Abstract

Background: Evidence is lacking on long-term outcomes in unselected patients surviving the first year following myocardial infarction (MI).

Methods and results: The TIGRIS (long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease in post-myocardial infarction patients) prospective registry enrolled 9176 eligible patients aged ≥50 years, 1–3 years post-MI, from 25 countries. All had ≥1 risk factor: age ≥65 years, diabetes mellitus, second prior MI, multivessel coronary artery disease, chronic kidney disease (CKD). Primary outcome was a composite of MI, unstable angina with urgent revascularization, stroke, or all-cause death at 2-year follow-up. Bleeding requiring hospitalization was also recorded. 9027 patients (98.4%) provided follow-up data: the primary outcome occurred in 621 (7.0%), all-cause mortality in 295 (3.3%), and bleeding in 109 (1.2%) patients. Events accrued linearly over time. In multivariable analyses, qualifying risk factors were associated with increased risk of primary outcome (incidence rate ratio [RR] per 100 patient-years [95% confidence interval]): CKD 2.06 (1.66, 2.55), second prior MI 1.71 (1.38, 2.10), diabetes mellitus 1.63 (1.39, 1.92), age ≥65 years, 1.53 (1.28, 1.83), and multivessel disease 1.24 (1.05, 1.48). Risk of bleeding events was greater in older patients (vs <65 years) 65–74 years, 2.68 (1.53, 4.70), ≥75 years 4.62 (2.57, 8.28), and those with CKD 1.99 (1.18, 3.35).

Conclusion: In stable patients recruited 1–3 years post-MI, recurrent cardiovascular and bleeding events accrued linearly over 2 years. Factors independently predictive of ischemic and bleeding events were identified, providing a context for deciding on treatment options.

Two-year outcomes among stable high-risk patients following acute MI. Insights from a global registry in 25 countries

Short header: Two-year outcomes in post-MI patients

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[1]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Conflicts of interest

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1. Introduction

Recent improvements in the medical management of myocardial infarction (MI) have provided significant reduction in mortality [1-3], and a growing population of MI survivors. These patients remain at high risk of future cardiovascular (CV) events [1, 2, 4-7] with risk of recurrent events varying widely [8]. Clinical features including advanced age, diabetes mellitus, chronic kidney disease (CKD), prior MI, and documented history of multi-vessel coronary artery disease (CAD) are all associated with increased risk of recurrent CV events [9-12].

Recent trials have shown that, in a range of populations with stable vascular disease, including those post-MI, antithrombotic treatment combinations, such as prolonged dual antiplatelet therapy (DAPT) or combined antiplatelet and anticoagulant therapies, can reduce ischemic events but increase bleeding [13, 14]. Translation into clinical practice requires an understanding of absolute ischemic and bleeding event rates in unselected patients. However, incidence rates of recurrent ischemic and bleeding events in stable post-MI patients vary substantially across studies, reflecting differences in methods of data acquisition and populations studied [8, 13, 15].

Management of these patients is further complicated by patients at increased risk of ischemic events very often also being at increased risk of bleeding [16]. One challenge of long-term antithrombotic therapy in stable patients is the identification of those in whom escalated antithrombotic therapy offers the most benefit without undue risk of bleeding [17].

The TIGRIS (long-Term rIsk, clinical manaGement and healthcare Resource utilization of stable coronary artery dISease in post-myocardial infarction patients) global registry was undertaken to provide contemporary insights into ischemic and bleeding event rates in an

international cohort of stable high-risk post-MI patients. Here, the primary outcomes from this study are reported.

2. Methods

2.1. Objectives

Details of the TIGRIS study have been reported elsewhere [18, 19]. The primary objective was to describe the incidence rates of first occurrence of the primary composite outcome of MI, unstable angina with urgent revascularization, stroke, or death from any cause during the 2-year follow-up period in a patient population with a history of MI 1–3 years ago and high risk of further atherothrombotic events. The incidence rates of cardiovascular death, non-cardiovascular death, and bleeding events requiring hospitalization during the 2-year follow-up were secondary objectives.

2.2. Patients

Patients had stable CAD, were aged 50 years or older with a documented history of MI occurring 1–3 years prior to enrollment, and had ≥1 of the following risk factors: (a) age ≥65 years; (b) diabetes mellitus requiring medication; (c) documented history of a second prior presumed spontaneous MI (>1 year prior to enrollment); (d) angiographic evidence of multivessel CAD; and/or (e) chronic non-end-stage kidney disease (CKD) (creatinine clearance [by Cockcroft Gault equation] 15 mL/min to <60 mL/min).

Patients were excluded if any of the following were present: (a) any condition/circumstance that could significantly limit the complete follow-up of the patient; (b) serious/severe co-morbidities that could limit life expectancy (<1 year); (c) ongoing participation in a blinded randomized clinical trial; and/or (d) patients receiving treatment of ticagrelor beyond 12 months post-MI (which represented off-label use of ticagrelor at the time of study initiation).

2.3. Follow-up

Data entry used a standardized electronic case report form. Baseline data included relevant medical history, demographics, details regarding the index MI before enrollment, variables from routine physical examination, and laboratory testing where available.

Patients were contacted every 6 months for a follow-up period of 2 years, either by phone call or personal visit to the hospital. All outcome events were confirmed by the treating physician or hospital, including determination of final diagnosis, primary cause of hospitalization, duration of hospital stay, procedures, and interventions. If a death occurred, efforts were made to identify the cause (CV-related or non-CV) through the death certificate where available, or through relatives, physicians, or hospitals.

2.4. Ethics

The TIGRIS study was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and applicable legislation on non-intervention studies. All patients provided written informed consent. The study protocol and informed consent was reviewed and approved by the corresponding health authorities and ethics boards for all participating study sites. This includes China HGR approval of inclusion of 750 Chinese patients. The study was registered at Clinical Trials.gov (clinical trial identifier NCT01866904).

2.5. Statistical analysis

Consistent with an observational study without predefined hypothesis testing, no formal power calculation was undertaken; instead, sample size was based on precision of the primary endpoint. The sample size was initially estimated at 10,170 patients but delays in ethical approval in some countries meant 9225 patients were recruited. Furthermore,

reallocation of resources to ensure complete follow-up in all countries meant the minimum follow-up duration was reduced from 3 to 2 years.

Incidence rates per 100 patient-years for the primary composite, all-cause mortality, and bleeding requiring hospital admission were calculated for 2-year follow-up. Kaplan–Meier (KM) plots of cumulative incidence from time of enrollment for the primary endpoint and each of the components, as well as bleeding, were developed. A left-truncated KM estimate [20, 21] from time of index MI was constructed for incident events in the primary composite, total mortality, and bleeding events. Patients entered the left-truncated plot from their time of enrollment (1–3 years post-MI) and were right-censored 2 years later.

The association of qualifying risk factors (age ≥65, diabetes mellitus requiring medication, second prior MI, multi-vessel CAD, and CKD), sex, index MI characteristics and region with the incidence of the primary composite, total mortality and bleeding events at 2-year follow-up were explored and are described as incidence rates per 100 patient-years. These variables were selected as they were known from previous studies to be associated with increased risk of events. A sensitivity analysis was also performed for association of the same variables with the primary composite endpoint but excluding unstable angina with urgent revascularization, the most subjective component of the composite endpoint, which therefore may be difficult to classify correctly in a real-world study. Since KM plots showed a linear accumulation of events over time, we used Poisson regression to estimate incidence rate and corresponding 95% CIs for each risk factor for the primary outcome, total mortality, and bleeding events (time to first event, in each case). Multivariate Poisson regression was used to calculate rates and rate ratios adjusted for the patient characteristics described above. Age was considered a

continuous variable in a sensitivity analysis. Statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA).

