Comparison of De-escalation of DAPT Intensity or Duration in East Asian and Western Patients with ACS Undergoing PCI: A Systematic Review and Meta-analysis

Running title: DAPT De-escalation in East Asian versus Westerners

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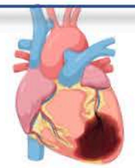
Summary slide

De-escalation of DAPT Intensity or Duration in East Asian and Western Patients

ACS  **plus**  **PCI**

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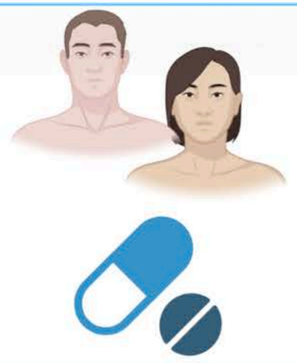
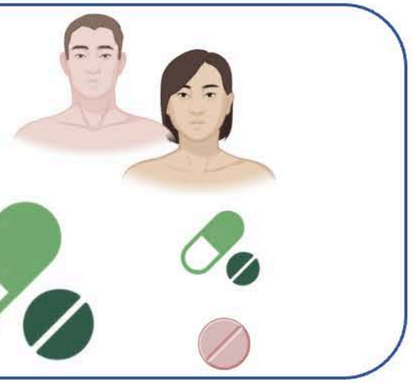
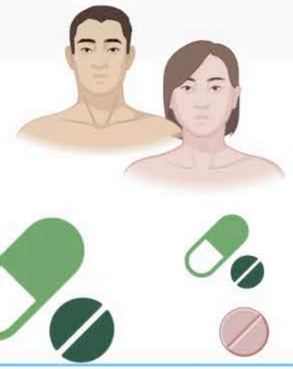
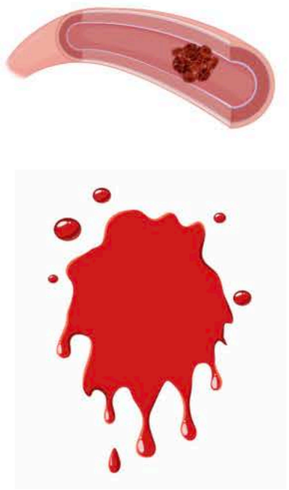
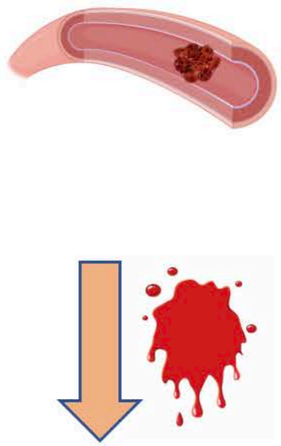
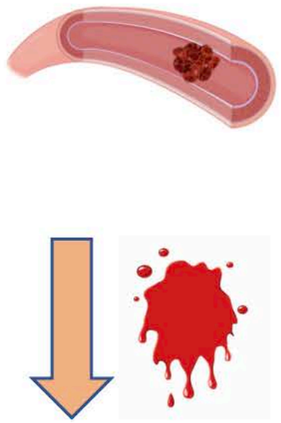
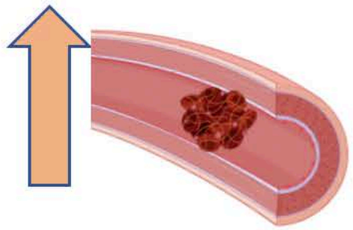
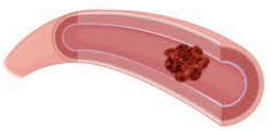
			
DAPT	Aspirin + Ticagrelor/Prasugrel 12 m	Reduced Intensity DAPT	Reduced duration DAPT	Reduced Intensity DAPT	Reduced duration DAPT
Balance of thrombosis vs. bleeding risk					

Abstract

Background

Guideline-recommended dual antiplatelet therapy (DAPT; aspirin plus prasugrel/ticagrelor) for 12 months in acute coronary syndrome (ACS) patients increases bleeding, with East Asians (EA) exhibiting higher bleeding and lower ischaemic risk, compared to non-East Asians (nEA). We sought to compare DAPT "de-escalation" strategies in EA and nEA populations.

Methods

A systematic review and meta-analysis of randomised controlled trials assessing reduction of DAPT intensity or duration in ACS patients undergoing percutaneous coronary intervention, in EA and nEA, was performed using a random effects model.

Results

Twenty-three trials assessed reduction of DAPT intensity (n=12) or duration (n=11). Overall, reduced DAPT intensity attenuated major bleeding (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.65-0.94, p=0.009), without impacting net adverse cardiovascular events (NACE) or major adverse cardiovascular events (MACE). In nEA, this increased MACE (OR 1.20, 95% CI 1.09-1.31, p<0.0001) without impacting NACE or bleeding; whilst in EA, it reduced major bleeding (OR 0.71, 95% CI 0.53-0.95, p=0.02) without affecting NACE or MACE.
Overall, abbreviation of DAPT duration reduced NACE (OR 0.90, 95% CI 0.82-0.99, p=0.03) due to major bleeding (OR 0.69, 95% CI 0.53-0.99, p=0.006), without impacting MACE. In nEA, this strategy did not impact NACE, MACE or major bleeding; whilst in EA, it reduced major bleeding (OR 0.60, 95% CI 0.4-0.91, p=0.02) without impacting NACE or MACE.

Conclusion

In EA, reduction of DAPT intensity or duration can minimise bleeding, without safety concerns. In nEA, reduction of DAPT intensity may incur an ischaemic penalty, whilst DAPT abbreviation has no overall benefit.

Word count: 248

Key words:
Dual antiplatelet therapy, de-escalation, acute coronary syndrome, bleeding, East Asian

Abbreviations

ACS = acute coronary syndrome

BARC = bleeding academic research consortium

DAPT = dual antiplatelet therapy

MACE = major adverse cardiovascular events

MI = myocardial infarction

NACE = net adverse cardiovascular events

PCI = percutaneous coronary intervention

RCT = randomised controlled trial

SAPT = single antiplatelet therapy

STEMI = ST-elevation myocardial infarction

INTRODUCTION

Dual antiplatelet therapy (DAPT) is the cornerstone of treatment for patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). Current ESC guidelines recommend 1 year of DAPT unless contraindicated or the presence of excess bleeding risk.[1,2,3] The guidelines, based predominantly on the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38)[4] and Study of Platelet Inhibition and Patient Outcomes (PLATO)[5] trials, recommend use of a potent $P2Y_{12}$ inhibitor, ticagrelor or prasugrel, over clopidogrel.[1-3] However, this duration and intensity of DAPT exposes patients to an increased risk of bleeding, which is emerging as at least an equal, if not potentially greater concern, than the ischaemic risk, with significant impact on mortality.[6-8] Importantly, in both TRITON-TIMI 38 and PLATO, more intense DAPT led to a reduction in ischaemic events within the first 30 days, whilst excess bleeding events were more frequently observed beyond this period.[4,5]

Increased awareness of the prognostic importance of bleeding, together with observed increase in bleeding rates have prompted studies that consider alternatives to 12 months of high-intensity DAPT to identify the optimal strategy to balance thrombotic and bleeding risks. Several randomised controlled trials (RCTs) have investigated various de-escalation strategies in patients with ACS undergoing PCI, either by reducing the intensity of DAPT, through switching from more potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor to clopidogrel, or by shortening the duration of DAPT and continuing with single antiplatelet therapy (SAPT).

East Asians have been shown to derive less anti-ischaemic benefit from and experience increased bleeding risk with antithrombotic medications, compared to Westerners.[9] East Asians exhibit reduced platelet inhibition in response to clopidogrel compared with Caucasians.[10] This can in part be attributed to a well described higher prevalence of the cytochrome P450 *2C19*(*CYP2C19*) *loss-of-function allele* which is twice as prevalent in East Asians as in Caucasians.[10,11] Whilst this would suggest a higher ischaemic risk, including stent thrombosis, East Asians have in fact been shown to have a lower ischaemic risk than Westerners.[9,10] This phenomenon has been termed the "East Asian Paradox".[9] It is therefore not surprising that many studies examining the safety and efficacy of antiplatelet therapy de-escalation in ACS were conducted in East Asian populations. Caution must be exercised when extrapolating these findings to Western populations and vice-versa. Due to the excess bleeding risk, in much of East Asia reduced-dose prasugrel (loading/maintenance dose 20/3.75mg) or clopidogrel are used in ACS patients undergoing PCI.[12-14]

To date, there has been no formal comparison of DAPT de-escalation strategies in EA compared to non-East Asian patients with ACS. We sought to perform a systematic review and meta-analysis of the current evidence to determine the optimal de-escalation DAPT strategy for patients with ACS undergoing PCI, with separate evaluation of those studies in predominantly East Asian and non-East Asian populations.

METHODS

This review was conducted in accordance with the guidelines set by Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA). The study was registered on the PROSPERO database (ID CRD42022288577). For this meta-analysis, we defined "standard

DAPT" therapy for ACS as aspirin in combination with either ticagrelor or prasugrel, for a total of 12 months. We excluded studies assessing de-escalation based on platelet function testing or genotyping, because these techniques are still not widely available, and such studies have been mainly performed in non-East Asian populations, with insufficient comparative data in matched East Asian populations.

Search Strategy and Data Extraction

Digital databases (PubMed and Cochrane Library) were searched from inception through to June 2022, using various combinations of medical subject headings (MeSH) (Supplementary List 1). The subsets were combined in various combinations, with the search restricted to full length articles published in English in peer-reviewed journals. Abstracts were screened and potentially relevant articles underwent full-text review.

Two reviewers (MF and DAG) independently reviewed all titles, or titles and abstracts to identify articles that met the study inclusion criteria, with backward snowballing to retrieve studies that were missed on the initial database search. Selected studies were compared, and disagreement resolved by discussion and consensus. Data extraction was carried out independently and in duplicate by the study investigators. Articles selected for the final review were checked to avoid inclusion of duplicate data. Data was collected from each study on baseline characteristics, DAPT strategy, and efficacy and safety clinical outcomes at the longest follow-up.

Inclusion and Exclusion Criteria

The inclusion criteria were: 1) randomised controlled trials, 2) at least 2 comparator arms, 3) study population of patients with ACS, with either all or at least a clearly defined subgroup undergoing revascularization, 4) treatment with oral $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, or prasugrel), 5) reporting bleeding and ischaemic outcomes. Exclusion criteria were: 1) non-randomised trials, 2) trials that excluded ACS patients or those in which ACS patients formed only a minority of subjects, 3) trials that included alternative antiplatelet therapy other than clopidogrel, ticagrelor, or prasugrel in addition to aspirin, 4) trials that compared only DAPT containing ticagrelor with DAPT containing prasugrel, 5) studies that employed de-escalation "guided" by either platelet function tests or genotyping, 6) trials that focused on patients with an indication for oral anticoagulation, 7) studies in which randomisation occurred beyond 6 months after the index ACS, and 8) trials with follow-up of less than 6 months.

Study endpoints

The primary efficacy endpoint was the occurrence of net adverse cardiovascular events (NACE) defined as the composite of ischaemic endpoints (including major adverse cardiovascular events [MACE] comprising all cause death, recurrent myocardial infarction [MI] and cerebrovascular accident); secondary endpoints were trial-defined MACE and major bleeding at longest follow-up.

Statistical analysis

Pooled odds ratios (OR) with 95% confidence interval (CI) were estimated for binary variables using a random-effects model with the method of DerSimonian and Laird (14). Heterogeneity between individual studies was explored by X^2 statistic and characterized with I^2 statistic.

In addition to a comprehensive analysis of all "de-escalation" strategies, we performed a sensitivity analysis to analyse trials separately based on the type of antiplatelet strategy, namely (1) standard vs. lower intensity DAPT and (2) non-abbreviated vs. abbreviated duration of DAPT. Studies in each strategy were further analysed based on the ethnicity of trial participants.

Included studies were assessed using the Cochrane risk-of-bias tool by two authors.[13] We also used funnel plots to assess for publication bias. All analyses were performed using RevMan Version 5.3.5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

A total of 8,352 studies were identified, leaving 6,313 after removal of duplicates. A further 6,277 were excluded after review of the title and/or abstract. Twenty-three trials met our inclusion and exclusion criteria, which included the two landmark trials PLATO and TRITON-TIMI 38 (Figure 1).[4,5] Following the establishment of "standard DAPT" comprising of aspirin plus either ticagrelor or prasugrel for 1 year in patients with ACS,[4,5] subsequent trials assessing the safety and efficacy of various antiplatelet de-escalation strategies were those that compared

(i) standard versus reduced *intensity* DAPT, namely DAPT comprising of aspirin plus ticagrelor/prasugrel compared with DAPT containing aspirin plus clopidogrel, (Figure 2) or

(ii) non-abbreviated versus abbreviated *duration* of DAPT, namely DAPT comprising aspirin plus ticagrelor/prasugrel for 6-12 months compared with DAPT comprising aspirin plus ticagrelor/prasugrel only for 1-4 weeks followed by de-escalation from prasugrel/ticagrelor to clopidogrel or low-dose prasugrel (Figure 3).

Results are reported in accordance with the PRISMA guideline (Supplementary Table 1), with RCT-level definitions of outcomes (Tables 1-2, Supplementary Table 2). The overall risk of bias is considered moderate in the included studies (Supplementary Table 3), with funnel plots to reflect publication bias (Supplementary Figure 1).

