326	321	315
2015	508	477	469	457	453

Number at risk:

1995	759	671	663	655	653
2000	974	825	814	791	675
2005	1038	982	974	968	965
2010	1352	1265	1256	1248	1241
2015	1364	1306	1295	1259	1237

One-year mortality in ST-segment-elevation myocardial infarction (STEMI) population according to use of reperfusion therapy between 1995 and 2015.

adjustment on baseline characteristics, mortality at 1 month was significantly lower in 2015 vs 1995 (HR 0.33, 95% CI 0.22-0.48), with a consistent trend for mortality from 1 month to 1 year (HR 0.63, 95% CI 0.39-1.03). After further adjustment on early management, neither 30-day mortality (HR 0.78, 95% CI 0.51-1.20), nor mortality from 1 month to 1 year (HR 1.52, 95% CI 0.91-2.55) differed significantly from 1995.

In patients without reperfusion therapy, in the time-dependent analysis, most of the mortality gain

from 2015 to 1995 was also observed at 1 month (HR 0.23, 95% CI 0.13-0.38), while the HR for one-month to one-year mortality was 0.55, 95% CI 0.30-1.00. Mortality adjusted on baseline characteristics was significantly lower at 1 month (HR 0.19, 95% CI 0.10-0.37), with a consistent trend for mortality from 1 month to 1 year (HR 0.57, 95% CI 0.30-1.08). After further adjustment on early management, one-month mortality in 2015 remained significantly lower in 2015 than in 1995 (HR 0.48, 95% CI 0.23-0.97), and there was no significant difference for mortality from 1 month to 1 year (HR 1.49, 95% CI 0.76-2.92). In the sensitivity analysis censoring patients dying within 48 hours of admission, neither one-month nor one-month to one-year mortality differed significantly from 1995 (HR for one-month death: 0.57, 95% CI 0.26-1.28; HR for one-month to one-year death: 1.46, 95% CI 0.74-2.87).

Discussion

In patients with STEMI, the use of reperfusion therapy has increased by more than 50% over the past 20 years. At the same time, the profile of patients has changed, with opposite trends in those with or without reperfusion therapy: patients with reperfusion therapy at the end of 2015 were 1 year older and with shorter times from symptom onset to admission, while patients without reperfusion therapy were younger, and with longer times to admission, compared to 1995. Evidence-based treatments at the acute stage and at discharge have become extensively used in all STEMI patients, although slightly less in patients without reperfusion therapy. In STEMI patients with reperfusion therapy, one-year mortality has declined until 2010, reaching a plateau afterwards. In contrast, in those without reperfusion therapy, mortality has continued to decrease. Most of the decline in mortality, both for patients with and those without reperfusion therapy, is likely attributable to improved early management, including performance of secondary PCI in patients who had not received reperfusion therapy at the acute stage.

The decline in mortality in patients with STEMI over the last 20 years reported in several registries and large administrative databases has been attributed mainly to improved use of reperfusion therapy and recommended medications.[1-10] In the present study, use of reperfusion therapy increased over time, with a shift from fibrinolysis to pPCI. Little progress, however, has been observed from 2010 to 2015 (+1.9%). In the SWEDEHEART registry, similar trends have been reported from 1995 to 2014:[7] use of reperfusion therapy increased from 66.2% to 81.7%, with a shift from fibrinolysis to pPCI and only a small increase in the percentage of patients receiving reperfusion therapy from 2009 to 2014 (+3%).

Beside the increased use of primary PCI and reperfusion therapy, changes in early recommended medications were considerable from 1995 until 2010. After 2010, however, a decrease in use of recommended medications at the acute stage was observed in patients with reperfusion therapy, while it continued to increase, albeit slightly, in patients without reperfusion treatment. In the SWEDEHEART registry, the use of recommended medications also increased markedly until 2006, with only small changes afterwards; the differential prescription of recommended medications in patients with or without reperfusion therapy, however, was not reported.[7]

Both short-term and long-term mortality have been shown to decrease over the past decades in several,[8-10] but not all countries.[17-19] Beside an increasing use of reperfusion therapy, improvements in care, such as improved network organization or changes in patient risk profile are also likely to contribute to improved survival.[5-10,20,21] Of note, at least in some countries, mortality did not decrease further in the most recent years.[7,22] None of the previous reports, however, analyzed in detail trends in presentation and outcomes according to whether or not patients underwent reperfusion therapy.

In the present analysis, patients getting reperfusion therapy tended to have a poorer initial profile over time (using the simple risk index, P for trend = 0.025), while no significant trend was observed in those without reperfusion therapy (simple risk index P for trend = 0.130), whose age decreased over time. In patients without reperfusion therapy, median times from onset to first call and onset to admission were longer in the 2015 survey, suggesting that the main determinant of lack of reperfusion therapy in the most recent survey may have been delayed presentation. Mortality has continued to decline for the whole study period in STEMI patients without reperfusion therapy, while it has reached a plateau since 2010 in those with reperfusion therapy. This improvement persisted after adjustment on the patients' baseline characteristics. When adjusted on early management, 30-day mortality continued to decrease throughout the study period for those without reperfusion treatment, while no change was observed in those with reperfusion therapy. From 1 month to 1 year, there was a trend for improved survival in both patients with or without reperfusion therapy after adjustment on baseline characteristics; for both populations, however, this trend no longer existed when early management was taken into account, suggesting that the advances in terms of one-year survival were mainly related to improved management in the early phase. The importance of using appropriate medical therapy at the early stage was further confirmed by the analysis limited to those patients who did received appropriate medical treatment, in whom survey year was not related to one-year outcome, neither for those with nor those without reperfusion therapy. Concordant with the current findings, the SWEDEHEART registry found that both early and one-year mortality decrease over time was no

longer significant when adjusted on early management (reperfusion therapy and medications).[7]

When analyzing the decrease in mortality by type of reperfusion therapy (e-Figure 1), 30-day mortality remained stable in patients treated with primary PCI (3.3% in 2010 and 3.2% in 2015) and increased slightly from 2010 (2.1%) to 2015 (2.6%) in patients treated with fibrinolytic therapy. Overall, the pattern observed according to use and type of reperfusion therapy shows that the decrease in mortality over the past 20 years cannot be attributed solely to the increasing use of primary PCI and that considerable progress has also been made in patients not receiving reperfusion therapy.

