



## Impact of triple antithrombotic therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention in real-world practice

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On behalf of the Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) Registry Investigators.

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### Abstract

**Objective** The optimal antithrombotic regimen for patients on oral anticoagulation (OAC) after acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) remains debated. This study sought to evaluate the efficacy and safety of OAC plus clopidogrel with or without aspirin in a real-world setting. **Methods** We retrospectively analyzed data from an international, multi-center registry between 2003 and 2014 ( $n = 15,401$ ). Patients with ACS and receiving OAC after PCI were screened. The composite primary endpoint was 1-year all-cause death, re-infarction, or severe bleeding. **Results** The final analysis enrolled 642 patients including 62 patients (9.7%) with OAC and clopidogrel (dual therapy), and 580 patients (90.3%) with the combination of aspirin, OAC and clopidogrel (triple therapy). Patients on triple therapy were more often female and were more likely to have comorbidities. There was no significant difference regarding the primary end point between dual therapy with triple therapy patients [17.74% vs. 17.24%; unadjusted hazard ratio (HR): 1.035; 95% confidence interval (CI): 0.556–1.929; adjusted HR: 1.026; 95% CI: 0.544–1.937]. However, the re-infarction rate was significantly higher in dual therapy than triple therapy patients (14.52% vs. 5.34%; unadjusted HR: 2.807; 95% CI: 1.329–5.928; adjusted HR: 2.333; 95% CI: 1.078–5.047). In addition, there was no difference between two regimes in all-cause death and severe bleeding. **Conclusions** In real-life patients with ACS following PCI and with an indication of OAC, triple therapy was not associated with an increased rate of adverse outcomes compared to dual therapy. Moreover, it decreased risk of re-infarction and did not increase risk of severe bleeding.

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## 1 Introduction

Current guidelines support co-administration use of oral anticoagulation (OAC) and dual-antiplatelet (DAPT) in patients with a formal indication of anticoagulation after percutaneous coronary intervention (PCI).<sup>[1,2]</sup> The largest randomized controlled trial (WOEST) confirmed the use of dual antithrombotic therapy (DT) (combined OAC and clopidogrel, DT) was prior to triple antithrombotic therapy (TT) (combined OAC, aspirin and clopidogrel, TT) with better clinical net benefit.<sup>[3]</sup> Moreover, Lamberts, *et al.*<sup>[4]</sup> gave the same recommendation in patients with atrial fibrillation. However, in patients with acute coronary syndrome (ACS) and an indication of OAC, who were recognized at increased risks for both hemorrhagic and ischemic complications, were mentioned less in previous studies.<sup>[5–7]</sup> The optimal antithrombotic regimen for patients on OAC after ACS and PCI remains debated

Therefore, this sub-analysis of the Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) registry sought to evaluate the efficacy and safety of OAC plus clopidogrel with or without aspirin in a real-world setting. We expect to make a further understanding of antithrombotic strategy for the ACS patients undergoing PCI with an indication of OAC.

## 2 Method

### 2.1 Study population

The design and rationale of the international, multi-center, retrospective observational BleeMACS registry are prescribed previously.<sup>[8]</sup> In brief, we collected data from a total of 18,077 ACS patients undergoing PCI from 16 centers in 11 countries from 2003 to 2014. A patient is eligible if diagnosed with ACS, at least 18 years old and without in-hospital death. Data from North America (Canada), South America (Brazil), Europe (Germany, Netherlands, Poland, Spain, Italy, Macedonia, Greece), and Asia (Japan and China) are included in the final cohort ( $n = 15401$ ), except that from one center (Macedonia,  $n = 2676$ ), due to a high percentage of missing values. Patients using OAC and clopidogrel with or without aspirin at discharge were included in the final analysis cohort ( $n = 642$ ). The scientific committee vouches for the integrity of the data. This study was approved by the local ethics committee of each center (the Ethical committee of Beijing Anzhen Hospital, Capital Medical University, NO.2015009X). All authors have read and agreed to the final manuscript. More information can be found at [clinicaltrials.gov](http://clinicaltrials.gov) (Identifier: NCT02466854).

