

# High thrombotic risk increases adverse clinical events up to 5 years after acute myocardial infarction. A nationwide retrospective cohort study

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## Abstract

The risk of recurrent events among survivors of acute myocardial infarction (AMI) is understudied. The aim of this analysis was to investigate the role of residual high thrombotic risk (HTR) as a predictor of recurrent in-hospital events after AMI. This retrospective cohort study included 186,646 patients admitted with AMI from 2009 to 2010 in all Italian hospitals who were alive 30 days after the index event. HTR was defined as at least one of the following in the 5 years preceding AMI: previous myocardial infarction, ischemic stroke/other vascular disease, type 2 diabetes mellitus, renal failure. Risk adjustment was performed in all multivariate survival analyses. Rates of major cardiac and cerebrovascular events (MACCE) within the following 5 years were calculated in both patients without fatal readmissions at 30 days and in those free from in-hospital MACCE at 1 year from the index hos-

pitalization. The overall 5-year risk of MACCE was higher in patients with HTR than in those without HTR, in both survivors at 30 days [hazard ratio (HR), 1.49; 95% confidence interval (CI), 1.45-1.52;  $p < 0.0001$ ] and in those free from MACCE at 1 year (HR, 1.46; 95% CI, 1.41-1.51;  $p < 0.0001$ ). The risk of recurrent MACCE increased in the first 18 months after AMI (HR, 1.49) and then remained stable over 5 years. The risk of MACCE after an AMI endures over 5 years in patients with HTR. This is also true for patients who did not have any new cardiovascular event in the first year after an AMI. All patients with HTR should be identified and addressed to intensive preventive care strategies.

## Introduction

Despite the improvement in management of acute myocardial infarction (AMI), long-term risk of fatal and non-fatal cardiovascular events is still increasing over time [1-11]. Accordingly, several studies investigated the long-term effect of different secondary prevention strategies on prognosis of post-myocardial infarction (MI) patients [12-15]. However, the time course of residual ischemic risk remains unclear, particularly for patients who did not have any new cardiovascular event during the first year after AMI and then could apparently be considered not at high risk. Aim of this study is to investigate the prognostic significance of residual high thrombotic risk (HTR) features in a large population surviving AMI in order to identify patients who could potentially benefit from more intensive secondary prevention care strategies [1].

## Patients and Methods

### Study design

This is a retrospective cohort study based on data from the Italian National Registry of Hospital Discharge Records (ItHDR), the administrative database including all Italian hospital admissions and discharges. Given the retrospective nature of the study and the use of anonymized patient data, ethical approval was not required.

### Study population

The ItHDR, including all records over two years, from January 1<sup>st</sup> 2009 to December 31<sup>st</sup> 2010, was used to identify the study population. ItHDR from January 1<sup>st</sup> 2004 to December 31<sup>st</sup> 2008 and

