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Impact of myocardial revascularization on long-term outcomes in a nationwide cohort of first acute myocardial infarction survivors

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KEYWORDS
Acute myocardial infarction;
Percutaneous coronary intervention;
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Secondary prevention;
Conservative management

The long-term clinical benefits of myocardial revascularization in a contemporary, nationwide cohort of acute myocardial infarction (AMI) survivors are unclear. We aimed to compare the mortality rates and clinical outcomes at 8 years of patients admitted in Italy for a first AMI managed with or without myocardial revascularization during the index event. This is a national retrospective cohort study that enrolled patients admitted for a first AMI in 2012 in all Italian hospitals who survived at 30 days. The outcomes of interest were all-cause mortality, major cardio-cerebrovascular events (MACCE), and re-hospitalization for heart failure (HF) at 8 years. Time to events was analysed using a Cox and Fine and Gray multivariate regression model. A total of 127 431 patients with AMI were admitted to Italian hospitals in 2012. The study cohort consisted of 62 336 AMI events, of whom 63.8% underwent percutaneous or surgical revascularization $\leq$30 days of the index hospital admission. At 8 years, the cumulative incidence of all-cause death was 36.5% (24.6% in revascularized and 57.6% in not revascularized patients). After multiple corrections, the hazard ratio (HR) for all-cause mortality in revascularized vs. not revascularized patients was 0.61 ($P < 0.0001$). The rate of MACCE was 45.7% and 65.8% (adjusted HR 0.83; $P < 0.0001$), while re-hospitalizations for HF occurred in 17.6% and 29.8% (adjusted HR 0.97; $P = 0.16$) in AMI survivors revascularized and not revascularized, respectively. In our contemporary nationwide cohort of patients at their first AMI episode, those who underwent myocardial revascularization within 1 month from the index event compared to those not revascularized presented an adjusted 39% risk reduction in all-cause mortality and 17% in MACCE at 8-year follow-up.

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Introduction

Care for patients with acute myocardial infarction (AMI) has advanced substantially during the past decades, with novel pharmacological therapies and rapid access to successful myocardial revascularization facilitated by AMI networks of care.[1-4] The early benefits of these interventions include lower mortality and a better quality of life.[1-4] In contrast, less is known about the long-term impact of myocardial revascularization in AMI, and few nationwide studies providing unbiased estimates of clinical events have been reported in contemporary series.[5-10]

We aimed at analysing the clinical impact of myocardial revascularization at long-term follow-up in AMI survivors using a nationwide, comprehensive, and universal administrative database of AMI events.

Methods

Study design

This was a retrospective cohort study that enrolled all patients admitted to all public and private hospitals in Italy for an AMI event from 1 January to 31 December 2012. The Italian National Registry of Hospital Discharge Records (HDR), provided by the Italian Ministry of Health, and other administrative databases available through a collaboration with the Italian National Program for Outcome Evaluation (PNE-AGENAS) were used as sources of data.

Study population

The Italian HDR database was used as the source of data to identify the study population. All HDR of patients aged 18–100 years, resident in Italy, admitted in 2012 and reporting a primary diagnosis of AMI [International Classification of Disease, 9th Revision, Clinical Modification (ICD 9 CM) 410] or a secondary diagnosis of AMI with any concomitant AMI complication within the primary diagnosis (ICD-9-CM codes 411, 413, 414, 426, 427, 428, 423.0, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 518.81, 780.01, 780.2, 785.51, 799.1, 997.02, and 998.2) were selected (*Outcomes evaluation National program [PNE]* Ed. 2020; available at https://pne.agenas.it/).

Patients discharged to home within 2 days from admission (probable false AMI cases) and AMI patients who died within 30 days from the index hospital admission were excluded. Furthermore, to avoid the inclusion of multiple admissions due to the same event, duplicate records and records concerning both transfers of patients to another hospital and patients with a previous AMI admission within 30 days of the index admission were excluded.[11]

For the purpose of this analysis, to define a cohort of first AMI events, all patients having had an AMI event or a percutaneous coronary intervention (PCI; ICD-9-CM codes 00.66, 36.01, 36.02, 36.05, 36.06, 36.07) and/or coronary artery bypass grafting procedure (CABG; ICD-9CM codes 36.10–36.19) in the previous 5 years were excluded. Patients meeting the cohort definition criteria were classified as having myocardial revascularization if they underwent PCI or CABG during the index admission for AMI or within the subsequent 30 days.

