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Long-term antiplatelet therapy in medically managed non-ST-segment elevation acute coronary syndromes: The EPICOR Asia study

Juan Zhou [a,b], Chee Tang Chin [c], Xin Huang [a], Ning Guo [a], Yue Wu [a], Bo Yu [d], Shubin Qiao [e], Jiyan Chen [f], Yaling Han [g], Junbo Ge [h], Stuart J. Pocock [i], Yong Huo [j], Zhaohong Wang [k], Zuyi Yuan [a,b,*]

[a] First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, PR China
[b] Key Laboratory of Environment and Genes Related to Diseases (Xi'an Jiaotong University), Ministry of Education, Xi'an, PR China
[c] National Heart Centre Singapore, Singapore
[d] Second Affiliated Hospital of Harbin Medical University, Harbin, PR China
[e] Fuwai Hospital, Xicheng District, Beijing, PR China
[f] Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[g] General Hospital of Shenyang Military Region, Liaoning, PR China
[h] Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China
[i] London School of Hygiene and Tropical Medicine, London, UK
[j] Peking University People's Hospital, Beijing, PR China
[k] AstraZeneca, Beijing, PR China

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ABSTRACT

Objectives: To describe long-term antithrombotic management patterns (AMPs) in medically managed Asian patients with non-ST-segment myocardial infarction (NSTEMI) or unstable angina (UA).
Background: Current guidelines support an early invasive strategy in NSTEMI and UA patients, but many are medically managed, and data are limited on long-term AMPs in Asia.
Methods: Data were analyzed from medically managed NSTEMI and UA patients included in the prospective, observational EPICOR Asia study (NCT01361386). Survivors to hospital discharge were enrolled (June 2011 to May 2012) from 8 countries/regions across Asia. Baseline characteristics and AMP use up to 2 years post-discharge were collected. Outcomes were major adverse cardiovascular events (MACE: myocardial infarction, ischemic stroke, and death) and bleeding.
Results: Among 2289 medically managed patients, dual antiplatelet therapy (DAPT) use at discharge was greater in NSTEMI than in UA patients (81.8% vs 65.3%), and was significantly associated with male sex, positive cardiac markers, and prior cardiovascular medications ($p < 0.0001$). By 2 years, 57.9% and 42.6% of NSTEMI and UA patients, respectively, were on DAPT. On multivariable Cox regression analysis, risk of MACE at 2 years was most significantly associated with older age (HR [95% CI] 1.85 [1.36, 2.50]), diagnosis of NSTEMI vs UA (1.96 [1.47, 2.61]), and chronic renal failure (2.14 [1.34, 3.41]), all $p \leq 0.001$. Risk of bleeding was most significantly associated with region (East Asia vs Southeast/South Asia) and diabetes.
Conclusions: Approximately half of all patients were on DAPT at 2 years. MACE were more frequent in NSTEMI than UA patients during follow-up.

1. Introduction

Current international guidelines support the use of an early invasive strategy in the management of male and female adult patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS), comprising non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) [1–5]. Nevertheless, many of these patients do not undergo revascularization and have poorer long-term outcomes compared with NSTE-ACS patients managed invasively [6]. Reasons for non-revascularization are unclear but are possibly associated with

Abbreviations: AMP, antithrombotic management pattern; DAPT, dual antiplatelet therapy; EPICOR, Long-tErm Follow-uP of antithrombotIc Management Patterns In Acute CORonary Syndrome Patients; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; SAPT, single antiplatelet therapy; UA, unstable angina.

* Corresponding author at: Department of Cardiology, 1# Jiankang Road, First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an 710061, Shaanxi, China.
E-mail address: zuyiyuan@mail.xjtu.edu.cn (Z. Yuan).

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high-risk comorbidities [7], an unfavorable coronary anatomy [7], or cultural reluctance among some patients [6].

There is no consensus regarding the management of medically managed NSTE-ACS patients, and there are few data relating to antithrombotic management patterns (AMPs) used and long-term outcomes in these patients in Asia [6]. This analysis used data from non-revascularized NSTEMI and UA patients from the EPICOR Asia (Long-tErm Follow-uP of antithrombotIc Management Patterns In Acute CORonary Syndrome Patients in Asia) study (NCT01361386) [8] who survived to discharge, and were followed up for up to 2 years post-discharge, to describe AMPs used post-index event and outcomes, including major cardiovascular and bleeding events.