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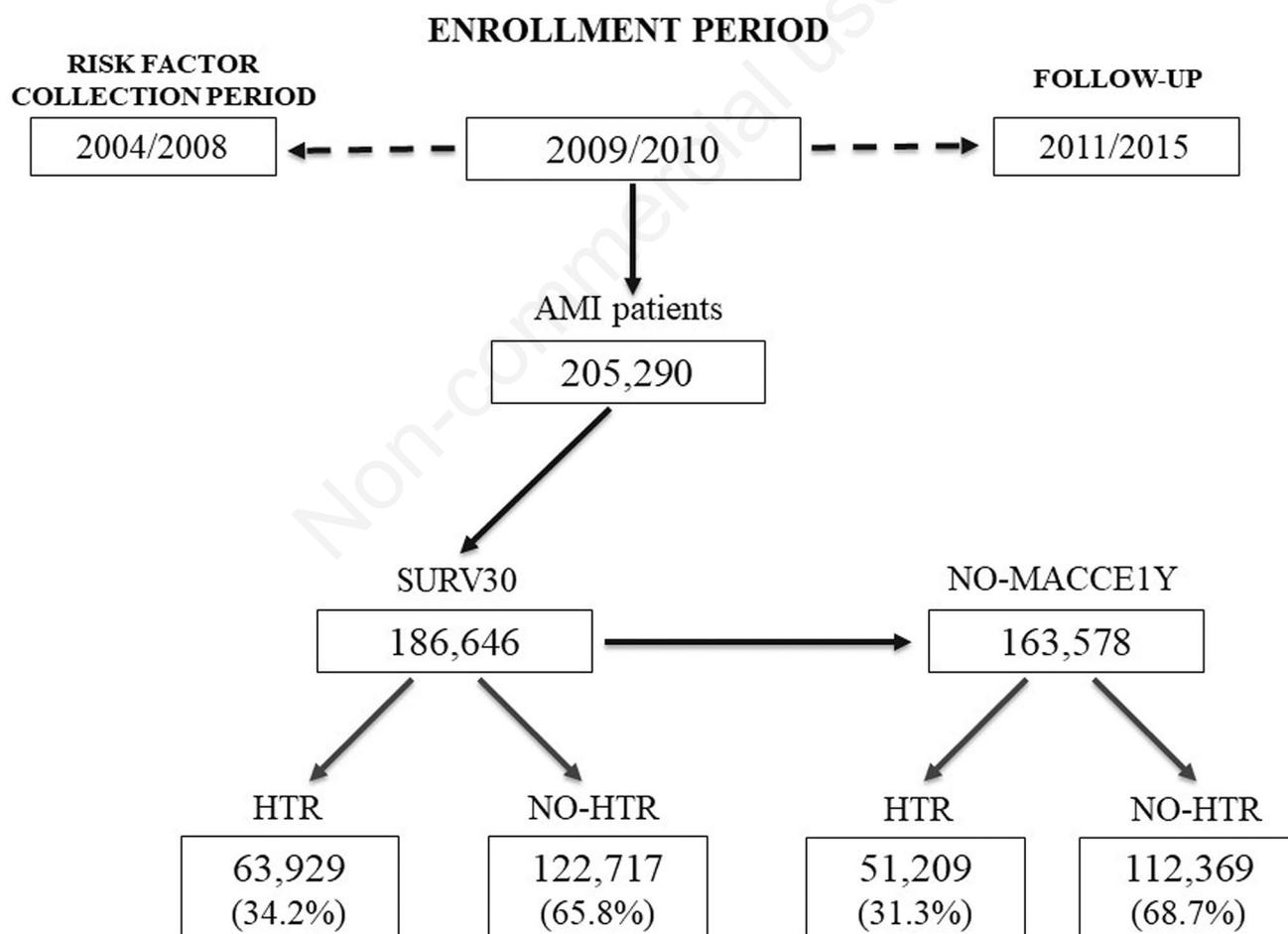
ItHDR from January 1<sup>st</sup> 2011 to December 31<sup>st</sup> 2015 was then used to detect previous and subsequent hospitalizations for the study population (Hospital Discharge Records database -Italian Ministry of Health). All hospital discharge records of patients aged 18-100 years, resident in Italy, and reporting a primary diagnosis of AMI [International Classification of Disease, 9<sup>th</sup> Revision, Clinical Modification (ICD 9 CM) 410] or a secondary diagnosis of AMI with any concomitant 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). Information on patient age, gender, risk factors, and comorbidities was also retrieved. ICD codes used to define outcomes and comorbidities have been reported in Table S1.

Patients discharged within 48 h from admission and those with a previous AMI admission within 30 days from the index admission were excluded to minimize the inclusion of false diagnosis of AMI and multiple admissions due to the same event [16,17]. For the purpose of this study, only patients without fatal in-hospital events 30 days after the index event entered into the current analysis (SURV30). Moreover, all patients free from in-hospital major adverse cardiac and cerebrovascular events (MACCE) resulting in

hospitalization within the first 1 year from the index AMI, which is currently considered the period of greatest exposure to risk of recurrences, were also analyzed (NO-MACCE1Y). According to diagnostic criteria used in previous epidemiological [11] and clinical studies [12,13] patients were classified as having high thrombotic risk (HTR) on the basis of the presence of at least one of the following characteristics recorded either in the index admission or in the previous 5-year hospitalizations: previous AMI, previous ischemic stroke (IS), other vascular disease, type 2 diabetes mellitus, or renal failure (National Kidney Foundation stage  $\geq 3$ ). Following the same methodology, information on patient age, gender, risk factors, and comorbidities was also retrieved. Figure 1 shows the flowchart of the study.

## Outcomes

MACCE (*i.e.*, death from any cause, AMI or IS) and recurrent AMI within 5 years were considered as the main adverse outcomes. They were evaluated both in SURV30 and in NO-MACCE1Y.