3. Results

3.1. Patient population

Of 9225 patients enrolled in TIGRIS from June 2013 to November 2014, 9176 were subsequently confirmed as eligible at baseline, and 9027 (98.4%) of these had follow-up data for the present analysis. Patients were enrolled in 25 countries and 334 sites from the following regions: Europe, North America, Latin America, and Asia. A full description of the enrolling countries and sites has already been published [18]. Of the 369 recruiting physicians, 96% were cardiologists.

Baseline clinical characteristics have been described previously and are presented in the Supplementary material online (Table SI) [19]. Patients were enrolled a median 1.8 years post-MI (52% with ST-segment elevation MI [STEMI]), median age 67 years (63% ≥65 years), 24% women, 66% Caucasian, 31% had diabetes mellitus requiring medication, 10% second prior MI >1 year prior, 66% multivessel disease, and 8% CKD. Management at the time of the index MI included percutaneous coronary intervention (PCI; 80.7%), coronary artery bypass surgery (CABG; 7.4%), or medical treatment only (11.9%). At enrollment, 98% of the 9027 patients were taking an antithrombotic drug, most commonly aspirin (90%), with 26% on DAPT. When compared by timing of enrollment from index MI (1–2 years vs 2–3 years), patients were similar; second prior MI and region did show statistically significant but clinically unimportant differences (Supplementary material online Table SII).

Prior to the first follow-up visit, 198 (2.1%) of the 9225 enrolled patients either withdrew consent or were not confirmed eligible and so did not contribute information for the primary composite outcome. The remaining 9027 patients are the subject of the present

report. During the 2-year follow-up period, a further 292 (3.2%) patients withdrew or were lost to follow-up.

3.2. Ischemic and bleeding events

The primary outcome occurred in 621 patients (7.0%) at 2 years, including 295 deaths (3.3%), comprising 178 CV and 117 non-CV deaths (2.0% and 1.3%, respectively) (Table 1). Rates of the primary composite outcome by time since enrollment (6-month intervals) and time since index myocardial infarction (2-year intervals) are shown in Supplementary material online Table SIII. There were 119 bleeding events requiring hospitalization, reported in 109 patients (1.2%) (Table 1). Approximately one-quarter of these (23.5%, 28 bleeding events) were associated with hemodynamic compromise. Over 40% of the total bleeding events (44.0%, 48 events) were gastrointestinal in origin (Supplementary material online Table SIV). However, no information on hemodynamic compromise was reported for 79 of the bleeding events.

Events accrued linearly throughout the follow-up period for the primary outcome, all its components, and bleeding events (Fig. 1, and Supplementary material online Fig. SI). Left-truncated Kaplan–Meier estimates indicated that this linear accumulation of events was apparent in patients enrolled as early as 1 year following their index MI (Supplementary material online Fig. SII). This pattern was observed both when analyzed as time since index MI (over the 1–5 years post-MI, *p*-value testing for non-linearity=0.46), or in an analysis of time since enrollment (over 2 years of follow-up; *p*-value testing for non-linearity 0.63).

Unadjusted incidence rates per 100 patient-years for the primary outcome, total mortality, and bleeding events by patient characteristics are shown in Table 2 and Supplementary

material online (Table SV). Primary composite incidence rate varied by each qualifying risk factor: CKD 8.6 per 100 patient-years, second prior MI 6.7, diabetes mellitus requiring medication 5.0, age ≥65 years old, 4.1, and multivessel disease 3.7. STEMI index MI showed a lower unadjusted incidence rate (3.1) than non-ST-segment elevation MI (NSTEMI) (4.2), but not in the adjusted analysis.

Timing of enrollment from index MI (1–2 years vs 2–3 years) did not affect the incidence rate of the primary composite endpoint. However, patients who had not been revascularized at the time of their index MI showed a markedly higher event rate (6.8) compared with those who had undergone PCI (3.2) or CABG (3.0). Some regional variation was observed, with highest incidence rates in North America (4.6) and lowest in Asia and Australia combined (3.0). All-cause death varied within subgroups in a pattern consistent with the primary composite endpoint. The highest unadjusted mortality rate was seen in patients ≥75 years (3.4), patients with diabetes mellitus requiring medication, or a second prior MI (2.5), those with CKD (5.8), and patients who were medically managed (4.2). Incidence rates of bleeding requiring hospitalization were >1 per 100 person-years in patients ≥75 years, and those with CKD.

3.3. Predictors of risk

Figure 2 shows the results of multivariable (adjusted) analyses for the primary composite outcome, all-cause death, and bleeding requiring hospitalization, which simultaneously assessed the association of all these patient enrollment factors with outcome. Independent predictors of the primary outcome included older age, diabetes mellitus requiring medication, second prior MI, multivessel disease, CKD, and medical management of index MI. Similar findings were obtained following exclusion of unstable angina requiring revascularization from the composite endpoint (Supplementary material

online Fig. SIII). Risk factors independently associated with all-cause death included older age, diabetes mellitus requiring medication, and medical management of index MI. Multivessel disease had a similar risk ratio for all-cause mortality as the composite outcome but did not reach significance due to the smaller number of events. Second prior MI was not associated with increased all-cause death. The incidence rate ratio of bleeding events requiring hospitalization was significantly greater in patients aged 65–74 years compared to patients <65; and patients with CKD. For all outcomes, older age remained independently associated with outcomes when analyzed categorically, or continuously (footnote Fig. 2). After adjusting for variations in prevalence of high-risk characteristics, region was not predictive of composite ischemic events, total mortality, or bleeding events (Supplementary material online Table SVI).

The five eligibility criteria of high risk plus medical management of the index MI were identified as risk factors for the primary composite endpoint. Supplementary material online Fig. SII shows a stepwise risk increase according to the number of risk factors present in a patient. Only older age (>65, with further increase in risk for patients >75) and the presence of CKD were significantly associated with higher risk of bleeding requiring hospitalization. Supplementary material online Fig. SIV also shows how the number of risk factors for bleeding (from 0 to 3) is strongly related to the incidence of bleeding events.

4. Discussion

This contemporary study of over 9000 high-risk patients, 1–3 years post-MI, from 25 countries, followed for 2 years, describes the natural history of this condition with emphasis on subpopulations at high risk of subsequent events. In our overall population, the primary composite outcome occurred in 7.0% of patients and bleeding requiring hospitalization in 1.2%. Each qualifying risk factor was associated with greater risk of the primary composite endpoint, but only older age and CKD were independently associated with increased risk of bleeding.

Event rates in observational studies generally exceed those in randomized trials due to inclusion of higher risk patients [22]. However, compared with studies derived from data extracted from administrative datasets, prospective clinical registries that require specific eligibility criteria and patient informed consent may more closely resemble clinical trials [23, 24].

The TIGRIS cohort is likely to be an accurate reflection of the general population of post-MI patients for whom decisions regarding secondary preventative therapy would be entertained. Firstly, those enrolled were identified in a broad range of outpatient (mostly cardiology) practices in 25 countries; secondly, there were few exclusion criteria; and thirdly, no intervention was mandated, removing a disincentive for patients to participate.

There have been relatively few published international prospective registries documenting intermediate term outcomes in stable patients post-MI [8, 25]. The REACH (Reduction of Atherothrombosis for Continued Health) registry recruited outpatients with established or those at risk of vascular disease between 2003 and 2004 and included a significant portion of patients with coronary disease [8] Event rates in this coronary population at 1 year were substantially greater than ours (mortality in REACH 2.89% vs

1.7% in TIGRIS, stroke in REACH 1.38% vs 0.4% in TIGRIS), while recurrent MI rates were comparable (1.44% in REACH, 1.3% in TIGRIS). The true difference in outcomes is likely greater as REACH included lower risk cardiology patients without prior MI [26], and suggests important improvements in outcomes in these patients over the last decade.