Limitations

Our study provides a detailed description of the profile and outcomes of STEMI patients in relation with the use of reperfusion therapy, rarely available from real-world data. It suffers, however, the same limitations as all observational studies. Comparisons between patients with reperfusion therapy and those without reperfusion therapy were obviously not randomized and, despite careful adjustments on a large number of potentially confounding variables, the results can only be considered indicative. Further observations will show whether the trends observed up to 2015 remain the same in the coming years. Patients who died before reaching the hospital, such as patients with out-of-hospital cardiac arrest, were not included; the mortality figures reported here are therefore likely to minimize the true mortality figures of MI on a population basis. Finally, comprehensive data on time delays were not available in all surveys; for instance, time from symptom onset to first call was not available in the 1995 survey. We therefore could not adjust for such variables in the overall analysis.

Conclusions

In STEMI patients, one-year mortality has considerably declined from 1995 to 2015, both related to increased use of reperfusion therapy but also to progress in overall patient management, as evidenced by the continuous decrease in mortality also found in patients without reperfusion therapy. In patients with reperfusion therapy, mortality has reached a plateau since 2010, while it has continued to decline in patients without reperfusion therapy. Our study suggests that the margin for improvement should be focused on shortening time delays between symptom onset and first call (e.g. public media information on optimal behavior of the population in case of prolonged chest pain), in order to decrease the percentage of patients without reperfusion, and also by improved use of recommended medications in those who still do not undergo reperfusion therapy.

Acknowledgements

The authors are deeply indebted to all patients who accepted to participate in the surveys, and to the physicians who took care of the patients at the participating institutions.

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. None of the companies had a role in the design and conduct of the study, data collection and management. They were not involved in the analysis and interpretation of the data, nor in the preparation, review, or approval of the manuscript.

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;125:1848-57.
2. 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;156:1026-34.
3. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155-65.
4. Fox KAA, Steg PG, Eagle KA, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007;297:1892-900.
5. Puymirat E, Simon T, Steg PG, et al. 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.
6. Puymirat E, Simon T, Cayla G, et al. USIK, USIC 2000, and FAST-MI investigators. 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. Circulation 2017;136:1908-19.
7. Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. Eur Heart J 2017;38:3056-65.
8. Jernberg T, Johanson P, Held C, et al. SWEDEHEART/RIKS-HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;305:1677-84.
9. Gale CP, Allan V, Cattle BA, et al. 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 Br Card Soc 2014;100:582-9.
10. Stolt Steiger V, Goy J-J, Stauffer J-C, et al, Plus Investigators AMIS. Significant decrease in in-hospital mortality and major adverse cardiac events in Swiss STEMI patients between 2000 and December 2007. Swiss Med Wkly 2009;139:453-7.
11. 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: 1598-605.
12. Hanania G, Cambou J-P, 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 Br Card Soc 2004;90:1404-10.
13. Cambou J-P, Simon T, Mulak G, et al. 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;100:524-34.
14. 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 Br Card Soc 2012;98:699-705.
15. Belle L, Cayla G, Cottin Y, et al. 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;110:366-78.
16. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
17. Aliprandi-Costa B, Morgan L, Snell LC, et al. ST-Elevation Acute Myocardial Infarction in Australia-Temporal Trends in Patient Management and Outcomes 1999–2016. Heart Lung Circ 2018 Jun 11. pii: S1443-9506(18)30697-8.
18. Zandecki Ł, Sadowski M, Janion M, et al. Survival benefit from recent changes in management of men and women with ST-elevation myocardial infarction treated with percutaneous coronary interventions. Cardiol J 2018 Jun 20, https://doi.org/10.5603/CJ.a2018.0057.
19. Li X, Murugiah K, Li J, et al. China PEACE Collaborative Group. Urban-Rural Comparisons in Hospital Admission, Treatments, and Outcomes for ST-Segment-Elevation Myocardial Infarction in China From 2001 to 2011: A Retrospective Analysis From the China PEACE Study (Patient-Centered Evaluative Assessment of Cardiac Events). Circ Cardiovasc Qual Outcomes 2017;10. pii: e003905.
20. Filgueiras Filho NM, Feitosa Filho GS, Solla DJF, et al. Implementation of a Regional Network for ST-Segment-Elevation Myocardial Infarction (STEMI) Care and 30-Day Mortality in a Low- to Middle-Income City in Brazil: Findings From Salvador's STEMI Registry (RESISST). J Am Heart Assoc 2018;7. pii: e008624.
21. Schoenenberger AW, Radovanovic D, Windecker S, et al. AMIS Plus Investigators. Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome. Eur Heart J 2016;37: 1304-11.
22. Tran DT, Welsh RC, Ohinmaa A, et al. Temporal Trends of Reperfusion Strategies and Hospital Mortality for Patients With STEMI in Percutaneous Coronary Intervention-Capable Hospitals. Can J Cardiol 2017;33:485-92.