### 2.2 Data collection and follow-up

Baselines of patient characteristics were collected, including patient demographics, medical history, concomitant diseases, chronic medical treatment and main diagnosis, as well as data on laboratory tests, index angioplasty and adjunctive therapy. Patients were followed up by telephone or face-to-face at discharge and at 1-year. Duration and adjustment of antithrombotic regimens were determined by physicians according to local guidelines. Data on the mortality, re-infarction and severe bleeding events and medical therapy were also documented at each follow-up point.

### 2.3 Study end points and definitions

The primary end point for BleeMACS and for this analysis was a composite end point of all-cause death, re-infarction, or severe bleeding events. All-cause death included both cardiovascular and other deaths. The definition of re-infarction is the simultaneous occurrence of ischemic symptoms (or new electrocardiographic changes) and new elevated troponin and/or creatine kinase or creatine kinase-MB. Severe bleeding event is defined as any TIMI (Thrombolysis In Myocardial Infarction) major bleeding, or any GUSTO (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded arteries definition for bleeding) severe or moderate bleeding, or any BARC (Bleeding Academic Research Consortium) type 3 bleeding intracranial bleeding or any other bleeding leads to hospitalization and/or red blood transfusion. Surgery related bleeding and/or transfusion were excluded from the analysis.

Prior bleeding includes any episode of severe bleeding previous to the qualifying of ACS hospitalization. The definition of complete revascularization in our study is a final angiographic result without coronary stenosis  $\geq 70\%$  in left anterior descending, left circumflex, or right coronary arteries, or stenosis  $\geq 50\%$  in left main coronary artery. The measurements of serum creatinine are standardized according to the recommendations of the National Kidney Disease Educational Program (NKEDP) and the European Federation of Clinical Chemistry and Laboratory Medicine, to reduce inter-laboratory variation in creatinine assay calibration.

### 2.4 Statistical analysis

Baseline clinical characteristics are described according to dual therapy versus triple therapy. Continuous and categorical variables were presented by using means and proportions respectively, and compared by using respective ANOVA and chi-square tests.

Kaplan-Meier estimates of outcomes, such as all-cause death event rates within one year, severe bleeding event

rates within one year, and re-infarction event rates according to different therapies were reported. Propensity scores were estimated with dual therapy versus triple therapy, by using a logistic regression model. Afterwards, a 1:1 balanced sample was selected by matching similar probabilities which were assigned to each patient. Unadjusted and adjusted Cox proportional hazard models were fit for each outcome of interest before and after ps-matching: unadjusted models included discharge therapy (dual therapy or triple therapy) as the sole variable, and concomitant variables, such as age, sex, diabetes mellitus, hypertension, peripheral arterial disease, malignancy, serum creatinine at admission, hemoglobin at admission and antithrombotic therapy, were applied in adjusted models. Hazard ratios (HRs) for triple therapy versus dual therapy and corresponding 95% confidence intervals (CIs) were reported by tables and forest plot.