This is reinforced by outcomes from the more recent Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease (CLARIFY) which followed over 33,000 outpatients enrolled between 2009 and 2010 [25]. Two-year event rates varied according to the presence of angina and/or ischemia, but were comparable to those observed in our study (mortality 2.62–3.52% in CLARIFY vs 3.3% in TIGRIS, MI 1.27–2.36% in CLARIFY vs 2.2% in TIGRIS, stroke 0.73–1.06% in CLARIFY vs 0.7% in TIGRIS). Although CLARIFY was not restricted to the post-MI population, the consistency of outcomes across the two registries further supports the robustness of our findings.

In the TIGRIS study, the incidence rates of the primary composite endpoint, each of its components and bleeding requiring hospitalization remained constant over the follow-up period. Similar findings have been reported by others [26, 27]. Our left-truncated KM curve illustrates that events occurred at a constant rate from 12 months post-MI, as also demonstrated in PEGASUS-TIMI 54. These consistent findings suggest that events occurring as early as 1-year post-MI may reflect the underlying atherothrombotic disease process, against a stable bleeding hazard, rather than being a residual manifestation of the original MI or its treatment.

We previously reported regional differences in the prevalence of qualifying risk factors in the TIGRIS population [19], and on follow-up found these differences were associated with variations in ischemic outcomes. Following adjustment for these, and other baseline

risk characteristics, statistically significant regional differences in risk of the primary composite outcome or total mortality were no longer evident.

TIGRIS enrolled patients with features known to predict poorer outcomes following acute MI. Given the relative paucity of data on the impact of high-risk features on outcomes in the post-MI population in the longer term, we further interrogated patients with high-risk clinical characteristics. Each of the 5 qualifying high-risk characteristics of age ≥65 years, diabetes mellitus, second prior MI, CKD, and multivessel disease, together with no revascularization at index MI [28-31], was associated with an increased rate of the primary composite endpoint, consistent with the presumption that the associated increased risk of recurrent ischemic events and deaths post-MI persists in the longer-term. Only two of these features, older age and CKD, were associated with an increased bleeding risk, suggesting high-risk patients without these characteristics might gain a favorable benefit–risk balance from prolonged anticoagulant therapy.

Our findings suggest the trade-off in ischemic vs bleeding absolute event rates, derived from representative high-risk patients enrolled in well-executed clinical registries, may inform the application of prolonged antithrombotic therapies. Although it is well known that patients at high risk of ischemic events are also at high risk of bleeding, this appears clustered towards specific risk factors (i.e. advanced age and CKD). Others have reported similar findings, and indeed a number of tools such as the DAPT score, the Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) score, and the Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE DAPT) score have been developed to assist in the evaluation of bleeding vs ischemic complications to guide longer term antiplatelet or anticoagulant therapy [32-34]. However, these aids have been developed

in the post-PCI population, and have not been validated in broader post-MI populations such as our own. Furthermore, they rely on information collected at the time of the index procedure, which may be difficult to determine and of questionable relevance in the stable patient some years following their event. Our findings also provide impetus for the development of risk-management tools allowing evaluation of potential trade-offs between prevention of ischemic events and bleeding complications in the stable post-MI population.

There are several limitations to our study. Despite our initial intention to recruit from a broad range of clinical practices that included general practitioners and general physicians, most patients were recruited from cardiology outpatient practices. This likely explains why a high proportion of patients had undergone previous revascularization. This, however, does represent the setting in which most discussion on antiplatelet continuation and other therapies occur. Patients were recruited from a diversity of countries and may have experienced diverse outcomes. We did not have sufficient numbers of patients from individual countries to explore this. Furthermore, while national lead investigators were asked to select practices that represented the diversity of those around the country, in some smaller recruiting countries this was not possible. Although treatment-related data was collected, this was self-reported in most instances and not independently validated. Additionally, information collected on treatment targets (blood pressure, lipid levels) achieved was not comprehensive. Patients receiving ticagrelor more than 12 months following a MI were excluded; however, recruitment into the study was conducted before approval of this therapy for prolonged use in any country so these exclusions constituted a handful of patients only and do not limit generalization of the results. Although follow-up was comprehensive for an observational analysis, outcomes were not independently adjudicated as they would be in a randomized clinical trial. Since

all patients needed to have some risk factor for inclusion, the associations of individual factors with outcomes may be altered. Our observations pertain to specific high-risk clinical populations similar to other studies [9-12, 35]. In view of the dearth of outcomes data in this relatively understudied population, we restricted our subgroup interrogation to a limited number of clinically recognized high-risk sub-populations. Our data provide some justification for consideration of a comprehensive tool incorporating all collected clinical variables to arrive at predictive algorithms for ischemic events and/or bleeding.

In conclusion, the TIGRIS study has provided insight into outcomes of stable post-MI patients at high risk of future events treated in the outpatient setting across 25 countries. Beyond 12 months following a MI, the incidence of recurrent ischemic events and death remains constant over 2 years of follow-up, consistent with progression of the underlying atherosclerotic process rather than continued manifestation of the index acute MI. It is possible to identify clinical factors that predict an increased risk of ischemic but not bleeding events in this stable post-MI population. These insights are applicable to representative patients in routine clinical practice and provide a context for deciding on treatment options. They should be appreciated by clinicians and shared with their patients to better inform discussions on the potential benefits and harms of long-term therapies.

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Figure legends

Figure 1. Kaplan–Meier plots of primary composite outcome and its components, and bleeding over 2-year follow-up. Events accrued linearly throughout the follow-up period for all outcomes and bleeding events.

P-value testing for non-linearity for primary composite outcome = 0.46.

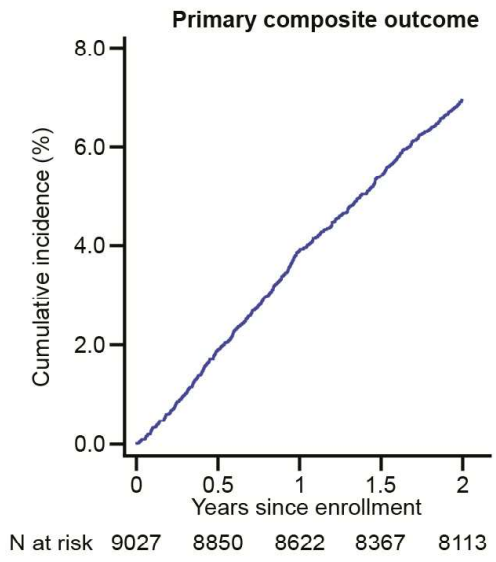
Figure 2. Adjusted rate ratios for primary composite outcome, all-cause death, and bleeding requiring hospitalization each obtained from a multivariable regression.* Independent predictors of the primary outcome included age 65–74 years, age ≥75 years, diabetes mellitus requiring medication, CKD, and medical management of index MI.

