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► **To cite this version:**

Frédéric Bouisset, Edouard Gerbaud, Vincent Bataille, Pierre Coste, Etienne Puymirat, et al.. Percutaneous Myocardial Revascularization in Late-Presenting Patients With STEMI. *Journal of the American College of Cardiology*, 2021, 78 (13), pp.1291-1305. 10.1016/j.jacc.2021.07.039 . hal-03626432

**HAL Id: hal-03626432**

**<https://hal.science/hal-03626432v1>**

Submitted on 16 Oct 2023

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## **Percutaneous Myocardial Revascularization in Late-Presenting Patients with STEMI**

**Brief title:** Myocardial revascularization in latecomer STEMI patients

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### ***Sources of funding***

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

### ***Disclosures***

Dr Frederic **Bouisset** reports personal fees from MSD, Abbott, Bayer, B-Braun and Amgen.

Dr Edouard **Gerbaud** is a consultant for Terumo.

Dr Vincent **Bataille** reports no conflicts of interest

Prof Pierre **Coste** reports personal fees from Amgen, Sanofi, Servier, AstraZeneca, and Abiomed

Prof Etienne **Puymirat** reports fees for lectures and/or consulting from Amgen, AstraZeneca, Bayer, Biotronik, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, The Medicine Company, Sanofi, Saint Jude Medical, Servier, Siemens.

Dr Loic **Belle** reports unrestricted grants for research from Boston Scientific, Medtronic, Abbott, Biotronik, speaker fees and consulting with Astra-Zeneca and MSD

Dr Clément **Delmas** reports consulting fees from the company Boston Scientific, grants/research support from the companies Maquet, Abiomed, Abbott and Terumo, lecture fees from the companies Abiomed, Thoratec and Abbott.

Prof Guillaume **Cayla** reports speaker or congress fees and has received research grants/consultant fees/ lectures fees from Amgen, AstraZeneca, Abbott, Bayer, Biotronik, Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis.

Prof Pascal **Motreff** reports consulting fees from Terumo and Abbott Medical.

Prof Gilles **Lemesle** reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Daiichi Sankyo, Lilly, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, and Servier

Prof Nadia **Aissaoui** reports no conflicts of interest

Dr Didier **Blanchard** reports no conflicts of interest

Prof François **Schiele** reports personal fees from Amgen, Astra Zeneca, Bayer, BMS, MSD, Pfizer, and Sanofi.

Prof Tabassome **Simon** reports grants from AstraZeneca, Daiichi-Sankyo, EliLilly, GSK, MSD, Novartis, Sanofi, and personal fees for board membership and/or consultancy and/or lectures from AstraZeneca, BMS, Sanofi, and Novartis

Prof Nicolas **Danchin** reports having received grants, speaking fees, consulting fees, or nonfinancial support from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Intercept, Novo-Nordisk, Pfizer, Sanofi and Servier

Prof Jean **Ferrières** reports grants and personal fees from Akcea, Amarin, Amgen, MSD, Sanofi and Servier

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#### **Acknowledgments**

The authors acknowledge the patients who accepted to participate to this study and all physicians who took care of them. We acknowledge the help of ICTA (Fontaine-lès-Dijon, France), and Axonal (Nanterre, France) for data collection. Our gratitude to the personnel of URCEST (Assistance Publique des Hôpitaux de Paris and University Paris Sorbonne). Special thanks to Benoît Pace (Société Française de Cardiologie) who designed the electronic CRF, to Geneviève Mulak, Pharm D. and Nicole Naccache, Pharm D. (Société Française de Cardiologie) for their help, and to Elodie Drouet, MSc, who supervised patients' follow-up.

## **Abstract**

**Background:** The optimal management of patients with ST-elevation Myocardial Infarction (STEMI) presenting late - over 12 hours following symptoms 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:** We analyzed the data of three nationwide observational studies from the French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) program, conducted over a one 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 6273 STEMI patients were included in the three cohorts, 1169 (18.6%) of whom were latecomers. After exclusion of patients treated with fibrinolysis and patients deceased within 2 days after admission, 1077 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 of 58 months, the rate of all-cause death was 30.4 [25.7 - 35.9] for 1000 patient-years in the revascularized latecomers group vs 78.7 [67.2 - 92.3] for 1000 patient-years in the non-revascularized latecomers group ( $p < 0.001$ ). In multivariate analysis, revascularization of latecomers STEMI patients was independently associated with a significant reduction of mortality occurrence during follow-up: HR= 0.65 [0.50 - 0.84],  $p < 0.001$ .