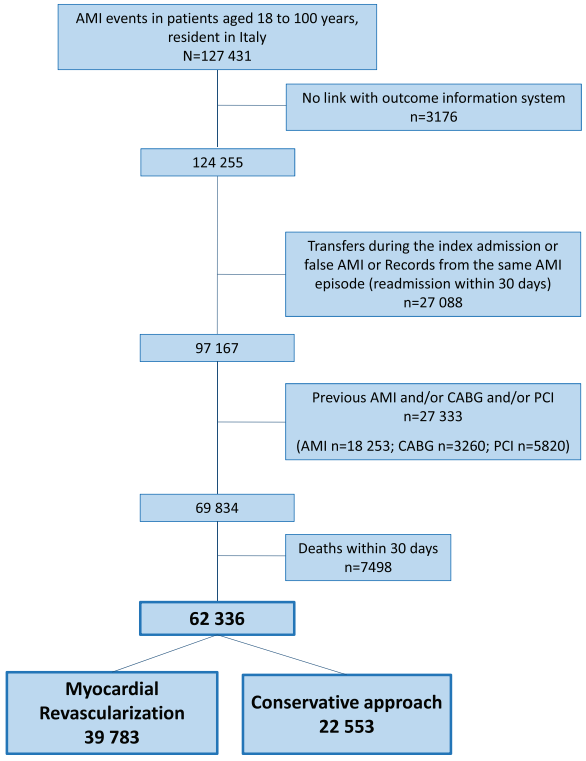

Figure 1 Study flowchart. AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Hospital Discharge Records from 1 January 2007 were used to detect previous hospitalizations for the study population. Data on patient risk factors and comorbidities, according to the ICD9-CM codes reported in Supplementary material online, *Table S1*, were retrieved either from the index admission or the previous 5-year hospitalizations.

Outcomes

All-cause mortality at 8-year follow-up represented the main adverse outcome. We also evaluated the long-term incidence of major adverse cardio-cerebrovascular events (MACCE), defined as all-cause death or re-hospitalizations for MI, stroke, and/or myocardial revascularization, and the rate of new admissions for heart failure (HF) at 8 years, as secondary endpoints.

Statistical analysis

The prevalence of risk factors and comorbidities were presented as counts and percentages; age was expressed as the mean ± standard deviation. Cox regression models were used to analyse time to death and MACCE, while Fine and Gray models were used to analyse time to re-hospitalization for HF, AMI, stroke, and myocardial revascularization, with death as a competing risk.

To provide adjusted outcome data, age, gender, and patients' risk factors and comorbidities were included in the multivariate models as potential confounding factors; stepwise procedures were used to identify independent associations with each of the considered outcomes. Since some chronic comorbidities recorded in the index hospitalization show a paradoxical protective effect,[12] the same