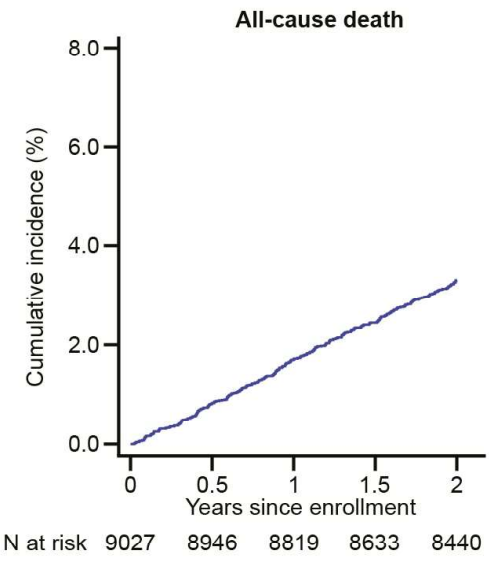
*Primary composite outcome is first occurrence of the composite of MI, unstable angina with urgent re-vascularization, stroke, or death from any cause.

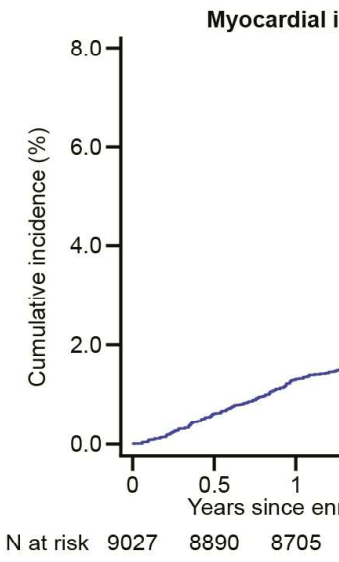
†Multivariable Poisson regression simultaneously adjusted for all risk factors in figure plus geographical region.

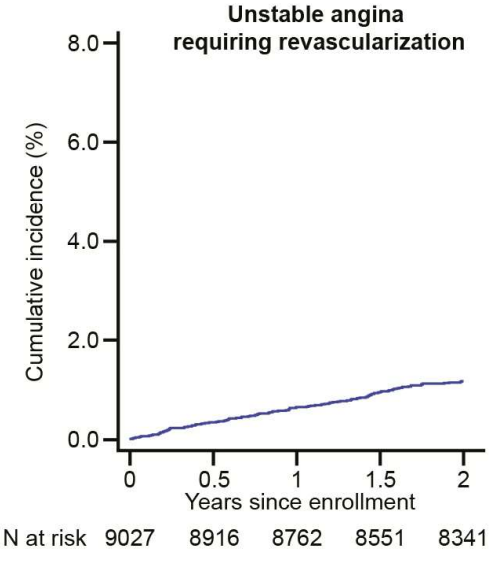
#Age when analyzed as a continuous variable (per year older), HR (95% CI): composite endpoint 1.03 (1.02, 1.04), all-cause death 1.07 (1.05, 1.08), and bleeding 1.06 (1.03, 1.08).

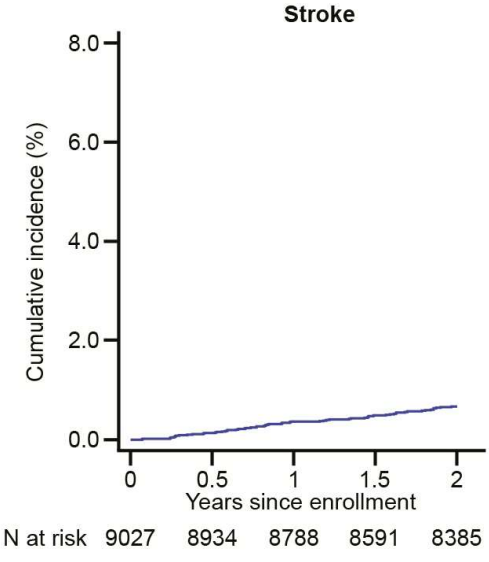
CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

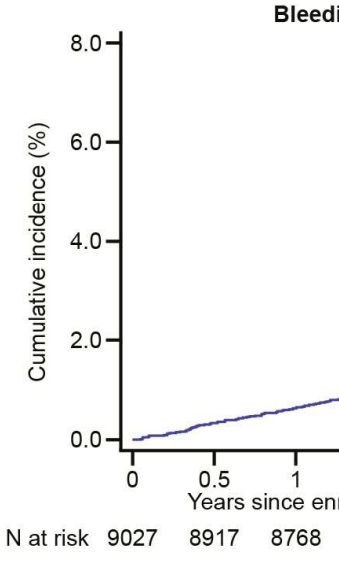

Primary composite outcome
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
1.5
2
Years since enrollment
N at risk 9027 8850 8622 8367 8113


All-cause death
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
1.5
2
Years since enrollment
N at risk 9027 8946 8819 8633 8440


Myocardial i
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
Years since en
N at risk 9027 8890 8705


Unstable angina
requiring revascularization
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
1.5
2
Years since enrollment
N at risk 9027 8916 8762 8551 8341


Stroke
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
1.5
2
Years since enrollment
N at risk 9027 8934 8788 8591 8385


Bleedi
Cumulative incidence (%)
8.0
6.0
4.0
2.0
0.0
0
0.5
1
Years since en
N at risk 9027 8917 8768