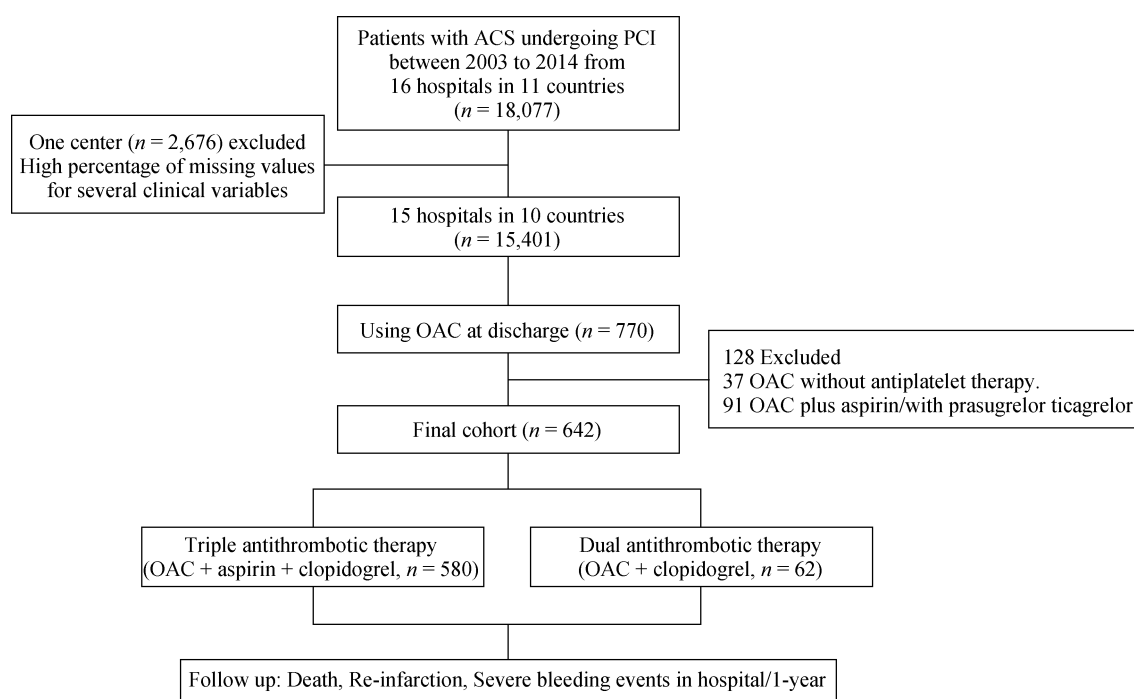
To consolidate our findings, we carried out a propensity score adjusted cox model in which propensity score was included besides aforementioned factors. A Cox model was used to estimate propensity score. In this Cox model, age, sex, diabetes mellitus, hypertension, peripheral arterial disease, history of malignancy, serum creatinine at admission, hemoglobin at admission and antithrombotic therapy were included according to variables screening (backward method) or prespecified (sex, diabetes mellitus and hemoglobin at admission).

In order to further analyze the impact of anticoagulation and antiplatelet therapy on re-infarction, we performed subgroup analyses using the Cox models on ten subsets.

Since the DT (or TT) records of our study subjects are complete with no missing data, we did not conduct an imputation. All *P* values were two-sided, and a *P* value of less than 0.05 was considered statistical significance. All analyses were performed using the SAS (Statistical software version 9.4, SAS Institute Inc.; Cary, NC).

### 3 Results

Data from 15,401 patients with ACS after PCI between 2003 and 2014 in 10 countries from 15 centers were included in the BleeMACS final database. Of them, 770 (5.0%) patients are prescribed OAC at discharge. We excluded 91 patients with single antiplatelet therapy with aspirin/with prasugrel or ticagrelor, and 37 OAC without antiplatelet therapy. Therefore, 642 patients using OAC and clopidogrel with or without aspirin at discharge were selected for the final analysis (Figure 1). Among them, 62 patients (9.7%) were prescribed OAC and clopidogrel (DT group) at discharge, others ( $n = 580$ , 90.3%) were treated with OAC, clopidogrel and aspirin (TT group); while 190 (29.6%) patients were at least 75 years old, 99 (15.4%) patients were female and 19 (3.0%) patients had prior bleeding.



**Figure 1. Study selection flow chart.** ACS: acute coronary syndrome; OAC: on oral anticoagulation; PCI: percutaneous coronary intervention.

Table 1 shows the baseline clinical characters of patients. Significant differences between groups were found in terms of gender ratio (16.2% *vs.* 8.1%,  $P = 0.0110$ , respectively), medical history of hypertension (50.3% *vs.* 16.1%,  $P < 0.01$ , respectively) and dyslipidemia (34.5% *vs.* 14.5%,  $P = 0.0350$ , respectively). Patients in the TT group experienced more heart failure at admission (killip class  $\geq 2$ ) than the DT group (21.4% *vs.* 4.8%,  $P = 0.0050$ , respectively). Patients in the TT group were more likely to have an index diagnosis of ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). Drug eluting stent (DES) was implanted in

the 103 patients (17.8%) of the TT group, while only 9.7 % of the DT group had received a DES ( $P = 0.0160$ ). Moreover, the use of Statins was more common in the TT group (61.2% *vs.* 11.3%,  $P = 0.0040$ , respectively).

