De-escalation of Antiplatelet Therapy Retains P2Y12 Inhibitor After Percutaneous Coronary Intervention Among East Asians and Non-East Asians: A Meta-Analysis of Randomized Controlled Trials

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Research Article

Keywords: antiplatelet therapy, de-escalation, meta-analysis, percutaneous coronary intervention, randomized controlled trials

Posted Date: July 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-709986/v1

Abstract

Background: The impact of de-escalation of antiplatelet therapy retains P2Y12 inhibitor on major bleeding and ischemic outcomes after percutaneous coronary intervention (PCI) among East Asians and non-East Asians was unclear.

Methods: We systematically searched PubMed, Embase and the Cochrane Library for randomized controlled trials through September 2020. Eight trials were included, which studied de-escalation of DAPT (D-DAPT, switching to P2Y12 inhibitor monotherapy or decreasing the intensity of P2Y12 inhibitor after 1 to 3 months) versus 12 months standard DAPT (S-DAPT). The primary outcomes data were conducted with random effects models.

Results: Among 8 included trials with 37,775 patients, 62.6% of patients presented with acute coronary syndrome. The median follow-up duration ranged from 12 to 24 months. Compared with S-DAPT, D-DAPT was associated with a lower risk of major bleeding (RR=0.64, 95%CI: 0.47-0.88, *p*=0.006), but this was only observed among East-Asians (RR=0.55, 95%CI: 0.38-0.81, *p*=0.002). Among non-East Asians, the rate of major bleeding was similar between two groups (RR=0.73, 95% CI: 0.46-1.14, *p*=0.17). There was no significant difference of MACE between D-DAPT and S-DAPT treatment among both East Asians (RR=0.84, 95%CI: 0.66-1.08, *p*=0.18) and non-East Asians (RR=0.89, 95%CI: 0.79-1.00, *p*=0.05).

Conclusions: De-escalation strategy retains P2Y12 inhibitor after PCI was associated with reduced risk of bleeding events, which was only demonstrated in East Asians patients, but not in non-East Asians patients.

Background

Current, the American College of Cardiology (ACC)/American Heart Association (AHA), European, and Chinese guidelines all recommend that patients with acute coronary syndrome (ACS) undergoing percutaneous coronary interventions (PCI) should receive 12 months of dual antiplatelet therapy (DAPT) and those with stable coronary artery diseases (SCAD) undergoing PCI should receive 6 months of DAPT as a standard therapy (aspirin plus a P2Y12 inhibitor [1-6]). Given that most of bleeding complications might be occurred at 1 to 3 months after PCI, several large RCTs have evaluated the effect of de-escalation strategies [7-14], but the results are conflicting. Recently, several studies have reported that East Asian populations have different ischemia and bleeding profiles and might be more susceptible to bleeding [15-17], so they may not benefit from more potent antithrombotic strategies [7-10]. Therefore, we conducted this meta-analysis to evaluate the impact of de-escalation strategies retains P2Y12 inhibitor on both bleeding and ischemic events among East Asian and non-East Asian populations. We present the following article in accordance with the PRISMA reporting checklist.

Methods

Data Sources and Search Strategies

We searched PubMed, Embase and the Cochrane Library for randomized control trials (RCTs) through September 2020 by two independent investigators (G. W. and X. W.) without language restrictions. The following key words were used: “de-escalation” or “switch” and “percutaneous coronary intervention” or “PCI” or “acute coronary syndrome” or “ACS” and “antiplatelet therapy” or “prasugrel” or “ticagrelor” or “clopidogrel” (Figure 1).

Study Selection and Eligibility Criteria

Two investigators (G. W. and X. W.) independently assessed studies considered for inclusion by screening the titles and abstracts. The inclusion criteria were: (1) RCTs that compared de-escalation of DAPT (D-DAPT, switching to monotherapy that followed by P2Y12 receptor inhibitor, switching from a potent P2Y12 receptor inhibitor to clopidogrel or dose reduction of P2Y12 inhibitor) with standard DAPT (S-DAPT); (2) reporting on ischemic and bleeding events; (3) sample size >500 patients. Studies that focused on duration of DAPT for ACS undergoing PCI and reported on pharmacodynamics and pharmacokinetic of drugs were excluded.

Data Extraction and Quality Assessment

Data extraction and adjudication were performed independently by two investigators (G. W. and X. W.) using a standardized electronic form. Any discrepancies were judged and solved by a senior author (S.N.). We recorded the following information: time span, region, demographic characteristics, timing of de-escalation, switching strategy, number of events and participants, follow-up duration, and outcomes.

The potential risk of bias of selected RCTs was assessed using the Cochrane Risk of Bias Tool[18]. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[19].

Outcome Measures

The primary outcome was major adverse cardiovascular events (MACE), including all-cause or cardiovascular death, myocardial infarction, repeat revascularization, stent thrombosis or stroke, which was reported by studies or integrated with ischemic events of each study. The primary safety outcome was major bleeding, defined as Bleeding Academic Research Consortium (BARC) ≥3, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding. Secondary efficacy outcomes included cardiovascular death, all-cause death, myocardial infarction (MI), definite or probable stent thrombosis, repeat revascularization, and stroke. According to ethnicity, we compared the outcomes between two strategies among East Asian and non-East Asian populations.