2. Methods

2.1. Patients

Data were analyzed from NSTE-ACS patients treated with medication only in EPICOR Asia, a prospective, multinational, observational cohort study. Patients with ACS who survived to hospital discharge were enrolled between June 2011 and May 2012 from 8 countries/regions across Asia. Patient data relating to final diagnosis, baseline demographics and clinical characteristics, and AMPs used in hospital, at discharge, and up to 2 years post-discharge, were collected. Post-discharge data on AMPs and cardiovascular and bleeding events were collected by means of telephone interviews at 6 weeks and then every 3 months, and events were validated based on real-time reports. Predefined in-hospital major cardiovascular complications included myocardial infarction (MI) and ischemic stroke, and post-discharge major adverse cardiovascular events (MACE) included MI, ischemic stroke, and death. These were recorded both as composite and individual endpoints.

Study procedures adhered to International Conference on Harmonization (ICH) Good Clinical Practice guidance, the Declaration of Helsinki, and local regulations. Institutional Review Board/Ethics Committee approval was obtained at each participating center in each country. All patients provided written informed consent.

2.2. Objectives

To describe in-hospital, discharge, and long-term AMPs, and ischemic and bleeding outcomes in medically managed Asian patients surviving hospitalization for NSTEMI or UA who were followed for up to 2 years post-discharge.

2.3. Statistical analysis

To describe real-world outcomes, an intention-to-treat assessment of index event, AMPs used, and outcomes was performed, unadjusted for baseline differences in patient characteristics or treatment selection; therefore, as this was an observational rather than a randomized study, a causal association between AMPs and outcomes could not be established. Low use of antithrombotic therapy was defined as 0–1 antiplatelet +0–1 heparin/anticoagulant and no glycoprotein (GP) IIb/IIIa inhibitor. Dual antiplatelet therapy (DAPT) was defined as 2 or more antiplatelet agents. In-hospital cardiovascular complications included MI and ischemic stroke but not death, as patients who died in hospital were excluded from the study. Comparisons of baseline patient characteristics between single antiplatelet therapy (SAPT) and DAPT use at discharge were performed. Exploratory analysis of risk factors for cardiovascular and bleeding events up to 2 years post-discharge was performed using multivariable Cox regression analysis – with models containing AMP at discharge (≥2 antiplatelets [no anticoagulant] vs 1 antiplatelet [no anticoagulant], and any anticoagulant vs 1 antiplatelet [no anticoagulant]), diagnosis (NSTEMI, UA), age, gender, region, hypertension, hypercholesterolemia, diabetes mellitus, family history of coronary artery disease (CAD), current smoking, obesity (body mass index >30 kg/m^2), prior MI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft, coronary angiogram diagnostic for CAD, chronic angina, heart failure, atrial fibrillation, transient ischemic attack/stroke, peripheral vascular disease, and chronic renal failure – and presented in terms of hazard ratio (HR) and associated 2-sided 95% confidence intervals (CIs). Covariates were selected based on clinical evaluation of potential prognostic value, informed by other investigations that had taken place on the EPICOR [9] and EPICOR Asia studies.

3. Results

3.1. Patient characteristics

Of 6306 NSTE-ACS patients included in EPICOR Asia, 2289 (36.3%) were treated with medication only, of whom 996 (43.5%) had a diagnosis of NSTEMI and 1293 (56.5%) UA. Mean ages were 63.7 and 63.0 years in NSTEMI and UA patients, respectively, with 20.0% and 14.2% being over 75 years of age in each category. Most patients (70.1% and 60.2%, respectively) were male, 33.5% and 27.5% had diabetes, and 26.6% and 18.7% were current smokers (eTable 1).