Trials of standard versus reduced intensity DAPT

Since the initial landmark studies which established the standard for DAPT in ACS,[4,5] there have been 10 trials which compared standard with lower intensity DAPT (Table 1),[16-25] including 7 in East Asian populations.[16-22] Characteristics of the trial participants, including ACS type and cardiovascular risk factors, are shown in Figures 4 and 5.

Overall, reduced intensity DAPT had no impact on NACE (OR 0.87, 95% CI 0.73-1.04, p=0.13) or MACE (OR 1.06, 95% CI 0.91-1.23, p=0.43) but significantly reduced major bleeding (OR 0.78, 95% CI 0.65- 0.94, p=0.009) (Figure 6).

Trials comparing standard DAPT with potent $P2Y_{12}$ inhibitors vs. reduced intensity DAPT in non-East Asians

Reducing the intensity of DAPT had no impact on NACE (OR 0.94, 95% CI 0.77-1.13, p=0.50), but significantly increased MACE (OR 1.20, 95% CI 1.09-1.31, p<0.0001) without reduction in major bleeding (OR 0.82, 95% CI 0.65-1.03, p=0.08) (Figure 7). All 3 studies in this category were open-label, and two were conducted specifically in elderly populations. The Elderly-ACS 2 trial,[24] which enrolled patients ≥ 75 years undergoing revascularization, was prematurely terminated for futility after an interim analysis showing no difference in the primary endpoint. The Clopidogrel versus ticagrelor or prasugrel in patients aged

70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE) trial in patients aged ≥ 70 years included only non-ST-elevation MI patients (STEMI excluded) and less than half the patients underwent revascularization.[23] Notably, in the Timing Of Platelet Inhibition after acute Coronary syndrome (TOPIC) trial,[25] de-escalation of DAPT occurred at 1 month post-index MI, unlike in the other two studies. Further, MI was not included in the composite primary endpoint, but urgent re-hospitalisation requiring revascularisation was included and would likely have captured a significant proportion of MIs. Taken together, three studies would appear underpowered to assess the safety of low intensity DAPT, especially in the first month, in the majority of ACS patients undergoing revascularisation, particularly in those with STEMI. Both TOPIC and the Elderly-ACS 2 trials included minor, in addition to major bleeding in the safety endpoint.

Trials comparing DAPT with potent $P2Y_{12}$ inhibitors vs. reduced intensity DAPT in East Asians

Compared to standard DAPT, use of lower intensity DAPT had no impact on NACE (OR 0.87, 95% CI 0.62-1.23, p=0.43) or MACE (OR 0.98, 95% CI 0.68-1.41, p=0.91), but significantly reduced major bleeding (OR 0.71, 95% CI 0.53-0.95, p=0.02) (Figure 8). Whilst most trials randomised patients to the different DAPT strategies within the index admission, in the Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI)[21] and Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS)[22] trials, de-escalation occurred 1-month post-ACS. In Efficacy and Safety of Adjusted-Dose Prasugrel Compared With Clopidogrel in Japanese Patients With Acute

Coronary Syndrome (PRASFIT-ACS),[16] DAPT comprising of prasugrel 3.75mg daily plus aspirin significantly reduced MACE compared with clopidogrel plus aspirin, reflecting the benefit seen in TRITON-TIMI 38[4] with full dose prasugrel compared to clopidogrel in predominantly non-East Asians. In the HOST-REDUCE-POLYTECH-ACS trial,[22] only a third of participants had MI. The PHILO trial showed no significant difference between ticagrelor and clopidogrel, in addition to aspirin, on bleeding or ischaemic endpoints, although the event rate was rather low and some clinical risk factors were more prevalent in the ticagrelor group.[17] The Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management (TICAKOREA) study comparing ticagrelor with clopidogrel as part of DAPT, showed a lower risk of major bleeding with ticagrelor, but was not designed to assess ischaemic endpoints.[20] In the TALOS-AMI study, de-escalation from ticagrelor plus aspirin to clopidogrel plus aspirin one month post-ACS significantly reduced bleeding, including major bleeding, without an increase in ischaemic endpoints.[21] By comparison, a small study of elderly patients with STEMI showed that ticagrelor effectively reduced the composite of cardiovascular death, MI and stroke compared to clopidogrel without impact on bleeding.[24]

Trials of standard (non-abbreviated) versus abbreviated DAPT duration

Eleven trials assessed shortening of DAPT duration (Table 2),[27-38] of which 7 were conducted in East Asian populations.[27-29,34-37] The characteristics of the trial participants, including ACS-type and cardiovascular risk factors, are shown in Figures 9 and 10.

Compared to non-abbreviated DAPT duration, abbreviated DAPT reduced NACE (OR 0.90, 95% CI 0.82-0.99, p=0.03), without effect on MACE (OR 1.01, 95% CI 0.90-1.12, p=0.93)

and a very significant reduction in major bleeding (OR 0.69, 95% CI 0.53-0.99, p=0.006) (Figure 6).

Trials comparing non-abbreviated vs. abbreviated DAPT duration in non-East Asians

Reducing the duration of DAPT had no significant impact on NACE (OR 0.93, 95% CI 0.85-1.00, p=0.06), MACE (OR 0.92, 95% CI 0.83-1.03, p=0.14) or major bleeding (OR 0.79, 95% CI 0.58-1.06, p=0.12) (Figure 11).

Importantly, in 3 out 4 studies in this category, de-escalation from DAPT involved switching to monotherapy with a $P2Y_{12}$ inhibitor. The GLOBAL LEADERS[30] and Ticagrelor with or without Aspirin in High-Risk Patients after PCI (TWILIGHT)[33] trials assessed de-escalation of DAPT from aspirin plus ticagrelor, to ticagrelor monotherapy, after 1-3 months of DAPT, respectively. The GLOBAL LEADERS trial randomised patients undergoing PCI for stable coronary disease or ACS, and in the ACS cohort, compared a strategy of aspirin plus ticagrelor for 12 months followed by aspirin, with a strategy of aspirin plus ticagrelor for 1 month, followed by 23 months of ticagrelor monotherapy.[31] Ticagrelor monotherapy had no impact on ischaemic or bleeding endpoints compared to DAPT, including in ACS patients. However, in TWILIGHT, de-escalation of DAPT to ticagrelor monotherapy significantly reduced clinically-relevant bleeding, without an ischaemic penalty.[33] In Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk (MASTER DAPT),[38] 1 month of DAPT followed by clopidogrel (54%) or aspirin monotherapy, significantly reduced major or clinically-relevant nonmajor bleeding, and was noninferior to ≥3 months DAPT with respect to NACE. Notably, patients were at high bleeding risk although ACS patients comprised only 40%, with a significant proportion taking anticoagulation.

Trials comparing non-abbreviated vs. abbreviated DAPT duration in East Asians

Reducing the duration of DAPT had no impact on NACE (OR 0.88, 95% CI 0.74-1.06, p=0.18) or MACE (OR 1.11, 95% CI 0.93-1.33, p=0.26), but significantly reduced major bleeding (OR 0.60, 95% CI 0.4-0.91, p=0.02) (Figure 12).

Almost all trials in this category were open label and in more than half, de-escalation involved switching to $P2Y_{12}$ inhibitor monotherapy. In the STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent)[35] trial in which ACS patients comprised only 38% of participants, abbreviated DAPT for 1 month followed by clopidogrel monotherapy significantly reduced the secondary endpoint of major bleeding and met the criteria for noninferiority for NACE, including in the ACS subgroup. In the subsequent STOPDAPT-2 ACS trial,[36] de-escalation of DAPT after 1-2 months to clopidogrel monotherapy, compared with 12 months DAPT, reduced the secondary endpoint of bleeding, but did not meet criteria for non-inferiority with respect to NACE, with a signal for harm with a 2-fold increase in MI. This signal was also seen in the SMART-DATE study,[29] in which de-escalation of DAPT after 6-months to aspirin met the criteria for non-inferiority with respect to the composite of all cause death, MI or stroke, but a significant increase in MI was observed with abbreviated DAPT, without reduction in bleeding. In the SMART-CHOICE (Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention) trial,[34] two-thirds of patients had ACS and de-escalation at 3 months reduced the occurrence of bleeding without an ischaemic penalty. In the Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome (TICO) trial,[37] de-escalation of DAPT after 3 months to ticagrelor monotherapy reduced NACE, driven by a significant reduction in major bleeding. Sub-analysis of the

TWILIGHT trial focusing on the 13% of patients enrolled in China showed that 3 months of DAPT followed by ticagrelor monotherapy compared to 12-month DAPT reduced the primary end point of BARC type 2, 3 or 5 bleeding (3.5% vs. 6.2%, 95% CI 0.31–0.99; p=0.048), with no significant difference in the composite of all-cause death, MI or stroke.[39]

DISCUSSION

Whilst there have been previous reviews of DAPT de-escalation options and strategies in ACS patients undergoing PCI,[45,46] ours is the first systematic review and meta-analysis to directly address the differences in outcomes amongst these studies between East Asian and non-East Asian patients. Our study is unique in showing that there are significant ethnic differences between East Asian and non-East Asian patients with respect to strategies that involve either reducing DAPT intensity or duration (Central Illustration). We summarise our analyses below.

Use of lower intensity vs. standard intensity DAPT

Overall, reducing the intensity of DAPT significantly reduced major bleeding, without impacting NACE or MACE. This benefit was mainly evidenced in East Asian patients, where use of lower intensity DAPT had no impact on NACE or MACE, but very significantly reduced major bleeding.

In comparison, in non-East Asian patients, although there was a trend for lower intensity DAPT to reduce major bleeding, this approach significantly increased the risk of MACE, without overall impact on NACE.

This indicates that reduced intensity DAPT should be considered in East Asian patients where it can reduce bleeding without adverse ischaemic effects. On the other hand, in predominantly non-East Asian populations, the PLATO[5] and TRITON-TIMI 38[4] studies showed reduction in ischaemic risk with standard compared to low intensity DAPT and our data support this, indicating that reduction of DAPT intensity may have an ischaemic penalty in non-East Asians. Furthermore, reduction of DAPT intensity in non-East Asians was predominantly assessed in the elderly, and findings therefore cannot be extrapolated to younger patients.

Use of abbreviated vs. non-abbreviated duration DAPT

Overall, abbreviated DAPT reduced NACE, a benefit driven by very significant reduction in major bleeding, with no adverse effect on MACE. In non-East Asian patients, abbreviation of DAPT showed a trend towards reduction of NACE, but without effect on MACE or major bleeding. On the other hand, in East Asian patients, abbreviation of DAPT significantly reduced major bleeding, without impacting NACE or MACE.
This would indicate that abbreviated DAPT should be considered in East Asian patients, to reduce bleeding. Evidence for a benefit in non-East Asians is lacking, although there is no apparent signal for harm with this approach.

De-escalation of DAPT intensity -when to de-escalate?

The benefit of reduced DAPT intensity was predominantly seen in East Asians. Of the 7 trials, 5 initiated reduced intensity DAPT during the index hospitalisation[16-20] and the others at one-month post-ACS.[21-22] Of those that randomised during the index admission, two

demonstrated an increase in ischaemic endpoints and the others showed overall reduction in MACE. The two largest studies assessing reduced DAPT intensity in East Asians.[21,22] both de-escalated at 1-month post-ACS, and neither showed an excess ischaemic risk. Therefore, in East Asians, it may be safest to de-escalate at one-month post-ACS.

De-escalation of DAPT duration -when to reduce and which monotherapy?

The net benefit of abbreviated DAPT was mainly seen in East Asians. Amongst these, DAPT was stopped at 6 months in 3 studies, at 3 months in 2 studies, and at 1 month in 2 studies. The two largest studies stopped DAPT at 1 month and showed the greatest reduction in bleeding. However, one of these showed a signal for increase in ischaemic events,[36] suggesting that perhaps abbreviation of DAPT at 3 months may be safer.
Following abbreviated DAPT, 3 studies continued with aspirin, whereas the subsequent 4 larger studies de-escalated to a $P2Y_{12}$ inhibitor, with no significant difference in outcomes between the monotherapies. Importantly, $P2Y_{12}$ inhibitor monotherapy did not increase bleeding compared to aspirin monotherapy in East Asians.

Possible explanations for ethnic differences

The "East Asian Paradox" refers to enhanced pharmacokinetic and pharmacodynamic profiles with most antithrombotic medications in East Asian compared to Caucasian subjects, including $P2Y_{12}$ inhibitors and oral anticoagulants, resulting in more frequent bleeding complications, with consequent recommendations for reduced dose antithrombotic prescribing regimens in East Asian patients.[11-14] Additionally, East Asians appear to have a lower genetic predisposition to coronary disease but a higher propensity for bleeding

compared to non-East Asians. Interaction between genetic and epigenetic factors also likely contributes. East Asians tend to manifest lower body mass index (BMI) and total cholesterol, and more frequent hypertension[40], although in this meta-analysis, risk factors including BMI were similar, apart from smoking which was more prevalent in East Asians (Figures 5, 10).[40] Lower coagulant and inflammatory profiles have also been reported in East Asians compared with Caucasians.[41-44]

What is not known

Firstly, there has been no head-to-head comparison of the two "de-escalation" approaches, namely reduced intensity vs. reduced duration DAPT, overall, and no comparisons by ethnicity. The optimal timing for de-escalation to lower intensity DAPT, the optimal time to abbreviate DAPT and the subsequent optimal SAPT are unclear. Finally, the optimal patient for de-escalation of DAPT intensity or duration, is not clearly defined. We consider that the ideal study should be a 2 x 2 factorial design, comparing de-escalation of DAPT intensity and de-escalation of DAPT duration, and comparing the two strategies in East Asian and non-East Asian patients.