**Figure 1.** Flowchart of the study. The study population was identified from the Italian National Registry of Hospital Discharge Records (ItHDR) including all hospital discharge records of patients aged 18-100 years, resident in Italy, and reporting a primary diagnosis of AMI, over two years, from January 1<sup>st</sup> 2009 to December 31<sup>st</sup> 2010. The previous (2004-2008) and following (2011-2015) four years were used to detect previous and subsequent hospitalizations (Hospital Discharge Records database).

## Statistical analysis

All the statistical analyses were performed separately for SURV30 and NO-MACCE1Y. Prevalence of risk factors and comorbidities were presented as counts and percentages; age was expressed as the mean  $\pm$  SD. Time to event distribution was analyzed according to the event type (MACCE or recurrent AMI). A Cox regression model was used for analysis of time to MACCE. Proportional hazards and time-dependent effects were checked using Schoenfeld residuals and the Kolmogorov-Smirnov test. Fine and Gray models were used for competing risk analysis of time to recurrent AMI, with death as the competing risk. Selection of variables was performed by stepwise multiple regression with the Akaike information criterion for selection. Cumulative incidence function (CIF) of MACCE and recurrent AMI was plotted separately for patients with HTR and those without HTR. The effect of covariates on the CIF was also evaluated using a proportional hazard model where the effect of HTR was allowed for time-varying over the 5 years of follow-up; the effect of all the other covariates was considered constant. Two-sided statistics were performed with a significance level of 0.05. SAS version 9.2 and R 3.0.3 software [18] was used for all analyses.

## Results

Of the 205,290 patients admitted for AMI to an Italian hospital in 2009-2010, 186,646 patients (90.9%) did not have fatal in-hos-

pital events 30 days after the event (SURV30); furthermore, 163,578 out of 186,646 (87.6%) were free from in-hospital MACCE at 1 year (NO-MACCE1Y). Of the SURV30 group, 63,929 (34.2%) were identified as having HTR; of the NO-MACCE1Y group, the HTR condition was detected in 51,209 (31.3%) patients (Figure 1).

The general characteristics as well as the prevalence and distribution of risk factors and main comorbidities in the SURV30 and NO-MACCE1Y groups are shown in Table 1. More than half of patients underwent percutaneous coronary intervention (PCI) at the index hospitalization (53.6% of the SURV30 group and 56% of the NO-MACCE1Y group); previous PCI was detected in 11% of patients in both groups. The proportion of patients with previous stable coronary heart disease was about 20% in both groups (20.9% and 19%, respectively).

A previous AMI was the most prevalent ischemic risk factor in both SURV30 and in NO-MACCE1Y (17.3% and 15.8%, respectively). The other most prevalent risk factors were type 2 diabetes mellitus (15.3% and 13.6% in SURV30 and NO-MACCE1Y, respectively), renal failure (10.8% and 9.2%, respectively), other vascular disease (6.89% and 6.0%, respectively) and IS (2.8% and 2.4%, respectively) (Table 1).

Prevalence of clinical characteristics in patients with and without HTR has been reported in Table S2 and Figure S1.

### Long-term incidence of MACCE

The overall 5-year cumulative incidence of MACCE after AMI was higher in patients with HTR compared with those without

**Table 1. Prevalence of baseline characteristics and comorbidities in survivors at 30 days (SURV30) and patients free from MACCE at 1 year (NO-MACCE1Y) from the index hospitalization for acute myocardial infarction (2009-2010).**

	SURV30 (n=186,646)		NO-MACCE1Y (n=163,578)	
Age (years), mean and SD	69.7	13.3	68.8	13.3
Gender (F)	64,903	34.8	55,462	33.9
Arterial hypertension	50,756	27.2	41,011	25.1
Dyslipidemia	16,469	8.8	13,761	8.4
Obesity	7095	3.8	6149	3.8
PCI at the index admission	100,052	53.6	91,602	56.0
Stable coronary heart disease	38,936	20.9	31,134	19.0
Heart failure	40,568	21.7	31,301	19.1
Cardiomyopathies	6437	3.4	5011	3.1
Arrhythmias	19,379	10.4	15,112	9.2
Rheumatic heart disease	4316	2.3	3330	2.0
Cardiac complications	5471	2.9	4212	2.6
Peripheral vascular disease	10,061	5.4	7984	4.9
Non-ischemic stroke or transient ischemic attack	16,390	8.8	12,867	7.9
Anemia	11,973	6.4	8895	5.4
Chronic obstructive pulmonary disease	14,630	7.8	11,380	7.0
Inflammatory chronic diseases	5192	2.8	4400	2.7
Tumors	13,607	7.3	10,952	6.7
Previous PCI	21,929	11.7	18,406	11.3
Previous coronary artery bypass graft	8626	4.6	6829	4.2
Other previous cardiac surgery	2706	1.4	2112	1.3
Previous vascular surgery	4263	2.3	3294	2.0
Previous cerebral revascularization	2171	1.2	1651	1.0

MACCE, major cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; values are number and percentage except where indicated otherwise.