3.2. In-hospital AMPs

The AMP used most frequently in-hospital was ≥2 antiplatelets plus heparin/anticoagulant, and no GP IIb/IIIa inhibitor (53.1% of patients); this regimen was used more in NSTEMI (63.3%) than in UA (45.2%) patients (eTable 2). Patients with UA were more frequently managed with ≥2 antiplatelets only (no anticoagulant/no GP IIb/IIIa inhibitor) compared with NSTEMI patients (34.4% vs 19.0%). Unadjusted analysis showed a tendency for higher in-hospital cardiovascular complications with low antithrombotic therapy use in NSTEMI patients (5.6%) compared with greater use (1.3% for ≥2 antiplatelets plus heparin/anticoagulant but no GP IIb/IIIa inhibitor, and 1.4% for ≥2 antiplatelets only and no anticoagulant or GP IIb/IIIa inhibitor) (eTable 3). Bleeding rates were also higher with greater versus lower antithrombotic therapy use (1.7% vs 0.2%, respectively), and were slightly higher in NSTEMI versus UA patients (eTable 3). As stated previously, however, causality cannot be inferred.

3.3. Discharge and long-term AMPs and outcomes

At discharge, the majority of patients were receiving ≥2 antiplatelets without an anticoagulant; this was higher in NSTEMI (81.8%) compared with UA patients (65.3%) (Fig. 1 and eTable 4). Use of any anticoagulant was low during follow-up (<1% of the overall NSTE-ACS population at each time point, eTable 4). Among 2192 patients discharged on SAPT ($n = 585$) or DAPT ($n = 1607$), there were notable differences by patient characteristics, including greater DAPT use associated with NSTEMI, male sex, positive cardiac markers, initial creatinine >1.2 mg/dl, and pre- or in-hospital use of cardiovascular medications, including aspirin, clopidogrel, and anticoagulants (Table 1). There were also significant differences across hospital type and country of residence.

The overall proportion of patients receiving DAPT gradually decreased from 72.6% at discharge to 49.1% at 2 years, whereas the proportion of patients receiving SAPT increased from 26.4% to 41.1%, and those receiving no antiplatelet rose from 0.1% to 8.9% over the same period (eTable 4). By the end of the 2-year follow-up, more UA than NSTEMI patients were on 0–1 antiplatelet (56.6% vs 41.0%), whereas more NSTEMI (57.9%) than UA patients (42.6%) were on DAPT.

The overall incidence of MACE at 2 years was somewhat higher in patients discharged on DAPT than on SAPT (15.5% vs 10.9%, Table 2), but NSTEMI patients (i.e. higher risk patients) were more likely to receive DAPT than SAPT. Thus, risk of MACE in NSTEMI patients was 18% on SAPT and 20% on DAPT, with corresponding values in UA patients