Table 1 Baseline characteristics of the enlisted population

	Not revascularized ($n = 22\,553$)	Revascularized ($n = 39\,783$)	*P* value
Age (years), mean ± SD	74.98 ± 13.66	65.41 ± 12.50	<0.0001
Age ≥ 75, *n* (%)	12 922 (57.3)	9731 (24.5)	<0.0001
Gender (F), *n* (%)	11 994 (53.2)	10 218 (25.7)	<0.0001
Hypertension, *n* (%)	5756 (25.5)	5204 (13.1)	<0.0001
Diabetes, *n* (%)	3001 (13.3)	3076 (7.7)	<0.0001
Heart failure, *n* (%)	2125 (9.4)	801 (2.0)	<0.0001
Ill-defined descriptions and complications of heart disease, *n* (%)	479 (2.1)	226 (0.6)	<0.0001
Cerebrovascular disease, *n* (%)	2568 (11.4)	1912 (4.8)	<0.0001
Cerebrovascular disease (ind. adm.), *n* (%)	1520 (6.7)	1162 (2.9)	<0.0001
Vascular disease, *n* (%)	1386 (6.2)	1312 (3.3)	<0.0001
Vascular disease (ind. adm.), *n* (%)	839 (3.7)	1047 (2.6)	<0.0001
Chronic coronary syndromes, *n* (%)	2598 (11.5)	1896 (4.8)	<0.0001
Arrhythmias, *n* (%)	2630 (11.7)	1494 (3.8)	<0.0001
Anaemia, *n* (%)	1323 (5.9)	656 (1.7)	<0.0001
Anaemia (ind. adm.), *n* (%)	1419 (6.3)	651 (1.6)	<0.0001
Blood clotting defects, *n* (%)	67 (0.3)	49 (0.1)	<0.0001
Blood clotting defects (ind. adm.), *n* (%)	15 (0.1)	9 (0.02)	0.0073
Other hematological diseases, *n* (%)	167 (0.7)	154 (0.4)	<0.0001
Other hematological diseases (ind. adm.), *n* (%)	99 (0.4)	125 (0.3)	0.0124
Cardiomyopathy, *n* (%)	406 (1.8)	186 (0.5)	<0.0001
Cardiomyopathy (ind. adm.), *n* (%)	586 (2.6)	346 (0.9)	<0.0001
Rheumatic heart disease, *n* (%)	325 (1.4)	155 (0.4)	<0.0001
Rheumatic heart disease (ind. adm.), *n* (%)	489 (2.2)	286 (0.7)	<0.0001
Endocarditis and acute myocarditis, *n* (%)	30 (0.1)	18 (0.05)	0.0001
Other chronic heart conditions, *n* (%)	390 (1.7)	167 (0.4)	<0.0001
Other chronic heart conditions (ind.adm.), *n* (%)	592 (2.6)	383 (1.0)	<0.0001
Chronic kidney disease, *n* (%)	1575 (7.0)	961 (2.4)	<0.0001
Chronic kidney diseases (ind. adm.), *n* (%)	2728 (12.1)	1972 (5.0)	<0.0001
Other chronic disease (liver, pancreas, intestine), *n* (%)	544 (2.4)	714 (1.8)	<0.0001
Other chronic disease (liver, pancreas, intestine) (ind. adm.), *n* (%)	199 (0.9)	152 (0.4)	<0.0001
Obesity, *n* (%)	419 (1.9)	467 (1.2)	<0.0001
Obesity (ind. adm.), *n* (%)	529 (2.4)	1107 (2.8)	0.0010
Chronic obstructive pulmonary disease, *n* (%)	2056 (9.1)	1406 (3.5)	<0.0001
Malignant neoplasms, *n* (%)	2295 (10.2)	2465 (6.2)	<0.0001
Previous vascular surgery, *n* (%)	1068 (4.7)	1235 (3.1)	<0.0001
Previous cerebral revascularization, *n* (%)	209 (0.9)	261 (0.7)	0.0002
Other previous cardiac surgery than CABG, *n* (%)	256 (1.1)	137 (0.3)	<0.0001

ind. adm, comorbidity information retrieved at the index admission.

comorbidities recorded in the previous hospitalizations were also forced into the models.

All-cause mortality was also analysed by stratifying by gender (male or female) and age (< or ≥75 years old).

All assumptions of statistical methods were explicitly checked. Statistical analyses were performed using SAS 9.4 (Cary, NC, USA).

Results

Out of the overall 127 431 AMI hospitalizations that occurred in Italy in 2012, our study cohort consisted of 62 336 AMI events (*Figure 1*): 63.8% treated with myocardial revascularization (92.7% with PCI only, 4.6% with CABG only and 2.7% with PCI and CABG) and the remaining 36.2% managed without revascularization. Among the study cohort, 35.5% were females and 36.3% were aged ≥75 years (*Table 1*).

At an 8-year follow-up, the cumulative incidence of all-cause mortality was 36.5% (24.6% in revascularized and 57.6% in not revascularized patients). After multiple corrections, the hazard ratio (HR) for all-cause mortality in revascularized vs. not revascularized patients was 0.61 ($P < 0.0001$) (*Table 2* and *Figure 2*). Acute myocardial infarction patients who received myocardial revascularization within 48 h from hospital admission had a 45% reduced risk of all-cause death as compared to not revascularized patients (HR 0.55; $P < 0.0001$), while those revascularized from 48 h to 30 days had a 29% reduced risk (HR 0.71; $P < 0.0001$) (*Figure 2*).