### 3.1 Clinical outcome according to discharge antithrombotic regimen

Table 2 shows the Kaplan–Meier analysis on 1-year event rates of the DT and the TT group. 111 (17.29%) patients adjudicated all-cause deaths, re-infarctions or severe bleeding events were registered. There was no differences of primary end point between two regimens (17.74% *vs.*

**Table 1. Baseline characteristics by therapies.**

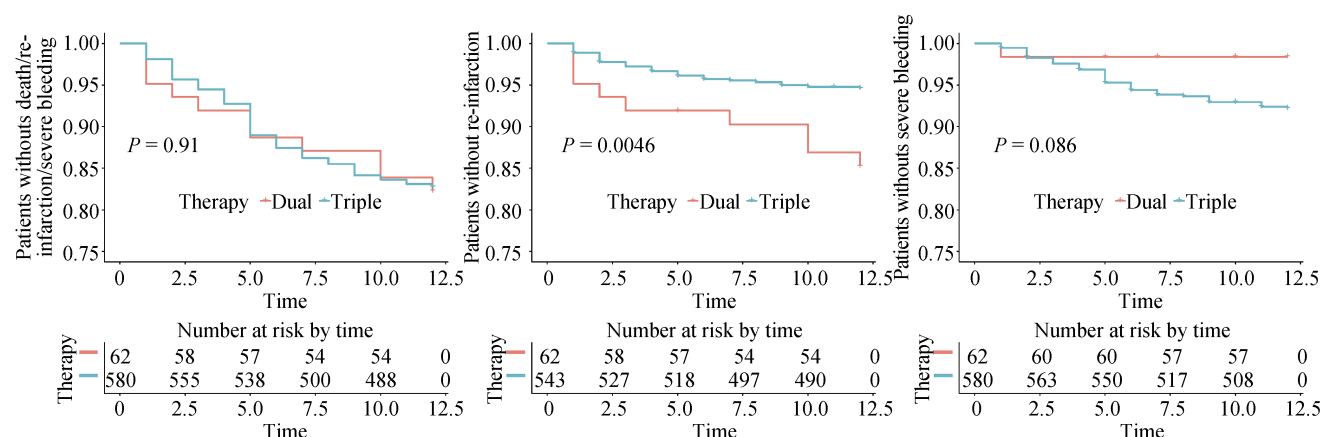
Characteristics	Triple antithrombotic therapy ( $n = 580$ )	Dual antithrombotic therapy ( $n = 62$ )	Total ( $n = 642$ )	$P$ Value
Age, yrs	70.61 $\pm$ 11.74	68.12 $\pm$ 12.52	70.37 $\pm$ 11.83	0.1145
$\geq 75$	184 (31.7%)	6 (9.7%)	190 (29.6%)	0.6720
Female	94 (16.2%)	5 (8.1%)	99 (15.4%)	0.0110
Medical history				
Hypertension	292 (50.3%)	10 (16.1%)	302 (47.0%)	0.0030
Dyslipidemia	200 (34.5%)	9 (14.5%)	209 (32.6%)	0.0350
Diabetes	129 (22.2%)	3 (4.8%)	132 (20.6%)	0.7550
Malignancy	34 (5.9%)	2 (3.2%)	36 (5.6%)	0.9250
Prior stroke	47 (8.1%)	3 (4.8%)	50 (7.8%)	0.6650
Congestive Heart Failure	36 (6.2%)	0 (0.0%)	36 (5.6%)	0.8860
Prior Bleeding	18 (3.1%)	1 (1.6%)	19 (3.0%)	0.4600
Prior AMI	68 (11.7%)	3 (4.8%)	71 (11.1%)	0.9280
Prior CABG	33 (5.7%)	0 (0.0%)	33 (5.1%)	0.2200
Prior PCI	56 (9.7%)	4 (6.5%)	60 (9.3%)	0.9350
Peripheral Arterial Disease	41 (7.1%)	2 (3.2%)	43 (6.7%)	0.2000
Index event type				
STEMI	175 (30.2%)	2 (3.2%)	177 (27.6%)	
Unstable Angina	48 (8.3%)	5 (8.1%)	53 (8.3%)	0.0001
NSTEMI	192 (33.1%)	6 (9.7%)	198 (30.8%)	
Clinical characteristic				
Baseline hemoglobin, g/dL	13.70 $\pm$ 1.91	13.41 $\pm$ 1.88	13.68 $\pm$ 1.91	0.2475
Baseline creatinine, mg/dL	1.07 $\pm$ 0.80	1.05 $\pm$ 0.44	1.07 $\pm$ 0.77	0.8659
Killip class at admission $\geq 2$	124 (21.4%)	3 (4.8%)	127 (19.8%)	0.0050
LVEF, %	47.61 $\pm$ 14.14	44.82 $\pm$ 8.42	47.54 $\pm$ 14.03	0.5157
Index PCI intervention				
Drug-eluting stent	103 (17.8%)	6 (9.7%)	109 (17.0%)	0.0160
PCI without Stent	19 (3.3%)	0 (0.0%)	19 (3.0%)	0.5030
Thrombolysis	9 (1.6%)	0 (0.0%)	9 (1.4%)	0.3230
Complete revascularization	252 (43.4%)	7 (11.3%)	259 (40.3%)	0.1440
Prescribed drugs				
$\beta$ -blocker	307 (52.9%)	7 (11.3%)	314 (48.9%)	0.9150
ACEI/ARB	333 (57.4%)	8 (12.9%)	341 (53.1%)	0.3500
Statins	355 (61.2%)	7 (11.3%)	362 (56.4%)	0.0040