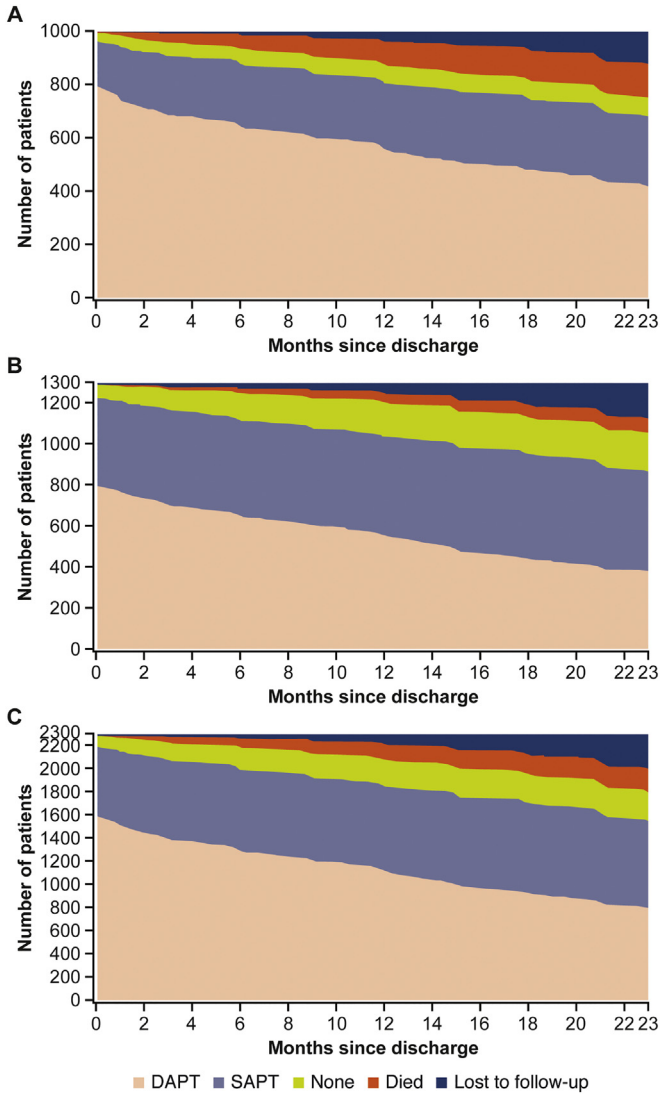

Fig. 1. Antithrombotic management patterns (AMPs) in **(A)** Non-ST-segment elevation myocardial infarction (NSTEMI), **(B)** Unstable angina, and **(C)** All non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients up to 2 years post-discharge. Legend: Number of patients on each AMP type over time, including patients who died or were lost to follow-up. DAPT, dual antiplatelet therapy; None, no antiplatelet therapy; SAPT, single antiplatelet therapy.

Table 1
Patient characteristics by antiplatelet therapy at discharge following NSTE-ACS in medically managed patients ($n = 2192$).

	N	SAPT ($n = 585$ [26.7%])	DAPT[a] ($n = 1607$ [73.3%])
Index event diagnosis			
NSTEMI	964	164 (17.0)	800 (83.0)
Unstable angina	1228	421 (34.3)	807 (65.7)
Age (yrs), mean (SD)	2192	63.5 (11.4)	63.1 (11.7)
>75	361	95 (26.3)	266 (73.9)
Male sex	1415	332 (23.5)	1083 (76.5)
Positive cardiac markers[b]	961	163 (17.0)	798 (83.0)
Risk factors for CVD	1643	427 (26.0)	1216 (74.0)
Hypertension	1388	363 (26.2)	1025 (73.8)
Hypercholesterolemia	456	101 (22.1)	355 (77.9)
Diabetes mellitus	658	159 (24.2)	499 (75.8)
Family history of CAD	205	46 (22.4)	159 (75.6)
Current smoking	484	114 (23.6)	370 (76.4)
Obesity (BMI >30 kg/m^2)	138	41 (29.7)	97 (70.3)
Prior CVD	900	238 (26.4)	662 (73.6)
Prior MI	310	74 (23.9)	236 (76.1)
Prior PCI	278	57 (20.5)	221 (79.5)
Prior CABG	66	17 (25.8)	49 (74.2)
CAG diagnostic for CAD	380	90 (23.7)	290 (76.3)
Chronic angina	518	148 (28.6)	370 (71.4)
Heart failure	129	30 (23.3)	99 (76.7)
Atrial fibrillation	60	21 (35.0)	39 (65.0)
TIA/stroke	128	41 (32.0)	87 (68.0)
PVD	33	4 (12.1)	29 (87.9)
Chronic renal failure	80	15 (18.8)	65 (81.2)
Initial creatinine >1.2 mg/dl	399	75 (18.8)	324 (81.2)
Antiplatelet therapy[c]	2192	585 (26.7)	1607 (73.3)
Aspirin	2066	488 (23.6)	1578 (76.4)
Clopidogrel	1944	397 (20.4)	1547 (79.6)
Other prior cardiovascular medication			
β-blocker	1527	374 (24.5)	1153 (75.5)
ACEi/ARB	1382	327 (23.7)	1055 (76.3)
Statin	2019	522 (25.9)	1497 (74.1)
Anticoagulants	1343	257 (19.1)	1086 (80.9)
Discharge hospital type			
Community	176	48 (27.3)	128 (72.7)
Non-university general ($n = 496$)	496	87 (17.5)	409 (82.5)
University general ($n = 1198$)	1198	331 (27.6)	867 (72.4)
Other hospital/clinic ($n = 322$)	322	119 (37.0)	203 (63.0)
Cath lab facilities			
Coronary/ICU ($n = 2106$)	2106	561 (26.6)	1545 (73.4)
Cath lab ($n = 2038$)	2038	551 (27.0)	1487 (73.0)
Place of residence			
Rural ($n = 716$)	716	162 (22.6)	554 (77.4)
Metropolitan ($n = 1476$)	1476	423 (28.7)	1053 (71.3)
Insurance type[d]			
Government ($n = 1543$)	1543	422 (27.3)	1121 (72.7)
Private ($n = 186$)	186	39 (21.0)	147 (79.0)
Employer-provided ($n = 25$)	25	9 (36.0)	16 (64.0)
Other ($n = 64$)	64	9 (14.1)	55 (85.9)
None ($n = 391$)	391	111 (28.4)	280 (71.6)
Country of residence			
China ($n = 1374$)	1374	396 (28.8)	978 (71.2)
Hong Kong ($n = 37$)	37	13 (35.1)	24 (64.9)
India ($n = 407$)	407	121 (29.7)	286 (70.3)
Malaysia ($n = 50$)	50	7 (14.0)	43 (86.0)
Singapore ($n = 17$)	17	2 (11.8)	15 (88.2)
South Korea ($n = 50$)	50	18 (36.0)	32 (64.0)
Thailand ($n = 220$)	220	25 (11.4)	195 (88.6)
Vietnam ($n = 37$)	37	3 (8.1)	34 (91.9)