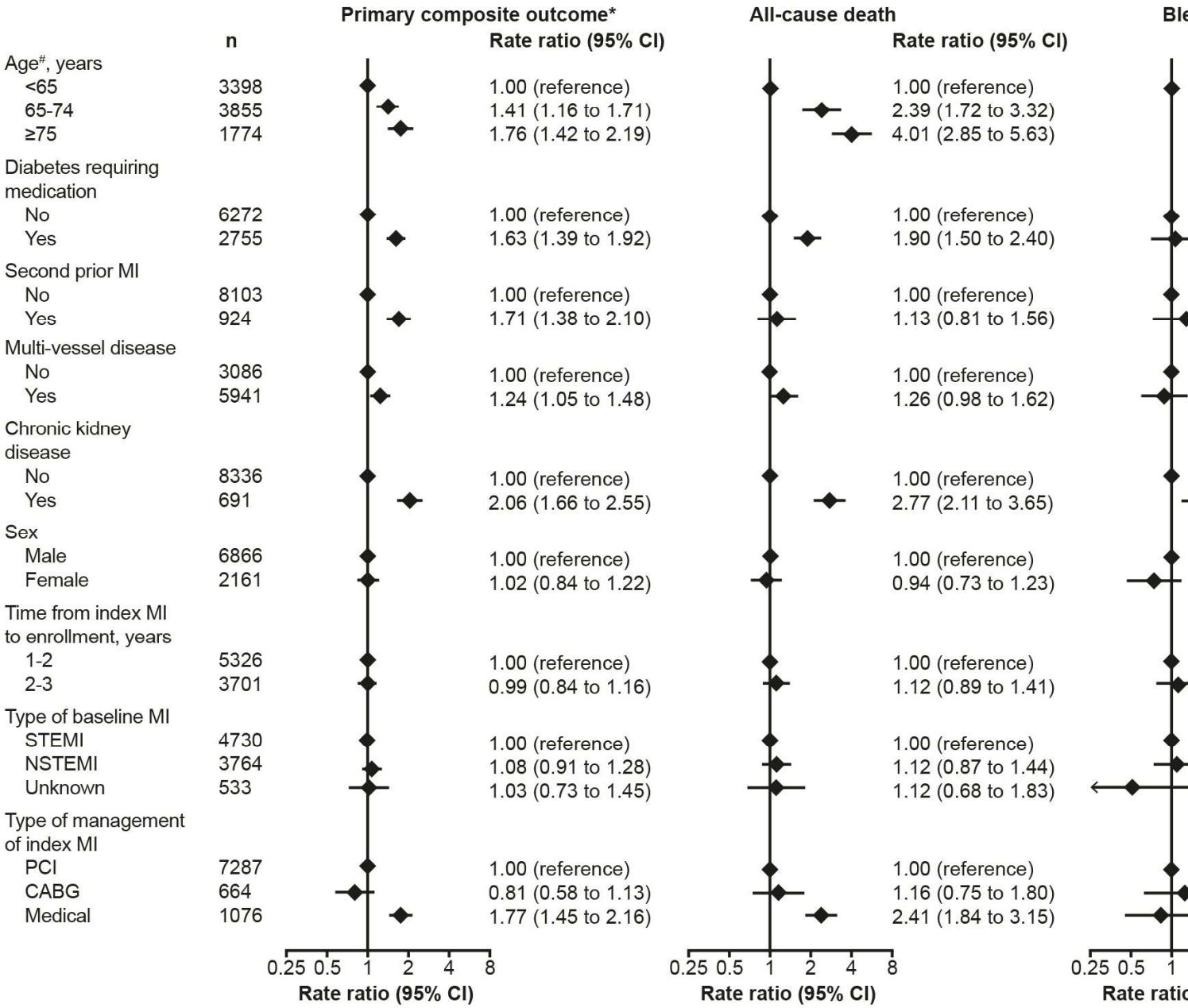

Primary composite outcome*
All-cause death
Ble
n
Rate ratio (95% CI)
Rate ratio (95% CI)
Age#, years
<65 3398 1.00 (reference) 1.00 (reference)
65-74 3855 1.41 (1.16 to 1.71) 2.39 (1.72 to 3.32)
≥75 1774 1.76 (1.42 to 2.19) 4.01 (2.85 to 5.63)
Diabetes requiring medication
No 6272 1.00 (reference) 1.00 (reference)
Yes 2755 1.63 (1.39 to 1.92) 1.90 (1.50 to 2.40)
Second prior MI
No 8103 1.00 (reference) 1.00 (reference)
Yes 924 1.71 (1.38 to 2.10) 1.13 (0.81 to 1.56)
Multi-vessel disease
No 3086 1.00 (reference) 1.00 (reference)
Yes 5941 1.24 (1.05 to 1.48) 1.26 (0.98 to 1.62)
Chronic kidney disease
No 8336 1.00 (reference) 1.00 (reference)
Yes 691 2.06 (1.66 to 2.55) 2.77 (2.11 to 3.65)
Sex
Male 6866 1.00 (reference) 1.00 (reference)
Female 2161 1.02 (0.84 to 1.22) 0.94 (0.73 to 1.23)
Time from index MI to enrollment, years
1-2 5326 1.00 (reference) 1.00 (reference)
2-3 3701 0.99 (0.84 to 1.16) 1.12 (0.89 to 1.41)
Type of baseline MI
STEMI 4730 1.00 (reference) 1.00 (reference)
NSTEMI 3764 1.08 (0.91 to 1.28) 1.12 (0.87 to 1.44)
Unknown 533 1.03 (0.73 to 1.45) 1.12 (0.68 to 1.83)
Type of management of index MI
PCI 7287 1.00 (reference) 1.00 (reference)
CABG 664 0.81 (0.58 to 1.13) 1.16 (0.75 to 1.80)
Medical 1076 1.77 (1.45 to 2.16) 2.41 (1.84 to 3.15)
0.25 0.5 1 2 4 8
Rate ratio (95% CI)
0.25 0.5 1 2 4 8
Rate ratio (95% CI)
0.25 0.5 1
Rate ratio

Table 1. Cumulative incidence of the primary composite cardiovascular outcome and its components, and bleeding from enrollment to 1 and 2 years of follow-up

	Events (Kaplan–Meier %)	
	1-year	**2-year**
Primary composite outcome	352 (3.9%)	621 (7.0%)
All-cause death	154 (1.7%)	295 (3.3%)
CV death	100 (1.1%)	178 (2.0%)
Non-CV death	54 (0.6%)	117 (1.3%)
Myocardial infarction	117 (1.3%)	195 (2.2%)
Stroke	32 (0.4%)	58 (0.7%)
Unstable angina requiring revascularization	58 (0.6%)	103 (1.2%)
Bleeding requiring hospitalization	56 (0.6%)	109 (1.2%)

CV, cardiovascular.

Table 2. Patient characteristics at enrollment and corresponding incidence rate of the primary composite outcome

	Patients (%)	Number with primary outcome	Incidence rate per 100 person years	*P*-value
All patients	9027	621	3.6 (3.3, 3.9)	
Age, years				
<65	3398 (37.6%)	181	2.8 (2.4, 3.2)	
65-74	3855 (42.7%)	271	3.7 (3.3, 4.1)	
≥ 75	1774 (19.7%)	169	5.1 (4.4, 5.9)	<0.0001
Diabetes requiring medication				
No	6272 (69.5%)	364	3.0 (2.7, 3.4)	
Yes	2755 (30.5%)	257	5.0 (4.4, 5.6)	<0.0001
Second prior MI*				
No	8103 (89.8%)	506	3.3 (3.0, 3.6)	
Yes	924 (10.2%)	115	6.7 (5.6, 8.1)	<0.0001
Multi-vessel disease				
No	3086 (34.2%)	198	3.4 (2.9, 3.9)	
Yes	5941 (65.8%)	423	3.7 (3.4, 4.1)	0.22
Chronic kidney disease				
No	8336 (92.3%)	514	3.2 (2.9, 3.5)	

	Patients (%)	Number with primary outcome	Incidence rate per 100 person years	*P*-value
Yes	691 (7.7%)	107	8.6 (7.0, 10.4)	<0.0001
Sex				
Male	6866 (76.1%)	462	3.5 (3.2, 3.9)	
Female	2161 (23.9%)	159	3.9 (3.3, 4.5)	0.29
Time from index MI to enrollment				
1-2 years	5326 (59.0%)	372	3.7 (3.3, 4.1)	
2-3 years	3701 (41.0%)	249	3.5 (3.1, 4.0)	0.67
Type of baseline MI				
STEMI	4730 (52.4%)	282	3.1 (2.8, 3.5)	
NSTEMI	3764 (41.7%)	301	4.2 (3.8, 4.7)	
Unknown	533 (5.9%)	38	3.7 (2.6, 5.1)	0.0008
Type of management of index MI				
PCI	7287 (80.7%)	448	3.2 (2.9, 3.5)	
CABG	664 (7.4%)	38	3.0 (2.1, 4.1)	
Medical	1076 (11.9%)	135	6.8 (5.7, 8.1)	<0.0001
Region				
Asia + Australia	2815 (31.2%)	165	3.0 (2.6, 3.5)	
Europe	4126 (45.7%)	284	3.6 (3.2, 4.1)	

	Patients (%)	Number with primary outcome	Incidence rate per 100 person years	*P*-value
North America	982 (10.9%)	84	4.6 (3.7, 5.7)	
Latin America	1104 (12.2%)	88	4.2 (3.4, 5.2)	0.0079

Primary composite outcome is first occurrence of the composite of MI, unstable angina with urgent re-vascularization, stroke, or death from any cause. *P*-values were calculated using univariable Poisson regression.

*Second prior MI any time before index MI.

CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Two-year outcomes among stable high-risk patients following acute MI. Insights from a global registry in 25 countries

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.