Limitations

Our review has number of limitations. Amongst the 3 trials of reduced intensity DAPT in non-East Asians, two were conducted in elderly populations,[23,24] so the benefit of this approach in younger patients is unclear. There was heterogeneity in reporting bleeding, including BARC, PLATO, TIMI classifications. Even amongst studies that included the same classification (e.g. BARC), some included grades 2, 3 and 5, whilst others only grades 3 and

5 bleeding. For studies not formally reporting NACE,[7,16-20,33] we compiled extrapolated NACE by amalgamating ischaemic (MACE) and bleeding risks, a potential source of error. There was also some heterogeneity in reporting MACE, and where possible, we limited MACE in the analysis to cardiovascular death, MI and stroke. There was heterogeneity in trial participants, with some including chronic coronary syndrome or medically-managed ACS patients, and some including a minority of patients on anticoagulation. Antiplatelet regimens and doses varied, particularly in East Asians. Abbreviated DAPT durations ranged from 1-6 months, with further heterogeneity in monotherapy following DAPT. Amongst studies investigating reduced DAPT intensity, there was heterogeneity in the "intense" regimen. Many studies were open label and generally, high risk bleeding patients were under-represented. The studies included span a period of 14 years and the stents used have changed significantly over that period, and the stent-type may affect the safety of de-escalation. In earlier trials, some 50% of patients undergoing PCI received bare metal stents,[16] whereas subsequently trials used predominantly drug-eluting stents. Even amongst the latter, there is significant heterogeneity over time and more recent studies employing the latest generation drug-eluting stents may evidence more the benefit of a de-escalation strategy. The overall duration of follow-up was shorter for some studies recruiting East Asian patients than for some recruiting non-East Asian patients. Among studies assessing de-escalation of DAPT intensity, all East Asian studies and the majority of non-East Asian studies had 12 months follow up. For de-escalation of DAPT duration, all East Asian patients and more than half of all non-East Asian patients had follow-up of 18 m or less. Although it is possible, we feel this difference in follow-up overall is unlikely to have affected the results of the analyses.

In the REDUCE trial, some 30% of the population were East Asians. Lastly, we grouped together East Asians from several countries who may not share similar genetic profiles,

whilst significant differences may exist within non-East Asian populations, that include Caucasian, South Asian, Black, American Indian, and Hispanic ethnicities.

Conclusions

In the first head-to-head comparison between East Asian and non-East Asian ACS patients, we show that there are significant ethnic differences in risk and benefit between strategies that involve either reducing DAPT intensity or duration.

In East Asians, evidence supports reduction in either DAPT intensity or duration, to minimise the risk of bleeding, with no safety concerns. Abbreviation of DAPT could occur at 1-6 months post-ACS, and beyond that, monotherapy with aspirin or a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) can be used. In non-East Asians, reduced intensity DAPT should be avoided, as it may incur an ischaemic penalty. Abbreviation of DAPT duration can be considered, but without proven benefit.

Although standard DAPT favours patients at high ischaemic risk, while shorter or less intense DAPT may benefit those at high bleeding risk, many patients have overlapping risk factors. Individualisation of DAPT strategy may be preferable to personalise care based on both ethnicity and prevailing risks.

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List of Figures

Figure 3. Trials assessing non-abbreviated versus abbreviated DAPT

Studies were conducted predominantly in East Asian (EA) or Western (W) populations, with duration of DAPT in months shown in brackets on panels.

A=aspirin, T=ticagrelor, P=prasugrel. Studies are grouped based on the duration of abbreviated dual antiplatelet strategy (DAPT) employed and the monotherapy chosen to follow cessation of DAPT.

Figure 4. ACS-type and PCI undertaken in trials comparing standard versus reduced intensity DAPT

ACS=acute coronary syndrome, DAPT=dual antiplatelet therapy, NSTEMI=non-ST-segment elevation myocardial infarction, STEMI=ST-segment elevation myocardial infarction, PCI=percutaneous coronary intervention, UA=unstable angina

Figure 5. Cardiovascular risk factors in trials assessing standard versus reduced intensity DAPT

BMI=body mass index.

Figure 6. Impact of reduction in DAPT intensity or duration on net adverse cardiovascular events (all studies)

Panels (A) studies comparing standard intensity with lower intensity DAPT, (B) studies comparing standard duration with lower intensity DAPT.

DAPT=dual antiplatelet therapy, NACE=net adverse cardiovascular events

Figure 7. Comparison of standard versus reduced intensity DAPT in Western patients

Panels (A) net adverse cardiovascular events (NACE), (B) major adverse cardiovascular events (MACE) and (C) major bleeding.

Figure 8. Comparison of standard versus reduced intensity DAPT in East Asian patients

Panels (A) net adverse cardiovascular events (NACE), (B) major adverse cardiovascular events (MACE) and (C) major bleeding.

Figure 9. ACS-type and PCI undertaken in trials comparing standard versus abbreviated DAPT

ACS=acute coronary syndrome, DAPT=dual antiplatelet therapy, NSTEMI=non-ST-segment elevation myocardial infarction, STEMI=ST-segment elevation myocardial infarction, PCI=percutaneous coronary intervention, UA=unstable angina

Figure 10. Cardiovascular risk factors in trials assessing standard versus reduced intensity DAPT

BMI= body mass index.

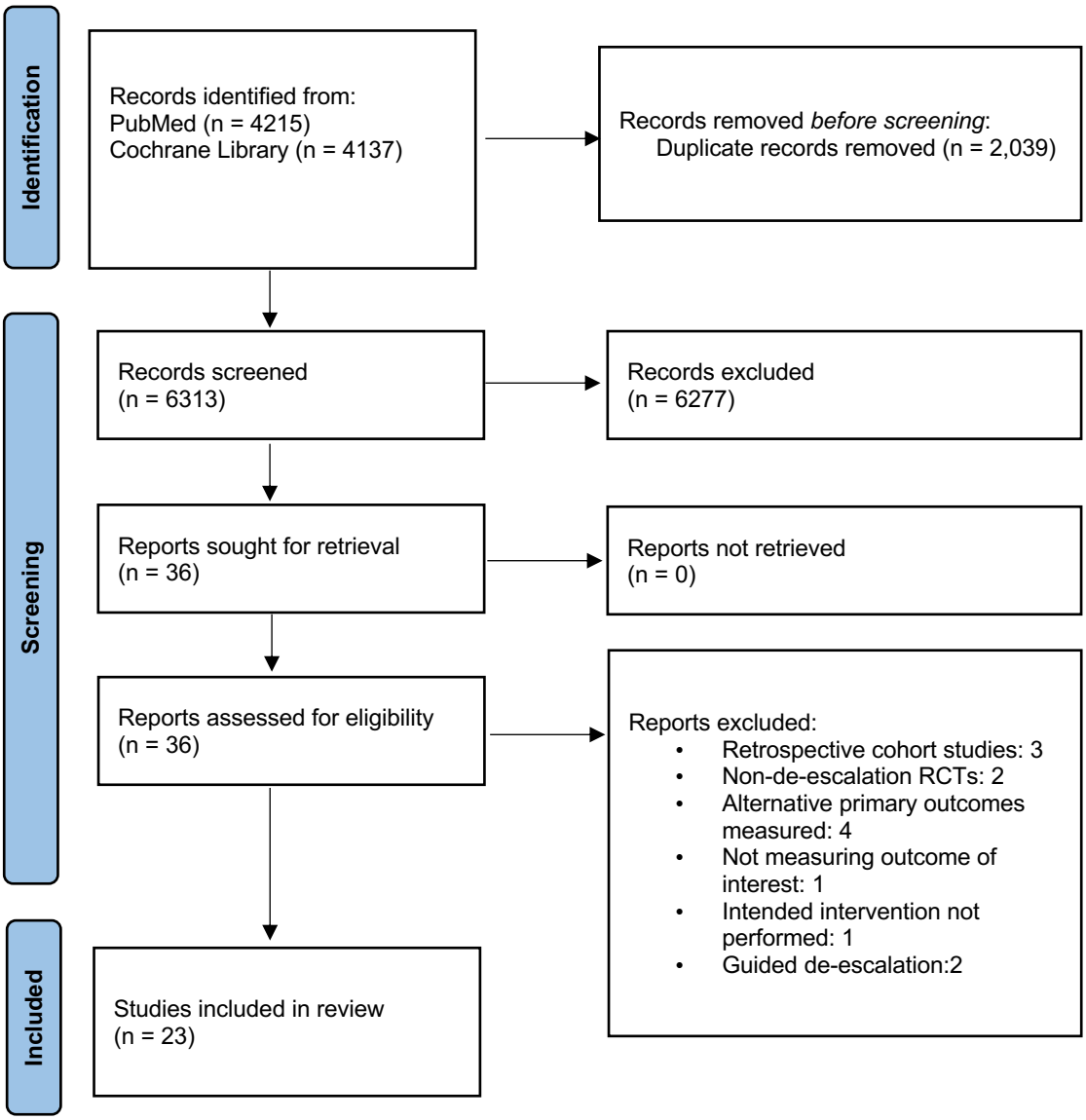
Figure 11. Comparison of standard versus abbreviated DAPT in Western patients

Panels (A) net adverse cardiovascular events (NACE), (B) major adverse cardiovascular events (MACE) and (C) major bleeding.

Figure 12. Comparison of standard versus abbreviated DAPT in East Asian patients

Panels (A) net adverse cardiovascular events (NACE), (B) major adverse cardiovascular events (MACE) and (C) major bleeding.

Figure 1.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Cochrane Library (n = 4137)
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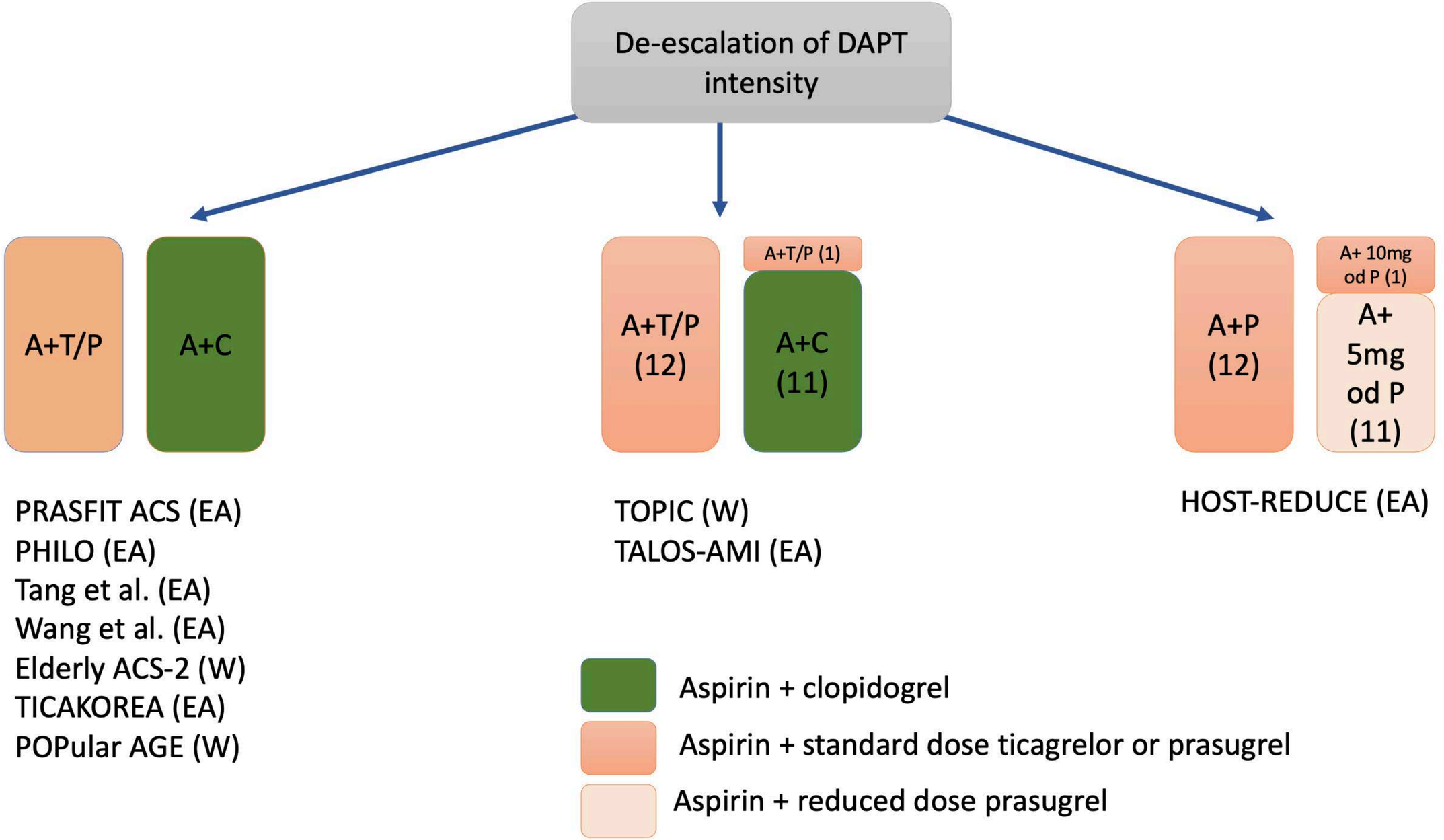
Duplicate records removed (n = 2,039)
Screening
Records screened
(n = 6313)
Records excluded
(n = 6277)
Reports sought for retrieval
(n = 36)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 36)
Reports excluded:
• Retrospective cohort studies: 3
• Non-de-escalation RCTs: 2
• Alternative primary outcomes measured: 4
• Not measuring outcome of interest: 1
• Intended intervention not performed: 1
• Guided de-escalation:2
Included
Studies included in review
(n = 23)

Figure 2.