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAG, coronary angiography; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; ICU, intensive care unit; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SAPT, single antiplatelet therapy; SD, standard deviation; TIA, transient ischemic attack.
Values are *n* (%), unless otherwise indicated and represent number of subjects discharged on SAPT or DAPT out of those subjects with the row characteristic of interest.
[a] ≥2 antiplatelet agents.
[b] Positive cardiac markers were defined as elevated CK-MB and troponins (at least 1 value >99th percentile of the upper reference limit).
[c] For patients with no in-hospital antiplatelet use recorded, any discharge antiplatelet is assumed to have also been used in hospital.
[d] Patients may have more than 1 insurance.

of 8% and 11%. Causality of treatment effect cannot be inferred for reasons such as potential confounders, as described in the limitations section of the discussion. With the same proviso, bleeding event rates were similar regardless of discharge antiplatelet therapy.

Table 2
2-year outcomes according to discharge antithrombotic management pattern[a].

	NSTEMI		UA		All patients	
	SAPT (n = 164)	DAPT (n = 800)	SAPT (n = 421)	DAPT (n = 807)	SAPT (n = 585)	DAPT (n = 1607)
MACE	30 (18.3)	160 (20.0)	34 (8.1)	89 (11.0)	64 (10.9)	249 (15.5)
Death	24 (14.6)	99 (12.4)	18 (4.3)	49 (6.1)	42 (7.2)	148 (9.2)
Myocardial infarction	10 (6.1)	69 (8.6)	8 (1.9)	28 (3.5)	18 (3.1)	97 (6.0)
Ischemic stroke	1 (0.6)	19 (2.4)	11 (2.6)	18 (2.2)	12 (2.1)	37 (2.3)
Bleeding	3 (1.8)	34 (4.3)	26 (6.2)	64 (7.9)	29 (5.0)	98 (6.1)
Major bleeding[b]	0	10 (1.3)	2 (0.5)	12 (1.5)	2 (0.3)	22 (1.4)
Bleeding by region[c]						
Overall	41/996 (4.1)		94/1293 (7.3)		135/2289 (5.9)	
East Asia	34/452 (7.5)		93/1072 (8.7)		127/1524 (8.3)	
Southeast/South Asia	7/544 (1.3)		1/221 (0.5)		8/765 (1.0)	

DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular event; NSTEMI, non-ST-segment elevation myocardial infarction; SAPT, single antiplatelet therapy; UA, unstable angina.
Values are n (%).
[a] Causality of treatment effect cannot be inferred due to treatment allocation bias and baseline confounding; i.e., there are multiple variables associated with SAPT or DAPT beyond those created by the treatment alone.
[b] Confirmed events only; bleed severity was not recorded for approximately 5% of bleed events.
[c] For bleeding events by region, SAPT and DAPT at discharge were combined.

