Archives of Cardiovascular Disease (2019) 112, 459—468

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CLINICAL RESEARCH

Outcome associated with prescription of cardiac rehabilitation according to predicted risk after acute myocardial infarction: Insights from the FAST-MI registries

Évolution associée à la prescription d'une réadaptation cardiaque selon le risque après un infarctus du myocarde :enseignements tirés des registres FAST-MI

Etienne Puymirat[a,b,*], Marc Bonaca[c], Marie-Christine Iliou[d], Victoria Tea[a,b], Grégory Ducrocq[e], Hervé Douard[f], Marc Labrunee[g], Philoktimon Plastaras[h], Pierre Chevallereau[i], Guillaume Taldir[j], Vincent Bataille[k,l,m], Jean Ferrières[k,l,m], François Schiele[n], Tabassome Simon[o,p,q], Nicolas Danchin[a,b], for the FAST-MI investigators

[a] *Department of Cardiology, hôpital Européen Georges-Pompidou (HEGP), AP-HP, 75015 Paris, France*
[b] *Université Paris-Descartes, 75006 Paris, France*
[c] *TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital; and Harvard Medical School, Boston, MA 02115, USA*
[d] *Department of cardiac Rehabilitation, hôpital Corentin-Celton, AP-HP, 92130 Issy-les-Moulineaux, France*

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CR, cardiac rehabilitation; FAST-MI, French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction; HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; 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, TIMI Risk Score for Secondary Prevention.

* Corresponding author at: Hôpital Européen Georges-Pompidou, 20, rue Leblanc, 75015 Paris, France.
E-mail address: etienne.puymirat@aphp.fr (E. Puymirat).

https://doi.org/10.1016/j.acvd.2019.04.002

[e] *Department of cardiology, hôpital Bichat, AP-HP, 75877 Paris, France*
[f] *Department of cardiology, hôpital Haut-Lévèque, 33600 Pessac, France*
[g] *Department of Cardiac Rehabilitation, Toulouse University Hospital, 31073 Toulouse, France*
[h] *Department of cardiology, hôpital de Colmar, 68000 Colmar, France*
[i] *Department of cardiology, Centre hospitalier de Libourne, 33500 Libourne, France*
[j] *Department of cardiology, Centre hospitalier de Saint-Brieuc, 22000 Saint-Brieuc, France*
[k] *Department of cardiology B, Toulouse university hospital, 31059 Toulouse, France*
[l] *Department of epidemiology, Toulouse university hospital, 31073 Toulouse, France*
[m] *UMR Inserm 1027, 31000 Toulouse, France*
[n] *Department of Cardiology, Jean-Minjoz University Hospital, 25000 Besançon, France*
[o] *Department of Clinical Pharmacology and Unité de Recherche Clinique (URCEST), hôpital Saint-Antoine, AP-HP, 75012 Paris, France*
[p] *Université Pierre et Marie-Curie (UPMC-Paris 06), 75005 Paris, France*
[q] *Inserm U-698, 75877 Paris, France*

Received 13 January 2019; received in revised form 14 March 2019; accepted 2 April 2019
Available online 22 May 2019

KEYWORDS
Atherothrombotic risk stratification;
Acute myocardial infarction;
Cardiac rehabilitation;
Score

Summary
Background. — Cardiac rehabilitation is strongly recommended in patients after acute myocardial infarction.
Aims. — To assess cardiac rehabilitation prescription after acute myocardial infarction according to predicted risk, and its association with 1-year mortality, using the FAST-MI registries.
Methods. — We used data from three 1-month French nationwide registries, conducted 5 years apart from 2005 to 2015, including 13130 patients with acute myocardial infarction admitted to coronary or intensive care units. Atherothrombotic risk stratification was performed using the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS-2P). Patients were classified into three categories: Group 1 (low risk; no or one risk indicator; score of 0 or 1); Group 2 (intermediate risk; two risk indicators; score of 2); and Group 3 (high risk; at least three risk indicators; score of ≥ 3).
Results. — Among the 12291 patients, cardiac rehabilitation prescription was 43.6% (49.9% in Group 1; 43.0% in Group 2; 35.2% in Group 3). Using Cox multivariable analysis, cardiac rehabilitation prescription was associated with lower mortality at 1 year in the overall population (3.8% vs. 8.2%; hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.61—0.85; $P < 0.001$). Cardiac rehabilitation was associated with improved 1-year mortality, with homogeneous relative risk reductions in low- and intermediate-risk categories (HR 0.70, 95% CI 0.51—0.94) compared with high-risk patients (HR 0.72, 95% CI 0.59—0.88). In absolute terms, however, mortality decrease associated with cardiac rehabilitation was positively correlated with risk level (Group 1, 0.9% vs. 2.4%; Group 2, 3.0% vs. 4.2%; Group 3, 10.5% vs. 17.3%).
Conclusion. — Cardiac rehabilitation prescription was inversely correlated with patient risk. A positive association between cardiac rehabilitation and 1-year survival after acute myocardial infarction was present whatever the risk level, but the greatest mortality reduction was observed in high-risk patients.