Statistical Analysis

A random effect model was used to evaluate all outcomes of interest among East Asians and non-East Asians patients, which were reported as Risk Ratio (RR) with 95% confidence intervals (CI). The Cochran Q test and I^2 statistic were used to assess heterogeneity. I^2 statistic scores of 25%, 50%, 75% respectively represents low, moderate and high heterogeneity. Sensitivity analyses were performed to evaluate the reasons for heterogeneity or the potential bias. Forest plot was used to evaluate the overall effect of trials, and funnel plots was used to assess the publication bias. All data analysis was performed with Cochrane Review Manager software (version 5.4). A 2-sided *p* value <0.05 was considered statistically significant.

Results

From 7013 publications, 176 trials were assessed for full-text eligibility. After reading the full manuscripts, 168 studies were excluded, of which 53 studies were systematic reviews or meta-analysis, 31 studies were not RCTs, and 25 studies did not report on outcomes of interest. Finally, a total of 8 trials with 37775 patients were included in this meta-analysis (Figure 1). Overall, 23637 patients (62.6%) presented as ACS, and the follow-up duration ranged from 12 to 24 months. Five trials evaluated a P2Y12 inhibitor monotherapy comparing with DAPT, and two trials evaluated a potent P2Y12 inhibitor switching to clopidogrel, and one trial evaluated switching the dose of prasugrel from 10mg to 5mg. The detailed characteristics of all included studies are described in Table 1. The baseline clinical characteristics of each study are summarized in Table 2. Quality assessment were reported in Supplement Fig. A.3. Among the 8 included studies, 87.5% had high risk of blinding of intervention, and 100% had a low risk of blinding of outcome assessment.

Primary Efficacy and Safety Outcomes

We analyzed the effect of D-DAPT on major bleeding in 8 trials, a total of 679 major bleeding events occurred in all participants. Treatment with D-DAPT was associated with a lower risk of major bleeding (RR=0.64, 95%CI: 0.47-0.88, *p*=0.006), but this was only observed in studies including East Asians patients (1.2% vs. 2.3%, RR=0.55, 95%CI: 0.38-0.81, *p*=0.002). Among non-East Asians, the rate of major bleeding was similar in D-DAPT and S-DAPT groups (1.6% vs. 2.0%, RR=0.73, 95% CI: 0.46-1.14, *p*=0.17) (Figure 2).

All trials reported outcome of MACE. Treatment with de-escalation DAPT strategy was associated with a decreased risk of MACE (RR=0.88, 95%CI: 0.79-0.98, *p*=0.02) in all participants. There was no significant difference of MACE between D-DAPT and S-DAPT treatment among both East Asians (RR=0.84, 95%CI: 0.66-1.08, *p*=0.18) and non-East Asians (RR=0.89, 95%CI: 0.79-1.00, *p*=0.05) (Figure 3).

Cardiovascular Death and All-cause Death

Among both East Asians and non-East Asians, there was no statistically significance in cardiovascular death (7 trials with 21807 patients) between D-DAPT and S-DAPT groups (Figure 4). Similarly, no statistical difference of all-cause death (7 trials with 37129 patients) was observed in both East Asians and non-East Asians (Figure 5).

Individual Cardiovascular Events

There were no statistical difference between D-DAPT and S-DAPT treatment in myocardial infarction (RR=0.79, 95%CI: 0.51-1.22, *p*=0.29 in East Asians; RR=0.99, 95%CI: 0.86-1.14, *p*=0.84 in non-East Asians), definite or probable stent thrombosis (RR=1.41, 95%CI: 0.59-3.33, *p*=0.44 in East Asians; RR=0.93, 95%CI: 0.69-1.26, *p*=0.65 in non-East Asians), repeat revascularization (RR=1.15, 95%CI: 0.91-1.46, *p*=0.24 in East Asians; RR=0.98, 95%CI: 0.82-1.18, *p*=0.84 in non-East Asians), and stroke (RR=0.95, 95%CI: 0.52-1.77, *p*=0.88 in East Asians; RR=0.99, 95%CI: 0.55-1.76, *p*=0.97 in non-East Asians) (Figure 6).

Sensitivity Analyses

There was a slight trend but no significant difference in MACE among non-East Asians between D-DAPT and S-DAPT groups. While the TROPICAL-ACS trial included a part of patients who were re-escalated to prasugrel, which maybe affect the ischemic outcomes. After removal of the TROPICAL-ACS trial, the risk of ischemic outcomes was similar among non-East Asians who received de-escalation of DAPT or standard DAPT. The risk of major bleeding events was significantly lower with de-escalation of DAPT in initial pooled analysis, but substantial heterogeneity was presented. After removal of the GLOBAL-LEADERS trial, the risk of major bleeding was still lower with de-escalation of DAPT, while the heterogeneity I^2 was reduced from 64% to 23%. This may be due to large sample size of this trial. Among non-East Asians, the risk of major bleeding events was similar between D-DAPT group and S-DAPT group. However, due to unavailability of data of individual patients in TWILIGHT trial which included one-sixth Asian, we pooled this trial into the subgroup of non-East Asians. After removal of the TWILIGHT trial, the risk of major bleeding was still similar between two groups among non-East Asians.