De-escalation of DAPT intensity
A+T/P
A+C
A+T/P (12)
A+T/P (1)
A+C (11)
A+P (12)
A+ 10mg od P (1)
A+ 5mg od P (11)
PRASFIT ACS (EA)
PHILO (EA)
Tang et al. (EA)
Wang et al. (EA)
Elderly ACS-2 (W)
TICAKOREA (EA)
POPular AGE (W)
TOPIC (W)
TALOS-AMI (EA)
HOST-REDUCE (EA)
Aspirin + clopidogrel
Aspirin + standard dose ticagrelor or prasugrel
Aspirin + reduced dose prasugrel

1

Figure 3.

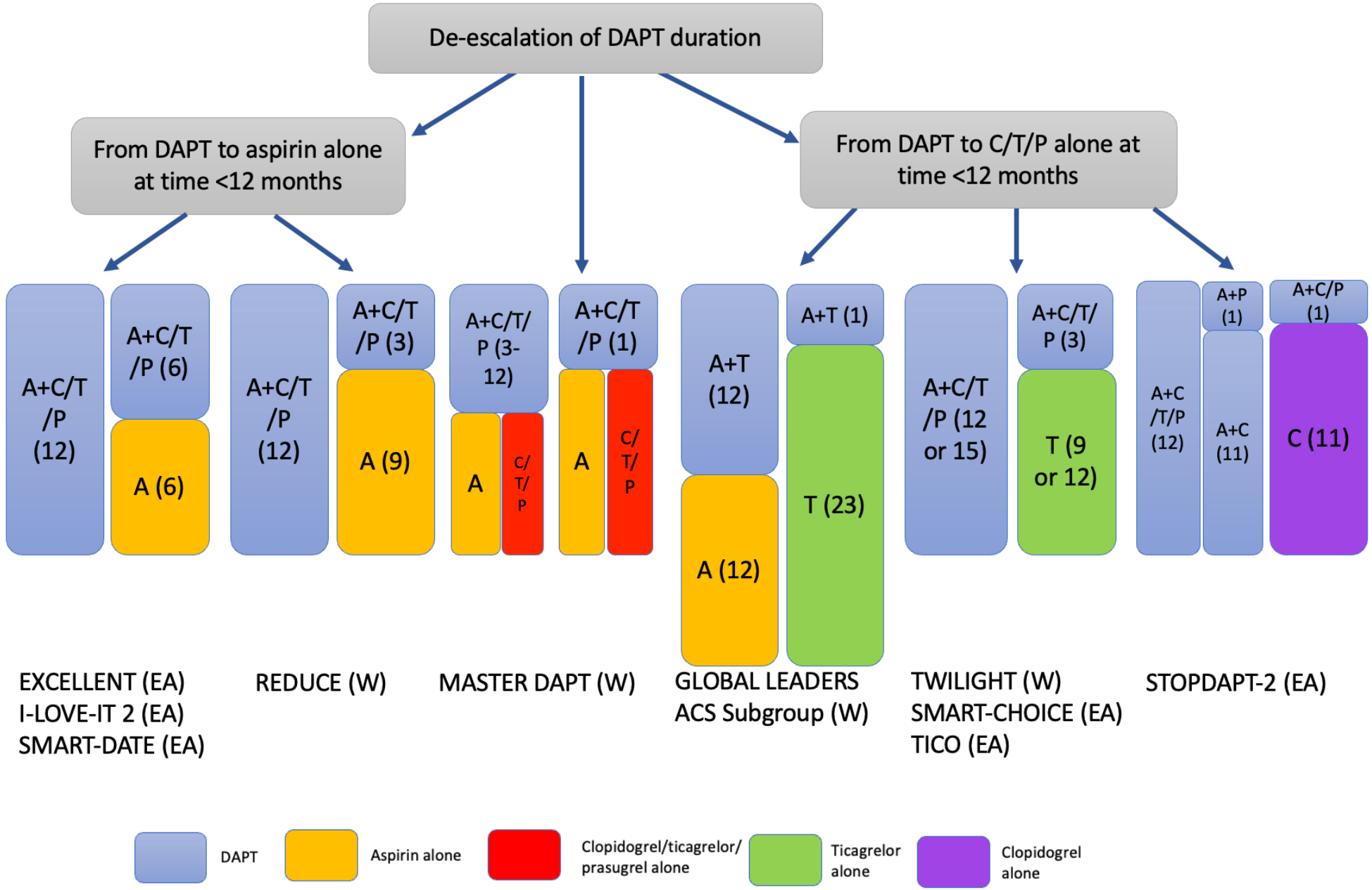
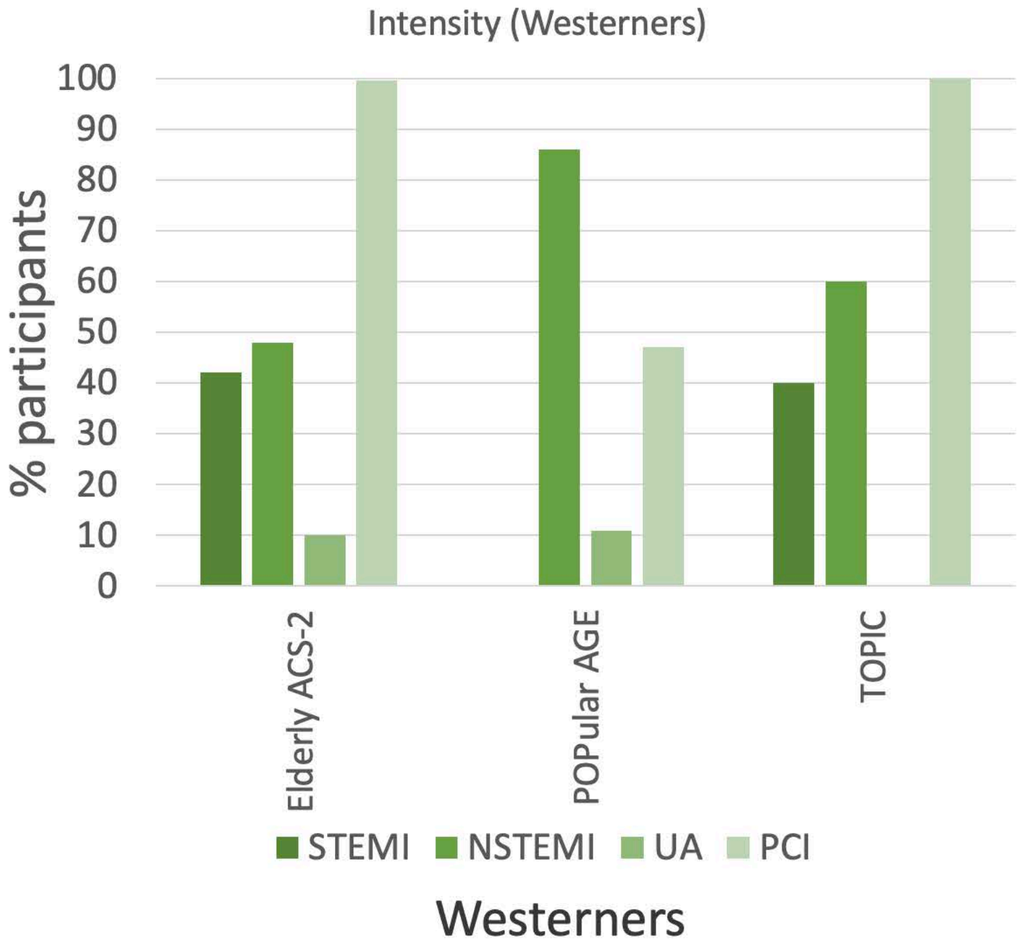

De-escalation of DAPT duration
From DAPT to aspirin alone at time <12 months
From DAPT to C/T/P alone at time <12 months
A+C/T/P (12)
A+C/T/P (6)
A (6)
A+C/T/P (12)
A+C/T/P (3)
A (9)
A+C/T/P (3-12)
A
C/T/P
A+C/T/P (1)
A
C/T/P
A+T (12)
A (12)
A+T (1)
T (23)
A+C/T/P (12 or 15)
A+C/T/P (3)
T (9 or 12)
A+C/T/P (12)
A+C (11)
A+P (1)
C (11)
A+C/P (1)
EXCELLENT (EA)
I-LOVE-IT 2 (EA)
SMART-DATE (EA)
REDUCE (W)
MASTER DAPT (W)
GLOBAL LEADERS
ACS Subgroup (W)
TWILIGHT (W)
SMART-CHOICE (EA)
TICO (EA)
STOPDAPT-2 (EA)
DAPT
Aspirin alone
Clopidogrel/ticagrelor/prasugrel alone
Ticagrelor alone
Clopidogrel alone

Figure 4.


Intensity (Westerners)
% participants
100
90
80
70
60
50
40
30
20
10
0
Elderly ACS-2
POPular AGE
TOPIC
STEMI
NSTEMI
UA
PCI
Westerners

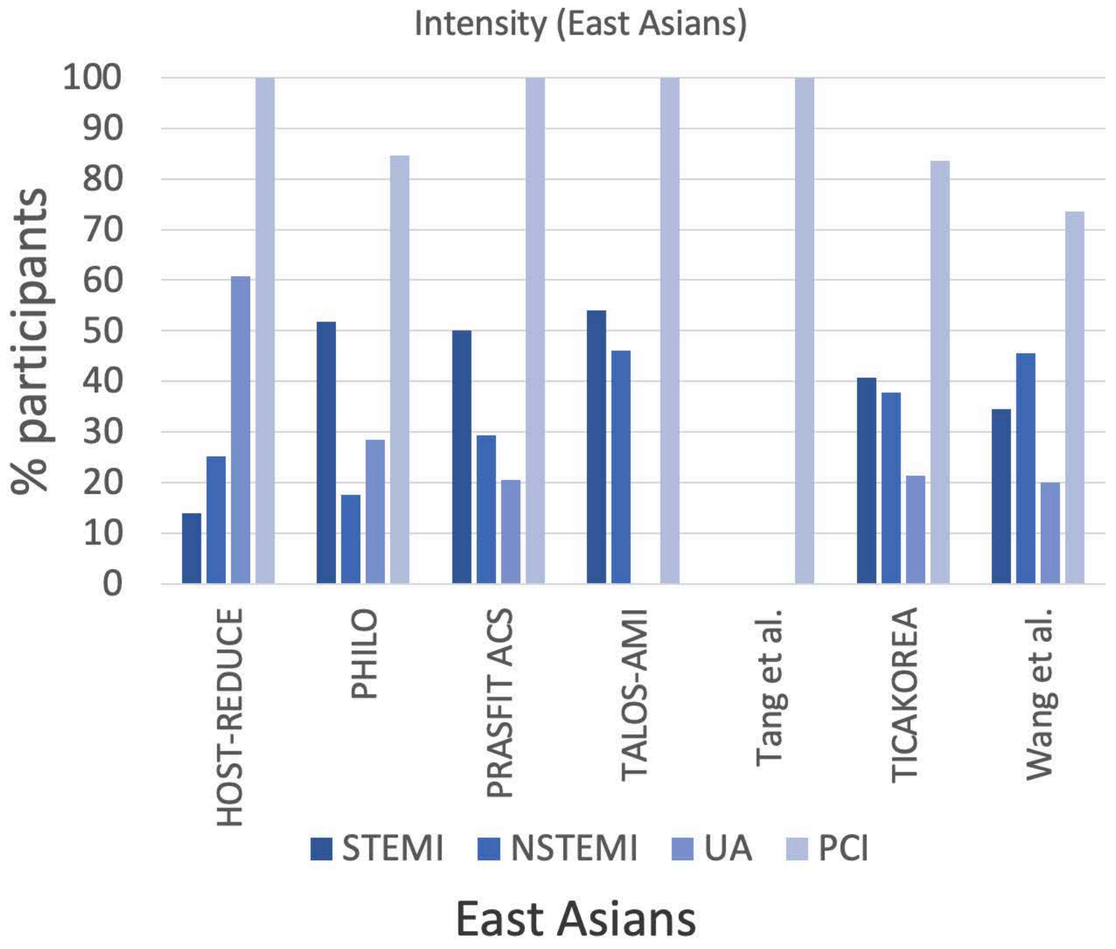

Intensity (East Asians)
% participants
100
90
80
70
60
50
40
30
20
10
0
HOST-REDUCE
PHILO
PRASFIT ACS
TALOS-AMI
Tang et al.
TICAKOREA
Wang et al.
STEMI
NSTEMI
UA
PCI
East Asians

Figure 5.