MOTS CLÉS
Stratification risque athérothrombotique ;
Infarctus du myocarde ;
Réadaptation cardiaque ;
Score

Résumé
Contexte. — La réadaptation cardiaque (RC) est fortement recommandée chez les patients après un infarctus du myocarde (IdM).
Objectifs. — Évaluer la prescription de la RC au décours d'un IdM selon un score de risque et son association sur la mortalité à un an, en utilisant les registres FAST-MI.
Méthodes. — Nous avons utilisé 3 registres d'un mois, conduits tous les 5 ans entre 2005 à 2015, incluant 13130 patients admis dans une unité de soins intensifs en France pour un IDM. Le score de risque athérothrombotique utilisé était le TIMI Risk Score for Secondary Prevention

(TRS-2P). Les patients étaient répartis en 3 catégories: Groupe 1 (bas risque; TRS-2P = 0/1); Groupe 2 (risque intermédiaire; TRS-2P = 2); et, Groupe 3 (haut risque; TRS-2P ≥ 3).
Résultats. — Sur les 12291 patients survivants, la prescription de la RC était de 43,6 % (Groupe 1, 49,9 %; Groupe 2, 43,0 %; Groupe 3, 35,2 %). En analyse multivariée, la prescription de la RC était associée à une baisse de la mortalité à un an dans la population globale (3,8 % vs 8,2 %; HR 0,72; IC95 % 0,61—0,85; $p < 0,001$), avec des réductions de risques relatifs homogènes dans les catégories de risque faible et intermédiaire (HR 0,70, IC95 % 0,51—0,94) comparées aux patients à haut risque (HR 0,72, IC95 % 0,59—0,88). En revanche, en valeur absolue, la baisse de la mortalité associée à la RC était corrélée au niveau de risque (Groupe 1, 0,9 % vs 2,4 %; Groupe 2, 3,0 % vs 4,2 %; Groupe 3, 10,5 % vs 17,3 %).
Conclusions. — La prescription de la RC était inversement corrélée au niveau de risque des patients. La baisse de la mortalité à 1 an a été observée quel que soit le niveau de risque des patients, avec toutefois une réduction plus marquée en valeur absolue chez les patients à haut-risque.

Background

Cardiac rehabilitation (CR), including graduated cardiovascular exercise, risk factor modification, education, stress management and psychological support, is strongly recommended in current European guidelines in patients after acute myocardial infarction (AMI) [1—3]. Participation in CR after AMI is a safe and effective intervention that is associated with decreased mortality and morbidity [4—8]. Specifically, participation in CR has been correlated with lower rates of unplanned readmissions, higher quality-of-life metrics, healthy lifestyle behavioural choices and improved exercise capacity [4—10]. To our knowledge, the benefits of CR have not been evaluated according to atherothrombotic risk stratification.

Few risk stratification tools are validated and used in clinical practice to assist with long-term therapeutic decision making for secondary prevention in patients discharged alive after AMI [11—23]. Recently, the Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS-2P) has been proposed to identify high-risk patients who have the greatest potential to benefit from more intensive secondary prevention therapy, such as antithrombotic or lipid-lowering therapy [24—26]. In addition, the TRS-2P has been recently validated in other trial populations and observational studies [27,28].

The aim of the present study was to analyse the relationship between prescription of CR and 1-year survival according to risk level defined by the TRS-2P score in patients with AMI discharged alive, using the FAST-MI registries (French registry of Acute ST-elevation or non — ST-elevation Myocardial Infarction) [29—31].

Methods

Population

Three nationwide French registries were conducted 5 years apart over a 10-year period (2005 to 2015): FAST-MI 2005 (NCT00673036) [30]; FAST-MI 2010 (NCT01237418) [31]; and FAST-MI 2015 (NCT02566200) [29]. The methods used for these registries have been detailed previously [29—31]. Briefly, their primary objectives were to evaluate the characteristics, management and outcomes of patients with AMI as seen in routine clinical practice, on a country-wide scale (Appendix A).

All registries consecutively included patients with ST-segment elevation myocardial infarction (STEMI) or non — ST-segment elevation myocardial infarction (NSTEMI) admitted to cardiac intensive care units within 48 hours of symptom onset, during a specified 1-month period (October to December 2005, 2010 and 2015), with a possible extension of up to 1 additional month. AMI was defined by increased levels of cardiac biomarkers (troponins, creatine kinase or creatine kinase MB), together with either compatible symptoms or electrocardiogram changes. Participation in the study was offered to all institutions, including university teaching hospitals, general and regional hospitals and private clinics that received AMI emergencies. A total of 13,130 patients (52% STEMI) were included in the three surveys.

The study was conducted in accordance with the guidelines on good clinical practice and French law (Appendix A). 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 all three surveys.

Data collection

Data on baseline characteristics, including demographics, risk and medical history, were collected as described previously [29—31]. Information on the use of cardiac procedures, including the use of percutaneous coronary intervention and 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 (Appendix A). Mortality follow-up at 1 year was obtained in more than 99% of patients.

TRS-2P score

Each patient was assessed for the presence of any of the nine risk indicators described previously in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic

Ischemic Events (TRA-2P)-TIMI 50 trial at baseline [24—26]: age ≥ 75 years; diabetes mellitus; hypertension; peripherical 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/1.73 m^2 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 no or one risk indicator (Group 1; score of 0 or 1), an intermediate-risk category with two risk indicators (Group 2; score of 2) and a high-risk category with at least three risk indicators (Group 3; score of ≥ 3).