Data was presented as mean  $\pm$  SD, or  $n$  (%). ACEI: angiotensin converting enzyme inhibitor; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; LVEF: Left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

**Table 2.** Unadjusted and propensity-score adjusted hazard ratios for 1-year endpoint in patients with dual or triple therapy.

	Dual antithrombotic therapy (n = 62) (%)	Triple antithrombotic therapy (n = 580) (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P for treatment
All-cause death/re-infarction/severe bleeding	11 (17.74%)	100 (17.24%)	1.035 (0.556–1.929)	1.026 (0.544–1.937)	0.9211
All-cause death/re-infarction	11 (17.74%)	64 (11.03%)	1.669 (0.880–3.164)	1.516 (0.786–2.926)	0.1181
All-cause death	6 (9.68%)	47 (8.10%)	1.196 (0.512–2.798)	1.059 (0.445–2.520)	0.6686
Re-infarction	9 (14.52%)	29 (5.34%)	2.807 (1.329–5.928)	2.333 (1.078–5.047)	0.0048
Severe bleeding	1 (1.61%)	44 (7.59%)	0.209 (0.029–1.519)	0.246 (0.034–1.804)	0.0799

Unadjusted and adjusted HR (95% CI) showing the relationship between OAC and clinical outcomes. CI: confidence intervals; HR: hazard ratios; OAC: on oral anticoagulation.

**Figure 2.** Kaplan-Meier analysis of 1-year primary endpoint (all-cause death/re-infarction/severe bleeding) in dual versus triple therapy.

17.24%; unadjusted HR: 1.035; 95% CI: 0.556–1.929; adjusted HR: 1.026; 95% CI: 0.544–1.937). The rate of re-infarction was significantly higher in patients with the DT than those with the TT (14.52% vs. 5.34%; unadjusted HR: 2.807; 95% CI: 1.329–5.928; adjusted HR: 2.333; 95% CI: 1.078–5.047). In addition, compared with DT, TT was not associated with an increased risk of all-cause death/re-infarction and all-cause death, or a decreased risk of severe bleeding (Table 2, Figure 2).