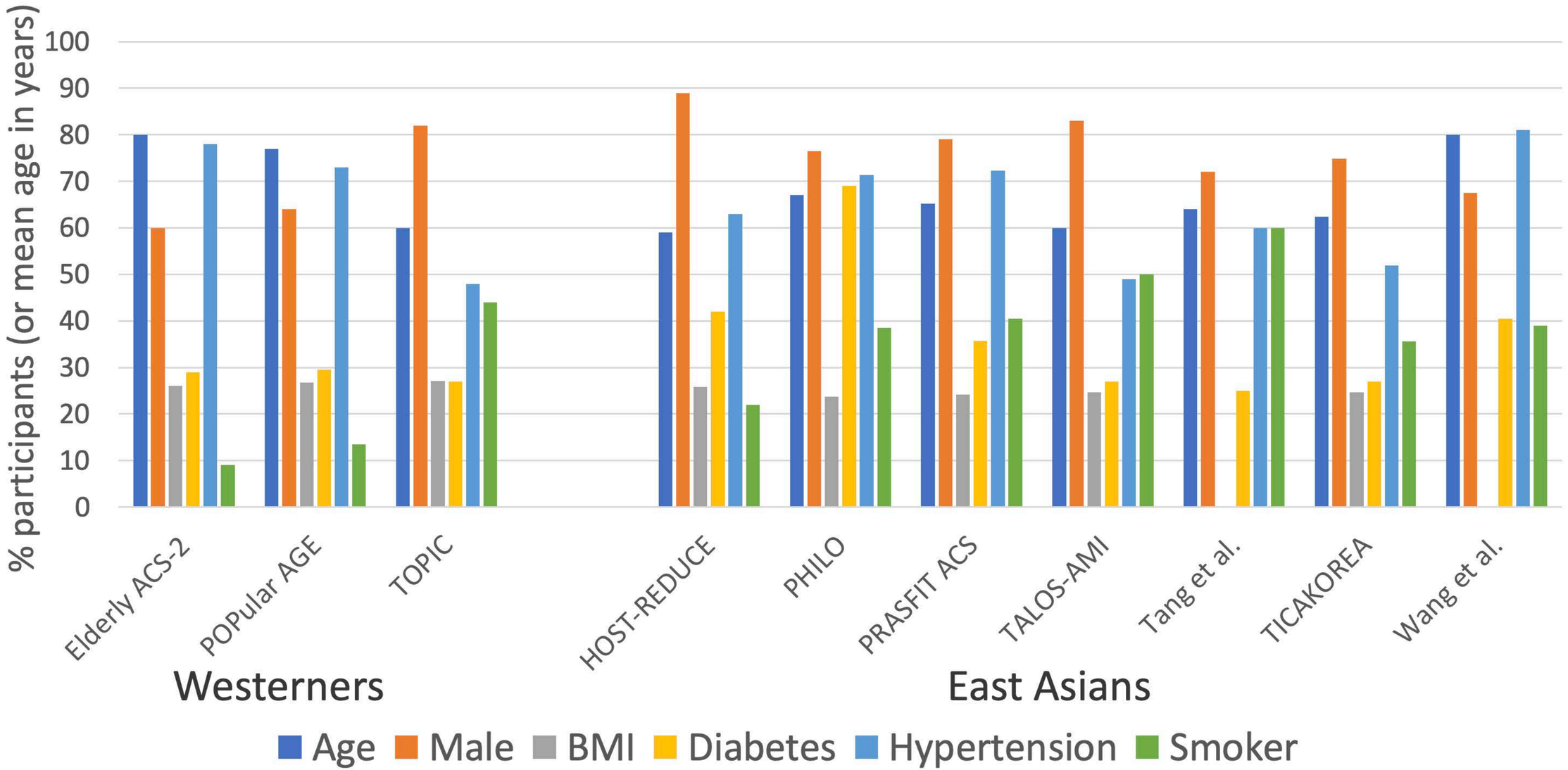
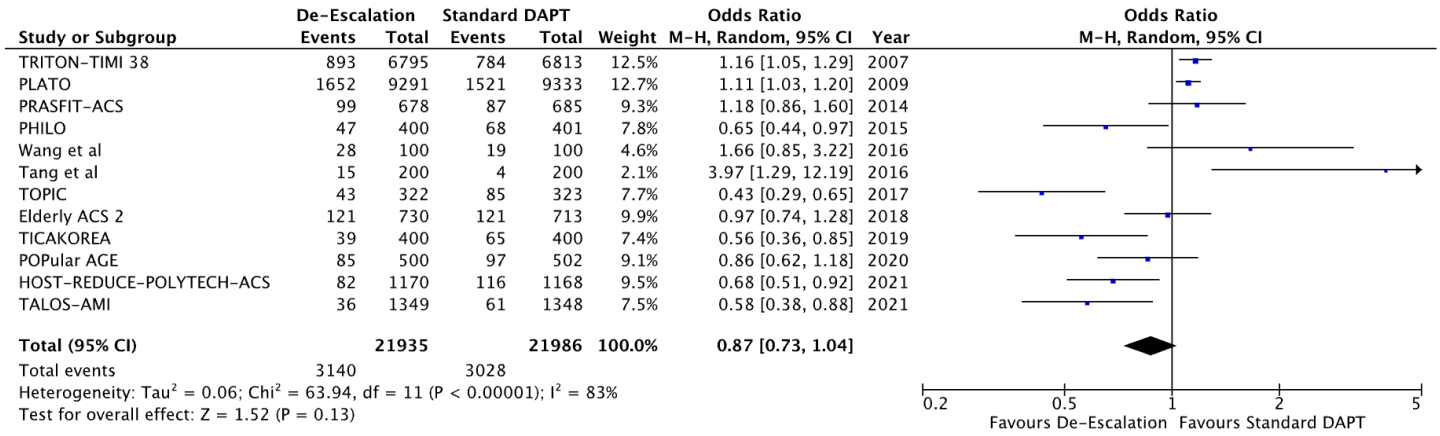

% participants (or mean age in years)
100
90
80
70
60
50
40
30
20
10
0
Elderly ACS-2
POPular AGE
TOPIC
HOST-REDUCE
PHILO
PRASFIT ACS
TALOS-AMI
Tang et al.
TICAKOREA
Wang et al.
Westerners
East Asians
Age
Male
BMI
Diabetes
Hypertension
Smoker

Figure 6.

A


De-Escalation
Standard DAPT
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
TRITON-TIMI 38 893 6795 784 6813 12.5% 1.16 [1.05, 1.29] 2007
PLATO 1652 9291 1521 9333 12.7% 1.11 [1.03, 1.20] 2009
PRASFIT-ACS 99 678 87 685 9.3% 1.18 [0.86, 1.60] 2014
PHILO 47 400 68 401 7.8% 0.65 [0.44, 0.97] 2015
Wang et al 28 100 19 100 4.6% 1.66 [0.85, 3.22] 2016
Tang et al 15 200 4 200 2.1% 3.97 [1.29, 12.19] 2016
TOPIC 43 322 85 323 7.7% 0.43 [0.29, 0.65] 2017
Elderly ACS 2 121 730 121 713 9.9% 0.97 [0.74, 1.28] 2018
TICAKOREA 39 400 65 400 7.4% 0.56 [0.36, 0.85] 2019
POPular AGE 85 500 97 502 9.1% 0.86 [0.62, 1.18] 2020
HOST-REDUCE-POLYTECH-ACS 82 1170 116 1168 9.5% 0.68 [0.51, 0.92] 2021
TALOS-AMI 36 1349 61 1348 7.5% 0.58 [0.38, 0.88] 2021
Total (95% CI) 21935 21986 100.0% 0.87 [0.73, 1.04]
Total events 3140 3028
Heterogeneity: Tau² = 0.06; Chi² = 63.94, df = 11 (P < 0.00001); I² = 83%
Test for overall effect: Z = 1.52 (P = 0.13)
0.2 0.5 1 2 5
Favours De-Escalation Favours Standard DAPT

B

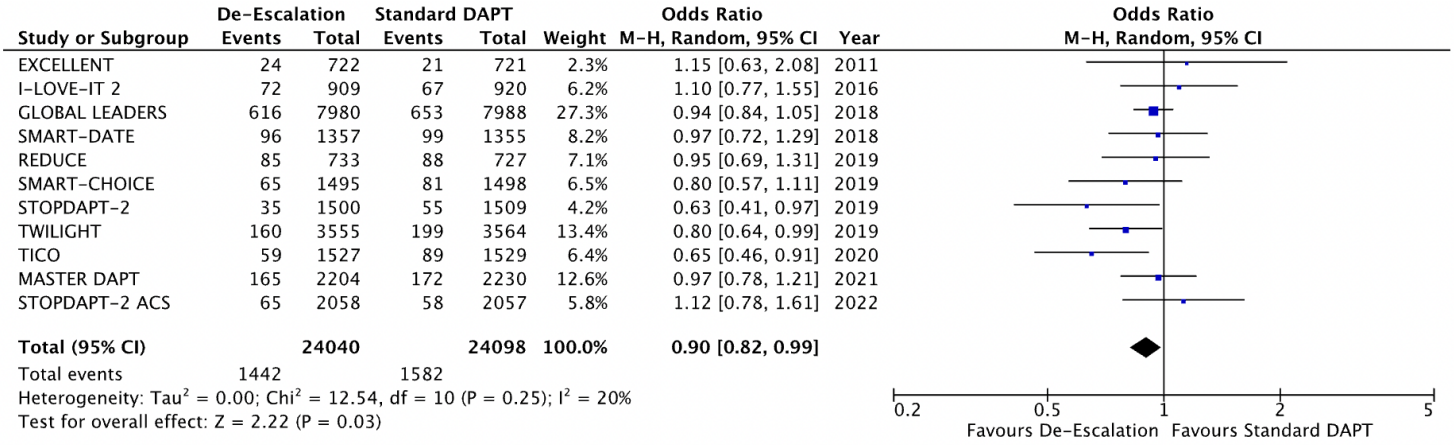
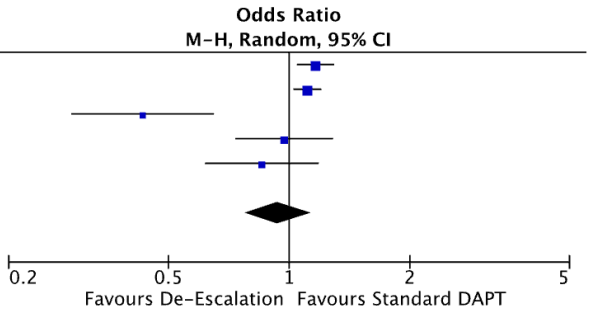

De-Escalation
Standard DAPT
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
EXCELLENT 24 722 21 721 2.3% 1.15 [0.63, 2.08] 2011
I-LOVE-IT 2 72 909 67 920 6.2% 1.10 [0.77, 1.55] 2016
GLOBAL LEADERS 616 7980 653 7988 27.3% 0.94 [0.84, 1.05] 2018
SMART-DATE 96 1357 99 1355 8.2% 0.97 [0.72, 1.29] 2018
REDUCE 85 733 88 727 7.1% 0.95 [0.69, 1.31] 2019
SMART-CHOICE 65 1495 81 1498 6.5% 0.80 [0.57, 1.11] 2019
STOPDAPT-2 35 1500 55 1509 4.2% 0.63 [0.41, 0.97] 2019
TWILIGHT 160 3555 199 3564 13.4% 0.80 [0.64, 0.99] 2019
TICO 59 1527 89 1529 6.4% 0.65 [0.46, 0.91] 2020
MASTER DAPT 165 2204 172 2230 12.6% 0.97 [0.78, 1.21] 2021
STOPDAPT-2 ACS 65 2058 58 2057 5.8% 1.12 [0.78, 1.61] 2022
Total (95% CI) 24040 24098 100.0% 0.90 [0.82, 0.99]
Total events 1442 1582
Heterogeneity: Tau² = 0.00; Chi² = 12.54, df = 10 (P = 0.25); I² = 20%
Test for overall effect: Z = 2.22 (P = 0.03)
0.2 0.5 1 2 5
Favours De-Escalation Favours Standard DAPT

Figure 7.

