



HAL
open science

Clinical outcomes with high-intensity statins according to atherothrombotic risk stratification after acute myocardial infarction: The FAST-MI registries

Edouard Desjobert, Victoria Tea, Tabassome Simon, Nicolas Danchin, Etienne Puymirat, François Schiele, Jean Ferrières

► To cite this version:

Edouard Desjobert, Victoria Tea, Tabassome Simon, Nicolas Danchin, Etienne Puymirat, et al.. Clinical outcomes with high-intensity statins according to atherothrombotic risk stratification after acute myocardial infarction: The FAST-MI registries. Archives of cardiovascular diseases, 2021, 114 (2), pp.88-95. 10.1016/j.acvd.2020.06.003 . hal-04353580

HAL Id: hal-04353580

<https://ut3-toulouseinp.hal.science/hal-04353580v1>

Submitted on 22 Jul 2024

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.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Clinical outcomes with high-intensity statins according to atherothrombotic risk stratification after acute myocardial infarction: The FAST-MI registries

Evolution clinique avec des statines de forte intensité selon le risque athérombotique après un infarctus du myocarde (à partir des registres FAST-MI)

Abbreviated title: TRS-2P and high-intensity statins

Abbreviated title: TRS-2P et statines de forte intensité

**Edouard Desjobert^a, Victoria Tea^a, François Schiele^b, Jean Ferrières^c, Tabassome Simon^d,
Nicolas Danchin^a, Etienne Puymirat^{a,*}, for the FAST-MI investigators**

^a *Department of Cardiology, Hôpital Européen Georges Pompidou (HEGP), AP-HP, 75015 Paris;
Université de Paris, 75006 Paris, France*

^b *Department of Cardiology, University Hospital Jean Minjoz, 25000 Besançon, France*

^c *Department of Cardiology, Rangueil Hospital, 31400 Toulouse, France*

^d *Department of Clinical Pharmacology and Unité de Recherche Clinique (URC-Est), Hôpital Saint-Antoine, AP-HP, 75012 Paris; Université Pierre et Marie Curie (UPMC-Paris 06), 75005 Paris, France*

* Corresponding author at: Department of Cardiology, HEGP, 20 rue Leblanc, 75015 Paris, France.
E-mail address: etienne.puymirat@aphp.fr (E. Puymirat).

Summary

Background. – Current guidelines strongly recommend high-intensity statin therapy after acute myocardial infarction.

Aims. – To analyse the relationship between prescription of high-intensity statin therapy at discharge and long-term clinical outcomes according to risk level defined by the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS-2P) after acute myocardial infarction.

Methods. – We used data from the FAST-MI 2005 and 2010 registries – two nationwide French surveys including 7839 consecutive patients with acute myocardial infarction. Level of risk was stratified in three groups using the TRS-2P score: Group 1 (low risk; TRS-2P = 0–1); Group 2 (intermediate risk; TRS-2P = 2); and Group 3 (high risk; TRS-2P ≥ 3).

Results. – Among the 7348 patients discharged alive with a TRS-2P available, high-intensity statin therapy was used in 41.3% in Group 1, 31.3% in Group 2 and 18.5% in Group 3. After multivariable adjustment, high-intensity statin therapy was associated with a non-significant decrease in major adverse cardiovascular events (death, stroke or recurrent myocardial infarction) at 5 years in the overall population compared with that in patients receiving intermediate- or low-intensity statins or without a statin prescription (14.3% vs 29.6%; hazard ratio 0.94, 95% confidence interval 0.81–1.09; $P = 0.42$). In absolute terms, the decrease in major adverse cardiovascular events was positively correlated with risk level (Group 1: 8.1% vs 10.7%; Group 2: 14.8% vs 21.6%; Group 3: 30.8% vs 51.6%). However, after adjustment, the benefits of high-intensity statin therapy were associated with lower mortality only in high-risk patients (hazard ratio 0.79, 95% confidence interval 0.64–0.97; $P = 0.02$).

Conclusions. – High-intensity statin therapy at discharge after acute myocardial infarction was associated in absolute terms with fewer major adverse cardiovascular events at 5 years, regardless of atherothrombotic risk stratification, although the highest absolute reduction was found in the high-risk TRS-2P class.

Résumé

Contexte. – La prescription des fortes doses de statine (FDS) est actuellement recommandée chez les patients après un infarctus du myocarde (IdM).

Objectifs. – Analyser la relation entre la prescription de FDS à la sortie et le devenir clinique à long terme selon le niveau de risque défini par le score de prévention secondaire TIMI (TRS-2P) après un IdM.