Supplementary material

Table SI Patient characteristics at enrollment (baseline) in the TIGRIS study population

Characteristic	Mean (SD) or n/N (%)
Age	66.9 (8.6)
Male	6866/9027 (76.1%)
Ethnicity	
Caucasian	5888/8882 (66.3%)
Black	92/8882 (1.0%)
Asian/Oriental	2465/8882 (27.8%)
Other	437/8882 (4.9%)
Region	
Asia + Australia	2815/9027 (31.2%)
Europe	4126/9027 (45.7%)
North America	982/9027 (10.9%)
Latin America	1104/9027 (12.2%)
BMI (kg/m2)	27.3 (4.7)
Waist circumference (cm)	97.7 (13.0)
SBP (mmHg)	131.5 (17.7)
DBP (mmHg)	76.6 (10.4)
Smoking status	
Never Smoked	3398/9025 (37.7%)
Former Smoker	4373/9025 (48.5%)
Current Smoker	1254/9025 (13.9%)
Heart rate (bpm)	68.4 (10.7)
Inclusion criteria and management of index MI	
Age >=65 years	5626/5626 (100.0%)
Diabetes requiring medication	2755/9027 (30.5%)

Second prior MI	924/9027 (10.2%)
Multi-vessel disease	5941/9027 (65.8%)
Chronic kidney disease	691/9027 (7.7%)
Type of index MI	
STEMI	4730/9027 (52.4%)
NSTEMI	3764/9027 (41.7%)
Unknown	533/9027 (5.9%)
Management of index MI	
PCI	7287/9027 (80.7%)
CABG	664/9027 (7.4%)
Medical	1076/9027 (11.9%)
Medical history	
Hyperlipidemia	5990/9027 (66.4%)
Hypertension	6508/9027 (72.1%)
Chronic anemia	258/9027 (2.9%)
Angina	898/9027 (9.9%)
CHF	1033/9027 (11.4%)
CABG	1282/9027 (14.2%)
PCI	7757/9027 (85.9%)
Stroke	402/9027 (4.5%)
TIA	192/9027 (2.1%)
Venous thrombo-embolism	149/9027 (1.7%)
Major bleed	253/9027 (2.8%)
Atrial fibrillation	727/9027 (8.1%)
Permanent pacemaker	200/9027 (2.2%)
Valve replacement/repair	99/9027 (1.1%)
PVD	601/9027 (6.7%)

COPD	645/9027 (7.1%)
Medications at baseline	
ACE/ARB	6707/9007 (74.5%)
Antiplatelet medication	
No APT	451/9007 (5.0%)
SAPT	6189/9007 (68.7%)
DAPT	2367/9007 (26.3%)
Anticoagulant	498/9007 (5.5%)
Beta-blocker	7128/9007 (79.1%)
Diuretic	2266/9007 (25.2%)
Statin	8287/9007 (92.0%)

ACEi, angiotensin-converting enzyme inhibitor; APT, antiplatelet; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; SBP, systolic blood pressure; STEMI, ST-segment elevation MI.

Table SII Patient characteristics by timing of enrollment from index event (1–2 years vs 2–3 years)

	Enrolled 1–2 years after index MI	Enrolled 2–3 years after index MI	*P*-value
Sex			0.1201
Male	4020 (75.5%)	2846 (76.9%)	
Female	1306 (24.5%)	855 (23.1%)	
Type of MI			0.6347
STEMI	2769 (52.0%)	1961 (53.0%)	
NSTEMI	2242 (42.1%)	1522 (41.1%)	
Unknown	315 (5.9%)	218 (5.9%)	
MI management			0.6815
PCI	4284 (80.4%)	3003 (81.1%)	
CABG	395 (7.4%)	269 (7.3%)	
Medical	647 (12.1%)	429 (11.6%)	
Diabetes requiring medication			0.7264
Yes	1633 (30.7%)	1122 (30.3%)	
No	3693 (69.3%)	2579 (69.7%)	
2nd prior MI			0.0295
Yes	576 (10.8%)	348 (9.4%)	
No	4750 (89.2%)	3353 (90.6%)	
Multi-vessel disease			0.1518
Yes	3537 (66.4%)	2404 (65.0%)	
No	1789 (33.6%)	1297 (35.0%)	
CKD			0.1637
Yes	425 (8.0%)	266 (7.2%)	

No	4901 (92.0%)	3435 (92.8%)	
Region			<0.0001
Asia + Australia	1684 (31.6%)	1131 (30.6%)	
Europe	2320 (43.6%)	1806 (48.8%)	
North America	593 (11.1%)	389 (10.5%)	
Latin America	729 (13.7%)	375 (10.1%)	

CABG, coronary artery bypass graft; CKD, chronic kidney disease; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Table SIII Rate of the primary composite outcome by time since enrollment and time since index myocardial infarction

	Number of events	Rate per 100 person-years, 95% CI
0–6 months	172	3.8 (3.3, 4.5)
6–12 months	180	4.1 (3.5, 4.8)
12–18 months	134	3.2 (2.6, 3.7)
18–24 months	135	3.3 (2.8, 3.9)
Time since index MI		
1–2 years	101	3.5 (2.8, 4.2)
2–3 years	269	3.8 (3.4, 4.3)
3–4 years	197	3.5 (3.0, 4.0)
4–5 years	53	3.3 (2.5, 4.3)

Table SIV Bleeding events with hemodynamic compromise, and location of bleeds, among 109 patients who required hospitalization for 119 bleeding events

	n (%) of events
Bleeding events with hemodynamic compromise	
Yes	28 (23.5)
No	0 (0)
Unknown	12 (10.1)
No information provided	79 (66.4)
Location of bleed*	
Gastrointestinal	48 (44.0)
Genitourinary	14 (12.8)
Epistaxis	10 (9.2)
Intracranial	10 (9.2)
Vascular access	3 (2.8)
Other (≤2 patients each)	40 (40.4)

*Some patients had multiple sites of bleeding.

Table SV Patient characteristics at enrollment and corresponding unadjusted incidence rates of all-cause death and bleeding requiring hospitalization

	No. of deaths (incidence rate per 100 person-years)	*P*-value	Number with bleeding outcome (incidence rate per 100 person-years)	*P*-value
All patients	295 (1.7)		109 (0.6)	
Age, years				
<65	51 (0.8)		17 (0.3)	
65–74	129 (1.7)		51 (0.7)	
≥75	115 (3.4)	<0.0001	41 (1.2)	<0.0001
Diabetes mellitus requiring medication				
No	163 (1.3)		76 (0.6)	
Yes	132 (2.5)	<0.0001	33 (0.6)	1.00
Second prior MI*				
No	250 (1.6)		95 (0.6)	
Yes	45 (2.5)	0.0041	14 (0.8)	0.35
Multi-vessel disease				
No	101 (1.7)		43 (0.7)	
Yes	194 (1.7)	0.98	66 (0.6)	0.24
Chronic non-end-stage renal dysfunction				
No	220 (1.4)		91 (0.6)	
Yes	75 (5.8)	<0.0001	18 (1.4)	0.0003
Sex				
Male	216 (1.6)		86 (0.6)	
Female	79 (1.9)	0.23	23 (0.6)	0.51
Time from index MI to enrollment				
1–2 years	168 (1.6)		61 (0.6)	

2–3 years	127 (1.8)	0.45	48 (0.7)	0.50
Type of index MI				
STEMI	122 (1.3)		56 (0.6)	
NSTEMI	154 (2.1)		50 (0.7)	
Unknown	19 (1.8)	0.0003	3 (0.3)	0.94
Type of management of index MI				
PCI	187 (1.3)		88 (0.6)	
CABG	23 (1.8)		9 (0.7)	
Medical	85 (4.2)	<0.0001	12 (0.6)	0.92
Region				
Asia + Australia	69 (1.2)		42 (0.8)	
Europe	129 (1.6)		48 (0.6)	
North America	48 (2.6)		12 (0.6)	
Latin America	49 (2.3)	0.0003	7 (0.3)	0.15

Primary composite outcome is first occurrence of the composite of MI, unstable angina with urgent re-vascularization, stroke, or death from any cause. *P*-values were calculated using univariable Poisson regression.