**Conclusions:** Coronary revascularization of latecomer STEMI patients is associated with better short and long-term clinical outcomes.

**Condensed Abstract:** A substantial proportion of STEMI patients still present late- i.e. over 12 hours following symptoms onset – and optimal management of these patients is still debated. The present study focuses on a population of 6273 STEMI patients among whom 1169 were latecomers (presenting between 12 and 48 hours). Our results demonstrate that revascularization within 48 hours after hospital admission is independently associated with a reduction of mortality both at 30-days and long term follow-up. These findings suggest that STEMI patients presenting late (between 12 and 48 hours) should be considered for coronary angiography and revascularization if appropriate.

**Keywords:** Acute myocardial infarction ; Acute coronary syndrome ; Percutaneous coronary revascularization ; Latecomer; Immortal time bias.

## **Abbreviations list:**

**AMI:** Myocardial Infarction

**ECG:** Electrocardiogram

**PCI:** Percutaneous Coronary Intervention

**MACE:** Major Adverse Cardiac Events

**STEMI:** ST-elevation Myocardial Infarction

## **Introduction**

A substantial proportion of ST-segment elevation myocardial infarction (STEMI) patients still present late after symptom onset (*i.e.* 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 PCI is reasonable in patients with STEMI if there is clinical and/or 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 h) after symptom onset (Class IIa, Level of Evidence: B) (7). However, the benefit of late PCI remains controversial, particularly in latecomers 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 over 12 h 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.

## **Methods**

### *Study population*

Three nationwide French registries were conducted over a one-month period, 5 years apart, over a 10-year period (2005 to 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 country-wide scale.

All 3 registries consecutively included patients with STEMI admitted to intensive cardiovascular care units (ICCU) within 48 hours of symptom onset, during a specified one-month period (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. A total of 13129 patients were included in the 3 surveys. Diabetics patients included in the FAST-MI 2005 extension phase were excluded (n=611) and only STEMI patients were kept in the present analysis (n=6637). After exclusion of patients for whom the “symptom onset to admission delay” was missing, (n=364), a total of 6273 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 two days after hospital admission (n=32) in order to exclude potential immortal time bias. A detailed flow-chart 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 these surveys.

### *Data collection*

Data on baseline characteristics, including demographics, and medical history and initial electrocardiogram (ECG) were collected as previously described (14-18). Patient-related delays, i.e. time from symptoms onset to first call or medical contact, time from symptoms 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 (i.e. time from symptoms onset to ICCU admission  $\leq 12$  hours) or latecomers (i.e. time from symptoms onset to ICCU admission  $> 12$  hours and  $\leq 48$  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 (pre-hospital or in-hospital), or intended primary PCI, i.e. coronary angiography with an intent to perform PCI. Use of medications administered in the pre-hospital 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 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 was 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 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 one physician from the research team. All cases of cardiovascular events were centrally reviewed by at least one physician. Cases in which the final diagnosis appeared unclear or debatable were reviewed by a three-member critical events committee.

### *Statistics*

Continuous data were expressed as mean  $\pm$  standard deviation when following a normal distribution, and as median (interquartile range) 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  $\chi^2$  or Fisher exact tests for categorical variables.



Complications incidence rates for occurrence during hospitalization and follow-up were computed. Outcomes incidence rates during follow-up are expressed for 1000 patient-years. Complications occurrences were compared between latecomers and early comers and between revascularized latecomers and non-revascularized 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 sub-population, 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 non-revascularized latecomers with similar conditions, was built in order 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, College Station, TX, USA).

## **Results**

### *Study population*

A total of 6273 STEMI patients with complete data were included in the 3 pooled FAST-MI registries (1943 subjects in FAST-MI 2005, 2274 in FAST-MI 2010 and 2346 in FAST-MI 2015). Among them, 1169 (18.6%) presented late (i.e. > 12 hours after symptoms onset) and were classified as *latecomers*. Median time from symptoms onset to ICU admission was 3.5 hours IQR[2.3 - 5.7] in the early comers population vs 20.2 hours IQR[15.4 – 27.9] in the latecomers population ( $p < 0.001$ ). Global median follow-up was 59 months IQR[40 - 110]. 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**).