Méthodes. – Nous avons utilisé les données des registres FAST-MI 2005 et 2010, 2 enquêtes nationales ayant inclus consécutivement 7839 patients avec un IdM. Le niveau de risque a été stratifié en 3 groupes selon le score TRS-2P : Groupe 1 (bas risque ; TRS-2P = 0–1) ; Groupe 2 (risque intermédiaire ; TRS-2P = 2) ; et le Groupe 3 (haut risque ; TRS-2P ≥ 3).

Résultats. – Sur les 7348 patients survivants (avec un TRS-2P disponible), la prescription de FDS était de 41,3 % (Groupe 1), 31,3 % (Groupe 2) et 18,5 % (Groupe 3). Après ajustement, la prescription de FDS était associée à une baisse (non significative) des événements cardiovasculaires majeurs (MACE, décès, accident vasculaire cérébral ou récurrence d'IdM) à 5 ans dans la population globale comparée aux patients avec une dose intermédiaire/faible de statines ou sans statine (14,3 % vs 29,6 % ; HR 0,94, IC95 % 0,81–1,09 ; $P = 0,42$). En valeur absolue, cependant la baisse des MACE était corrélée positivement au niveau de risque (Groupe 1 : 8,1 % vs 10,7 % ; Groupe 2 : 14,8 % vs 21,6 % ; Groupe 3 : 30,8 % vs 51,6 %). Les bénéfices des FDS étaient toutefois associés à une réduction de la mortalité après ajustement uniquement chez les patients à haut risque (HR 0,79, IC95 % 0,64–0,97 ; $P = 0,02$).

Conclusions. La prescription des FDS après un IdM était associée à une baisse des MACE à 5 ans en valeur absolue quelle que soit le niveau de risque athérombotique, bien que la réduction absolue la plus élevée ait été retrouvée dans la catégorie du TRS-2P à haut risque.

KEYWORDS

Myocardial infarction;

Percutaneous coronary intervention;

Risk stratification;

Statin

MOTS CLÉS

Infarctus du myocarde ;

Angioplastie coronaire percutanée ;

Stratification du risque ;

Statine

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; FAST-MI: French Registry of Acute ST-elevation or Non-ST-elevation Myocardial Infarction; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; OR, odds ratio; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; TRA 2P, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events; TRS-2P, Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

Background

Optimal lipid management for patients after an acute myocardial infarction is of paramount importance. Prompt initiation of high-intensity statin therapy is strongly recommended for any patient having an acute myocardial infarction – regardless of baseline low-density lipoprotein cholesterol (LDL-C) concentration – within 1–4 days of the index event [1, 2]. The Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS-2P) was developed in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P) trial, and has been recently validated in other trials and observational studies, such as the French Registry of Acute ST-elevation or Non-ST-elevation Myocardial Infarction (FAST-MI) [3-8]; it has recently been proposed for the identification of high-risk patients who derive the greatest benefit from the addition of antithrombotic or ezetimibe therapy for secondary prevention after acute coronary syndrome (ACS) [3-5, 7].

The aim of our study was to assess the association between high-intensity statin prescription at discharge and major adverse cardiovascular events (MACE) at 5 years, according to atherothrombotic risk stratification in a routine-practice population of patients with acute myocardial infarction.

Methods

Study population

The FAST-MI programme consists of three nationwide French registries of patients admitted to hospital for an acute myocardial infarction, conducted 5 years apart, since 2005. The methods used for these registries have been detailed previously [9-11]. Overall, their primary objective was to gather data on the characteristics, management and outcomes of patients hospitalized for ST-segment elevation myocardial infarction (STEMI) or non-STEMI in cardiac intensive care units within 48 hours of symptom onset, during a specified 1-month period (October–December) (see [Table A.1](#)). For the present study, we selected surveys with long-term clinical follow-up available (i.e. 5 years): FAST-MI 2005 (NCT00673036) [10] and FAST-MI 2010 (NCT01237418) [11], in which 7839 patients were included. The FAST-MI programme was conducted in accordance with the guidelines on good clinical practice and French law. 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 both surveys.

Data on baseline characteristics, including demographics, risk and medical history, were collected as described previously. Information on the use of cardiac procedures, including the use of percutaneous coronary intervention, and on the use of medications in the first 48 hours and at hospital discharge was collected. For all surveys, follow-up was centralized at the French Society of Cardiology. Mortality follow-up at 5 years was obtained in 95% of the patients.