Discussion

In the present meta-analysis, we found the following points: (1) Compared with S-DAPT, treatment with D-DAPT retains P2Y12 inhibitor was associated with lower risks of MACE and major bleeding complications; (2) Compared with S-DAPT, D-DAPT retains P2Y12 inhibitor was associated with a lower risk of major bleeding, but this was only observed among East Asians. Among non-East Asians, the rate of major bleeding was similar between two groups. (3) There were also no significant associations between D-DAPT retains P2Y12 inhibitor treatment with cardiovascular death, all-cause death and individual cardiovascular outcomes among East Asians and non-East Asians. Based on these results, compared with standard DAPT strategy, de-escalation of DAPT retains P2Y12 inhibitor treatment might be considered as an alternative DAPT strategy for East Asians.

It is well known that East Asians who received dual antiplatelet therapy after PCI have a higher risk of bleeding and a lower risk of ischemia[20]. This may be due to the lower body mass index (BMI) of the East Asians compared with non-East Asians. Previous studies have shown that obesity is associated with thrombosis[21], and it's a prethrombotic state that could cause a series of changes in the body to promote the formation of thrombus[22]. This may be one of

the reasons why the risk of ischemia in East Asians is lower than that in non-East Asians. Secondly, the genetic polymorphism between different races may also explain the profile of East Asians. Previous Multi-Ethnic Study of Atherosclerosis (MESA) studies [23]have shown that Blacks have highest levels of dysfunctional endothelial profile (such as factor VIII, D-Dimer, plasmin–antiplasmin, and von Willebrand factor), so they have the highest risk of thrombotic events, followed by Caucasians and Hispanics, and finally the Chinese participants. In addition, previous studies have shown that the level of inflammation can also affect thrombosis, and the level of inflammation in East Asians is lower than that in non-East Asians[24], which may also explain the low risk of ischemia in East Asians.

Previously, Bianco et al. (4 RCTS, 29089 patients) indicated that after short-term DAPT followed by $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of clinically relevant bleeding [odds ratio (OR) = 0.70, 95%CI: 0.58–0.86] for patients undergoing PCI, as compared with 12 months DAPT, without an increasing risk of 1-year cardiovascular events (OR = 0.90, 95%CI: 0.79–1.03) [25]. Similarly results was observed in the analysis of Michelle et al. (5 trials, 32,145 patients) [26]. But none of them included the latest research. Moreover, the population of these studies is very wide, and they did not consider the differences of ethnicity. Our research confirmed that for East Asians, de-escalation strategy retains P2Y12 inhibitor was associated with a lower risk of major bleeding, but this was not observed among non-East Asians.

During one-to-three months after stenting, which belongs to the high incidence phase of ischemic events after PCI, the thrombotic risk outweighs the bleeding risk. While bleeding events generally occurred during a longer period after stent implantation, which belongs to the chronic phase. From the studies we included, it was noted that most of the de-escalation strategies start at one or three months after receiving dual antiplatelet therapy. As mentioned before, East Asians have a profile of high risk of bleeding. Therefore, in the chronic phase, downgrading of dual antiplatelet therapy, so as to reduce the degree of platelet inhibition, might reduce the risk of bleeding events among East Asians[7–10]. This is consistent with the results of our meta-analysis. Among non-East Asians, we found that the effects of de-escalation of DAPT and standard DAPT on major bleeding events were similar and no significant difference. Although the TWILIGHT study[12] which across both East-Asians and non-East Asians showed downgrading therapy could reduce bleeding events with BARC $\geq$ 2 in Asians and Caucasians, de-escalation of DAPT cannot reduce the risk of major bleeding (HR = 0.49, 95CI%: 0.33–0.74). What's more, the study did not report the primary interest outcomes in East-Asians, the effect on major bleeding events between East-Asians and non-East Asians was not clear. And our sensitivity analysis showed that whether or not the study is removed, there is no significant effect on major bleeding outcomes of the non-East Asians subgroup. Therefore, the results of our meta-analysis can be considered reliable.

However, the results should be interpreted with caution. First, different definition might influence the incidence of outcomes, including MACE and major bleeding events. Second, various de-escalation strategies among different races included in this analysis might affect the pooled analysis results. Thirdly, the TWILIGHT trial included both East-Asians and non-East Asians. Due to lack of patient level data, we pooled all the data into non-East Asians group.

Limitations: This analysis has certain limitations. First, the rates of ischemic events were lower than anticipated in most of the included trials, resulting in limited statistical power for ischemia outcomes. Secondly, the included patients composed of both ACS and SCAD, and owing to lack of individual level data, we could not perform subgroup analysis for both groups. Thirdly, adherence of agents was not noted, which was a recognized and common factor associated with long-term outcomes. Fourth, the race was judged by the sites of the participating studies. Therefore, the possibility of the race mix-up was not excluded in those studies. And since patient category (East Asian versus other) is totally dependent upon study, it is possible that the racial differences are really just differences among the studies. Fifth, the current analysis just focused on major bleeding events, but minor bleeding was not reported, which more likely resulted in lower adherence of treatment in clinical practice. Finally, although we strictly performed the study searching and selection, some extent of potential publication or selection bias cannot be neglected.