#### *Patients presentation*

Latecomer patients were more frequently female (30.8% vs 25.2%,  $p < 0.001$ ) and significantly older (65.2 +/- 14.8 vs 62.6 +/- 14.1,  $p < 0.001$ ) 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 (EMS) (69.2% vs 43.9%,  $p < 0.001$ ). A description of patient characteristics 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 EMS prior admission in cardiology, they are presented in **Supplemental Table 2**.

#### *Patients 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 TIMI2/3 flow obtained in 80.4% of latecomers vs 88.5% of early

comers ( $p < 0.001$ ). At discharge, aspirin, P2Y12 inhibitors and statins were significantly less prescribed in latecomer patients. No differences were observed regarding ACE/ARB or beta blockers, whereas diuretics 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 non-revascularized latecomer patients*

After exclusion of patients treated by thrombolysis and patients deceased within two days after admission, 1077 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 utilization of coronary angiography in latecomers population increased from 85.4% to 96.8% ( $p < 0.001$ ) and, as a result, revascularization by PCI in this population raised 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, P2Y12 inhibitors, beta blockers, statins and ACE inhibitors or ARB) 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 years old  $\pm$  14.2 vs 70.2  $\pm$  14.5,  $p < 0.001$ ) 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 a family history of CAD (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%,  $p=0.004$ ), P2Y12 inhibitors (77.5% vs 61.9%,  $p<0.001$ ), ACE-I/ARB (76.1% vs 63.8%  $p<0.001$ ) and statin therapy (86.2% vs 76.7%,  $p<0.001$ ), but less frequently diuretics (21.4% vs 33.5%  $p<0.001$ ). In the latecomers group, median door to balloon time was 5.4 hours (1.9 – 24.5). Although this delay was longer than in the early comers group (1.4 hours (0.6 – 4.4)  $p<0.001$ ), 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 non-revascularized latecomer patients is presented in **Table 2**.

#### *Outcomes of revascularized vs non-revascularized 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 non-revascularized 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) were more frequent among non-revascularized latecomers (0.4 vs 2.0%  $p=0.016$ )

During follow-up, the all-cause death rate in the latecomer population was 44.9 [40.0 – 50.3] for 1000 patient-years, significantly lower in the revascularized latecomers population than in the non-revascularized population (30.4 [25.7 – 35.9] vs 78.7 [67.2 – 92.3] for 1000 patient-years,  $p<0.001$ ). Recurrent AMI was also significantly less frequent among revascularized latecomers than in non-revascularized latecomers (5.4 [3.5 – 8.5] vs 11.0 [6.8 – 17.7] for 1000 patient-years,  $p=0.03$ ) (**Table 3**).

In a multivariate analysis, after adjustment on year of admission, age, smoking status, family history of CAD, prior AMI or PCI, prior stroke or TIA, peripheral artery disease, chronic kidney disease, Killip at admission, and LVEF at discharge, revascularization remained independently associated with a reduction of the occurrence of mortality, HR= 0.65 [0.42 - 0.71], p=0.001 during follow-up (**Table 4, Central illustration**). No interaction was found between the year of inclusion and the benefit revascularization. Kaplan Meier curves comparing mortality according to revascularization status for each registry (2005, 2010, 2015) are shown in **Supplemental Figure 2**, (log rank test p<0.001 for all)

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

## **Discussion**

The present study investigated the characteristics, prevalence, management and outcomes of latecomer STEMI patients (i.e. admitted > 12 hours after symptoms onset) over a period of 10 years (2005 to 2015) in metropolitan France based on 3 registries conducted in a one month period (2005, 2010 and 2015 FAST-MI registries). We observed a reduction of the latecomer patients proportion from 22.7% in 2005 to 16.1% in 2015, and an increase of the utilization 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 literature. On the contrary, a prior history of MI was, in our study, independently related to a 35% reduction in the probability of late arrival, probably due to the patients' awareness of AMI symptoms - this phenomenon has already been described in the GRACE registry (21). Interestingly, female gender 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 due to an increasing awareness among physicians and the population of AMI symptoms in female patients, as these are more likely to be atypical.