Each patient was assessed for the presence of any of the nine previously described risk indicators in the TRA 2P-TIMI 50 trial at baseline [3, 5, 7]: age \geq 75 years, diabetes mellitus, hypertension, peripheral artery disease, previous stroke, previous coronary artery bypass grafting, history of heart failure, active smoking and renal dysfunction (defined by an estimated glomerular filtration rate $<$ 60 mL/min/1.73m² using the Modification of Diet in Renal Disease equation). All variables, with the exception of age and renal dysfunction, were determined on the basis of clinical history. As described, each atherothrombotic risk indicator was weighted evenly to define total risk for each patient as the arithmetic sum of risk indicators. Simple risk categories were defined to parallel the annualized risk of death observed in the derivation population from patients in TRA 2P, thus translating to a low-risk category with 0–1 risk indicators (Group 1), an intermediate-risk category with 2 risk indicators (Group 2), and a high-risk category with \geq 3 risk indicators (Group 3).

We defined high-intensity statin prescription as atorvastatin 80 mg daily or rosuvastatin 20 mg daily at discharge. Patients without a high-intensity statin prescription received a lower dose of atorvastatin (40/20/10 mg daily) or rosuvastatin (10/5 mg daily), another statin whatever the dose (simvastatin, pravastatin, fluvastatin) or none.

Statistical analysis

Continuous variables are reported as means \pm standard deviations. Discrete variables are described as counts and percentages. Groups were compared by analysis of variance for continuous variables, and by the χ^2 test (or Fisher's exact test) for discrete variables. Between-category trends were tested using linear-by-linear association tests for binary variables, and Jonckheere-Terpstra tests for continuous variables. Odds ratios (ORs) and hazard ratios (HRs) are presented with their 95% confidence intervals (CIs). Survival curves were estimated using the Kaplan-Meier estimators and compared using log-rank tests. Multiple logistic regression analysis was used to estimate ORs, and to find the strongest independent predictors of high-intensity statin prescription. Clinical presentation and

in-hospital complication variables were included in the model. The rates of MACE (defined as all-cause death, stroke or recurrent myocardial infarction) at 5 years were analysed according to TRS-2P categories, and the effect of high-dose statins at discharge was compared using a multivariable backward stepwise Cox analysis with a threshold of 0.10 for variable elimination, among the different risk groups. Besides time period, variables included in the final models were selected *ad hoc*, based on their physiological relevance and potential to be associated with outcomes; they comprised age, sex, risk factors, co-morbidities, type of myocardial infarction, TRS-2P categories, year and management. Sensitivity analyses were performed focused on patients without statins at discharge. Analyses were repeated using forward stepwise analysis to check the consistency of the results. Statistical analyses were performed using IBM SPSS 26.0 (IBM Corp., Armonk, NY, USA). For all analyses, two-sided *P* values < 0.05 were considered significant.

Results

Characteristics and clinical presentation of the population

A total of 7348 patients (93.7%) alive at discharge had all nine variables included in the TRS-2P score available and were included in the main analysis. Prevalence of high-intensity statin prescription at discharge was 41.3% in Group 1, 31.3% in Group 2 and 18.5% in Group 3, and increased between 2005 and 2010 in all TRS-2P categories ($P < 0.001$ for all; [Table A.2](#)). All doses of statins prescribed at discharge according to TRS-2P categories are summarized in [Fig. A.1](#).

Patient characteristics and clinical presentation according to high-intensity statin prescription and TRS-2P categories are detailed in [Table 1](#). In all TRS-2P categories, patients discharged without high-intensity statins had a higher cardiovascular risk profile. High-intensity statin prescription was preferentially used in patients with STEMI. Biomarkers of inflammation (i.e. C-reactive protein, fibrinogen) were lower in all risk categories for patients with high-intensity statins. Finally, over the 5-year period, the proportion of patients at high risk (i.e. Group 3) decreased from 41% to 24% ($P < 0.001$).