A

Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
TRITON-TIMI 38	893	6795	784	6813	26.5%	1.16 [1.05, 1.29]	2007
PLATO	1652	9291	1521	9333	27.4%	1.11 [1.03, 1.20]	2009
TOPIC	43	322	85	323	12.4%	0.43 [0.29, 0.65]	2017
Elderly ACS 2	121	730	121	713	17.9%	0.97 [0.74, 1.28]	2018
POPular AGE	85	500	97	502	15.8%	0.86 [0.62, 1.18]	2020
Total (95% CI)		**17638**		**17684**	**100.0%**	**0.94 [0.77, 1.13]**	
Total events	2794		2608				

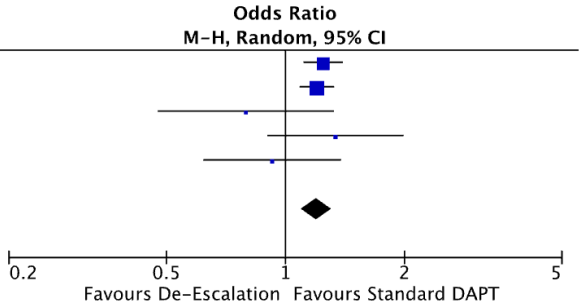
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 24.70$, df = 4 (P < 0.0001); $I^2 = 84\%$
Test for overall effect: Z = 0.67 (P = 0.50)



B

Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
TRITON-TIMI 38	781	6795	643	6813	40.1%	1.25 [1.12, 1.39]	2007
PLATO	1014	9291	864	9333	47.2%	1.20 [1.09, 1.32]	2009
TOPIC	30	322	37	323	3.0%	0.79 [0.48, 1.32]	2017
Elderly ACS 2	63	730	47	713	4.9%	1.34 [0.90, 1.98]	2018
POPular AGE	53	500	57	502	4.8%	0.93 [0.62, 1.38]	2020
Total (95% CI)		**17638**		**17684**	**100.0%**	**1.20 [1.09, 1.31]**	
Total events	1941		1648				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.92$, df = 4 (P = 0.30); $I^2 = 19\%$
Test for overall effect: Z = 3.91 (P < 0.0001)



C

Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
TRITON-TIMI 38	111	6716	146	6741	31.6%	0.76 [0.59, 0.97]	2007
PLATO	638	9186	657	9235	44.7%	0.97 [0.87, 1.09]	2009
TOPIC	1	322	4	323	1.1%	0.25 [0.03, 2.23]	2017
Elderly ACS 2	12	730	13	713	7.2%	0.90 [0.41, 1.99]	2018
POPular AGE	28	500	46	502	15.4%	0.59 [0.36, 0.96]	2020
Total (95% CI)		**17454**		**17514**	**100.0%**	**0.82 [0.65, 1.03]**	
Total events	790		866				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 7.87$, df = 4 (P = 0.10); $I^2 = 49\%$
Test for overall effect: Z = 1.73 (P = 0.08)

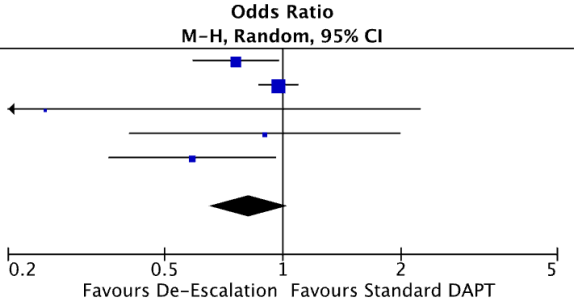
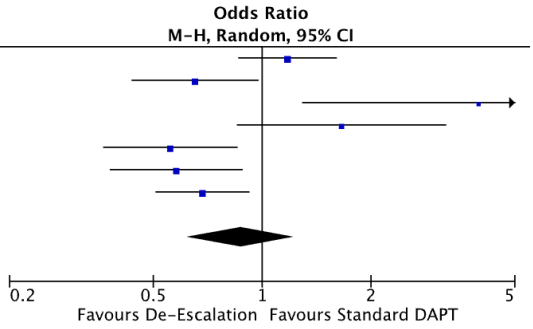


Figure 8.

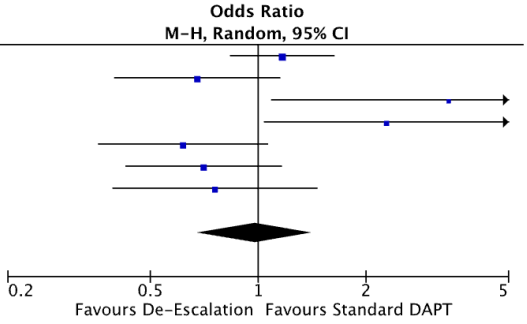
Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PRASFIT-ACS	99	678	87	685	17.4%	1.18 [0.86, 1.60]	2014
PHILO	47	400	68	401	15.9%	0.65 [0.44, 0.97]	2015
Tang et al	15	200	4	200	6.4%	3.97 [1.29, 12.19]	2016
Wang et al	28	100	19	100	11.5%	1.66 [0.85, 3.22]	2016
TICAKOREA	39	400	65	400	15.5%	0.56 [0.36, 0.85]	2019
TALOS-AMI	36	1349	61	1348	15.6%	0.58 [0.38, 0.88]	2021
HOST-REDUCE-POLYTECH-ACS	82	1170	116	1168	17.7%	0.68 [0.51, 0.92]	2021
Total (95% CI)		**4297**		**4302**	**100.0%**	**0.87 [0.62, 1.23]**	
Total events	346		420				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 25.61$, df = 6 (P = 0.0003); $I^2 = 77\%$
Test for overall effect: Z = 0.79 (P = 0.43)



Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PRASFIT-ACS	84	678	74	685	19.9%	1.17 [0.84, 1.63]	2014
PHILO	25	400	36	401	15.9%	0.68 [0.40, 1.15]	2015
Tang et al	13	200	4	200	7.2%	3.41 [1.09, 10.63]	2016
Wang et al	22	100	11	100	11.4%	2.28 [1.04, 5.00]	2016
TICAKOREA	23	400	36	400	15.6%	0.62 [0.36, 1.06]	2019
TALOS-AMI	27	1349	38	1348	16.5%	0.70 [0.43, 1.16]	2021
HOST-REDUCE-POLYTECH-ACS	16	1170	21	1168	13.5%	0.76 [0.39, 1.46]	2021
Total (95% CI)		**4297**		**4302**	**100.0%**	**0.98 [0.68, 1.41]**	
Total events	210		220				

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 16.97$, df = 6 (P = 0.009); $I^2 = 65\%$
Test for overall effect: Z = 0.11 (P = 0.91)



C

Study or Subgroup	De-Escalation Events	De-Escalation Total	Standard DAPT Events	Standard DAPT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
PRASFIT-ACS	15	678	13	685	14.8%	1.17 [0.55, 2.48]	2014
PHILO	22	400	32	401	26.4%	0.67 [0.38, 1.18]	2015
Tang et al	2	200	0	200	0.9%	5.05 [0.24, 105.86]	2016
Wang et al	6	100	8	100	6.9%	0.73 [0.25, 2.20]	2016
TICAKOREA	16	400	29	400	21.2%	0.53 [0.28, 1.00]	2019
TALOS-AMI	15	1349	28	1348	20.8%	0.53 [0.28, 1.00]	2021
HOST-REDUCE-POLYTECH-ACS	9	1170	8	1168	9.1%	1.12 [0.43, 2.92]	2021
Total (95% CI)		**4297**		**4302**	**100.0%**	**0.71 [0.53, 0.95]**	
Total events	85		118				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.85$, df = 6 (P = 0.44); $I^2 = 0\%$
Test for overall effect: Z = 2.34 (P = 0.02)

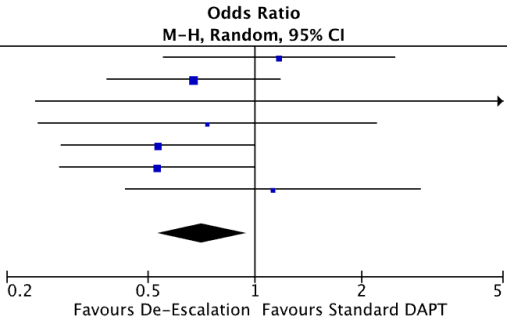
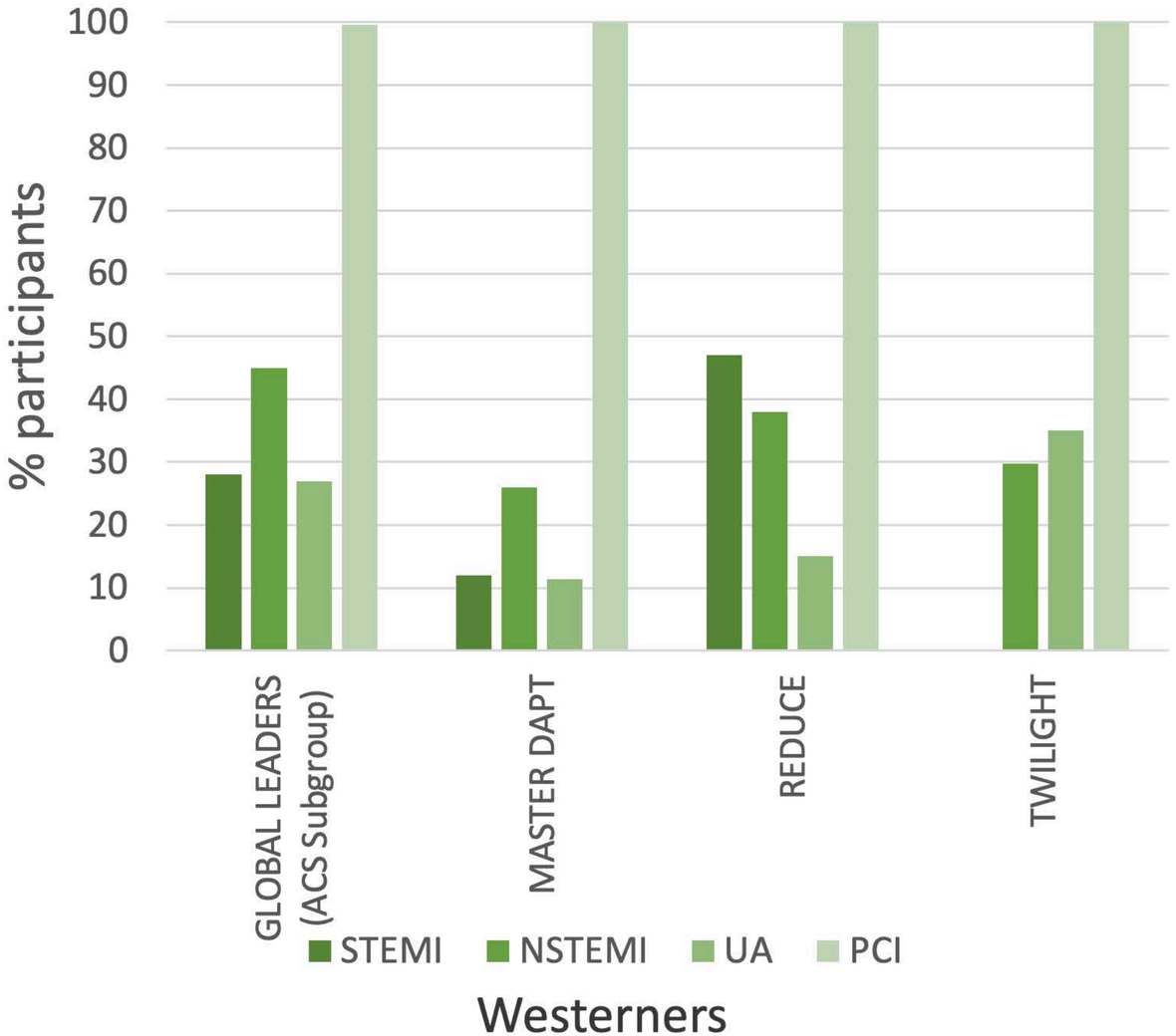


Figure 9.


100
90
80
70
60
50
40
30
20
10
0
% participants
GLOBAL LEADERS (ACS Subgroup)
MASTER DAPT
REDUCE
TWILIGHT
STEMI
NSTEMI
UA
PCI
Westerners