Myocardial revascularization was performed in 73.7% and 46.0% of males and females, and in 75.7% and 43.0% of patients aged < and ≥75 years, respectively. *Table 3* and *Figure 3* show the HR for all-cause death according to gender (male or female) and age (≥ or <75 years) in

Table 2 Cox regression analyses for primary and secondary endpoints at 8 years

	Death		MACCE		HF	
	HR	*P* value	HR	*P* value	HR	*P* value
Myocardial revascularization	0.61	<0.0001	0.83	<0.0001	0.97	0.1641
Age (years)	1.09	<0.0001	1.04	<0.0001	1.05	<0.0001
Gender (F)	0.87	<0.0001	0.86	<0.0001	1.03	0.2099
Hypertension	–	–	–	–	1.16	<0.0001
Diabetes	1.43	<0.0001	1.35	<0.0001	1.38	<0.0001
Heart failure	1.36	<0.0001	1.29	<0.0001	–	–
Cerebrovascular disease	1.19	<0.0001	1.16	<0.0001	0.93	0.0502
Cerebrovascular disease (ind. adm.)	1.28	<0.0001	1.22	<0.0001	–	–
Vascular disease	1.20	<0.0001	1.17	<0.0001	1.23	<0.0001
Vascular disease (ind. adm.)	1.15	<0.0001	1.09	0.0025	–	–
Chronic coronary syndromes	–	–	1.07	0.0013	1.20	<0.0001
Arrhythmias	1.04	0.1066	1.04	0.0516	1.22	<0.0001
Anaemia	1.23	<0.0001	1.15	<0.0001	0.93	0.1523
Anaemia (ind. adm.)	1.29	<0.0001	1.27	<0.0001	1.19	<0.0001
Other hematological diseases	1.22	0.0092	1.13	0.0786	–	–
Other hematological diseases (ind. adm.)	1.37	0.0009	1.19	0.0428	–	–
Cardiomyopathy	1.15	0.0066	1.04	0.4751	1.20	0.0996
Cardiomyopathy (ind. adm.)	1.29	<0.0001	1.18	<0.0001	2.10	<0.0001
Rheumatic heart disease	1.06	0.3319	1.06	0.2463	1.26	0.0272
Rheumatic heart disease (ind. adm.)	1.14	0.0043	1.13	0.0054	1.55	<0.0001
Other chronic heart conditions	1.08	0.1895	–	–	1.13	0.2268
Other chronic heart conditions (ind.adm.)	1.07	0.1037	–	–	1.21	0.0062
Chronic kidney disease	1.23	<0.0001	1.17	<0.0001	1.07	0.1711
Chronic kidney diseases (ind. adm.)	1.34	<0.0001	1.26	<0.0001	1.38	<0.0001
Other chronic disease (liver, pancreas, intestine)	1.23	<0.0001	1.12	0.0027	–	–
Other chronic disease (liver, pancreas, intestine) (ind. adm.)	1.54	<0.0001	1.27	0.0003	–	–
Obesity	–	–	–	–	1.23	0.0047
Obesity (ind. adm.)	–	–	–	–	1.23	0.0005
Chronic obstructive pulmonary disease	1.20	<0.0001	1.12	<0.0001	1.21	<0.0001
Malignant neoplasms	1.56	<0.0001	1.30	<0.0001	0.89	0.0004
Previous vascular surgery	1.39	<0.0001	1.19	<0.0001	–	–
Previous cerebral revascularization	0.90	0.0931	–	–	1.51	<0.0001
Other previous cardiac surgery than CABG	1.16	0.0346	–	–	–	–

HF, heart failure; ind. adm, comorbidity information retrieved at the index admission; MACCE, major averse cardiac and cerebrovascular events.

revascularized and not revascularized AMI survivors. Acute myocardial infarction patients aged ≥75 years and not revascularized presented the highest mortality rate, regardless of gender.