Our data describe a substantial reduction of latecomers prevalence, from 23.6% in 2005 to 16.1% in 2015. A recent study from Roberto *et al* 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, since the benefit of revascularization is known to be time-dependent (8,22), significant efforts in public health politics have been conducted in order 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 minutes 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-related artery beyond 12 hours remains debated. European guidelines on STEMI recommend the realization of PCI for patients presenting between 12h to 48h after symptoms 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 hours but no later than 24 hours after symptoms 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 70' with the description of "the wavefront phenomenon" by Reimer *et al* based on animals experimental studies (24). 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 six 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 symptoms onset (25-29) - which is precisely the origin of the 12-hour limit generally accepted to classify patients as latecomers. In order 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 six hours might be due to 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 antegrade blood flow. Finally, repetitive myocardial ischemia in patient presenting intermittent occlusion and recanalization prior to 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 six 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 latecomers STEMI patients with conflicting results. In the 90's and early 2000's, some reports suggested a potential benefit of revascularization over optimal medical treatment alone on LVEF (10), quality of life (40), and long-term MACE (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 SPECT – 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 latecomers STEMI patients, reported no benefit of revascularization at one year on a composite primary endpoint which associated cardiac death, non-fatal MI, or ventricular tachyarrhythmia (42). In 2006, the large OAT study (Occluded Artery Trial), which included



2166 stable latecomer STEMI patients randomized between a conservative therapy and PCI, failed to demonstrate any benefit of revascularization on a combined criteria (death, re-infarction, and heart failure) after 4 years of follow-up (HR=1,16 [0.92 -1.42] 95% CI, p=0.20) (43). The apparently conflicting results of the above trials can probably be explained by a significant difference among their population. Indeed, in the DECOPI and OAT trials - which both reported negatives results - patients were randomized with a median delay from symptoms onset of 5 and 8 days, respectively, whereas in the positive BRAVE 2 trials, patients presented much earlier, between 12 and 48 hours after symptoms onset. This suggests that revascularization of latecomers STEMI patients is relevant only in the relatively early period following symptoms onset. More recent studies confirm this observation, demonstrating that the myocardial salvage, assessed by SPECT (8) or MRI (9), remains substantial in a large proportion of latecomers provided that it was performed within 72 hours following symptoms 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 symptoms onset; these results also provide an adequate comparison of revascularized and non-revascularized latecomers, which was missing to date in the literature (44). Although late STEMI presentation is becoming rare in recent registries, they still represent 10% to 15% of STEMI patients (1,3). Moreover, these results are particularly relevant in the actual context of COVID 19 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 does not allow to affirm causality but only to describe statistically significant and independent associations between observed clinical outcomes and patients 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-related artery of latecomer STEMI patients admitted before 48 hours after symptoms onset is associated with better long-term clinical outcomes on hard end-points. Our results strengthen the current European guidelines that recommend to perform a PCI to STEMI patients up to 48 hours after symptoms onset.

**Clinical perspectives:**

**Competency in Patient Care and Procedural Skills:** Percutaneous coronary intervention (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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## Figure Legends

**Figure 1: Study flowchart.** The study population was derived from 3 French nationwide one-month registries of myocardial infarction (FAST MI registries) conducted in 2005, 2010 and 2015. STEMI = ST-elevation Myocardial Infarction ; non-STEMI : non-ST elevation Myocardial Infarction ; PCI = Percutaneous Coronary Intervention

**Figure 2: Mortality in the latecomer population in a propensity matched analysis.** In this propensity matched analysis which included two 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 [0.50 – 0.89]

**Central illustration: Mortality comparison in the latecomer population according to revascularization status.** 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 48h, revascularized within 48 hours following hospital admission, and after exclusion of patients who received thrombolysis.