3.4. Baseline risk factors for post-discharge clinical events

Risk of MACE up to 2 years post-discharge was associated with a number of baseline risk factors on multivariate Cox regression analysis, most significantly older age (HR [95% CI] 1.85 [1.36, 2.50], $p < 0.0001$), diagnosis of NSTEMI vs UA (1.96 [1.47, 2.61], $p < 0.0001$), and chronic renal failure (2.14 [1.34, 3.41], $p = 0.001$) (Fig. 2). A full list of results including non-significant covariates is shown in eTable 5. For bleeding events, baseline risk factors included residency in East Asia vs Southeast/South Asia (HR [95% CI] 5.58 [2.57, 12.10], $p < 0.0001$) and diabetes (2.07 [1.36, 3.15], $p < 0.001$). As the HR for region was very high for bleeding, an exploratory analysis was undertaken to investigate the possible effect of region and index event diagnosis as confounding factors (Table 2). The results confirmed that the two were not evenly distributed, with some small differences in bleeding between UA and NSTEMI patients within regions; that is, there was a comparatively high proportion of UA patients in East Asia, and a very small number of bleeding events in Southeast/South Asia.

4. Discussion

This analysis of data from medically managed NSTE-ACS patients enrolled in the EPICOR Asia study showed that, despite guideline recommendations [3,4], up to 40% of patients hospitalized with NSTE-ACS did not undergo coronary revascularization, and were treated only with medication. This may be due to cultural, financial, and/or educational reasons, or perhaps an inherent relatively high-risk profile of medically managed patients, who tend to be older, have a more prevalent history of cardiovascular disease and more cardiovascular disease risk factors and comorbidities, and a greater likelihood of treatment in a center with limited facilities for invasive management [6,7].

This study demonstrated that most patients were treated with DAPT until at least 12 months post-discharge (i.e., in accordance with guideline recommendations) [10–12], and around half were still on DAPT at 2 years, including 43% of UA patients, contrary to guidelines at the time the EPICOR Asia study was conducted [10,13]. At discharge, NSTEMI patients were more likely to receive DAPT than SAPT, with

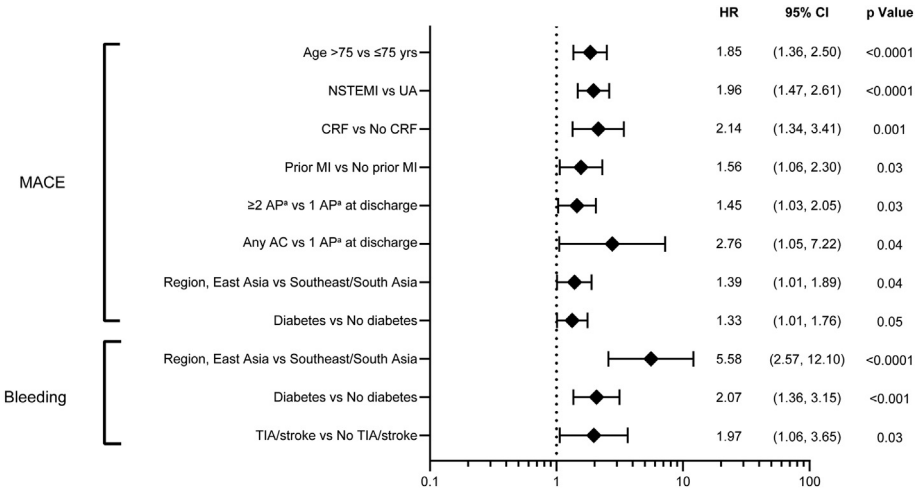

Fig. 2. Significant baseline risk factors of major adverse cardiovascular events and bleeding events up to 2 years post-discharge (Multivariate Cox Regression). Candidate covariates were: AMP at discharge (≥2 antiplatelets vs 1 antiplatelet [neither with anticoagulant], and any anticoagulant vs 1 antiplatelet [no anticoagulant]), diagnosis (NSTEMI, UA), age, gender, region, hypertension, hypercholesterolemia, diabetes, family history of coronary artery disease (CAD), current smoking, obesity (body mass index >30 kg/m^2), prior myocardial infarction, previous PCI, previous coronary artery bypass graft, coronary angiogram diagnostic for CAD, chronic angina, heart failure, atrial fibrillation, transient ischemic attack/stroke, peripheral vascular disease, and chronic renal failure. [a]No AC. AC, anticoagulant; AP, antiplatelet; CI, confidence interval; CRF, chronic renal failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; UA, unstable angina.

the opposite true for UA patients. This likely reflects the relative level of risk associated with each diagnosis. On unadjusted analysis, DAPT use was also more likely in males, and in patients with positive cardiac markers, elevated serum creatinine, and pre- or in-hospital use of cardiovascular medications. The results also showed that broad variability exists across countries in Asia in terms of discharge antiplatelet management strategy used for patients with NSTE-ACS, as also reported previously [6].