In-hospital management

Early management (i.e. during the first 48 hours), including medications and myocardial revascularization, differed according to TRS-2P categories and high-intensity statin prescription ([Table](#)

A.3). Overall, Group 3 patients were treated less optimally than patients in Groups 1 and 2. In all TRS-2P categories, however, patients with high-intensity statins received more recommended medications during the first 48 hours after admission, and the use of an invasive strategy was more frequent. Medications prescribed at discharge are listed in [Table 2](#). Overall, prescription of recommended treatments decreased progressively from low-risk to high-risk patients, and was significantly higher in patients with high-intensity statins in all risk categories. Statin prescription increased between the first 48 hours and discharge in all groups: 82% to 92.3% in Group 1, 78% to 89.3% in Group 2 and 69.5% to 81.1% in Group 3. Finally, in all statin-naïve patients who had an acute myocardial infarction (5283/7348), high-intensity statin prescription at discharge was 33.7%, with disparate results according to TRS-2P category (60.5% for Group 1, 24.2 for Group 2 and 15.2% for Group 3). After adjustment, high-intensity statins at discharge were prescribed less often in Groups 3 and 2 (OR 0.73, 95% CI 0.62–0.86 and OR 0.91, 95% CI 0.78–1.05, respectively) compared with Group 1.

Long-term clinical outcomes

High-intensity statin prescription was associated with a non-significant decrease in MACE at 5 years in the overall population compared with patients who received intermediate- or low-dose statins or had no statin prescription (14.3% vs 29.6%; Δ absolute risk = 15.3%; HR adjusted on baseline characteristics and management 0.94, 95% CI 0.81–1.09; $P = 0.42$). The decrease in MACE at 5 years was observed in all TRS-2P categories (Group 1: 8.1% vs 10.7%, Δ absolute risk = 2.6%; Group 2: 14.8% vs 21.6%, Δ absolute risk = 6.8%; Group 3: 30.8% vs 51.6%, Δ absolute risk = 20.8%). Finally, the association of high-intensity statins with 5-year MACE was not statistically significant in the low- and intermediate-risk groups (HR 1.07, 95% CI 0.76–1.51; $P = 0.71$; and HR 1.26, 95% CI 0.93–1.70; $P = 0.14$), whereas it was significant in high-risk patients (HR 0.79, 95% CI 0.64–0.97; $P = 0.02$) ([Fig. 1](#)). Similar results were found after excluding patients without statins at discharge (HR 0.80, 95% CI 0.65–0.98; $P = 0.04$) in high-risk patients.

Discussion

The main findings of this study are that, although it increased over time, the use of high-intensity statin therapy at discharge in patients with myocardial infarction remains low, especially in statin-naïve patients, despite current recommendations, and is inversely correlated with patient risk. This is a

concern, as the use of high-intensity statins at discharge was associated with a much lower risk of events in the higher-risk population.

High-intensity statin therapy in patients with ACS

Data from randomized controlled trials and meta-analyses indicate that routine early use of high-intensity statin therapy in patients with ACS is associated with rapid and sustained clinical benefits [12-16]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-TIMI 22 (PROVE IT-TIMI 22) trial demonstrated that high-intensity statin therapy (atorvastatin, 80 mg) early after ACS was associated with lower death, recurrent myocardial infarction or rehospitalization for recurrent ACS compared with standard therapy (pravastatin, 40 mg) at 30 days (3% vs 4.2%; HR 0.72, 95% CI 0.52–0.99; $P = 0.046$) [14].

Recent data with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors after ACS or in stable patients with previous myocardial infarction have shown that clinical benefits were correlated with LDL-C reduction, even when low levels of LDL-C were reached with high-intensity statins [17, 18]. Therefore, current guidelines from the European Society of Cardiology recommend the initiation of high-intensity statin therapy in all statin-naïve patients with ACS with no contraindication, regardless of initial LDL-C values [2]. The treatment goal is to reach a 50% LDL-C reduction from baseline, and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL). For those who have a recurrent event within 2 years while taking maximally tolerated statin therapy, a goal of < 1.0 mmol/L (< 40 mg/dL) for LDL-C should be considered. The intensity of statin therapy should be increased in those patients receiving low- or moderate-intensity statin treatment at presentation, unless there is a definite history of intolerance to high-intensity statin therapy.

Timing of statin treatment initiation

Based on current evidence, the initiation of high-intensity statin therapy is recommended during the first 1–4 days of hospitalization for the index ACS [2, 16, 19]. Moreover, pretreatment (or loading dose for patients already on a statin) with a high-intensity statin should be considered in patients with ACS with planned invasive management [2, 20]. Our data show that statin prescription is mainly done during the first 48 hours, especially in low- and intermediate-risk patients.