Statistical analysis

Continuous variables are reported as means ± standard deviations or medians and interquartile ranges (IQRs), as appropriate. 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. Temporal trends were tested using linear-by-linear association tests for binary and Jonckheere—Terpstra tests for continuous variables. Odds ratios and hazard ratios (HRs) are presented with their 95% confidence intervals (CIs). Survival curves were estimated using Kaplan—Meier estimators, and were compared using log-rank tests.

Multiple logistic regression analysis was used to estimate odds ratios, and to find the strongest independent predictors of referral to CR. Clinical presentation and in-hospital complication variables were included in the model. Correlates of 1-year mortality were determined using a multivariable backward stepwise Cox analysis, using a threshold of 0.10 for variable elimination. 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 with STEMI or NSTEMI separately, and in each of the three historical cohorts. Analyses were repeated using forward stepwise analysis to check the consistency of the results. Statistical analyses were performed using IBM SPSS 23.0 (IBM SPSS Inc., Armonk, NY, USA). For all analyses, two-sided *P* values < 0.05 were considered significant.

Results

CR prescription

A total of 12291 patients (93.6%) alive at discharge had all nine variables included in the TRS-2P score available, and were included in the main analysis. Prevalence of CR prescription was 49.9% in Group 1, 43.0% in Group 2 and 35.2% in Group 3, and increased between 2005 and 2015 in all TRS-2P categories (*P* < 0.001 for all), mainly as a result of increased prescription of outpatient CR (Fig. A.1). After adjustment, compared with Group 1, referral to CR was lower in Group 3 (HR 0.72, 95% CI 0.65—0.79; *P* < 0.001) and Group 2 (HR 0.83, 95% CI 0.75—0.91; *P* < 0.001) (Table A.1).

Clinical characteristics

Patient characteristics and clinical presentation according to CR and TRS-2P categories are detailed in Table 1 and Table A.2. In all TRS-2P categories, patients discharged without CR prescription were older and had a more severe cardiovascular risk profile. Current smokers were most frequently referred to CR centres in all risk categories. Patients referred to CR more often had STEMI or left ventricular dysfunction. In all TRS-2P categories, patients referred to CR had lower GRACE, Simple Risk Index and CRUSADE scores. Finally, biomarkers of inflammation (C-reactive protein, fibrinogen) were lower in all risk categories in patients referred to CR. In-hospital complications are described in Table A.3. The rates of cardiogenic shock, atrial fibrillation, major and minor bleedings and use of transfusions were higher in Group 3 patients.

In-hospital management

Early management, including medications and myocardial revascularization, differed according to TRS-2P categories and CR prescription (Table 2). Overall, Group 3 patients were treated less optimally than Group 1 and Group 2 patients. In all TRS-2P categories, however, patients referred to CR received more recommended medications during the first 48 hours after admission, and the use of invasive strategy was higher.

Medications prescribed at discharge are listed in Table 3. Overall, prescription of recommended treatments decreased progressively from low-risk to high-risk patients, and were significantly higher in patients referred to CR in all risk categories. The use of BASI combination therapy (beta-blocker, antiplatelet therapy, statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) at discharge was 61% in Group 1 (69% for patients referred to CR, 58% for patients not referred to CR), 62% in Group 2 (66% for patients referred to CR, 59.5% for patients not referred to CR) and 51% in Group 3 (58% for patients referred to CR, 47% for patients not referred to CR) (*P* for all < 0.001).

One-year mortality

Using Cox multivariable analysis, CR prescription was associated with lower mortality at 1 year in the overall population (3.8% vs. 8.2%; HR adjusted on baseline characteristics and management 0.72, 95% CI 0.61—0.85; *P* < 0.001). Risk stratification of death at 1 year according to CR prescription at discharge is presented in Fig. 1. CR was associated with improved outcomes in all risk categories, with homogeneous relative risk reductions in low- and intermediate-risk categories (HR 0.70, 95% CI 0.51—0.94;

Table 1 Baseline characteristics and clinical presentation, according to risk stratification[a].