At 8 years, the cumulative incidence of MACCE was 45.7% and 65.8% in revascularized and not revascularized AMI patients, respectively (adjusted HR 0.83; $P < 0.0001$), while re-hospitalizations for HF occurred in 17.6% of revascularized and in 29.8% of not revascularized patients (adjusted HR 0.97; $P = 0.16$) (*Table 2* and *Figure 4*). The adjusted HR for the single components of MACCE in revascularized vs. not revascularized AMI survivors are shown in *Table 4*.

Discussion

The main findings of this analysis of contemporary, nationwide administrative data are the following: (i) two-thirds of first AMI survivors hospitalized in Italy in 2012 received myocardial revascularization within 1 month from the index admission; (ii) patients revascularized presented a risk reduction of ∼40% in 8-year overall mortality compared to patients not revascularized, with a more pronounced survival benefit in elderly patients.

The use of myocardial revascularization in the contemporary management of AMI may vary according to randomized clinical trials and real-world data.[11,13-17] Recent trials conducted in all-comers AMI populations showed that approximately one-third of patients were managed without revascularization.[18] Similarly, recent surveys have suggested that ∼30–40% of AMI cases do not receive myocardial revascularization during hospitalization.[11,13,14] Data of this study are in accordance with these percentages and confirm that the medical management of AMI is still relatively frequent in clinical practice. Notably, patients not revascularized seem to receive suboptimal pharmacological treatment at the time of hospital discharge, which may contribute to their worse prognosis.[19] Possible reasons for not undergoing in-hospital revascularization include multiple and serious comorbidities, resource availability,

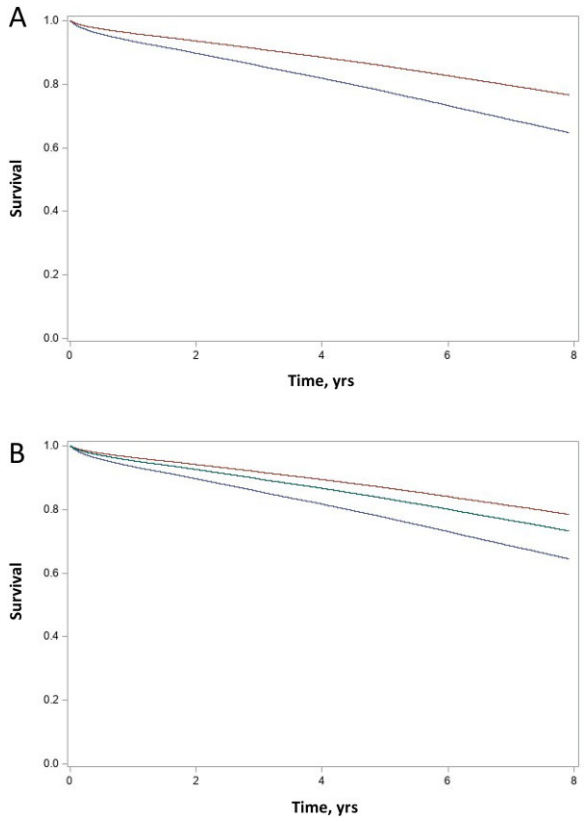

Figure 2 Adjusted survival curves for 8-year all-cause death in patients revascularized (red line) and not revascularized (blue line) (*A*) and in patients revascularized ≤48 h (red line) or >48 h to <30 days from the index hospitalization (green line) and not revascularized (blue line) (*B*).

Table 3 Adjusted hazard ratios of revascularized vs. not revascularized patients for 8-year all-cause mortality (females aged 75 years not revascularized as reference), according to gender and age

	HR Revasc vs. No-Revasc	*P* value
Males, <75 years, No Revasc	0.23	<0.0001
Males, <75 years, Revasc	0.12	<0.0001
Males, >75 years, No Revasc	1.01	0.5372
Males, >75 years, Revasc	0.53	<0.0001
Females, <75 years, No Revasc	0.21	<0.0001
Females, <75 years, Revasc	0.14	<0.0001
Females, >75 years, No Revasc	REF	REF
Females, >75 years, Revasc	0.51	<0.0001

No Revasc, no myocardial revascularization; Revasc, myocardial revascularization.

organizational issues, socioeconomic disparities, absence of significant coronary stenoses, patient refusal, or unfavourable coronary anatomy.