*Second prior MI any time before index MI.

CABG, coronary artery bypass graft; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Table SVI Adjusted* incidence rate ratios by region for primary composite outcome, all-cause death, and bleeding requiring hospitalization

Region	Number of patients	Rate ratios (95% CI)		
		Primary composite outcome	All-cause death	Bleeding
Asia + Australia	2815	0.87 (0.72 to 1.06)	0.83 (0.62 to 1.12)	1.34 (0.88 to 2.03)
Europe	4126	1.00 (reference)	1.00 (reference)	1.00 (reference)
North America	982	1.15 (0.90 to 1.46)	1.33 (0.95 to 1.86)	1.07 (0.57 to 2.03)
Latin America	1104	1.11 (0.87 to 1.41)	1.34 (0.96 to 1.86)	0.58 (0.26 to 1.29)

*Multivariable Poisson regression simultaneously adjusted for geographical region and variables in Figure III: age, diabetes mellitus requiring medication, second prior MI, multi-vessel disease, non-end-stage chronic kidney disease, sex, type of index MI, type of management of index MI, and time from index MI to enrollment.

CI, confidence interval; MI, myocardial infarction.

Figure SI. Kaplan–Meier plots of cardiovascular and non-cardiovascular death from enrollment over 2-year follow-up

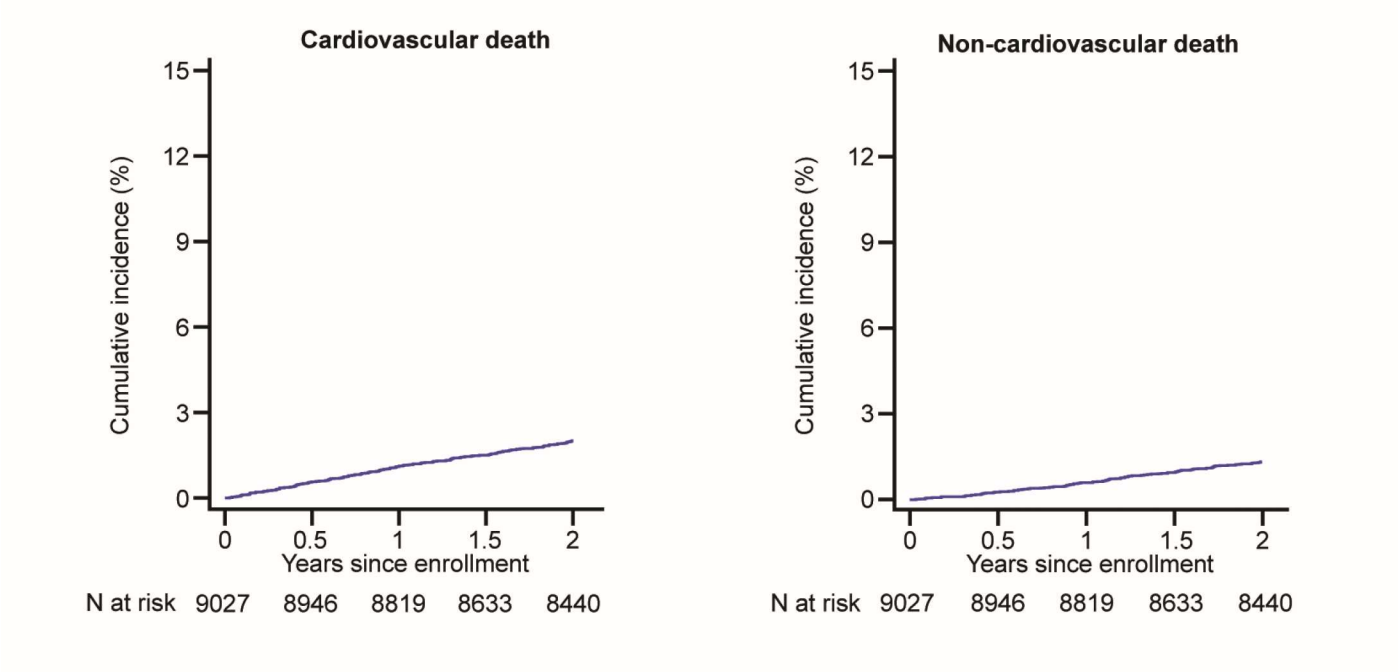
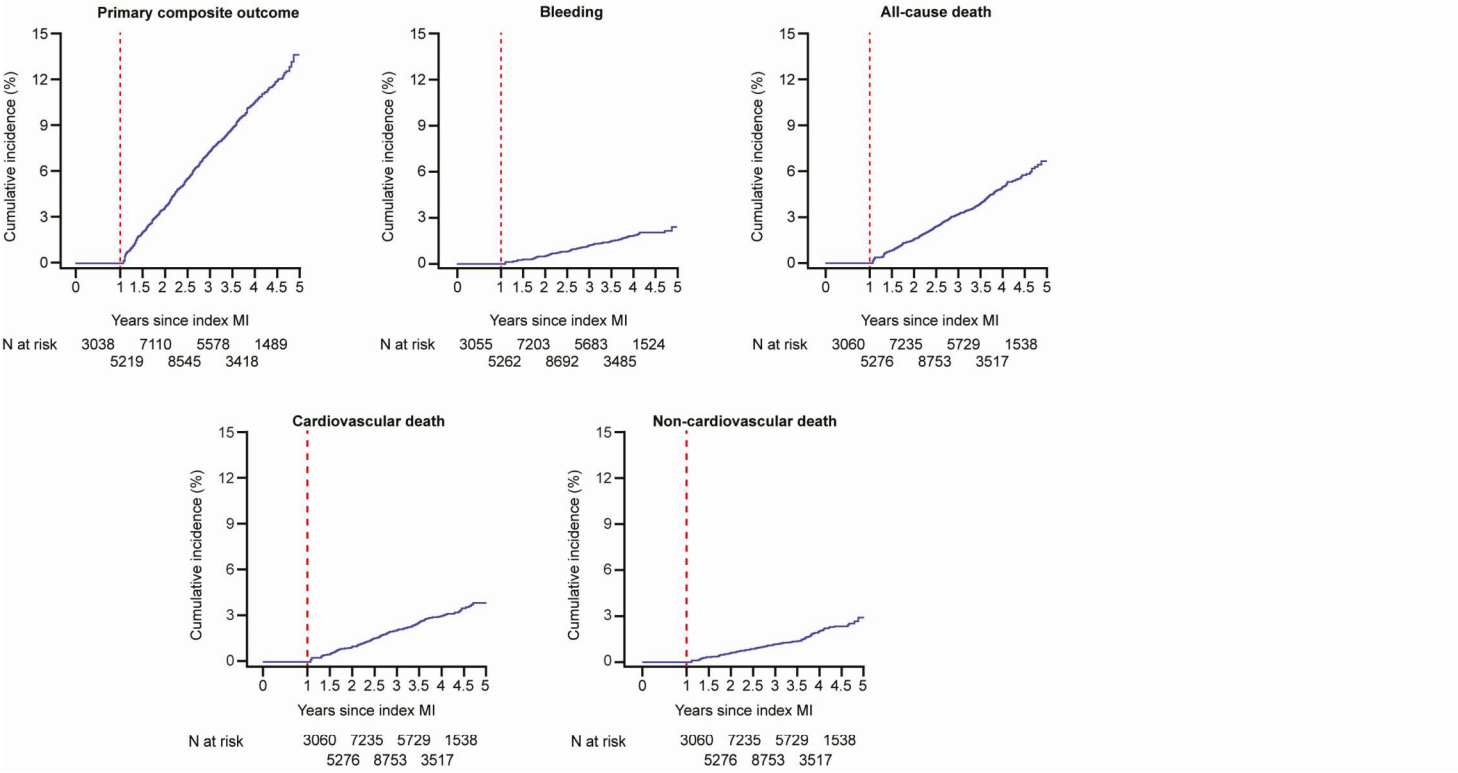