Conclusions

De-escalation strategy after PCI was associated with reduced risk of bleeding events, which was only demonstrated in East Asians patients, but not in non-East Asians patients. De-escalation of DAPT might be a safer and equally effective strategy for East Asians compared with standard DAPT strategy.

Abbreviations

DAPT
dual antiplatelet therapy
PCI
percutaneous coronary intervention
D-DAPT
de-escalation of DAPT
S-DAPT
standard DAPT
MACE
major adverse cardiovascular event
RR
Risk Ratio
CI
confidence intervals
ACC / AHA

American College of Cardiology / American Heart Association
ACS
acute coronary syndrome
SCAD
stable coronary artery diseases
RCTs
randomized control trials
BMI
body mass index
OR
odds ratio

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This study was funded by grants from Beijing Municipal Health Commission (grant numbers 2018-1-2061), Beijing Nova Program (grant numbers Z201100006820087), the Natural Science Foundation of Beijing, China (grant numbers 7191002), Beijing Municipal Administration of Hospitals (grant numbers ZYLX201710, DFL20180601), and Beijing Municipal Science and Technology Commission (grant numbers Z181100001718060).

Authors' contributions:

GW, XW and SN contributed to design the study and conduct the literature search and data extraction. GW and XW performed this meta-analysis. GW, XW, GZ, XH and RG contributed to interpretation of data. GW and XW wrote the draft of the manuscript, and all authors critically revised the manuscript and approved the final manuscript.

Acknowledgments:

Not applicable

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Tables

Table1 Study design and clinical characteristics of included studies

Study name	Period	Reigon	Center	Population	D-DAPT	S-DAPT	Timing of de-escalation	Switching strategy	MACE	Bleeding	Follow-up time
HOST-REDUCE-POLYTECH-ACS	2014-2018	Korea	M	ACS	1170	1168	1 month after PCI	Prasugrel 10mg-5mg	Cardiac death+ MI+ stent thrombosis+ ischemic stroke	BARC	1Y
TWILIGHT	2015-2017	North America+ Europe+ Asia	M	ACS+SCAD	3555	3564	3 months after discharge	ticagrelor monotherapy	all-cause death+ nonfatal MI+ nonfatal stroke	BARC	15 mon
TICO	2015-2018	Korea	M	ACS	1527	1529	3-months after DAPT	ticagrelor monotherapy	death+ MI+ stent thrombosis+ stroke+ target-vessel revascularization	TIMI	1Y
TOPIC	2014-2016	France	S	ACS	323	323	1 month after ACS	ticagrelor /prasugrel-clopidogrel	cardiovascular death+ unplanned urgent coronary revascularization+ stroke	TIMI	1Y
TROPICAL-ACS	2013-2016	European	M	ACS	1304	1306	P(1-week) +c(1-week) and PFT-guided therapy from day 14	prasugrel-clopidogrel (PFT-guided)	cardiovascular death+ MI+ stroke	BARC	1Y
SMART CHOICE	2014-2018	Korea	M	SCAD+ACS	1495	1498	3-months after DAPT	a P2Y12 inhibitor monotherapy	all-cause mortality+ MI+ stroke.	BARC	1Y
STOPDAPT-2	2015-2017	Japan	M	SCAD+ACS	1523	1522	1 month after DAPT	Clopidogrel monotherapy	cardiovascular death+ MI+ definite stent thrombosis+ stroke	BARC	1Y
GLOBAL-LEADERS	2013-2015	European	M	SCAD+ACS	7980	7988	1 month after DAPT	ticagrelor monotherapy	all-cause mortality+ stroke+ new Q-wave MI	BARC	2Y

RCT: randomized controlled trials; ACS: acute coronary syndrome; SCAD: stable coronary artery disease; PCI: percutaneous coronary intervention; M: multi-center; S: single center; MACE: major adverse cardiovascular events; BARC: Bleeding Academic Research Consortium; TIMI: Thrombolysis In Myocardial Infraction major bleeding; Y: year; mon: month; P: prasugrel; T:ticagrelor; PFT: platelet function testing; DAPT: dual antiplatelet therapy; D-DAPT: de-escalation of dual antiplatelet therapy; S-DAPT: standard dual antiplatelet therapy; MI: myocardial infraction.