	Low risk		Intermediate risk		High risk		*P*	
	CR (*n* = 2696)	No CR (*n* = 2712)	CR (*n* = 1307)	No CR (*n* = 1735)	CR (*n* = 1352)	No CR (*n* = 2489)	CR	No CR
Age (years)	57.7 ± 11.3	59.7 ± 12.2	63.8 ± 13.2	67.3 ± 13.2	73.1 ± 12.3	76.0 ± 10.9	< 0.001	< 0.001
Female sex	473 (18)	625 (23)	381 (29)	510 (29)	469 (35)	698 (39)	< 0.001	< 0.001
BMI (kg/m^2)	26.6 ± 4.2	26.6 ± 4.3	27.4 ± 4.7	27.2 ± 4.9	27.7 ± 5.1	27.3 ± 5.1	< 0.001	< 0.001
Risk factors								
Hypertension	552 (19)	570 (21)	985 (75)	1233 (71)	1196 (89)	2215 (89)	< 0.001	< 0.001
Diabetes	77 (3)	109 (4)	294 (23)	443 (25.5)	710 (52.5)	1378 (55)	< 0.001	< 0.001
Hypercholesterolaemia	919 (34)	1011 (37)	616 (47)	845 (49)	773 (57)	1382 (56)	< 0.001	< 0.001
Current smoking	1063 (39)	919 (34)	629 (48)	587 (34)	424 (31)	546 (22)	< 0.001	< 0.001
Medical history								
Myocardial infarction	191 (7)	304 (11)	168 (13)	326 (19)	372 (28)	765 (31)	< 0.001	< 0.001
PCI	205 (8)	304 (11)	168 (13)	317 (18)	339 (25)	643 (26)	< 0.001	< 0.001
CABG	14 (1)	29 (1)	30 (2)	70 (4)	171 (13)	315 (13)	< 0.001	< 0.001
Heart failure	8 (0.3)	6 (0.2)	19 (2)	33 (2)	158 (12)	356 (14)	< 0.001	< 0.001
Stroke	22 (1)	34 (1)	50 (4)	78 (5)	202 (15)	350 (14)	< 0.001	< 0.001
Peripheral artery disease	11 (0.4)	17 (1)	55 (4)	71 (4)	259 (19)	585 (24)	< 0.001	< 0.001
Chronic renal failure	11 (0.4)	12 (0.4)	20 (2)	43 (3)	158 (12)	334 (13)	< 0.001	< 0.001
Previous medications								
Aspirin	271 (10)	376 (14)	256 (20)	440 (25)	560 (41)	1041 (42)	< 0.001	< 0.001
Clopidogrel	67 (3)	145 (5)	84 (6)	182 (10.5)	246 (18)	597 (24)	< 0.001	< 0.001
Beta-blockers	333 (12)	348 (13)	350 (27)	509 (29)	533 (39)	1011 (41)	< 0.001	< 0.001
Statins	420 (16)	529 (20)	383 (29)	526 (30)	600 (44)	1071 (43)	< 0.001	< 0.001
ACE inhibitors or ARBs	454 (17)	391 (14)	485 (37)	724 (42)	705 (52)	1382 (56)	< 0.001	< 0.001
Clinical presentation								
STEMI	1852 (69)	1483 (55)	786 (60)	843 (49)	574 (42.5)	872 (35)	< 0.001	< 0.001
Killip class							< 0.001	< 0.001
I	2644 (98)	2654 (98)	1167 (89)	1554 (90)	863 (63)	1464 (59)		
II	36 (1)	42 (2)	92 (7)	122 (7)	283 (21)	567 (23)		
III	5 (0.2)	9 (0.3)	30 (2)	38 (2)	161 (12)	396 (16)		
IV	6 (0.2)	3 (0.1)	13 (1)	11 (1)	36 (3)	48 (2)		
LV function (%)	52.6 ± 10.0	55.2 ± 10.2	51.7 ± 11.0	53.4 ± 11.2	48.9 ± 12.1	49.3 ± 12.6	< 0.001	< 0.001
GRACE score	125.9 ± 26.1	126.6 ± 27.1	136.7 ± 30.5	139.6 ± 30.5	162.1 ± 34.3	166.5 ± 34.5	< 0.001	< 0.001
Simple Risk Index score	19.4 ± 9.4	20.7 ± 10.4	23.5 ± 11.5	26.2 ± 13.6	32.6 ± 15.4	35.0 ± 15.7	< 0.001	< 0.001
CRUSADE score	17.5 ± 10.6	20.0 ± 11.5	24.0 ± 12.7	27.3 ± 12.7	39.4 ± 15.3	43.6 ± 14.1	< 0.001	< 0.001
CRP	12.3 ± 36.0	12.6 ± 29.3	15.2 ± 33.8	15.1 ± 32.3	28.2 ± 51.1	31.9 ± 53.2	< 0.001	< 0.001
Fibrinogen	5.0 ± 13.0	5.8 ± 3.9	5.2 ± 10.8	6.7 ± 4.5	6.1 ± 12.3	8.2 ± 5.2	< 0.001	< 0.001

Data are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CABG: coronary artery bypass grafting; CR: cardiac rehabilitation; CRP: C-reactive protein: LV: left ventricular; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

[a] Low risk: no or one risk indicator (Group 1, score of 0 or 1); intermediate risk: two risk indicators (Group 2, score of 2); high risk: at least three risk indicators (Group 3, score of ≥ 3).

P = 0.02) compared with high-risk patients (HR 0.72, 95% CI 0.59—0.88; *P* = 0.01) (Fig. 2). In absolute terms, however, mortality decrease associated with CR was inversely correlated with risk level (Group 1: 0.9% vs. 2.4%, Δ absolute risk = 1.5; Group 2: 3.0% vs. 4.2%, Δ absolute risk = 1.2; Group 3: 10.5% vs. 17.3%, Δ absolute risk = 6.8). Similar results were found in patients with STEMI or NSTEMI separately, and in each of the three historical cohorts (data not shown).

Discussion

CR is under-prescribed in patients discharged alive after AMI, and is inversely correlated with patient risk. From 2005 to 2015, CR prescription has increased markedly in all risk categories, but the paradoxical lack of prescription of CR in higher-risk patients persists in the most recent survey. Lack of CR was associated with an increased risk of mortality whatever the patient risk profile, but the absolute increase

Table 2 In-hospital management, according to risk stratification[a,b].