HTR in both SURV30 and NO-MACCE1Y (Figure 2a). The hazard ratios (HR) of 5-year MACCE for HTR and for the single risk factors constituting it, in both SURV30 and NO-MACCE1Y, are shown in Table 2. After adjusting for the general characteristics, comorbidities and cardiac procedures reported in Table 1, multivariate analyses showed an increased risk for MACCE within 5 years of 49% in the HTR SURV30 group and of 46% in the HTR NO-MACCE1Y group, compared with the patients without HTR (NO-HTR). The 5-year incidence rates (IR) of in-hospital MACCE in the HTR SURV30 and HTR NO-MACCE1Y groups were 28.5% and 16.7%, respectively, with an absolute difference of 11.8%. Patients treated with PCI at the index hospitalization showed less long-term MACCE than those treated conservatively in the SURV30 group [HR, 0.56; 95% confidence interval (CI), 0.55-0.57] and in the NO-MACCE1Y group (HR, 0.65; 95% CI, 0.63-0.66). In patients with HTR, however, the increase of in-hos-

pital MACCE did not change after adjusting for PCI at the index hospitalization. When considered separately, all the risk factors determining HTR emerged as significant independent predictors of MACCE in both the SURV30 and NO-MACCE1Y group (Table 3). Although the hazard-proportionality has been respected at 5-year follow-up analysis, the trend of hazard ratios for developing in-hospital MACCE in SURV30 with HTR vs SURV30 without HTR showed a time-effect in the first 18 months, with a progressive increase of the excess risk of HTR from HR = 1.15 to HR = 1.50 and a subsequent stabilization (Figure 3a).

### Long-term incidence of AMI

The HR of 5-year recurrent AMI for HTR and for the single risk factors in both the SURV30 and NO-MACCE1Y group is shown in Table 2. After adjusting for the general characteristics and comorbidities reported in Table 1, multivariate analyses