Table 2 Baseline clinical characteristics of included studies

Study name	Age (y; m)	Female (n, %)	BMI (kg/m2; m)	DM (n, %)	Current smoker (n, %)	Prior MI (n, %)	Chronic kidney disease (n, %)	ACS (n, %)
HOST-REDUCE-POLYTECH-ACS[7]	58.8	252 (10.7)	25.8	990 (42.3)	838 (35.8)	90 (3.8)	64 (2.7)	2338 (100)
TWILIGHT[11]	65.2	1698 (23.9)	28.6	2620 (36.8)	1548 (21.8)	2040 (28.7)	1145 (16.8)	4614 (64.8)
TICO[9]	61	628 (20.5)	24.9	835 (27.3)	NA	113 (3.7)	620 (20.3)	3056 (100)
TOPIC[13]	60	114 (18)	27.2	177 (27)	286 (44)	NA	NA	646 (100)
TROPICAL-ACS[14]	58.8	2052 (78.6)	28.3	527 (20.2)	1182 (45.3)	293 (11.2)	67 (2.6)	2610 (100)
SMART CHOICE[8]	64.5	795 (26.6)	24.6	1122 (37.5)	791 (26.4)	127 (4.2)	97 (3.2)	1741 (58.2)
STOPDAPT-2[10]	68.6	672 (22.3)	24.3	1159 (38.5)	710 (23.6)	406 (13.5)	166 (5.5)	1148 (38.2)
GLOBAL-LEADERS[12]	64.6	3714 (23.3)	28.2	4038 (25.3)	4169 (26.1)	3710 (23.2)	2171 (13.6)	7484 (46.9)

BMI: Body-mass index; DM: diabetes mellitus; MI: myocardial infraction; ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infraction; y: years; m: mean; n: number; NA: not available