	Low risk		Intermediate risk		High risk		*P*	
	CR (*n* = 2696)	No CR (*n* = 2712)	CR (*n* = 1307)	No CR (*n* = 1735)	CR (*n* = 1352)	No CR (*n* = 2489)	CR	No CR
Aspirin	2528 (94)	2565 (95)	1209 (93)	1647 (95)	1235 (91)	2264 (91)	0.02	< 0.001
Clopidogrel	1084 (40)	1786 (66)	633 (48)	1241 (72)	798 (59)	1846 (74)	< 0.001	< 0.001
Ticagrelor	924 (34)	436 (16)	390 (30)	218 (13)	283 (21)	208 (8)	< 0.001	< 0.001
Prasugrel	671 (25)	440 (16)	204 (16)	179 (10)	87 (6)	95 (4)	< 0.001	< 0.001
Glycoprotein IIb/IIIa inhibitor	833 (31)	893 (33)	352 (27)	509 (29)	245 (18)	485 (20)	< 0.001	< 0.001
Unfractionated heparin	1010 (38)	1062 (39)	476 (36)	706 (41)	568 (42)	1184 (48)	0.005	< 0.001
LMWH	1452 (54)	1758 (65)	687 (53)	1032 (60)	582 (43)	1209 (49)	< 0.001	< 0.001
Bivalirudin	94 (4)	58 (2)	41 (3)	31 (2)	20 (2)	25 (1)	0.001	0.005
Fondaparinux	482 (18)	391 (14)	253 (19)	206 (12)	257 (19)	296 (12)	0.46	0.009
Statin	2267 (84)	2199 (81)	1057 (81)	1340 (77)	1016 (75)	1743 (70)	< 0.001	< 0.001
Beta-blocker	2143 (80)	2152 (79)	1015 (78)	1322 (76)	941 (70)	1666 (67)	< 0.001	< 0.001
ACE inhibitors or ARB	1673 (62)	1506 (56)	873 (67)	1067 (62)	857 (63)	1495 (60)	0.01	< 0.001
Procedures								
Coronary angiography	2689 (99)	2662 (98)	1293 (99)	1639 (95)	1246 (92)	2007 (81)	0.01	< 0.001
Coronary angiography results							< 0.001	< 0.001
No significant lesions (< 50%)	133 (5)	248 (9)	57 (4)	116 (7)	48 (4)	111 (6)		
One-vessel disease	1364 (51)	1267 (48)	558 (43)	645 (40)	354 (29)	562 (28)		
Two-vessel disease	753 (28)	757 (29)	406 (32)	475 (29)	381 (31)	579 (29)		
Three-vessel disease	407 (15)	344 (13)	234 (18)	326 (20)	286 (23)	479 (24)		
CABG	14 (1)	28 (1)	30 (2)	69 (4)	171 (14)	276 (14)		
PCI	2348 (87)	2113 (78)	1093 (84)	1305 (75)	913 (68)	1452 (58)	< 0.001	< 0.001
Drug-eluting stent	1486 (58)	1001 (44)	698 (57)	583 (42)	561 (48)	687 (42)	< 0.001	< 0.29
Reperfusion therapy (STEMI)							< 0.001	< 0.001
Primary PCI	1243 (67)	816 (55)	517 (66)	462 (55)	344 (60)	382 (44)		
Fibrinolysis	266 (14)	300 (20)	94 (12)	142 (17)	59 (10)	86 (10)		
Medical therapy	343 (19)	367 (25)	174 (22)	239 (28)	171 (30)	404 (46)		
Coronary angiography < 24 h (NSTEMI)	495 (59)	581 (49)	276 (54)	355 (43)	286 (41)	419 (33)	< 0.001	< 0.001
Complete myocardial revascularization	688 (26)	1322 (49)	366 (28)	749 (43)	390 (29)	745 (30)	< 0.001	< 0.001

Data are expressed as number (%). ACE:angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CR: cardiac rehabilitation; LMWH: low molecular weight heparin; NSTEMI: non — ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

[a] Low risk: no or one risk indicator (Group 1, score of 0 or 1); intermediate risk: two risk indicators (Group 2, score of 2); high risk: at least three risk indicators (Group 3, score of ≥ 3).

[b] Percentages based on available data.

was considerably higher in the high-risk group. Finally, risk stratification using scores such as the TRS-2P score can identify populations in whom special attention should be given to encourage CR.

CR prescription

Overall, only 44% of all 12291 patients had a referral recommendation for CR. This rate is in line with existing data from the European Cardiac Rehabilitation Inventory Survey and data from the EUROASPIRE study, demonstrating a wide range of referral rates from < 3% to 90% [32—34]. In EUROASPIRE IV, CR was recommended in 50.7% of patients, with 41.2% finally attending a CR programme [35]. Age limits, physical limitation and funding were the most prevalent reasons for exclusion. These reasons concur with our analysis showing that patients being referred to CR are significantly younger (63.0 vs. 67.4 years) with low risk (TRS-2P = 1: 39% vs. 50%). Data from the AMIS registry and a recent publication from the Israel Heart Society (Working Group on Cardiac Rehabilitation) found similar independent predictors for referral [36,37]. Data from the Get With The Guidelines programme also documented decreased use of CR in higher-risk patients, although the gap with lower-risk patients might have attenuated in recent years [38].

Patients with a prescription of CR at discharge were predominantly male; they were significantly younger, presented with fewer risk factors, such as dyslipidaemia, hypertension or diabetes, but were more likely to be obese and smokers, as reported recently in the AMIS registry [37]. In addition, our data showed that low risk (i.e. TRS-2P = 1) was an independent predictor of referral to CR.