In our study, somewhat more patients discharged on DAPT had experienced a MACE by 2 years than those discharged on SAPT, although it should be noted that NSTEMI patients (i.e., those with higher risk) were more likely to be discharged on DAPT than UA patients. Based on our data, DAPT patients were more likely to have positive cardiac markers, hypercholesterolemia, and higher initial creatinine, and more likely to take other cardiovascular medications, which may indicate that these patients have more serious cardiac, renal, and lipid metabolism disorders. As we know, these cardiovascular risk factors have a strong association with higher risk of MACE [14–16]. Thus, it is likely that the difference in event rates was due to SAPT patients being at lower cardiovascular risk rather than it being a treatment effect per se.

European Society of Cardiology guidelines recommend administration of DAPT with low-dose aspirin and a $P2Y_{12}$ receptor antagonist, preferably prasugrel or ticagrelor, for at least 12 months following an ACS event [4], but the influence of long-term AMPs on outcomes of medically managed NSTE-ACS patients remains to be elucidated. Interestingly, while overall bleeding rates were relatively low, we observed more bleeding events in UA than NSTEMI patients, even though UA patients were more likely than NSTEMI patients to receive SAPT (Table 2). However, as noted in the results, the numbers of patients with bleeding events were not evenly distributed by region and index event diagnosis. When included together in the model, it was region that appeared to be important. To our knowledge, this is the first report of bleeding events in medically managed NSTE-ACS up to 2 years post-discharge. Another EPICOR study report from Spain showed that 4.1% of NSTE-ACS patients had experienced at least 1 bleeding event at 2 years, with no significant difference between patients on DAPT or SAPT, but the authors did not provide separate bleeding event rates for UA and NSTEMI patients [17]. Bleeding complications following ACS management continue to occur in the long term after hospital discharge, and may increase the risk of mortality per se and MACE [18], so should be given serious consideration. Although the EPICOR Asia study did not collect data on coagulation function, a study by Mathur and colleagues showed that platelet behavior differs between UA and MI [19]. The authors observed that mean platelet volume was higher in UA than in MI patients (due to increased platelet size in UA), but platelet count and the percentage of platelets expressing P-selectin were lower in UA, indicating that coagulation states are different in these 2 patient groups.

4.1. Study limitations

In terms of potential limitations, and as stated earlier, this observational analysis did not allow assessment of comparative effectiveness of AMPs, and causality of treatment effect on cardiovascular and bleeding events cannot be inferred due to treatment allocation bias and baseline confounding; that is, there are multiple variables associated with SAPT or DAPT beyond those created by the treatment alone. Although the analysis can be clinically interpreted if SAPT and DAPT at discharge are viewed as markers for comorbidity and concurrent medications, the findings in relation to outcomes should be interpreted with caution. Furthermore, the study was carried out largely before the availability of the more potent antiplatelet agents, prasugrel and ticagrelor. Although prasugrel was not observed to achieve a significant reduction in cardiovascular event rates compared with clopidogrel in medically managed NSTE-ACS patients [20], ticagrelor showed consistent cardiovascular benefit versus clopidogrel in NSTE-ACS patients intended for medical management [21,22], and in Asian and non-Asian ACS patients [23].

5. Conclusions

In conclusion, this analysis of patients from EPICOR Asia provided a unique opportunity to describe long-term management patterns in medically managed NSTE-ACS patients across the Asian region. NSTEMI patients were more likely than UA patients to receive DAPT at discharge, and approximately half of all patients remained on DAPT by the end of the 2-year follow-up period. MACE occurred more frequently in NSTEMI than in UA patients during long-term follow-up. Although bleeding events appeared higher in UA patients, region was shown to be a confounder.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.11.015.

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