Atherothrombotic risk assessment and secondary prevention therapy

Atherothrombotic risk assessment may be useful to identify high-risk patients who have the greatest potential to benefit from more intensive secondary prevention therapy. In the TRA 2P-TIMI 50 trial, the risk stratification tool identified a gradient of risk for recurrent events, and distinguished a pattern of increasing absolute benefit with vorapaxar [3, 5, 7]. Similarly, using data from the IMPROVE IT trial, the TRS-2P score identified a strong gradient of risk for recurrent cardiovascular events, and an increasingly favourable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile [4]. Similarly, in our study, the use of the TRS-2P score in patients with myocardial infarction seems to be useful for identifying patients most likely to benefit from high-intensity statins. Use of a high-intensity statin at discharge was inversely correlated with patient risk; it was associated with larger absolute risk reductions in 5-year MACE in higher-risk categories and, after multivariable adjustment, the benefit of high-intensity statins was manifest only in high-risk patients. These findings are important, as they suggest that specific efforts should be made to increase high-intensity statin prescription rates in higher-risk populations.

Study limitations

The TRS-2P score was designed to be a simple tool, using readily available clinical data. There are other previously identified risk indicators and other yet to be identified variables that may provide additional refinement for stratification. However, the ability of this simple scoring system to identify differential treatment benefit for different classes of secondary prevention therapy supports its clinical utility. Our data are derived from an observational study of patients with acute myocardial infarction admitted to an intensive care unit, whereas TRS-2P was defined in a population of stable patients with previous myocardial infarction. In addition, our analyses were focused on mortality, recurrent myocardial infarction or stroke at 5 years, whereas this risk stratification tool was developed for all cardiovascular events at 3 years. The definition used for high-intensity statin is open to criticism and, in this analysis, we did not take into account co-prescription of ezetimibe (although ezetimibe was used in a small minority of our patients). Finally, we cannot exclude that factors other than those collected in the surveys could also explain the evolution observed according to TRS-2P category.

Conclusions

Use of high-intensity statins at discharge after acute myocardial infarction was inversely correlated with patient risk using the TRS-2P score. The increased hazard associated with lack of prescription of recommended medications was much greater in high-risk patients. Specific efforts should be directed towards better prescription of recommended treatment, particularly in high-risk patients.

Acknowledgements

The authors are deeply indebted to the patients who agreed to participate, and to 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 goes to the personnel of l'Unité de Recherche Clinique de l'Est Parisien (URC-Est) (Assistance Publique des Hôpitaux de Paris and University Paris 6). Special thanks to Vincent Bataille, PhD, (ADIMEP, Toulouse) for data management, Benoît Pace (Société Française de Cardiologie) who designed the electronic case report form, Geneviève Mulak, Pharm D., and Nicole Naccache, Pharm D., (Société Française de Cardiologie) for their help, and Elodie Drouet, MSc, who supervised patient follow-up.

Sources of funding

The FAST-MI 2005 and 2010 registries are the property of the French Society of Cardiology, and were funded by grants from the companies AstraZeneca, Daiichi Sankyo, Eli Lilly, GSK, MSD, Novartis, Pfizer, Sanofi and Servier, and by a grant from the French National Health Insurance body (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés [CNAM-TS]). None of the companies had a role in the design or conduct of the study, data collection or management.

Disclosure of interest

E. D. and V. T. have nothing to disclose. F. S. reports personal fees from Amgen, Astra Zeneca, Bayer, BMS, MSD, Pfizer, and Sanofi. J. F. reports grants and personal fees from Akcea, Amarin, Amgen, MSD, Sanofi and Servier. T. S. reports grants from AstraZeneca, Daiichi-Sankyo, Eli-Lilly, GSK, MSD, Novartis, Sanofi, and personal fees for board membership and/or consultancy and/or lectures from AstraZeneca, BMS, Sanofi, and Novartis. N. D. 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. E. P. 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.

References

- [1] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082-e143.
- [2] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.
- [3] Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic Risk Stratification and the Efficacy and Safety of Vorapaxar in Patients With Stable Ischemic Heart Disease and Previous Myocardial Infarction. *Circulation* 2016;134:304-13.
- [4] Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention. *J Am Coll Cardiol* 2017;69:911-21.
- [5] Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-13.
- [6] Puymirat E, Bonaca M, Fumery M, et al. Atherothrombotic risk stratification after acute myocardial infarction: The Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention in the light of the French Registry of Acute ST Elevation or non-ST Elevation Myocardial Infarction registries. *Clin Cardiol* 2019;42:227-34.
- [7] Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet* 2012;380:1317-24.
- [8] Williams BA, Chagin KM, Bash LD, et al. External validation of the TIMI risk score for secondary cardiovascular events among patients with recent myocardial infarction. *Atherosclerosis* 2018;272:80-6.
- [9] Belle L, Cayla G, Cottin Y, et al. 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.