**Table 1: Comparison of early- and latecomer patients characteristics and management**

	All (n=6273)	Early comers (n=5104)	Latecomers (n=1169)	p
<b>Demography</b>				
Age (years), mean +/- SD	63.1 +/- 14.3	62.6 +/- 14.1	65.2 +/- 14.8	< 0.001
Age ≥ 75, n(%)	1574 (25.1)	1203 (23.6)	371 (31.7)	< 0.001
Female, n(%)	1648 (26.3)	1288 (25.2)	360 (30.8)	< 0.001
<b>Risk factors</b>				
Hypertension, n(%)	2967/6253 (47.5)	2346/5086 (46.1)	621/1167 (53.2)	< 0.001
Hypercholesterolemia, n(%)	2511/6244 (40.2)	2023/5080 (39.8)	488/1164 (41.9)	0.187
Diabetes, n(%)	1036/6242 (16.6)	789/5080 (15.5)	247/1162 (21.3)	< 0.001
Current smoking, n(%)	2517/6120 (41.1)	2069/4974 (41.6)	448/1146 (39.1)	0.120
Family history of CAD, n(%)	1570/5928 (26.5)	1295/4822 (26.9)	275/1106 (24.9)	0.176
Obesity (BMI ≥ 30 kg/m <sup>2</sup> ), n(%)	1175/5860 (20.1)	948/4781 (19.8)	227/1079 (21.0)	0.370
<b>Cardiovascular history and comorbidities</b>				
Prior AMI, n(%)	730/6221 (11.7)	621/5061 (12.3)	109/1160 (9.4)	0.006
Prior PCI, n(%)	673/6237 (10.8)	579/5077 (11.4)	94/1160 (8.1)	0.001
Prior stroke/TIA, n(%)	294/6258 (4.7)	225/5091 (4.4)	69/1167 (5.9)	0.030
Peripheral artery disease, n(%)	321/6253 (5.1)	248/5086 (4.9)	73/1167 (6.3)	0.054
History of heart failure, n(%)	184/6254 (2.9)	126/5087 (2.5)	58/1167 (5.0)	< 0.001
Chronic kidney disease, n(%)	185/6254 (3.0)	147/5087 (2.9)	38/1167 (3.3)	0.505
Respiratory failure, n(%)	226/6243 (3.6)	184/5077 (3.6)	42/1166 (3.6)	0.971
History of cancer, n(%)	491/6243 (7.9)	383/5077 (7.5)	108/1166 (9.3)	0.049

**Medication prior AMI**

Antiplatelet therapy, n(%)	1392 (22.2)	1131 (22.2)	261 (22.3)	0.901
Statin, n(%)	1441 (23.0)	1168 (22.9)	273 (23.4)	0.731
Beta-blocking agent, n(%)	1289 (20.6)	1042 (20.4)	247 (21.1)	0.586
ACE-I or ARB, n(%)	1580 (25.2)	1245 (24.4)	335 (28.7)	0.002

**Clinical presentation**

SBP (mmHg), mean +/- SD	132 +/- 26	132 +/- 26	135 +/- 26	< 0.001
n	6068	4931	1137	
HR (bpm), mean +/- SD	78 +/- 18	77 +/- 18	80 +/- 19	< 0.001
n	6037	4910	1127	
LVEF (%), mean +/- SD	50.1 +/- 11.4	50.4 +/- 11.3	49.0 +/- 11.9	0.002
n	4625	3716	1127	
Anterior MI, n(%)	2583/5865 (44.0)	2102/4793 (43.9)	481/1072 (44.9)	0.546
Typical chest pain	5335/6217 (85.8)	4432/5066 (87.5)	903/1151 (78.5)	< 0.001
Cardiogenic shock, n(%)	100/6008 (1.7)	79/4889 (1.6)	21/1119 (1.9)	0.538
GRACE risk score, mean +/- SD	144 +/- 35	143 +/- 34	147 +/- 37	0.003
n	5851	4749	1102	
Killip class > 2, n(%)	284/6008 (4.7)	217/4889 (4.4)	67/1119 (6.0)	0.028
Out-of-hospital cardiac arrest, n(%)	151/6051 (2.5)	138/4934 (2.8)	13/1117 (1.2)	0.002
CRP (mg/l), median (IQR)	5 (3 - 13)	5 (3 - 10)	9 (4 - 30)	< 0.001
n	4556	3688	868	

**Delays**

Time from onset to first call or contact (h), median (IQR)	1.3 (0.5 - 4.2)	1.0 (0.5 - 2.4)	13.5 (8.0 - 21.0)	< 0.001
n	6229	5076	1153	