Figures

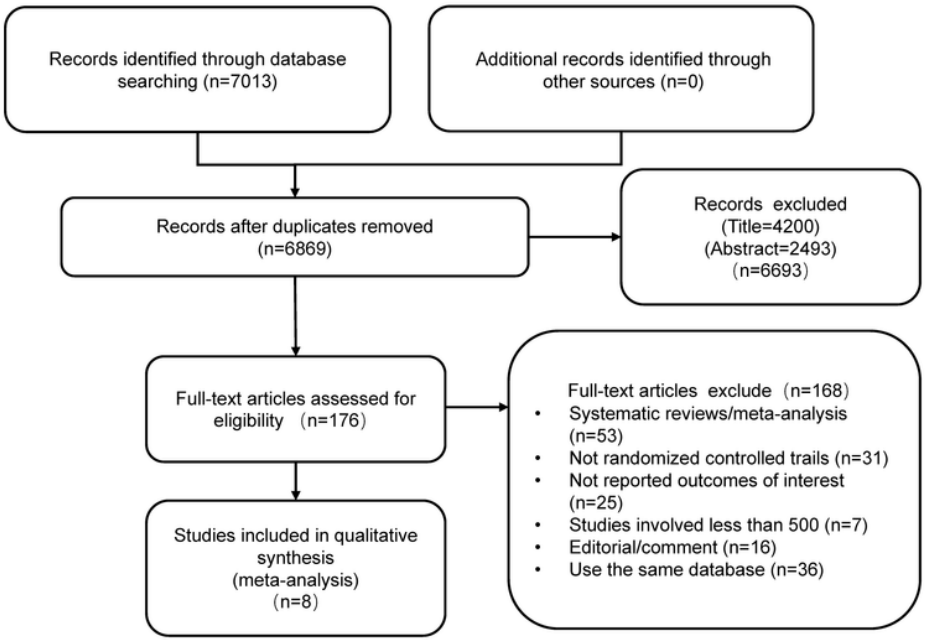

Figure 1

Flow chart of the study selection process of meta-analysis

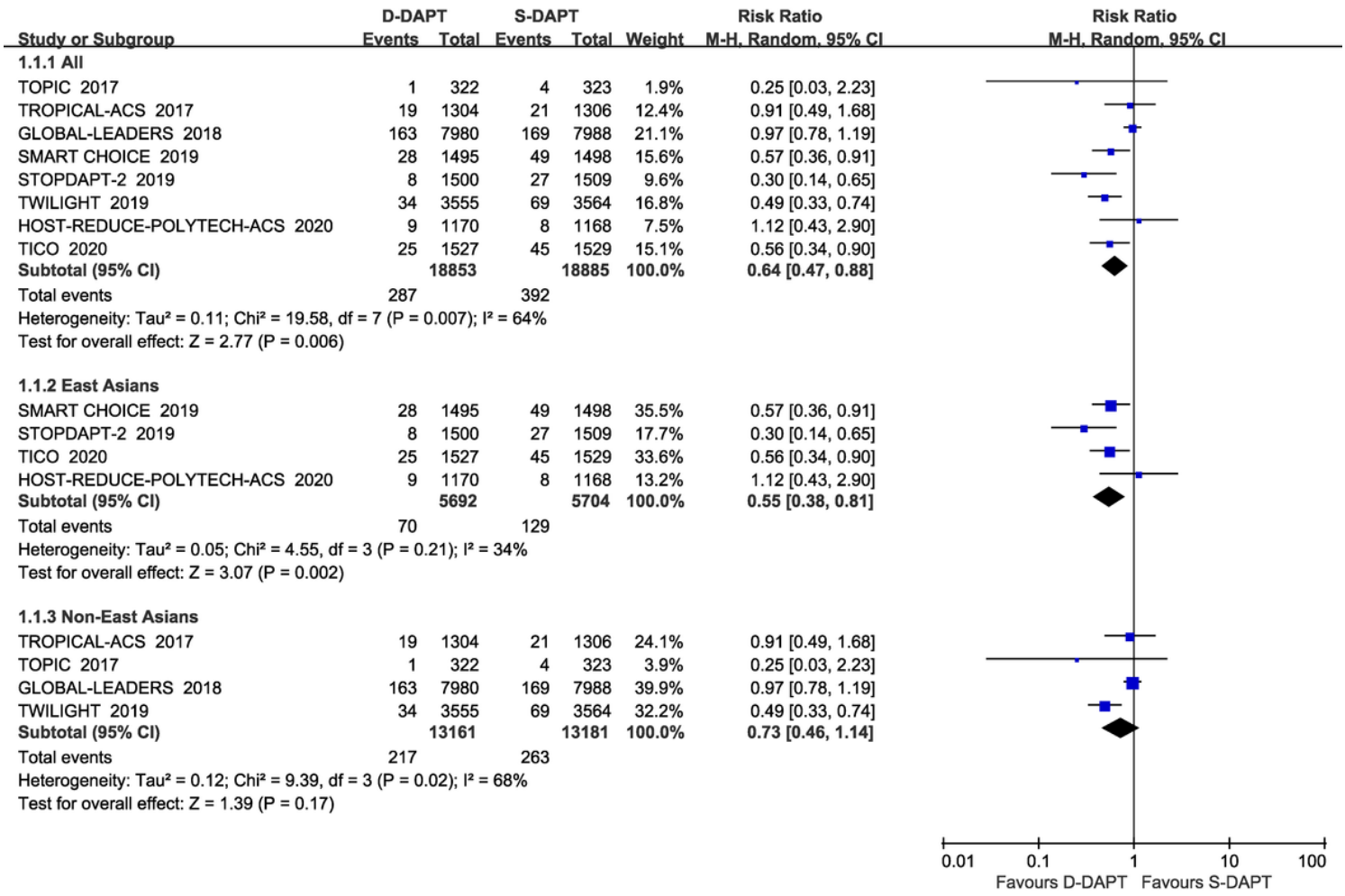

Figure 2

Forest plot of the risk estimates for major bleeding in patients treated with de-escalation of dual antiplatelet therapy (D-DAPT) compared to standard DAPT (S-DAPT)