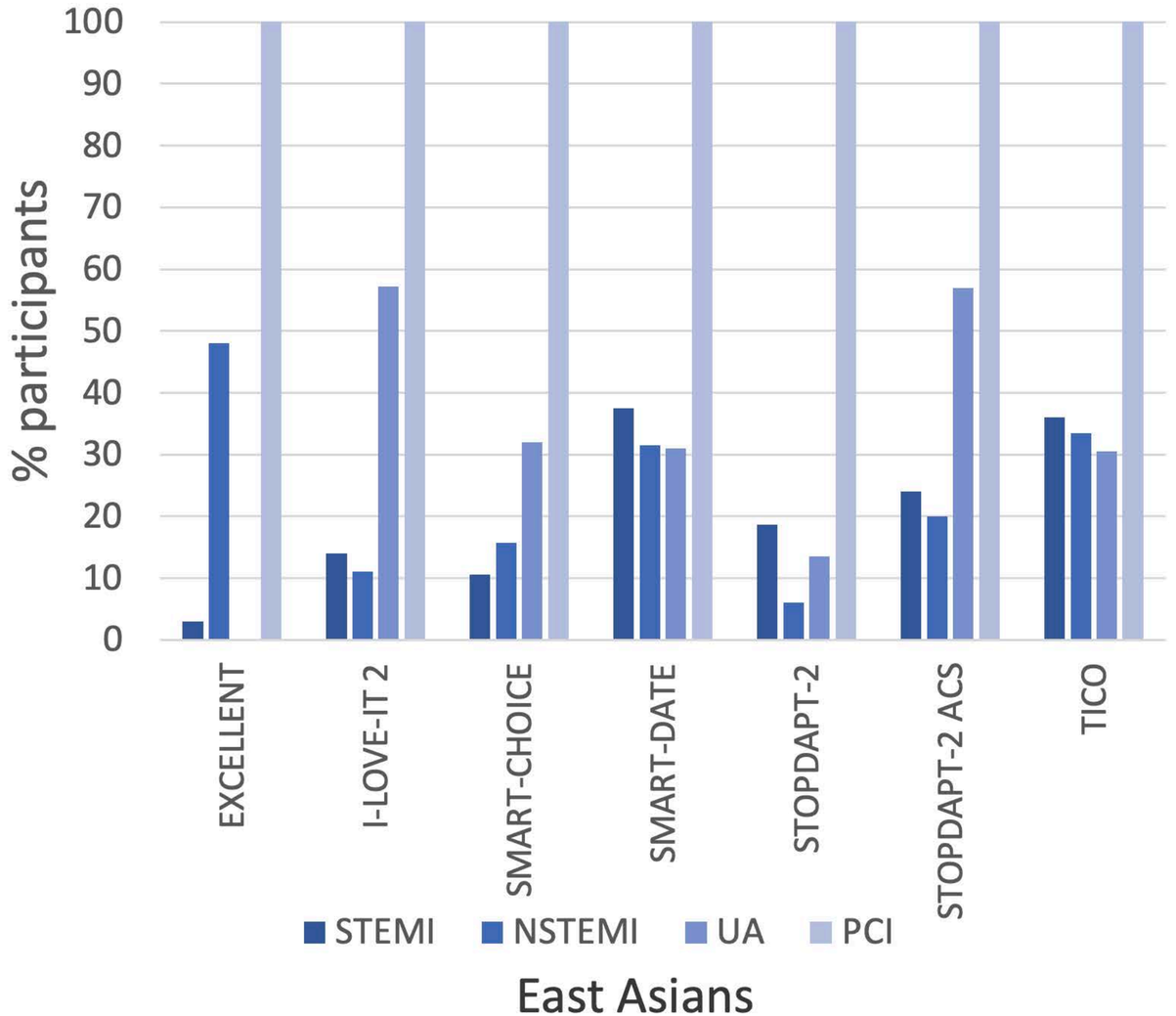
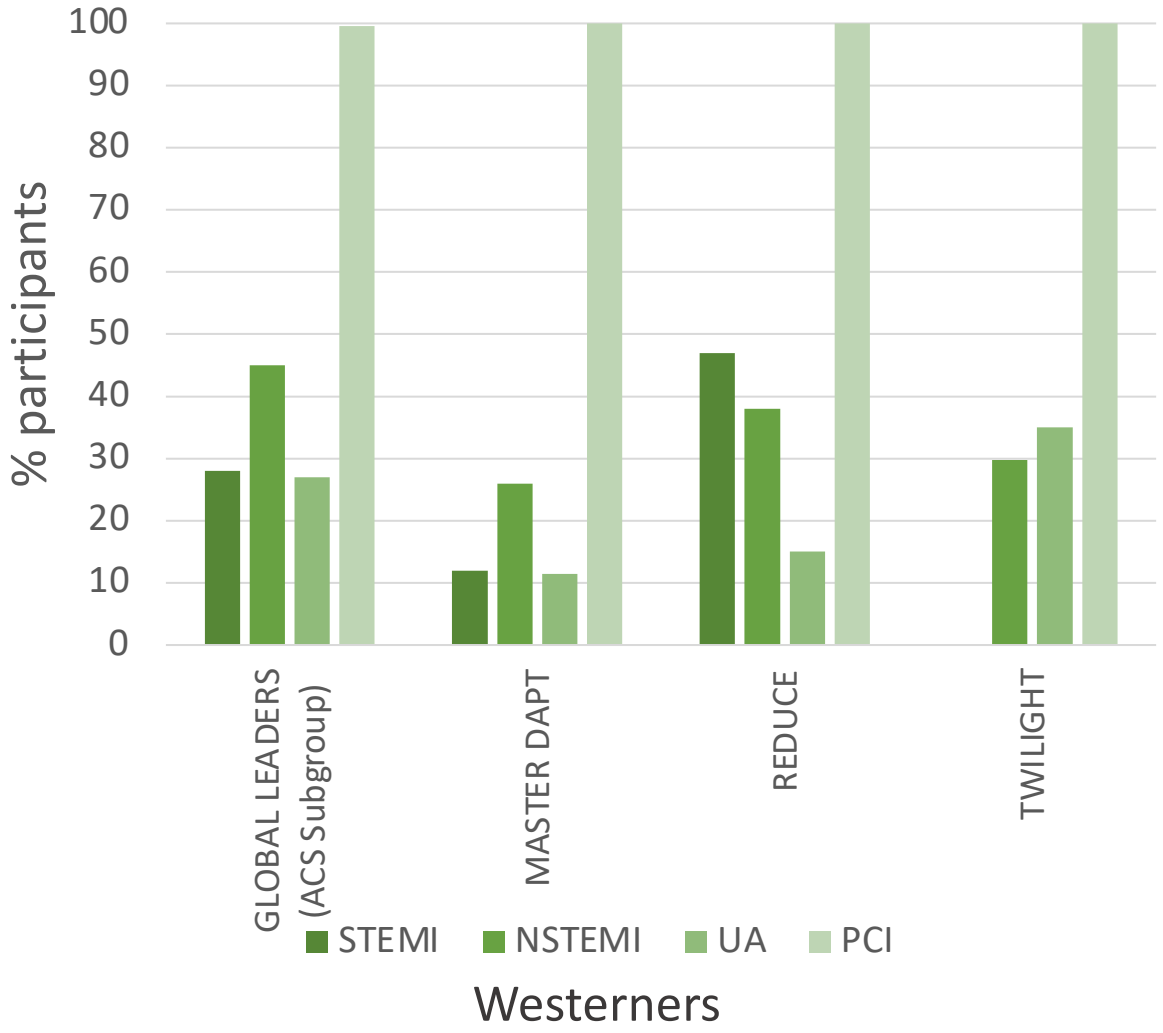

100
90
80
70
60
50
40
30
20
10
0
% participants
EXCELLENT
I-LOVE-IT 2
SMART-CHOICE
SMART-DATE
STOPDAPT-2
STOPDAPT-2 ACS
TICO
STEMI
NSTEMI
UA
PCI
East Asians

Figure 9.


100
90
80
70
60
50
40
30
20
10
0
% participants
GLOBAL LEADERS (ACS Subgroup)
MASTER DAPT
REDUCE
TWILIGHT
STEMI
NSTEMI
UA
PCI
Westerners

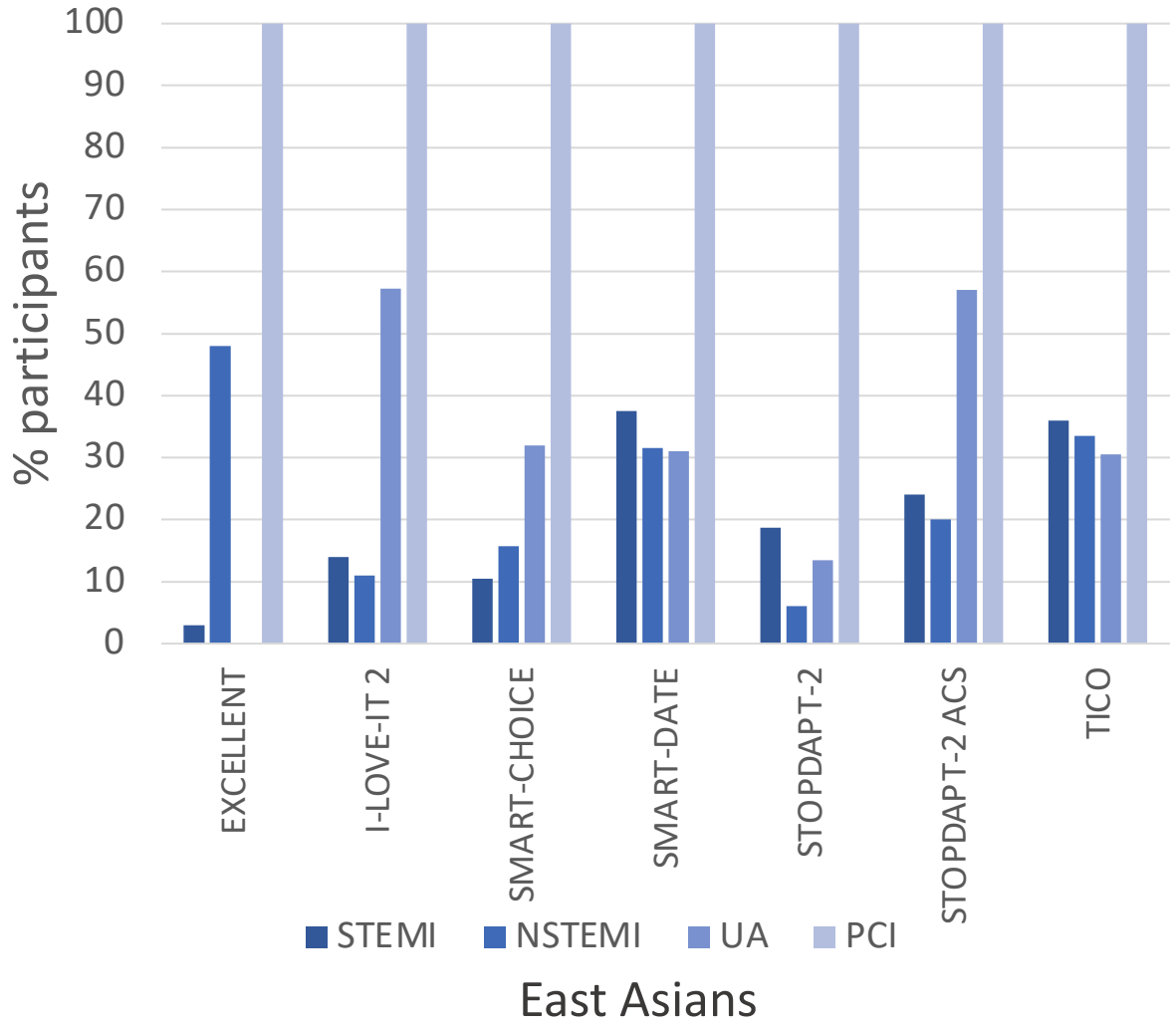

100
90
80
70
60
50
40
30
20
10
0
% participants
EXCELLENT
I-LOVE-IT 2
SMART-CHOICE
SMART-DATE
STOPDAPT-2
STOPDAPT-2 ACS
TICO
STEMI
NSTEMI
UA
PCI
East Asians

Figure 10.

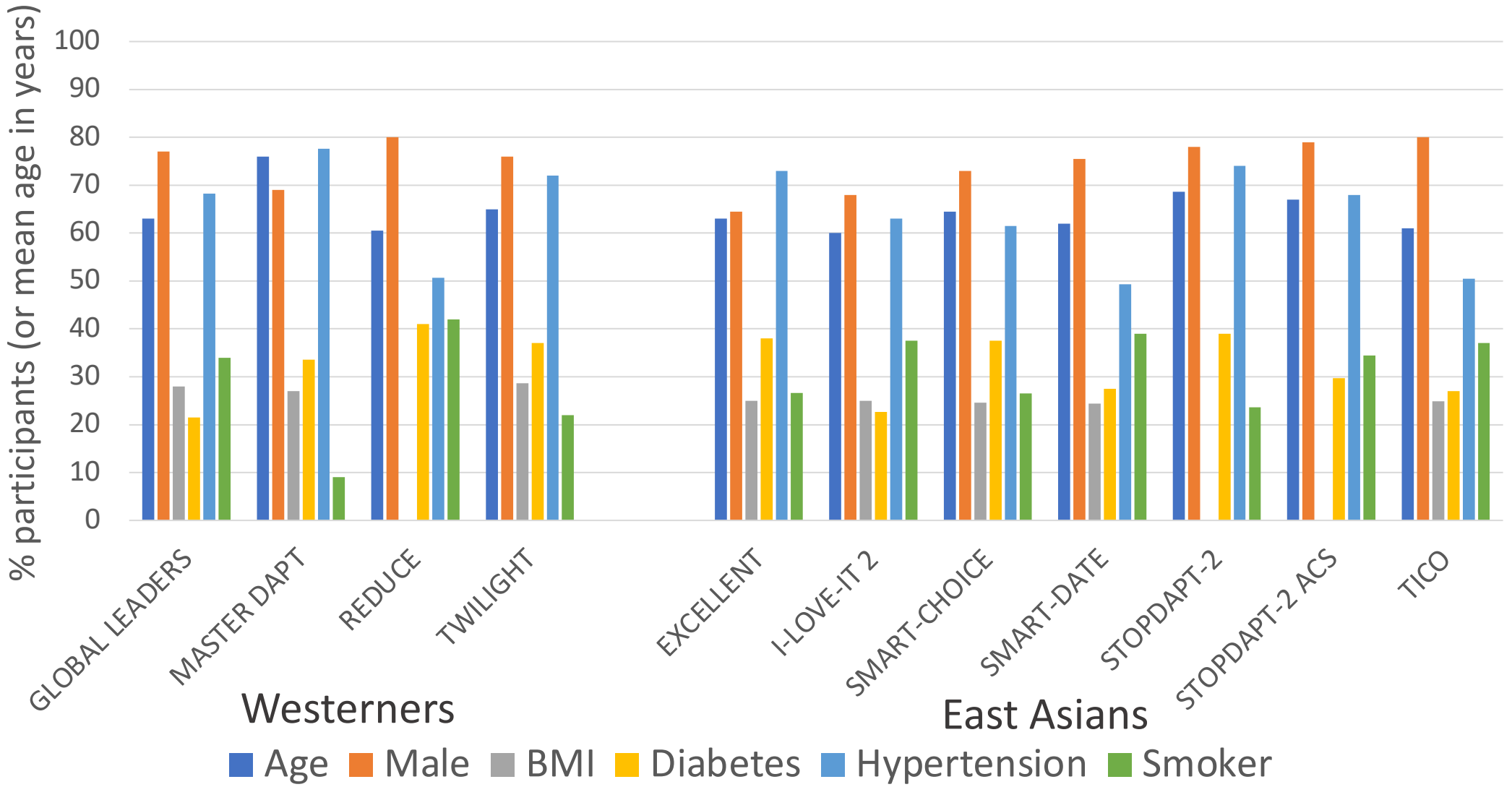
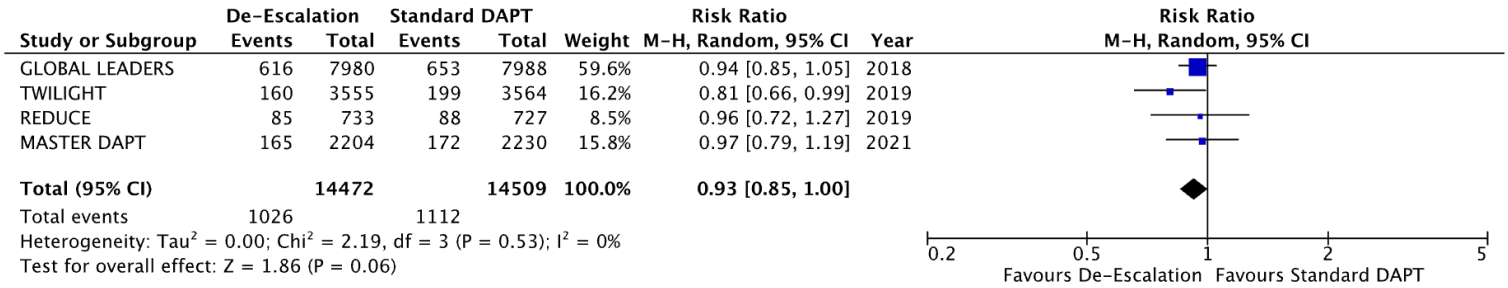
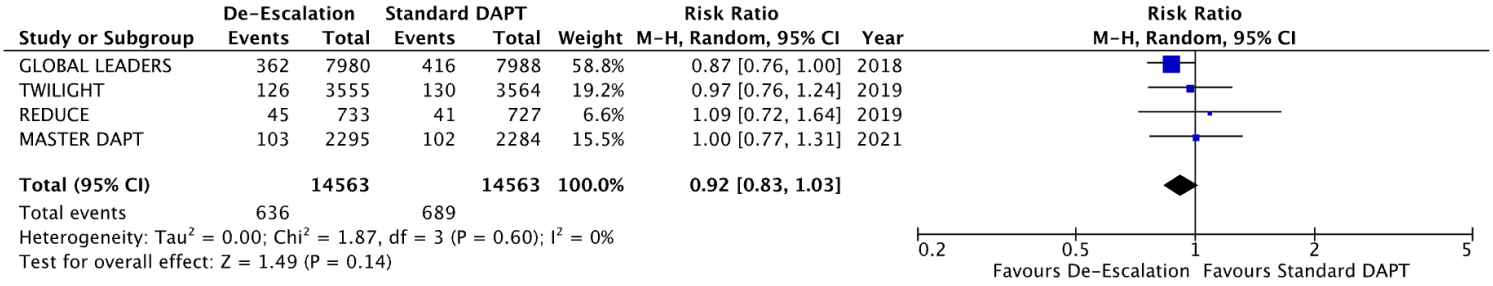