- [10] Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. *Arch Mal Coeur Vaiss* 2007;100:524-34.
- [11] Hanssen M, Cottin Y, Khalife K, et al. French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010. FAST-MI 2010. *Heart* 2012;98:699-705.
- [12] de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307-16.
- [13] Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Cardiol* 2014;113:1753-64.
- [14] Ray KK, Cannon CP, McCabe CH, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2005;46:1405-10.
- [15] Schwartz GG, Fayyad R, Szarek M, DeMicco D, Olsson AG. Early, intensive statin treatment reduces 'hard' cardiovascular outcomes after acute coronary syndrome. *Eur J Prev Cardiol* 2017;24:1294-6.
- [16] Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711-8.
- [17] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;376:1713-22.
- [18] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;379:2097-107.
- [19] Vale N, Nordmann AJ, Schwartz GG, et al. Statins for acute coronary syndrome. *Cochrane Database Syst Rev* 2014:CD006870.
- [20] Berwanger O, Santucci EV, de Barros e Silva PGM, et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. *JAMA* 2018;319:1331-40.

Figure legends

Figure 1. Five-year event-free survival according to the use of high-intensity statins in low-, intermediate- and high-risk patients. CI: confidence interval; G: group; HR: hazard ratio.

Figure A.1. Prescription of statins at discharge according to Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention categories. High-intensity statins at discharge were defined as rosuvastatin 20 mg daily or atorvastatin 80 mg daily. Moderate-intensity statins at discharge were defined as rosuvastatin 10 mg daily or atorvastatin 40 mg daily. Low-intensity statins were defined as rosuvastatin 5 mg daily or atorvastatin 10/20 mg daily or fluvastatin, pravastatin or simvastatin.

Table 1 Baseline characteristics and clinical presentation.

	Low risk (TRS-2P = 0–1)		Intermediate risk (TRS-2P = 2)		High risk (TRS-2P ≥ 3)		<i>P</i>	
	HIS (<i>n</i> = 1260)	No HIS (<i>n</i> = 1792)	HIS (<i>n</i> = 574)	No HIS (<i>n</i> = 1262)	HIS (<i>n</i> = 454)	No HIS (<i>n</i> = 2006)	HIS	No HIS
Age (years)	56.3 ± 11.1	59.3 ± 12.0 ^a	61.9 ± 12.9	67.5 ± 13.2 ^a	70.8 ± 11.9	75.9 ± 10.9 ^a	< 0.001	< 0.001
Female sex	196 (16)	419 (23) ^a	134 (23)	400 (32) ^a	123 (27)	818 (41) ^a	< 0.001	< 0.001
BMI (kg/m ²)	26.7 ± 4.2	26.6 ± 4.3	27.7 ± 4.9	27.0 ± 4.8 ^c	27.9 ± 5.2	27.3 ± 4.9 ^c	< 0.001	< 0.001
Risk factors								
Hypertension	224 (19)	391 (22)	420 (73)	879 (70)	398 (88)	1765 (88)	< 0.001	< 0.001
Diabetes	38 (3)	90 (5) ^b	117 (20)	359 (28) ^a	216 (48)	1150 (57) ^a	< 0.001	< 0.001
Hypercholesterolaemia	461 (37)	702 (39)	268 (47)	611 (48)	244 (54)	1096 (55)	< 0.001	< 0.001
Current smoking	564 (45)	566 (32) ^a	306 (53)	396 (31) ^a	167 (37)	425 (21) ^a	< 0.001	< 0.001
Medical history								
Previous MI	73 (6)	191 (11) ^a	66 (11.5)	217 (17) ^b	86 (19)	587 (29) ^a	< 0.001	< 0.001
Previous PCI	75 (6)	198 (11) ^a	61 (11)	215 (17) ^a	74 (16)	448 (22) ^b	< 0.001	< 0.001
Previous CABG	13 (0.6)	23 (1)	29 (1)	54 (4)	49 (2)	259 (13)	< 0.001	< 0.001
History of heart failure	0 (0)	7 (0.4) ^c	4 (0.7)	19 (1.5)	32 (7)	281 (14) ^a	< 0.001	< 0.001
History of stroke	6 (0.5)	18 (1)	21 (4)	58 (5)	52 (11.5)	294 (15)	< 0.001	< 0.001