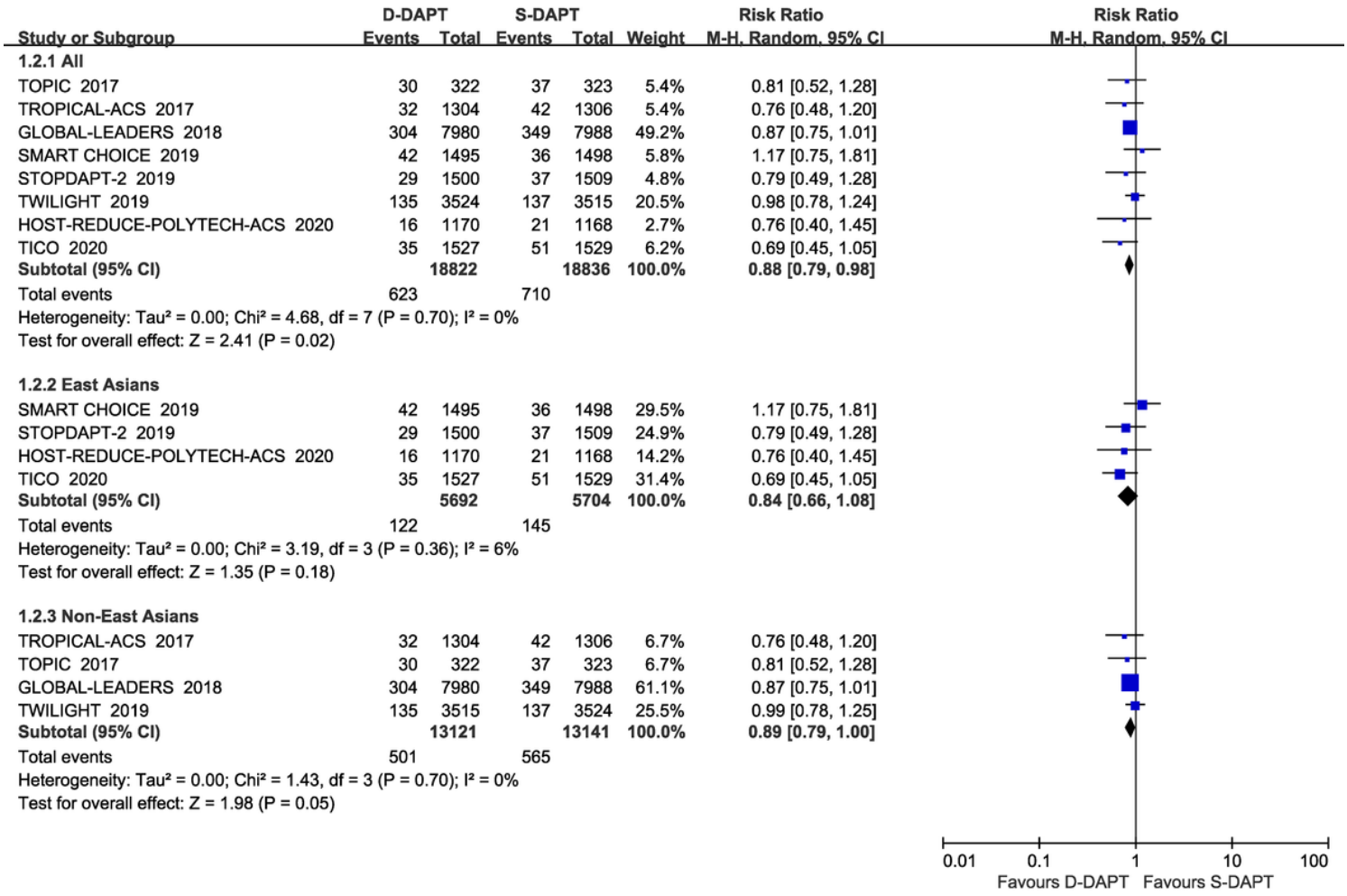

Figure 3

Forest plot of the risk estimates for major adverse cardiovascular events (MACE) in patients treated with de-escalation of dual antiplatelet therapy (D-DAPT) compared to standard DAPT (S-DAPT)

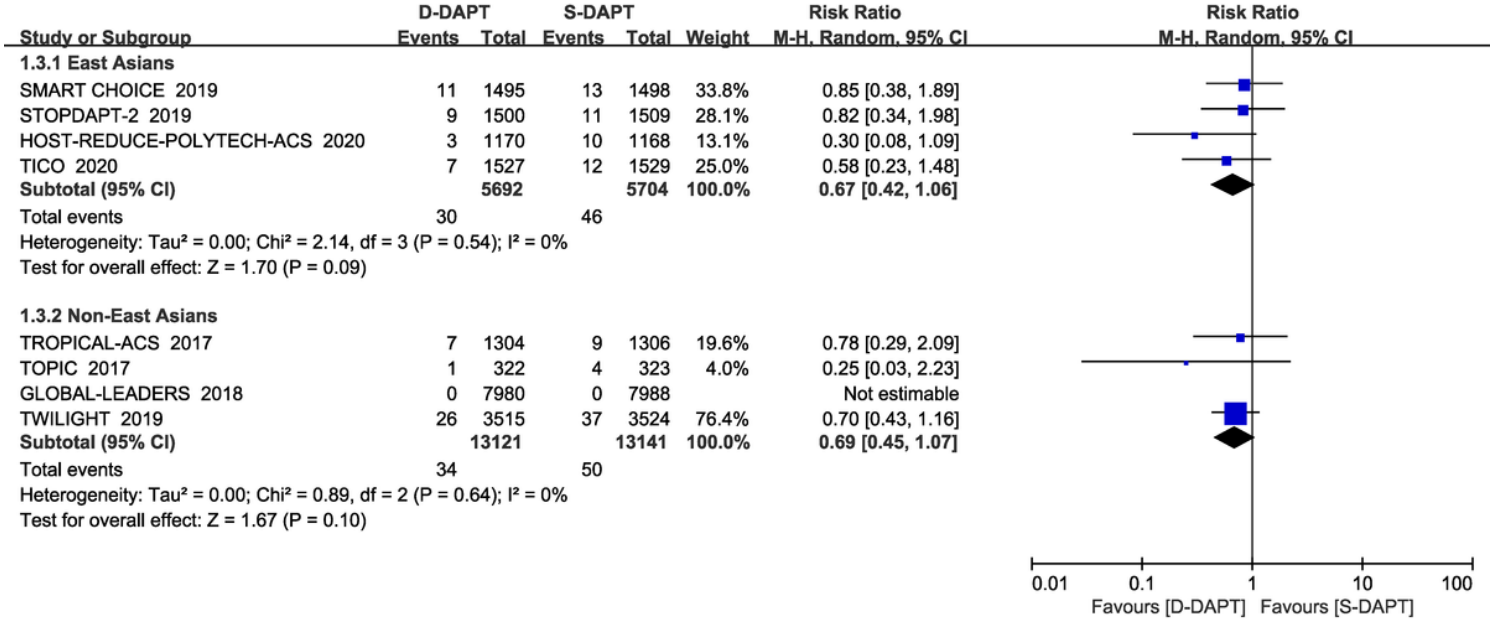

Figure 4

Forest plot of the risk estimates for cardiovascular death in patients treated with de-escalation of dual antiplatelet therapy (D-DAPT) compared to standard DAPT (S-DAPT)