Time from first call or contact to ICU admission (h), median (IQR)	2.2 (1.3 – 4.0) 6242	2.0 (1.3 – 3.2) 5089	4.8 (2.3 – 10.2) 1153	< 0.001
Time from onset to ICU admission (h), median (IQR)	4.3 (2.5 - 9.0) 6273	3.5 (2.3 - 5.7) 5104	20.2 (15.4 – 27.9) 1169	< 0.001
Time from onset to angiography (h), median (IQR)	5.6 (3.0 – 18.9) 5816	4.4 (2.8 – 9.1) 4783	27.5 (18.0 – 45.8) 1033	< 0.001
Time from onset to balloon (h), median (IQR)	5.8 (3.3 – 18.5) 5259	4.7 (3.0 – 9.5) 4364	26.5 (17.5 – 45.5) 895	< 0.001
Time from door to balloon (h), median (IQR)	1.7 (0.7 – 6.7) 5227	1.4 (0.6 – 4.4) 4346	5.4 (1.9 – 24.5) 881	< 0.001
Time from ICU admission to angiography (h), median (IQR)	0.7 (0.3 – 7.6) 4988	0.6 (0.3 – 3.1) 4106	3.3 (0.7 – 22.1) 882	< 0.001
Time from ICU admission to balloon (h), median (IQR)	1.0 (0.5 – 7.0) 4561	0.8 (0.5 – 3.2) 3806	3.2 (0.9 – 22.7) 755	< 0.001
<b>Pre-hospital pathway</b>				
Mobile ICU	4667/6247 (74.7)	4013/5086 (78.9)	654/1161 (56.3)	< 0.001
Patient's journey includes EMS	3036/6247 (48.6)	2233/5086 (43.9)	803/1161 (69.2)	< 0.001
<b>Reperfusion therapy, n(%)</b>				
None	821 (13.1)	564 (11.1)	257 (22.0)	
Thrombolysis	968 (15.4)	905 (17.7)	63 (5.4)	
No thrombolysis but PCI	4481 (71.5)	3634 (71.2)	847 (72.6)	
<b>Procedure during hospitalization, n(%)</b>				

Coronary angiography	5993/6269 (95.6)	4920/5101 (96.5)	1073/1168 (91.9)	< 0.001
PCI	5307/6268 (84.7)	4411/5101 (86.5)	896/1167 (76.8)	< 0.001
Pre-PCI TIMI Flow 2 or 3	1289/5258 (37.8)	1671/4280 (39.0)	318/978 (32.5)	< 0.001
Post-PCI TIMI Flow 2 or 3	4686/5384 (87.0)	39068/4414 (88.5)	780/970 (80.4)	< 0.001
CABG	115/6272 (1.8)	85/5104 (1.7)	30/1168 (2.6)	0.038
<b>Hemodynamic and respiratory support, n(%)</b>				
IAPB	116/6119 (1.9)	91/5071 (1.8)	25/1164 (2.2)	0.421
Other assistance	27/6235 (0.4)	23/5071 (0.5)	4/1164 (0.3)	0.607
Assisted ventilation	166/6205 (2.7)	133/5045 (2.6)	33/1160 (2.8)	0.691
<b>Medication within first 48h, n(%)</b>				
Aspirin	5779 (88.9)	4559 (89.3)	1020 (87.3)	0.042
Clopidogrel	3665 (58.4)	2881 (56.5)	784 (67.1)	< 0.001
Prasugrel	1330 (21.2)	1165 (22.8)	165 (14.1)	< 0.001
Ticagrelor	1304 (20.8)	1110 (21.8)	194 (16.6)	< 0.001
Glycoprotein IIb/IIIa inhibitors	332 (5.3)	249 (4.9)	83 (7.1)	0.002
Unfractionated heparin	2612 (41.6)	2117 (41.5)	495 (42.3)	0.588
LMWH	3458 (55.1)	2784 (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	3824 (61.0)	3135 (61.4)	689 (58.9)	0.116
Diuretic	1537 (24.5)	1202 (23.6)	335 (28.7)	< 0.001
Beta-blocker	4846 (77.3)	3992 (78.2)	854 (73.1)	< 0.001
Statin	5316 (84.7)	4357 (85.4)	959 (82.0)	0.004

<b>Medication at discharge, n(%)</b>				
Aspirin	5192/6027 (86.2)	4280/4923 (86.9)	912/1104 (82.6)	< 0.001
P2Y <sub>12</sub> inhibitor (any)	4566/6027 (75.8)	3769/4923 (76.6)	797/1104 (72.2)	0.002
ACE-I or ARB	4386/6027 (72.8)	3595/4923 (73.0)	791/1104 (73.0)	0.353
Statin	5137/6027 (85.2)	4223/4923 (85.7)	914/1104 (82.8)	0.011
Beta-blocker	5014/6292 (79.7)	4088/5114 (79.9)	926/1178 (78.6)	0.306
Diuretic	1246/6027 (20.7)	978/4923 (19.9)	268/1104 (24.3)	0.001
<b>Length of stay (days), median [IQR]</b>	7 [5 – 9]	7 [5 – 9]	7 [5 – 10]	0.003
<b>Cardio-vascular rehabilitation, n(%)</b>	641/6026 (10.6)	524/4922 (10.7)	117/1104 (10.6)	0.963