Peripheral artery disease	4 (0.3)	13 (0.7)	30 (5)	48 (4)	92 (20)	447 (22)	< 0.001	< 0.001
Chronic renal failure	3 (0.2)	4 (0.2)	11 (2)	26 (2)	44 (10)	246 (12)	< 0.001	< 0.001
Previous medications								
Aspirin	97 (8)	269 (15) ^a	94 (16)	306 (24) ^a	161 (35.5)	780 (39)	< 0.001	< 0.001
Clopidogrel	44 (3.5)	111 (6) ^c	39 (7)	145 (11.5) ^b	87 (19)	488 (24) ^c	< 0.001	< 0.001
Beta-blockers	125 (10)	242 (13.5) ^b	123 (21)	372 (29.5) ^a	165 (36)	762 (38)	< 0.001	< 0.001
Statins	181 (14)	373 (21) ^a	142 (25)	372 (29.5) ^c	183 (40)	814 (41)	< 0.001	< 0.001
ACE inhibitors or ARBs	146 (12)	266 (15) ^c	212 (37)	502 (40)	244 (54)	1108 (55)	< 0.001	< 0.001
Clinical presentation								
STEMI	890 (71)	1075 (60) ^a	362 (63)	666 (53) ^a	250 (55)	730 (36) ^a	< 0.001	< 0.001
Killip class							< 0.001	< 0.001
I	1236 (98)	1749 (98)	511 (89)	1117 (88.5)	279 (61.5)	1106 (55) ^c		
II	19 (1.5)	31 (1.7)	46 (8)	96 (8)	122 (27)	489 (24)		
III	3 (0.2)	7 (0.4)	11 (2)	34 (3)	43 (9.5)	348 (17)		
IV	2 (0.2)	3 (0.2)	6 (1)	9 (0.7)	9 (2)	53 (3)		
LV function (%)	54.0 ± 10.2	54.6 ± 11.0	52.6 ± 10.8	53.2 ± 11.9	49.6 ± 11.6	48.9 ± 13.4	< 0.001	< 0.001
GRACE score	122.5 ± 26.1	127.8 ± 29.5 ^a	132.8 ± 29.6	141.4 ± 30.4 ^a	155.9 ± 33.1	168.4 ± 34.8 ^a	< 0.001	< 0.001
SRI score	17.9 ± 8.5	20.4 ± 9.9 ^a	22.1 ± 11.1	26.5 ± 13.9 ^a	29.5 ± 13.9	35.4 ± 15.9 ^a	< 0.001	< 0.001
CRUSADE score	18.4 ± 10.4	20.7 ± 11.5 ^a	23.9 ± 12.2	28.5 ± 12.8 ^a	37.7 ± 13.4	44.8 ± 14.0 ^a	< 0.001	< 0.001

CRP	12.1 ± 42.4	13.8 ± 31.1	10.3 ± 20.0	17.8 ± 39.1 ^a	23.5 ± 44.6	34.1 ± 54.7 ^b	< 0.001	< 0.001
Fibrinogen	5.0 ± 13.0	5.8 ± 3.9 ^a	5.2 ± 10.8	6.7 ± 4.5 ^a	6.1 ± 12.3	8.2 ± 5.2 ^a	< 0.001	< 0.001

Values are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; BMI: body mass index; CABG: coronary artery bypass grafting; CRP: C-reactive protein; HIS: high-intensity statins; LV: left ventricular; MI: myocardial infarction; PCI: percutaneous coronary intervention; SRI: simple risk index; STEMI: ST-elevation myocardial infarction; TRS-2P: Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

Comparison of variables in each TRS-2P category (HIS versus no HIS):

^a $P < 0.001$.

^b $P < 0.01$.

^c $P < 0.05$.

Table 2 Medications in patients discharged alive according to risk stratification.