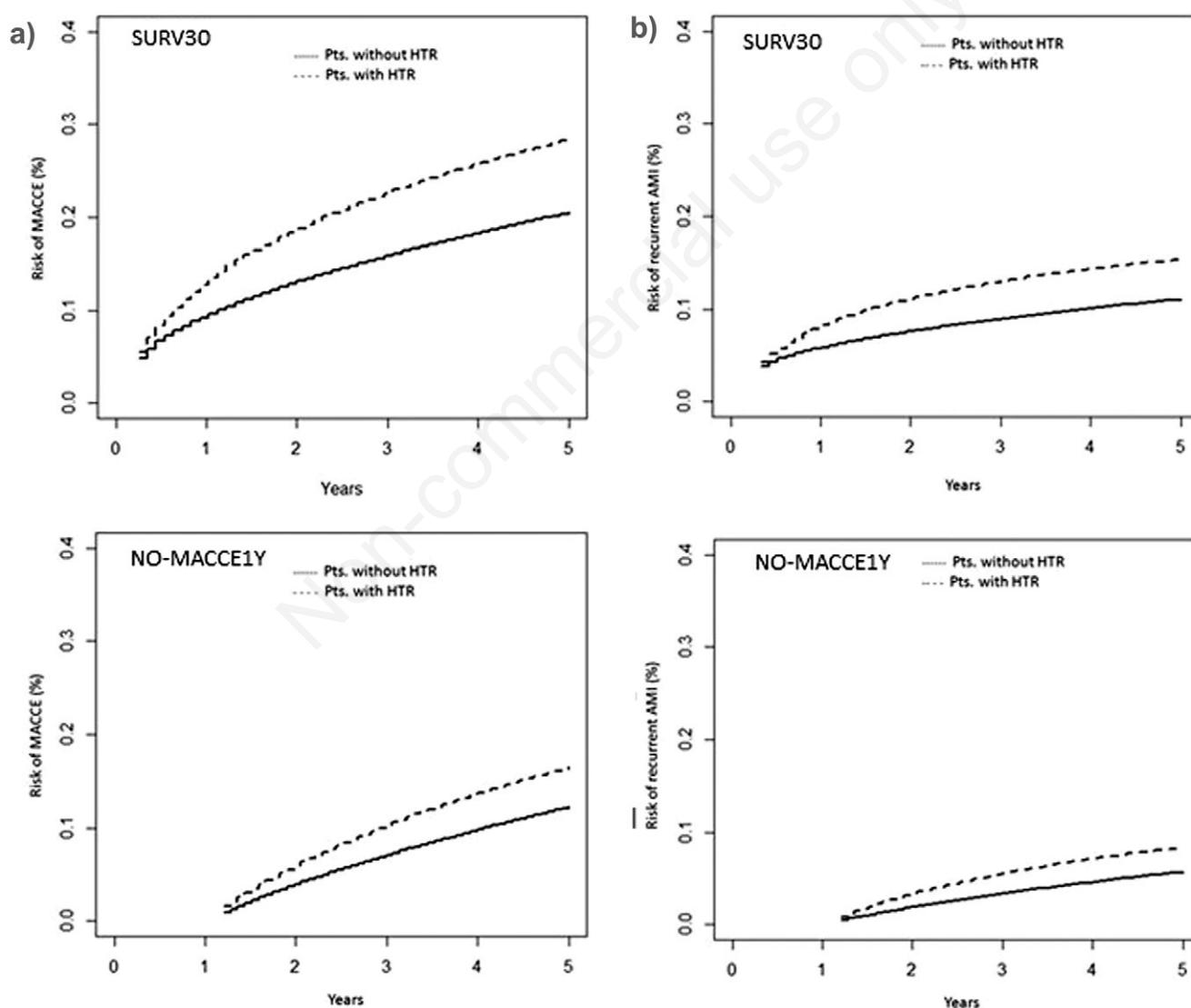


Figure 2. a) Cumulative incidence of in-hospital MACCE after AMI in patients with high thrombotic risk (HTR) (dotted line) and without high thrombotic risk (solid line) in survivors at 30 days (SURV30) and patients free from MACCE at 1 year (NO-MACCE1Y) from the index hospitalization for AMI (2009-2010). b) Cumulative incidence of recurrent in-hospital AMI after the index hospitalization for MI 2009-2010) in HTR (dotted line) and NO-HTR patients (solid line), in both SURV30 and in NO-MACCE1Y. Multivariate analysis.

showed an increased risk of 5-year AMI of 46% in the HTR SURV30 group (IR, 15.7%) and of 55% in the HTR NO-MACCE1Y group (IR, 8.2%), compared with the respective NO-HTR patients.

The cumulative incidence of recurrent AMI was significantly higher in HTR than in NO-HTR patients, both in the SURV30 and NO-MACCE1Y group (Figure 2b). The 5-years trend of HR for developing a recurrent MI in HTR SURV30 versus NO-HTR SURV30 showed a similar time effect as that observed for in-hospital MACCE, with a progressive increase in excess risk in the first 18 months after the index hospitalization and a subsequent stabilization until the fifth year of follow-up. Anyway, also for this analysis, the hazard-proportionality at 5-year follow-up was respected (Figure 3b).

## Discussion

The main finding of this study is that, after an AMI, the long-term risk of a new adverse clinical event is almost 50% higher in patients with HTR. Moreover, in contrast to what has been

believed so far, the excess risk of in-hospital MACCE in HTR *versus* NO-HTR patients remains high up to 5 years after the index hospitalization. Although the proportional hazard analysis considered the 5-year follow-up, the trend for the HR showed a time effect with a progressive increase in the HR from time zero to 18 months, and then the curve plateaued, indicating an enduring risk of recurrent MACCE or AMI in the long term.