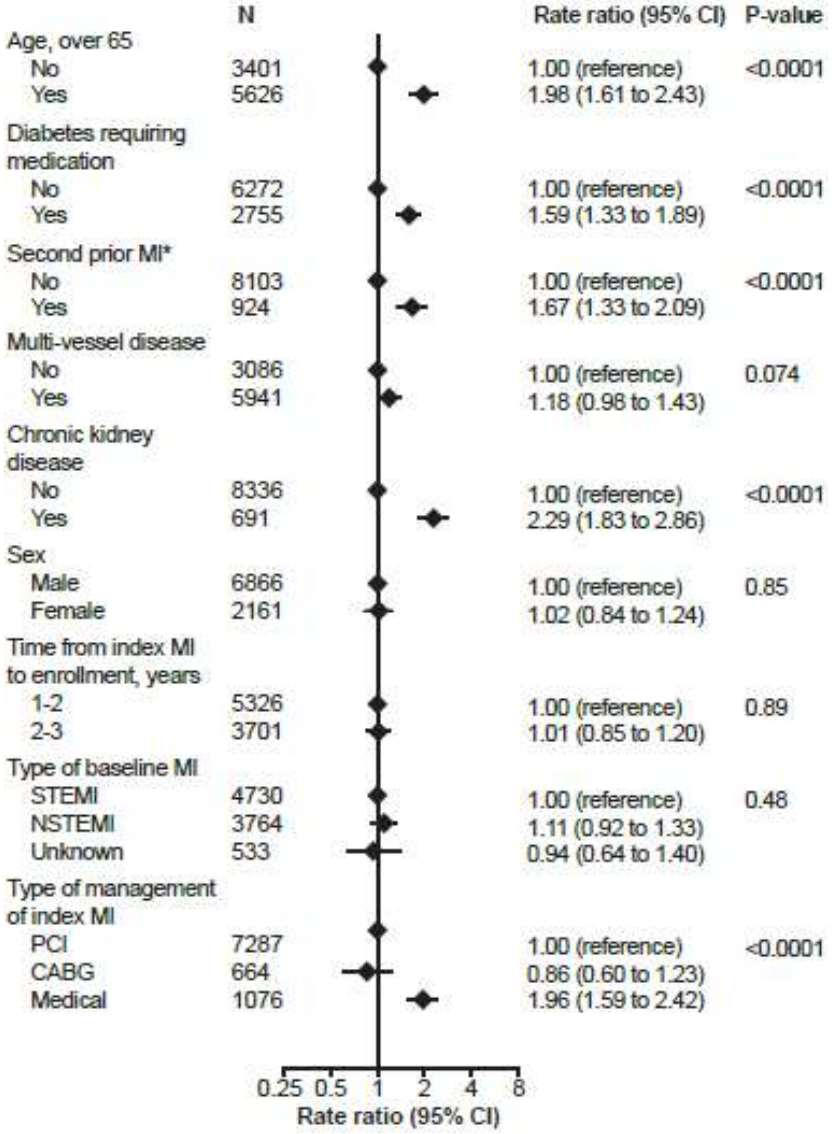
Figure SII. Left-truncated Kaplan–Meier plots of primary outcome, bleeding, all-cause death, and cardiovascular and non-cardiovascular death, showing cumulative risk from time of index myocardial infarction (MI)



P-value testing for non-linearity for primary composite outcome = 0.63.

MI, myocardial infarction.

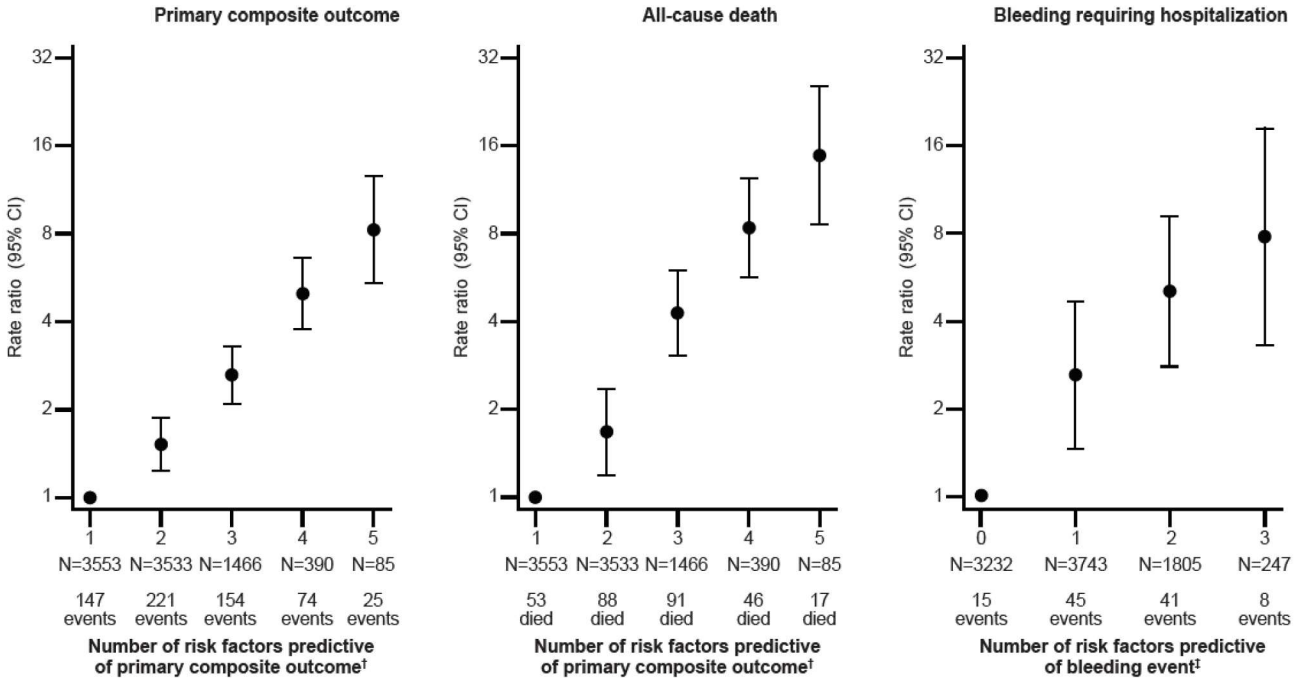
Figure SIII. Adjusted rate ratios for primary composite outcome excluding unstable angina requiring revascularisation, each obtained from a multivariable regression



*Second prior MI any time before index MI.

CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Figure SIV. Rate ratios for primary composite outcome, all-cause death, and bleeding events requiring hospitalization by number of predictive risk factors*



*Derived from univariable Poisson regression, using cohort with 1 risk factor as reference for primary composite endpoint outcome and all-cause death, respectively, and cohort with no risk factor as reference for bleeding event.

†Risk factors predictive of primary composite outcome: age ≥65, diabetes mellitus requiring medication, second prior MI, multi-vessel disease, CKD, medical management of index MI.

‡Risk factors predictive of bleeding requiring hospitalization: age ≥65, age ≥75 (equivalent to 2 risk factors), CKD

CKD, non-end-stage chronic kidney disease; CV, cardiovascular; MI, myocardial infarction.