Table 3 Medications in patients discharged alive, according to risk stratification[a].

	Low risk (0–1)		Intermediate risk (2)		High risk (≥ 3)		*P*	
	CR (*n* = 2696)	No CR (*n* = 2712)	CR (*n* = 1307)	No CR (*n* = 1735)	CR (*n* = 1352)	No CR (*n* = 2489)	CR	No CR
Aspirin	2621 (97)	2578 (95)	1264 (97)	1630 (94)	1271 (94)	2260 (91)	< 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-blocker	2392 (89)	2278 (84)	1139 (87)	1427 (82)	1112 (82)	1885 (76)	< 0.001	< 0.001
Statin	2562 (95)	2472 (91)	1202 (92)	1544 (89)	1160 (86)	2038 (82)	< 0.001	< 0.001
ACE inhibitors or ARB	2120 (79)	1894 (70)	1041 (80)	1326 (76)	1038 (77)	1770 (71)	0.18	< 0.001
Diuretic	342 (13)	253 (9)	324 (25)	398 (23)	653 (48)	1188 (48)	< 0.001	< 0.001
Aldosterone receptor antagonist	160 (6)	102 (4)	117 (9)	100 (6)	147 (11)	194 (8)	< 0.001	< 0.001
Calcium channel blocker	161 (6)	219 (8)	169 (13)	291 (17)	305 (23)	599 (24)	< 0.001	< 0.001
Proton pump inhibitor	1638 (61)	1520 (56)	859 (66)	1012 (58)	924 (68)	1555 (63)	< 0.001	< 0.001
Insulin	40 (2)	39 (1)	88 (7)	152 (9)	282 (21)	578 (23)	< 0.001	< 0.001
BASI	1869 (69)	1581 (58)	867 (66)	1032 (60)	786 (58)	1181 (47)	< 0.001	< 0.001

Data are expressed as number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BASI: combination therapy comprising beta-blocker, antiplatelet, statin and ACE inhibitor or ARB; CR: cardiac rehabilitation.
[a] Low risk: no or one risk indicator (Group 1, score of 0 or 1); intermediate risk: two risk indicators (Group 2, score of 2); high risk: at least three risk indicators (Group 3, score of ≥ 3).

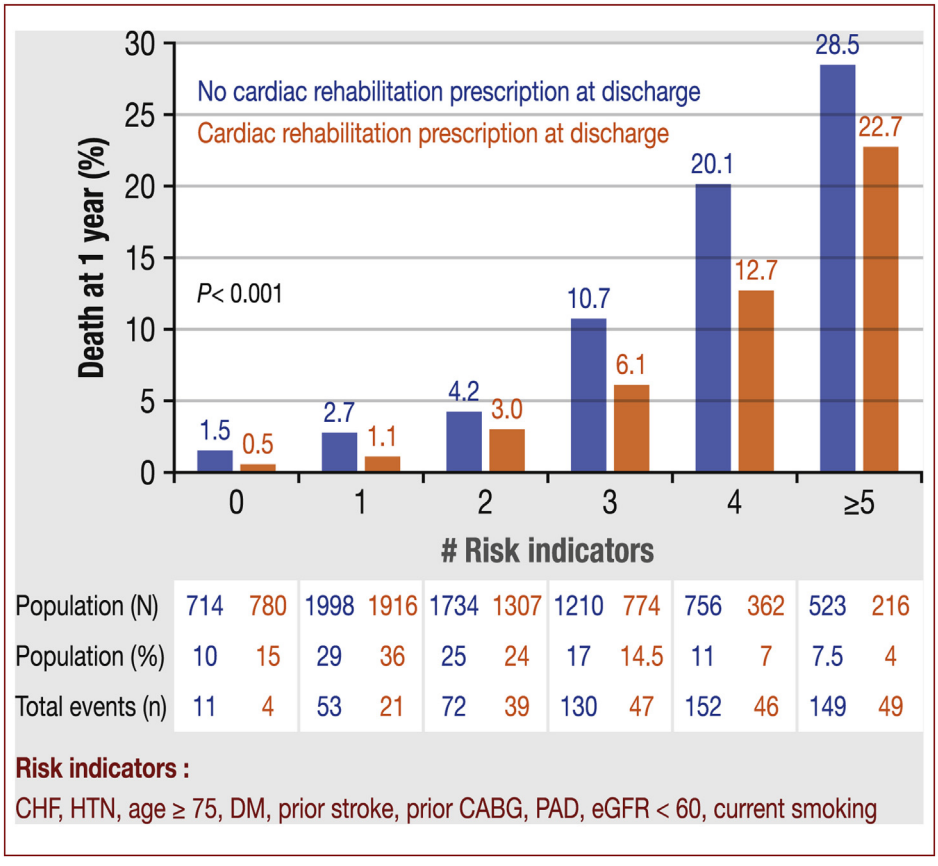

Figure 1. Death at 1 year by cardiac rehabilitation prescription at discharge according to number of risk indicators. One-year Kaplan–Meier estimates are shown. The *P* value is based on the χ^2 test for trend. CABG: coronary artery bypass graft; CHF: congestive heart failure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HTN: hypertension; PAD: peripheral artery disease.