The present study confirms and extends a previous observation from the Swedish registry in which advanced age, stroke, diabetes, heart failure, and the lack of revascularization during index AMI were each independently associated with a higher risk of ischemic events and death [11]. The cumulative risk of recurrent cardiovascular events in that study was high in the first year after the index hospitalization and remained high in the following 36 months. In our analysis we adjusted for all the confounding factors including heart failure, a strong predictor of recurrent ischemic events but also a major predictor of mortality. This allowed us to focus on the impact of HTR alone in a contemporary population in whom the use of PCI during the index admission was even higher than in the Swedish Register (53.6% *versus* 42.9%). In our study, patients treated with PCI at the index hospitalization showed less long-term in-hospital MACCE than those treated conservatively. However, in

**Table 2. Five-year MACCE and 5-year AMI adjusted hazard ratios for the high thrombotic risk and the single risk factors constituting it, in survivors at 30 days (SURV30) and patients free from MACCE at 1 year (NO-MACCE1Y) from the index hospitalization for AMI.**

5-year MACCE	SURV30		NO-MACCE1Y	
	HR	CI	HR	CI
High thrombotic risk	1.49	1.45–1.52	1.46	1.41–1.51
Type 2 diabetes	1.37	1.34–1.40	1.24	1.20–1.29
Previous AMI	1.24	1.21–1.27	1.21	1.17–1.25
Ischemic stroke	1.26	1.21–1.32	1.12	1.05–1.20
Other vascular disease	1.20	1.17–1.24	1.18	1.13–1.23
Renal failure	1.37	1.34–1.41	1.31	1.27–1.36
5-year AMI	SURV30		NO-MACCE1Y	
	HR	CI	HR	CI
High thrombotic risk	1.46	1.41–1.51	1.55	1.47–1.63
Type 2 diabetes	1.29	1.24–1.34	1.29	1.22–1.37
Previous AMI	1.39	1.34–1.44	1.45	1.38–1.53
Ischemic stroke	1.03	0.96–1.10	1.00	0.89–1.11
Other vascular disease	1.14	1.09–1.19	1.14	1.06–1.22
Renal failure	1.19	1.15–1.23	1.24	1.17–1.31

MACCE, major cardiac and cerebrovascular events (hazard ratio adjusted for general characteristics and comorbidities reported in Table 1, selected by a stepwise multiple Cox regression analysis). AMI, acute myocardial infarction (hazard ratio adjusted for general characteristics and comorbidities reported in Table 1, selected by a stepwise Fine and Gray multiple regression analysis; this methodology has been used to consider death as a competing risk).

**Table 3. Prevalence of single risk factors constituting high thrombotic risk in survivors at 30 days (SURV30) and patients free from MACCE at 1 year (NO-MACCE1Y) from the index hospitalization for AMI (2009-2010).**

	SURV30 (n=186,646)		NO-MACCE1Y (n=163,578)	
	n	%	n	%
Type 2 diabetes	28,585	15.32	22,245	13.6
Previous AMI	32,287	17.30	25,865	15.8
Ischemic stroke	5,219	2.80	3,895	2.4
Other vascular disease	12,869	6.89	9,749	6.0
Renal failure	20,185	10.81	14,980	9.2

MACCE, major cardiac and cerebrovascular events; AMI, acute myocardial infarction.

patients with HTR, the increase in MACCE did not change even after adjusting for PCI at the index hospitalization; in other words, the effect of HTR on prognosis was not mitigated by PCI performed at the index admission.

In the last 10 years, data from several observational studies and registries have shown a paradox in post-AMI morbidity and mortality trends, with in-hospital mortality continuing to decrease [19] and an increase in post-discharge mortality [1,20-22]. The aging population, the high prevalence of heart failure [23-27], as well as the lack of long-term adherence to evidence-based therapies [3,28,29], particularly the use of statins and antiplatelet agents [30,31], as well as the lack of access to secondary prevention programs [32] and cardiac rehabilitation facilities [33] have been advocated to explain this phenomenon. However, the role of ischemic risk factors as independent predictors of recurrent MACCE after discharge from an AMI is still debated. In addition,