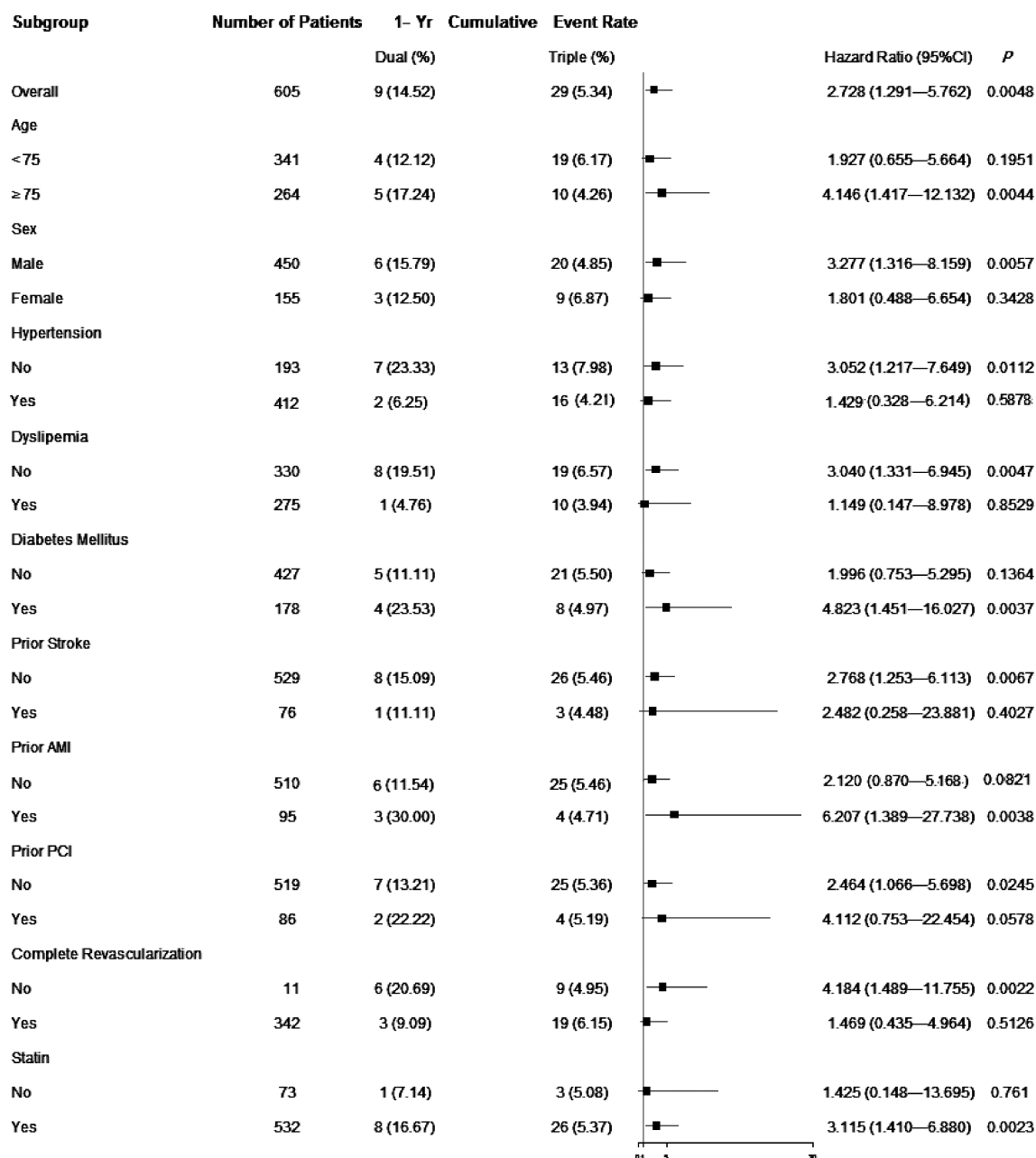
### 3.2 Subgroup analyses

We have performed analyses in ten subgroups: age, sex, hypertension, dyslipemia, diabetes, prior stroke, prior AMI, prior PCI, complete revascularization and use of statin for further understanding of the impact of anticoagulation and antiplatelet therapy on re-infarction. The results showed that the TT was superior to the DT in patients not younger than 75, male, having no medical history of hypertension, dyslipemia, diabetes, prior stroke or prior PCI, without complete revascularization. In contrast, patients with prior AMI and the use of statin were keen to benefit from the DT therapy (Figure 3).

## 4 Discussion

The main findings of this study were: (1) Compared with the DT, the use of TT was not associated with increased 1-year risk of the primary end point (all-cause death, re-infarction, or severe bleeding). (2) Unlike DT, TT decreased the risk of re-infarction and did not increase the risk of severe bleeding.