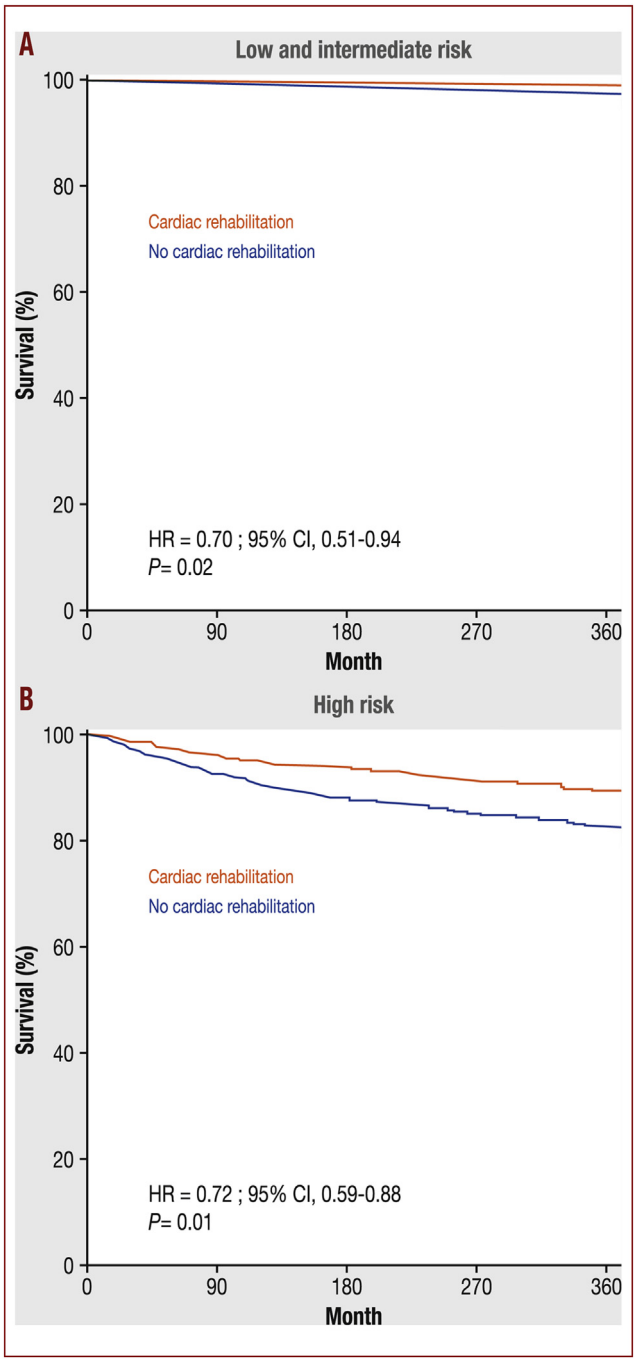

Figure 2. One-year survival according to risk stratification and cardiac rehabilitation prescription at discharge. CI: confidence interval; HR: hazard ratio. Low risk: no or one risk indicator (Group 1, score of 0 or 1); intermediate risk: two risk indicators (Group 2, score of 2); high risk: at least three risk indicators (Group 3, score of $\geq$ 3).

Clinical impact of CR

Based upon recent guideline recommendations, patients with STEMI and NSTEMI have a class I recommendation for CR [1—3]. Data from most recent meta-analyses about the impact of CR on mortality and morbidity after acute coronary syndrome further support this recommendation [39]. The CROS (Cardiac Rehabilitation Outcome Study) analysed 25 studies with 219702 patients, and demonstrated that CR after acute coronary syndrome was associated with reduced mortality.

To our knowledge, the potential benefits of referral to CR programme for patients after AMI according to atherothrombotic risk stratification have not been evaluated. Using the TRS-2P score, our results show that CR was associated with similar relative risk reductions in 1-year mortality in all risk categories, but in absolute terms, the increased hazard related to lack of prescription of CR was much greater in high-risk patients. Similarly, the TRS-2P score had previously demonstrated the capacity 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, this risk stratification tool identified a gradient of risk for recurrent events, and distinguished a pattern of increasing absolute benefit with vorapaxar [24—26]. Moreover, using data from the IMPROVE IT trial, the TRS-2P score identified an increasingly favourable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile [27].

Study limitations

As in any observational study, there are limitations to our analysis. In particular, causality between CR prescription and long-term outcome cannot be demonstrated; however, we did adjust our results on well-recognized determinants of long-term outcome, and sensitivity analyses confirmed our main findings. 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 clinically utility. In addition, our analyses were focused on the mortality at 1 year, while this risk stratification tool was developed for all cardiovascular events at 3 years. The rate of cardiovascular death was not available. Finally, the main limitation of this study is that we used the rate of CR prescription at discharge, because the rate of CR actually performed was not available. However, judging from the comparison of data from the 2010 FAST-MI survey (35.9% prescription rate) and the national figures of actual performance of CR in France in 2011 (33%), the difference between prescription and actual performance of CR appears to be small [40].

Conclusions

Despite favourable trends over the past 10 years, prescription of CR after AMI remains underutilized, and was inversely correlated with patient risk using the TRS-2P score. CR was associated with decreased 1-year mortality in all risk categories. In absolute terms, however, the increased hazard related to lack of prescription of CR was greater in high-risk patients. Specific efforts should be made to encourage prescription of CR, particularly in high-risk patients.