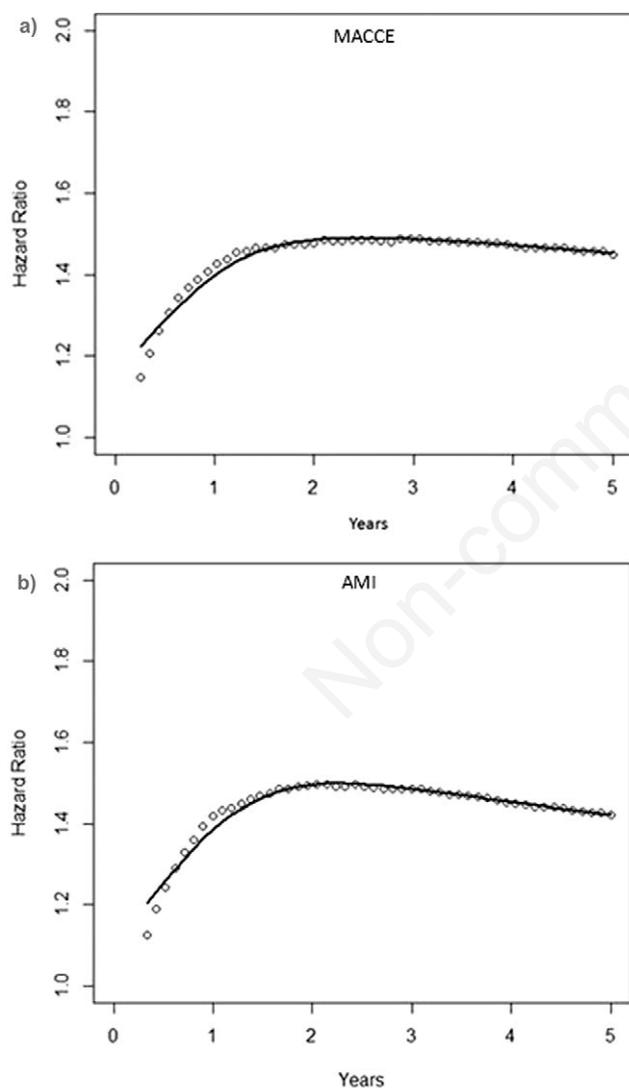
it is unclear if patients with HTR who have not experienced an event in the first year after AMI still have a higher risk of MACCE as compared to patients not at HTR [2].

Our data confirm the increase in long-term risk of MACCE also in HTR patients free from event in the first year after AMI. Moreover, our study suggests that the time period for which the risk appears to be increased in HTR subgroups is even longer than that reported in current clinical studies [12,13,34,35]. The excess risk due to HTR surprisingly increases up to 18 months then remains constant over time up to 5 years. One possible explanation of this finding is that adherence to therapy, including DAPT, decreases during the first year after AMI as suggested by current studies and registries [28-30,36-38]. Thus, the partial attenuation of the ischemic risk from pharmacological therapies is lost and it increases over time up to 18 months more markedly in patients with HTR. Hence, considering that the residual risk for recurrent ischemic events and re-hospitalization in patients after AMI can remain high despite optimal medical therapy, novel and/or more intense pharmacological interventions should be used over a longer period of time.

These results strongly suggest that careful selection, stratification, and long-term pharmacological management are to be warranted to this subgroup of patients, with relevant implications for organization of secondary prevention services [32,33].

### Study limitations

The present study is based on data from hospital discharge records. As reported in a previous work [1], although some reports have highlighted that ICD-9-CM coding adequately identifies definite or possible AMI according to the American Heart Association criteria the most common limitation of administrative data is the possible lack of strength as a basis for clinical research. Some difficulties in distinguishing between STEMI and NSTEMI must be also considered. Patients with previous AMI or ischemic stroke occurred more than 5 years before cannot be identified, and this may have led to an under-recognizing of some patients at risk. Some conditions as renal failure as defined as National Kidney Foundation stage  $\geq 3$  could be underreported. Moreover, the ItHDR cannot be systematically linked to comprehensive mortality registers, thus both fatal and non-fatal events refer only to those occurred during hospitalizations. As patients discharged after AMI could also have died out of the hospital, this hindrance might be considered a limitation of the study. However, there is evidence of consistency between the reported estimates of out-of-hospital mortality in patients discharged after hospitalization due to AMI [1] and our results. Finally, we do not have information on the real use of the recommended therapies, including ACE inhibitors, aspirin, clopidogrel,  $\beta$ -blockers, and statins at discharge and during follow-up. Because decrease in adherence to therapy is frequently reported even early after ACS in European and Italian registries [28,29-33,38], we can assume that undertreatment in the real world can amplify the excess risk particularly in patients with HTR.



**Figure 3.** Five-year trend of adjusted hazard ratios of high thrombotic risk (HTR) vs NO-HTR patients for in-hospital developed MACCE (a) and AMI (b) in survivors at 30 days (SURV30). The empty dots represent the hazard ratios point estimates and the solid line their interpolation.

### Conclusions

After an AMI, patients with HTR showed an overall higher risk of MACCE and recurrent AMI than those without HTR. This excess risk remains stable up to 5 years. Patients with HTR should be identified and treated with intensive pharmacological therapies and non-pharmacological strategies in order to improve their long-term prognosis.

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