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



**Table 2: Comparison of latecomer patients according to their revascularization status**

	Latecomers * (n=1077)	Revascularized** (n=729)	Non revascularized (n=348)	p
<b>Year of admission</b>				< 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)	
<b>Demography</b>				
Age (years), mean +/- SD	65.1 +/- 14.7	62.7 +/- 14.2	70.2 +/- 14.5	< 0.001
Age ≥ 75, n(%)	340 (31.6)	182 (25.0)	158 (45.4)	< 0.001
Female, n(%)	335 (31.1)	204 (28.0)	131 (37.6)	0.001
<b>Risk factors</b>				
Hypertension, n(%)	579/1076 (53.8)	354/729 (48.6)	225/347 (64.8)	< 0.001
Hypercholesterolemia, n(%)	449/1073 (41.9)	299/727 (41.1)	150/346 (43.4)	0.490
Diabetes, n(%)	227/1071 (21.2)	142/727 (19.5)	85/344 (24.7)	0.053
Current smoking, n(%)	415/1055 (39.3)	323/716 (45.1)	92/339 (27.1)	< 0.001
Family history of CAD, n(%)	256/1021 (25.1)	193/693 (27.9)	63/328 (19.2)	0.003
Obesity (BMI ≥ 30 kg/m <sup>2</sup> ), n(%)	216/1012 (21.3)	144/692 (20.8)	72/320 (22.5)	0.542
<b>Cardiovascular history and comorbidities</b>				
Prior AMI, n(%)	101/1069 (9.5)	71/725 (8.4)	40/344 (11.6)	0.093
Prior PCI, n(%)	84/1070 (7.9)	56/725 (7.7)	28/345 (8.1)	0.824
Prior stroke/TIA, n(%)	63/1076 (5.9)	37/729 (5.1)	26/347 (7.5)	0.114
Peripheral artery disease, n(%)	65/1076 (6.0)	33/729 (4.5)	32/347 (9.2)	0.003
History of heart failure, n(%)	53/1076 (4.9)	23/729 (3.2)	30/347 (8.7)	< 0.001

Chronic kidney disease, n(%)	34/1076 (3.2)	14/729 (1.9)	20/347 (5.8)	0.001
Respiratory failure, n(%)	42/1075 (3.9)	26/729 (3.6)	16/346 (4.6)	0.403
History of cancer, n(%)	100/1075 (9.3)	56/729 (7.7)	44/346 (12.7)	0.008
<b>Medication prior AMI</b>				
Antiplatelet therapy, n(%)	245 (22.8)	145 (19.9)	100 (28.7)	0.001
Statin, n(%)	250 (23.2)	170 (23.3)	80 (23.0)	0.904
Beta-blocking agent, n(%)	227 (21.1)	141 (19.3)	86 (24.7)	0.043
ACE-I or ARB, n(%)	312 (29.0)	197 (27.0)	115 (33.1)	0.042
<b>Initial presentation, n(%)</b>				
SBP (mmHg)	136 +/- 26	135 +/- 25	138 +/- 27	0.113
HR (bpm)	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, n(%)	54/1036 (5.2)	27/697 (3.9)	27/339 (8.0)	0.005
Out-of-hospital cardiac arrest, n(%)	9/1031 (0.9)	6/704 (0.9)	3/327 (0.9)	1.000
Anterior MI, n(%)	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
<b>Medication at discharge (in patients alive at discharge), n(%)</b>				
Aspirin	872/1046 (83.4)	612/715 (85.6)	260/331 (78.6)	0.004
P2Y <sub>12</sub> inhibitor	759/1046 (72.6)	554/715 (77.5)	205/331 (61.9)	< 0.001
ACE-I or ARB	755/1046 (72.2)	544/715 (76.1)	211/331 (63.8)	< 0.001
Statin	870/1046 (83.2)	616/715 (86.2)	254/331 (76.7)	< 0.001
Beta-blocker	823/1046 (78.7)	573/715 (80.1)	250/331 (75.5)	0.090
Diuretic	264/1046 (25.2)	153/715 (21.4)	111/331 (33.5)	< 0.001
<b>Length of stay (days), median [IQR]</b>	<b>7 [5 – 10]</b>	<b>6 [5 – 9]</b>	<b>9 [6 – 13]</b>	<b>&lt; 0.001</b>

<b>Cardiovascular rehabilitation, n(%)</b>	114/1046 (10,9)	83/715 (11.6)	31/331 (9.4)	0.279
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\* alive at day 2 and after exclusion of latecomers who received thrombolysis.