Rare study evaluated the efficacy and safety of triple antithrombotic therapy in ACS patients, our results confirm and extend the findings from observational studies or randomized trial that reported no associated risk of net clinical events in coronary artery disease (CAD) patients treated with TT,<sup>[9–15]</sup> but not holding the same opinions with the WOEST trial and several prior studies.<sup>[6,16,17]</sup> In our study, ACS patients who were treated with TT were older and had more comorbidities, thus indicating a cluster of patients with high risk of ischemic events. Probably, the optimal individualized antithrombotic strategy relates to the patient characteristics. It can be speculated that high-risk individuals are more prone to be prescribed for triple therapy and got benefit from the intensive antithrombotic therapy.



**Figure 3. Subgroup analyses of re-infarction.** CI: confidence interval; PCI: percutaneous coronary intervention.

Our finding was that in ACS patients with an indication of OAC after PCI, the triple therapy is superior to the dual therapy in respect to the prevention of ischemic outcomes of re-infraction while the risk of severe bleeding was similar. Notably, current guidelines recommend triple therapy in ACS patients under careful consideration of decreasing both the risk of ischemic event and bleeding event.<sup>[1,18]</sup> Meta-analysis on triple therapy shows a protection from ischemic events with no clear excess bleeding, compared to other regimens,<sup>[19,20]</sup> but most the studies performed in single center settings. On the basis of this multicenter experience,

the triple therapy is well tolerated in ACS patients with stent, and is associated with low rates of re-infarction events without elevated bleeding events. TT should be considered as an optional item for ACS patient with a high risk of ischemic and low risk of bleeding.<sup>[21]</sup>

Serval prior studies have reiterated that the optimal anti-thrombotic regimen for individuals with ACS should balance the risk of bleeding and ischemic events by their personal characteristics.<sup>[5,22–24]</sup> With regards to this, we performed a subgroup analysis for the re-infarction event for further understanding. We found that patients not younger

than 75 years old, male, absent of medical history of hypertension, dyslipidemia, diabetes, prior stroke or prior PCI, without complete revascularization were more likely to benefit from the TT therapy. Meanwhile, patients with prior AMI and use of statin may have a better outcome with the DT therapy. Consistent with these findings, results from numerous series of pre-existing investigations have disavowed the alleged higher anti-ischemic protection through the practice of adding two, rather than one, antiplatelet agent on top of OAC in patients with an indication for anticoagulation with stenting.<sup>[19,25–29]</sup> Due to statistical limitation, our experience from this retrospective study may not be applicable to all ACS-PCI practices. Prudent treatment decision should be made on a case by case basis, especially for risk groups with thrombosis and bleeding risk.

Limitations of this study should be acknowledged. The small sample size in the DT group limited the statistical power to revise the primary endpoint. We did a sensitivity analysis on a wider definition of dual antithrombotic therapy which included patients with all kinds of dual therapy ( $n = 153$ ): use of aspirin and OAC, clopidogrel and OAC, ticagrelor and OAC or prasugrel and OAC. There was no difference between the wider DT group and TT group in the primary endpoint (18.30% vs. 17.24%; unadjusted HR: 1.099; 95% CI: 0.723–1.671; adjusted HR: 1.208; 95% CI: 0.693–2.103). Based on the superiority of clopidogrel and OAC compared with other dual therapy regimens in Morten Lamberts *et al.* work, we used the most popular and reasonable dual therapy regimen (OAC + clopidogrel) and made a careful interpretation of our result.<sup>[4]</sup> Further studies are required in a larger population to give a firm recommendation in this specific population. Additionally, like the other observational studies, observation bias obviously existed. However, the primary endpoint was constituted with hard endpoints and was, therefore, less subject to the bias. This study should be more immune to inclusion bias, as it was based on an international, multi-center registry. Finally, clinical events could be under- or over-estimated because that individual information was collected by patients' self-report. Therefore the preliminary results of our study could be useful for further investigation in this field.

## 5 Conclusions

In the real-world registry of ACS patients following PCI and with an indication of OAC, triple therapy (combination of OAC, clopidogrel and aspirin) was not associated with an increased rate of adverse outcomes compared to dual therapy. Moreover, unlike DT, TT decreased the risk of re-infarction and did not increase the risk of severe bleeding.

Therefore, TT is an optional item in ACS patients after stenting, especially in patients with a higher risk of thrombosis.

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