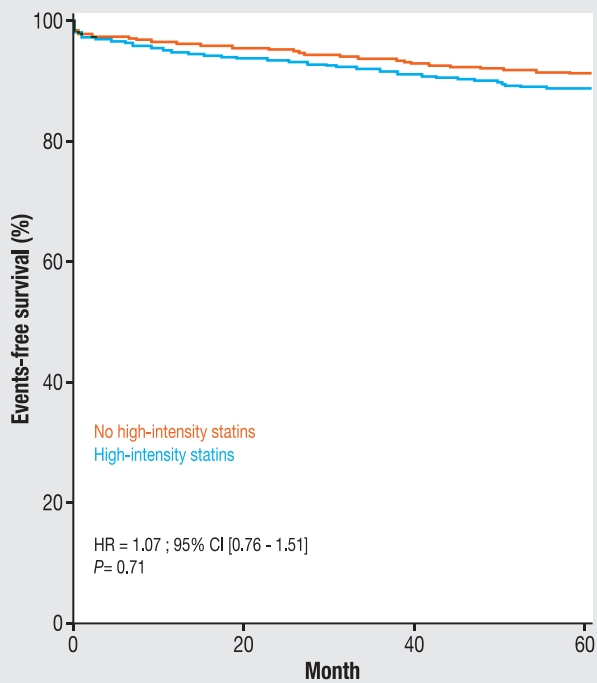
	Low risk (TRS-2P = 0–1)		Intermediate risk (TRS-2P = 2)		High risk (TRS-2P ≥ 3)		<i>P</i>	
	HIS (<i>n</i> = 1260)	No HIS (<i>n</i> = 1792)	HIS (<i>n</i> = 574)	No HIS (<i>n</i> = 1262)	HIS (<i>n</i> = 454)	No HIS (<i>n</i> = 2006)	HIS	No HIS
Aspirin	1227 (97)	1698 (95)	563 (98)	1177 (95)	436 (96)	1800 (90)	< 0.001	< 0.001
Clopidogrel	908 (34)	1476 (54)	561 (43)	1086 (63)	739 (55)	1647 (66)	< 0.001	< 0.001
Prasugrel or ticagrelor	1602 (59)	915 (34)	610 (47)	401 (23)	361 (27)	304 (12)	< 0.001	< 0.001
Beta-blockers	1174 (93)	1466 (82)	510 (89)	1023 (81)	389 (86)	1467 (73)	< 0.001	< 0.001
ACE inhibitors or ARBs	1022 (81)	1226 (68)	489 (85)	934 (74)	383 (84)	1437 (72)	0.18	< 0.001
Ezetemib	12 (1)	41 (2)	7 (1)	25 (2)	8 (2)	51 (2.5)	0.39	0.58
Diuretics	109 (9)	176 (10)	112 (19.5)	285 (23)	187 (41)	965 (48)	< 0.001	< 0.001
Aldosterone receptor antagonists	61 (5)	60 (3.5)	46 (8)	72 (6)	53 (12)	155 (8)	< 0.001	< 0.001
Calcium channel blockers	51 (4)	164 (9)	51 (9)	199 (16)	85 (19)	457 (23)	< 0.001	< 0.001
Proton pump inhibitors	713 (57)	948 (53)	343 (60)	707 (56)	306 (67)	1195 (60)	< 0.001	< 0.001
Insulin	20 (2)	31 (2)	53 (9)	105 (8)	88 (19)	477 (24)	< 0.001	< 0.001
BASl ^a	1148 (91)	1299 (73)	471 (82)	759 (61)	344 (76)	961 (48)	< 0.001	< 0.001

Data are expressed as number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HIS, high-intensity statins; TRS-2P:

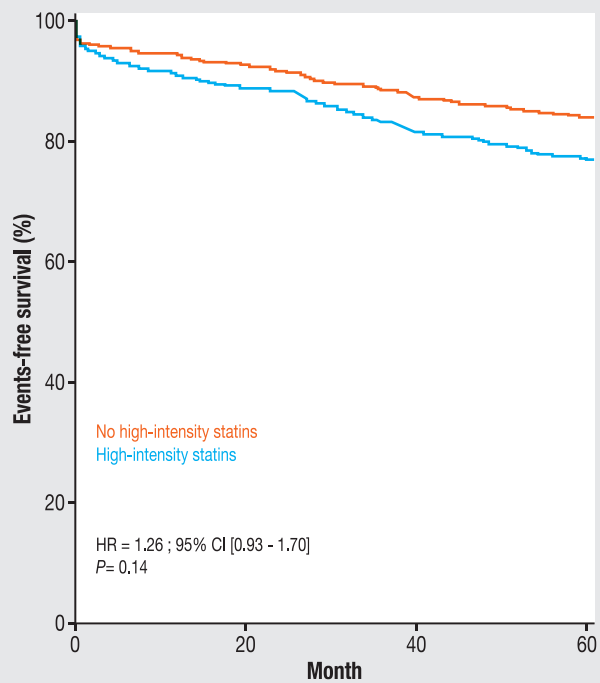
Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

^a Defined as the use of antiplatelet therapy, beta-blocker, statin and ACE inhibitor or ARB at discharge.

Low-risk (G1)



Intermediate-risk (G2)



High-risk (G3)