\*\* within 48 hours after hospital admission

SD: standard derivation; CAD: coronary artery disease; BMI: body mass index; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischemic attack; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin 2 receptor blocker; SBP: systolic blood pressure; HR: heart rate; MI: myocardial infarction

**Table 3: Early and long-term outcomes of latecomer patients according to their revascularization status**

	All (n=1077)	Revascularized latecomers (n=729)***	Non revascularized latecomers (n=348)	p
<b>Complications at 30-day (%)</b>				
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**	0.9%	0.4%	2.0%	0.016
<b>Long term complication*</b>				
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**	6.4 [4.5 – 9.0]	5.1 [3.2 – 8.2]	9.1 [5.4 – 15.4]	0.120

\* expressed as number of events for 1000 Patient years [95% confidence interval]

\*\* according to TIMI classification

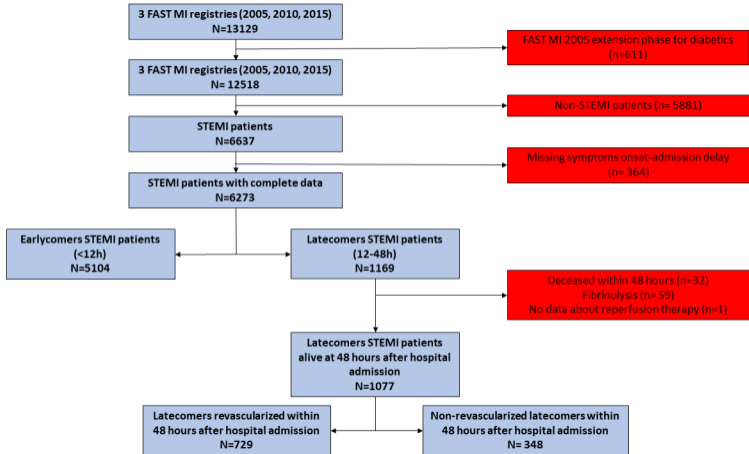
\*\*\* within 48 hours after hospital admission

AMI: acute myocardial infarction

**Table 4: Independent predictors of all-cause mortality during follow-up in the latecomer patients population**

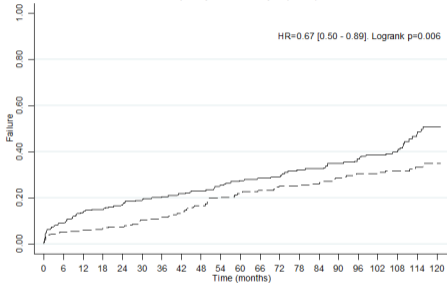
	<b>Hazard-Ratio</b>	<b>95% CI</b>	<b>p</b>
Year			
2005	1.00		
2010	1.11	0.84 - 1.47	0.470
2015	0.74	0.47 - 1.16	0.189
Age at entry (years)	1.07	1.06 - 1.09	< 0.001
Smoking	1.50	1.07 – 2.10	0.018
Family history of CAD			
No	1.00		
Yes	0.55	0.37 – 0.80	0.002
Unknown	1.99	1.09 – 3.60	0.024
Prior AMI / 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
<b>Revascularization within 48h after hospital admission</b>	<b>0.65</b>	<b>0.50 - 0.84</b>	<b>0.001</b>
LVEF at discharge			
≥ 40%	1.00		
< 40%	2.01	1.44 - 2.79	< 0.001
Unknown	1.25	0.94 - 1.66	0.123

CAD: coronary artery disease; AMI: acute myocardial infarction; TIA: transient ischemic attack ; PCI: percutaneous coronary intervention ; LVEF: left ventricular ejection fraction



## All-cause mortality

Propensity matched analysis (n=534)



Number at risk

No Revascularization within 48h	267	242	229	218	212	205	201	188	180	148	143	140	138	131	126	119	115	106	100	48	38
Revascularization within 48h	267	252	250	248	245	235	228	210	199	166	162	159	155	153	150	145	141	136	129	77	60

— No Revascularization within 48h    - - - - - Revascularization within 48h