Funding

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

Acknowledgements

The authors are deeply indebted to the patients who agreed to participate and to all the physicians who took care of them. For additional acknowledgements, see Appendix B.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2019.04.002.

References

[1] Piepoli MF, Corra U, Adamopoulos S, et al. Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 2014;21:664—81.

[2] Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267—315.

[3] Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569—619.

[4] Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1—12.

[5] Doll JA, Hellkamp A, Thomas L, et al. Effectiveness of cardiac rehabilitation among older patients after acute myocardial infarction. Am Heart J 2015;170:855—64.

[6] Dunlay SM, Pack QR, Thomas RJ, Killian JM, Roger VL. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. Am J Med 2014;127:538—46.

[7] Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011;162:571—8400.

[8] Pouche M, Ruidavets JB, Ferrieres J, et al. Cardiac rehabilitation and 5-year mortality after acute coronary syndromes: The 2005 French FAST-MI study. Arch Cardiovasc Dis 2016;109:178—87.

[9] Lee BJ, Go JY, Kim AR, et al. Quality of life and physical ability changes after hospital-based cardiac rehabilitation in patients with myocardial infarction. Ann Rehabil Med 2017;41:121—8.

[10] Zullo MD, Dolansky MA, Jackson LW. Cardiac rehabilitation, health behaviors, and body mass index post-myocardial infarction. J Cardiopulm Rehabil Prev 2010;30:28—34.

[11] Antoni ML, Hoogslag GE, Boden H, et al. Cardiovascular mortality and heart failure risk score for patients after ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention (Data from the Leiden MISSION! Infarct Registry). Am J Cardiol 2012;109:187—94.

[12] Battes L, Barendse R, Steyerberg EW, et al. Development and validation of a cardiovascular risk assessment model in patients with established coronary artery disease. Am J Cardiol 2013;112:27—33.

[13] Bavry AA, Kumbhani DJ, Gong Y, Handberg EM, Cooper-Dehoff RM, Pepine CJ. Simple integer risk score to determine prognosis of patients with hypertension and chronic stable coronary artery disease. J Am Heart Assoc 2013;2:e000205.

[14] Beatty AL, Ku IA, Bibbins-Domingo K, et al. Traditional risk factors versus biomarkers for prediction of secondary events in patients with stable coronary heart disease: from the heart and soul study. J Am Heart Assoc 2015:4.

[15] Fox KA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J 2010;31:2755—64.

[16] Goliasch G, Kleber ME, Richter B, et al. Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score. Eur Heart J 2012;33:2282—9.

[17] Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. Circulation 2010;121:2681—91.

[18] Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) Project. Int J Cardiol 2012;154:173—9.

[19] Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. Soroka acute myocardial infarction (SAMI) score predicting 10-year mortality following acute myocardial infarction. Int J Cardiol 2013;167:3068—70.

[20] Schmidt M, Jacobsen JB, Lash TL, Botker HE, Sorensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ 2012;344:e356.

[21] Wilson PW, D'Agostino Sr R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012;125:695—7030.

[22] Yap YG, Duong T, Bland M, et al. Potential demographic and baselines variables for risk stratification of high-risk post-myocardial infarction patients in the era of implantable cardioverter-defibrillator–a prognostic indicator. Int J Cardiol 2008;126:101—7.

[23] Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362:2155—65.

[24] 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.

[25] Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404—13.
[26] 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 degrees P-TIMI 50 trial. Lancet 2012;380:1317—24.
[27] Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention. J Am Coll Cardiol 2017;69:911—21.
[28] 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.
[29] 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.
[30] 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.
[31] 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.
[32] Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. Eur J Cardiovasc Prev Rehabil 2010;17:410—8.
[33] Chamosa S, Alarcon JA, Dorronsoro M, et al. Predictors of enrollment in cardiac rehabilitation programs in Spain. J Cardiopulm Rehabil Prev 2015;35:255—62.
[34] Kotseva K, Wood D, De Backer G, De Bacquer D, EUROASPIRE III Study Group. Use and effects of cardiac rehabilitation in patients with coronary heart disease: results from the EUROASPIRE III survey. Eur J Prev Cardiol 2013;20:817—26.
[35] Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol 2016;23:636—48.
[36] Chernomordik F, Sabbag A, Tzur B, et al. Cardiac rehabilitation following an acute coronary syndrome: Trends in referral, predictors and mortality outcome in a multicenter national registry between years 2006-2013: Report from the Working Group on Cardiac Rehabilitation, the Israeli Heart Society. Eur J Prev Cardiol 2017;24:123—32.
[37] Hermann M, Witassek F, Erne P, Radovanovic D, Rickli H. Referral for cardiac rehabilitation after acute myocardial infarction: Insights from nationwide AMIS Plus registry 2005-2017. Int J Cardiol 2018;261:1—5.
[38] Motivala AA, Cannon CP, Srinivas VS, et al. Changes in myocardial infarction guideline adherence as a function of patient risk: an end to paradoxical care? J Am Coll Cardiol 2011;58:1760—5.
[39] Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: a systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol 2016;23:1914—39.
[40] Gabet A, de Peretti C, Nicolau J, C. IM, Olié V. Évolution temporelle du recours à la réadaptation cardiaque après un infarctus du myocarde, France, 2010-2014. Bull Epidémiol Hebd 2016;43:764—74.