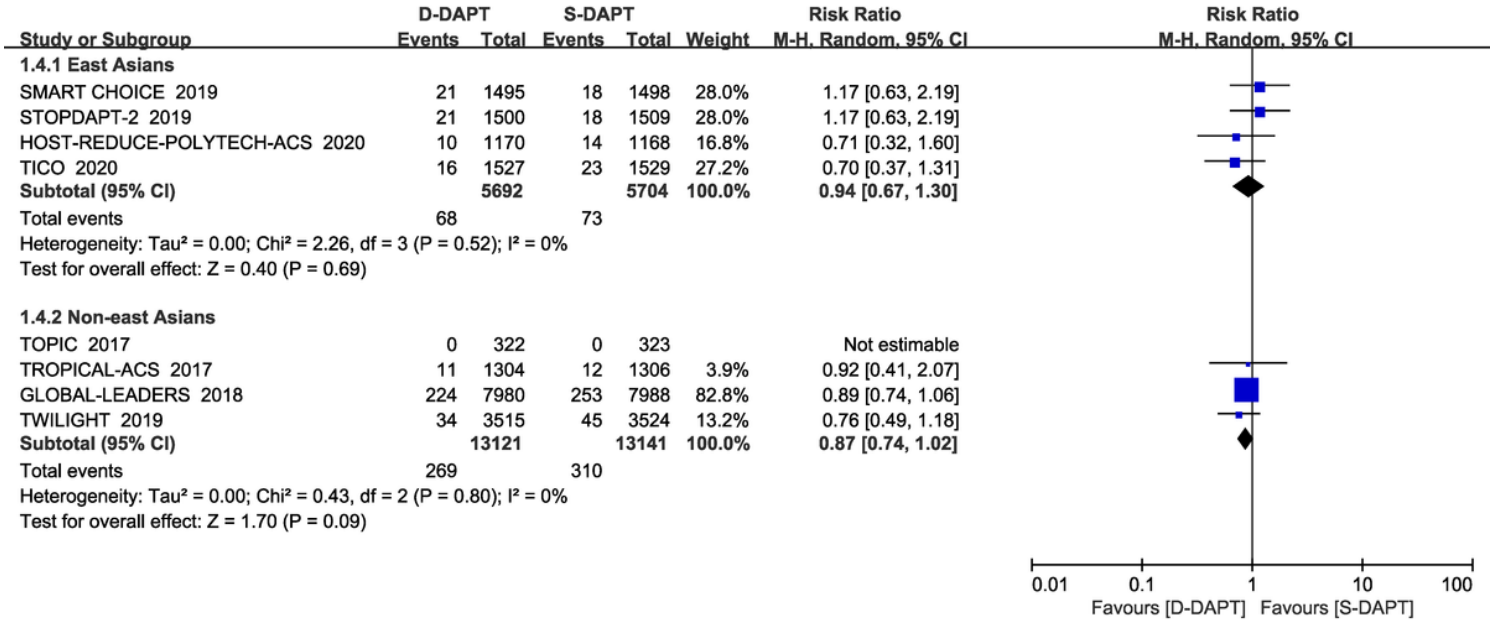

Figure 5

Forest plot of the risk estimates for all-cause death in patients treated with de-escalation of dual antiplatelet therapy (D-DAPT) compared to standard DAPT (S-DAPT)

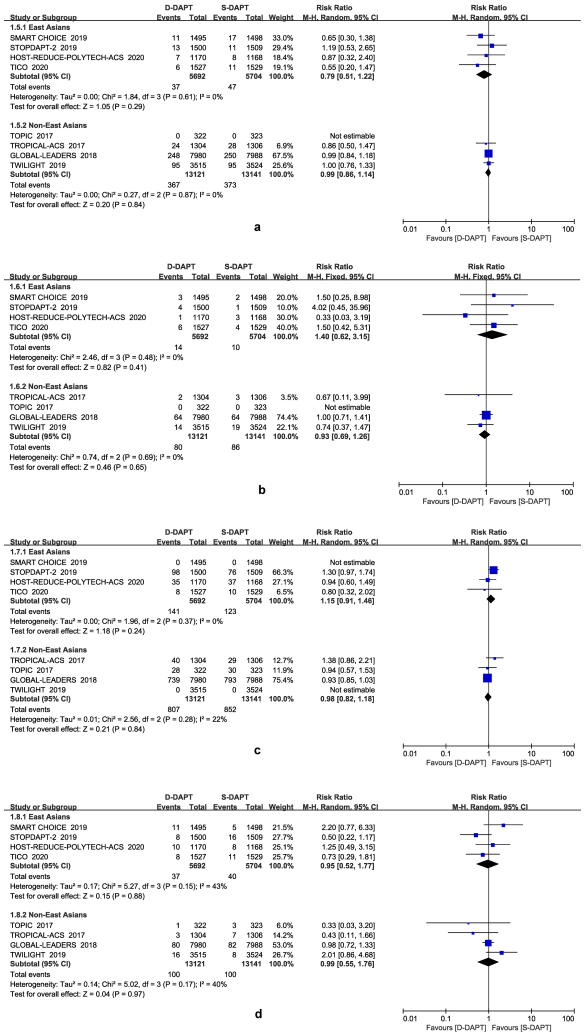

Figure 6

Forest plot of the risk estimates for individual cardiovascular events in patients treated with de-escalation of dual antiplatelet therapy (D-DAPT) compared to standard DAPT (S-DAPT). a. myocardial infraction (MI). b. stent thrombosis. c. repeat revascularization. d. stroke

Supplementary Files

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- Supplementarymaterial.pdf