There are few population studies of long-term survival after AMI.[1-4] In a cohort study conducted in the USA during 2003–06, 3-year mortality rate among patients aged ≥65 years with non-ST-elevation myocardial infarction (NSTEMI) was reported to be 40%.[20] In another study conducted in England from 2004 to 2010, 7-year mortality was 31% for men and 47% for women after a first AMI.[9] In a more recent analysis of data from Sweden (2013–14), the 7-year survival was about 70% for patients with ST-elevation myocardial infarction (STEMI) and 60% for those with NSTEMI.[7,8] Accordingly, in a cohort of AMI patients hospitalized in Australia and New Zealand from 2009 to 2015, the survival rate was 62% at 7 years.[21] An increased use of efficient secondary preventive strategies, high levels of access to timely reperfusion and changes in lifestyle are probably responsible for the improved survival rates observed in recent decades. Our data are in accordance with the recent literature: the crude 8-year survival rate was ∼64% in the overall population, reaching 75% in revascularized patients and 85% in those revascularized within 48 h from hospital admission. On the other hand, in elderly patients, long-term survival was approximately 50% in revascularized and 20% in non-revascularized AMI survivors, regardless of gender. In this regard, our data solicits the planning of educational campaigns and guidelines' adherence programmes focused on the acute management of elderly patients with AMI. Indeed, dedicated randomized clinical trials[22-24] and observational nationwide studies[25-27] documented a clear benefit of myocardial revascularization even in older and frail AMI patients. Based upon this evidence, the recent European guidelines on AMI recommend that elderly patients apply the same interventional strategies used for younger ones, considering on an individual case basis ischaemic and bleeding risks, estimated life expectancy, quality of life, patient values, and preferences.[28] Therefore, in daily practice, improving post-AMI care for older patients should require a multidisciplinary approach, carefully balancing the risks and benefits of secondary prevention strategies.

Limitations

There are several limitations of using an administrative health claims database. One is that the lack of specific clinical information may have affected the accuracy of the diagnosis and risk stratification of AMI. In addition, we cannot clearly classify from ICD-9 CM codes the type and severity of AMI. Another limitation is the deficiencies in the ICD-9 CM code descriptions that provide comprehensive data on in-hospital complications. Furthermore, we cannot determine the extent to which misclassification and coding errors may be present.

Conclusions

In the present contemporary, nationwide cohort of first AMI survivors, those who underwent myocardial revascularization within 1 month of the index event presented an adjusted 39% relative risk reduction in all-cause mortality and 17% in MACCE at 8-year follow-up compared to those not revascularized. These data further confirm the key role of appropriate, timely, and effective myocardial revascularization in the contemporary management of AMI, particularly in older patients.

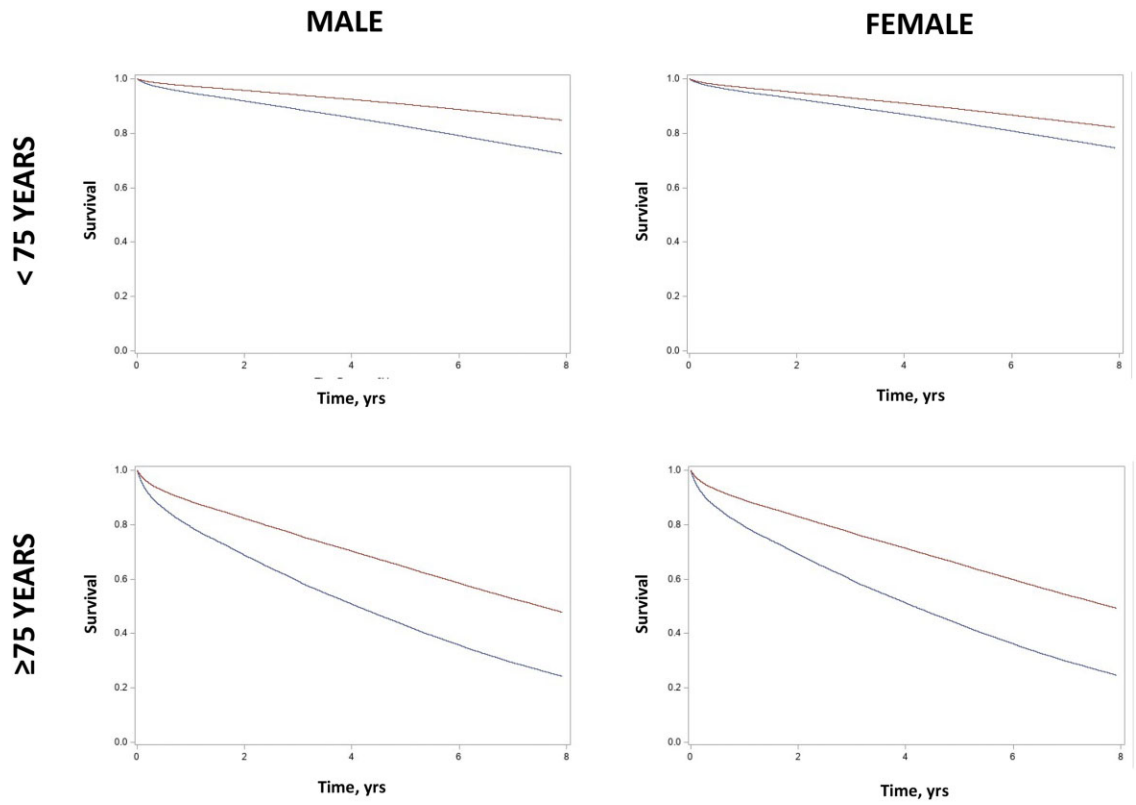

Figure 3 Adjusted survival curves for 8-year all-cause death in men, women, patients ≥ or <75 years old revascularized (red line) and not revascularized (blue line).

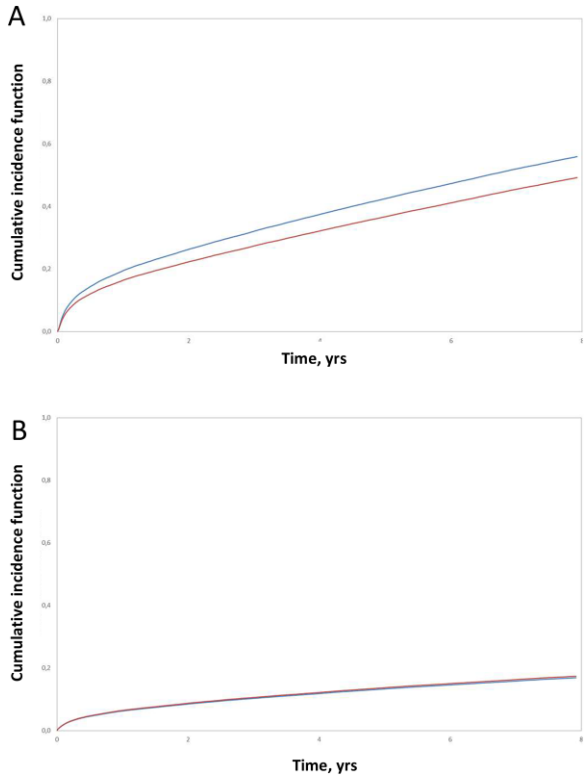

Figure 4 Cumulative incidence function of major cardio-cerebrovascular events (*A*) and heart failure (*B*) in patients revascularized (red line) and not revascularized (blue line) at 8-year follow-up.

Table 4 Adjusted hazard ratios of revascularized vs. not revascularized patients for 8-year major cardio-cerebrovascular events and its components

	HR	*P* value
MACCE	0.83	<0.0001
Death	0.61	<0.0001
Stroke	1.05	0.2388
AMI	0.93	0.0056
Re-PCI	2.40	<0.0001
Re-CABG	3.67	<0.0001

Supplementary material

Supplementary material is available at *European Heart Journal Supplements* online.

Conflict of interest: none declared.

Data availability

The data underlying this article were provided by AGENAS/ISS with permission. Data will be shared on request to the corresponding author with the permission of AGENAS/ISS.

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