% participants (or mean age in years)
100
90
80
70
60
50
40
30
20
10
0
GLOBAL LEADERS
MASTER DAPT
REDUCE
TWILIGHT
EXCELLENT
I-LOVE-IT 2
SMART-CHOICE
SMART-DATE
STOPDAPT-2
STOPDAPT-2 ACS
TICO
Westerners
East Asians
Age
Male
BMI
Diabetes
Hypertension
Smoker

Figure 11.

A



B



C

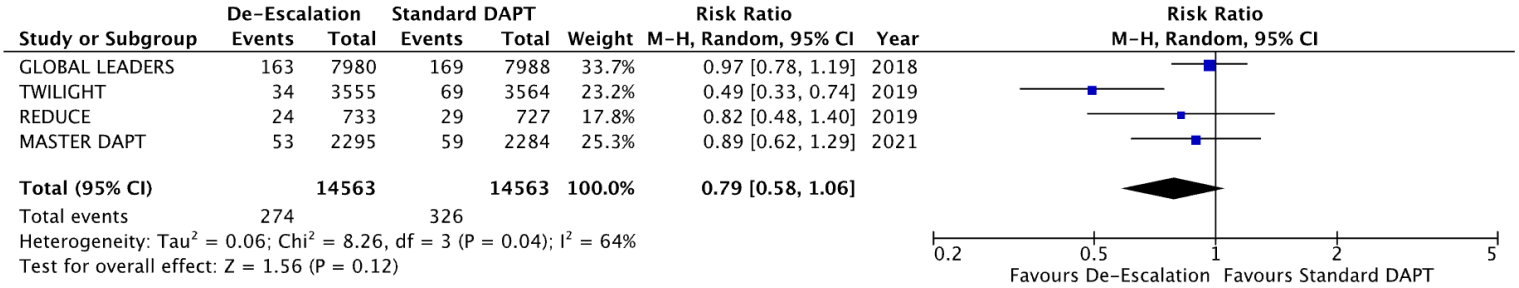
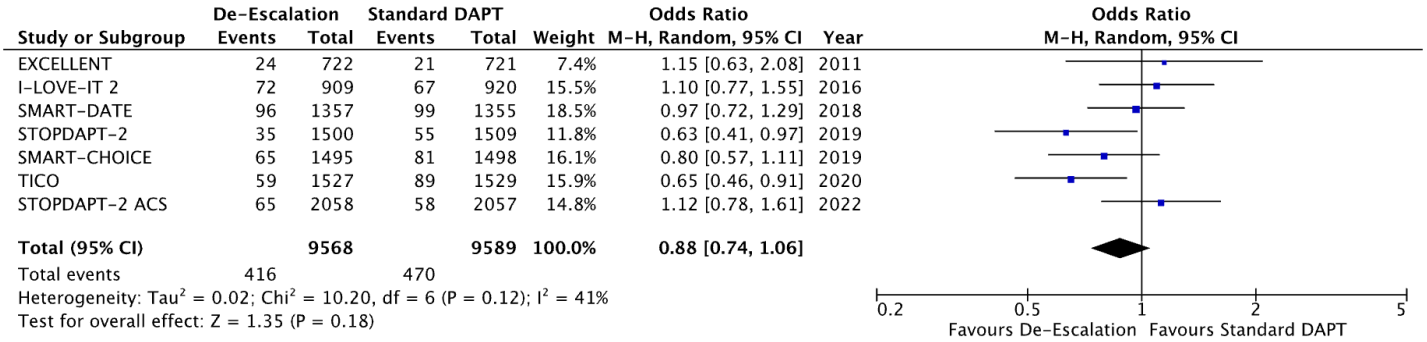


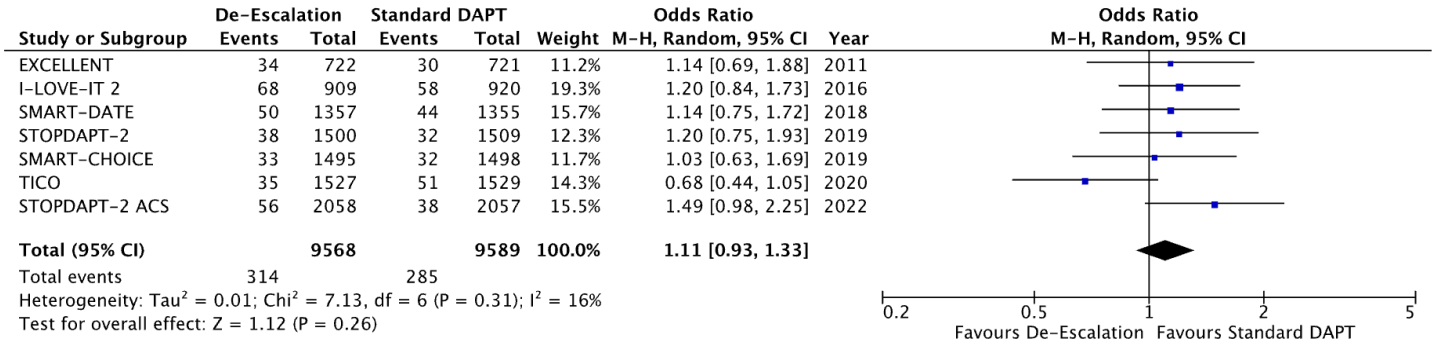
Figure 12.

Meta-analysis of studies comparing standard duration with reduced duration of DAPT in East Asian populations. Panel (A) shows net adverse cardiovascular events (NACE), panel (B) shows major adverse cardiovascular events (MACE) and panel (C) shows major bleeding.

A



B



C

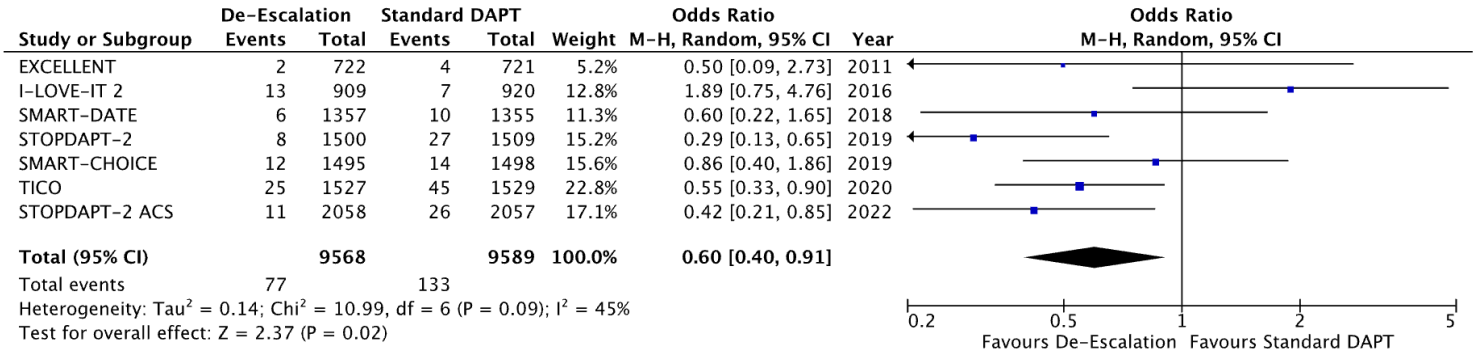
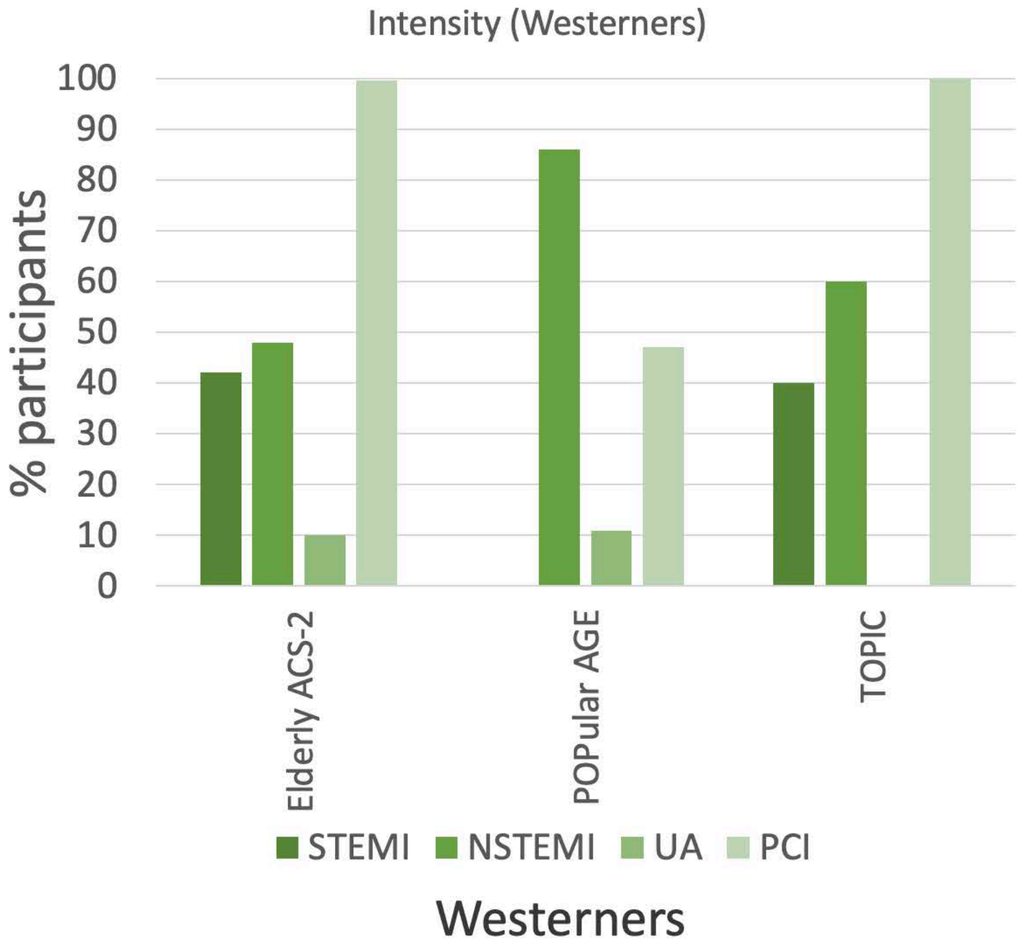
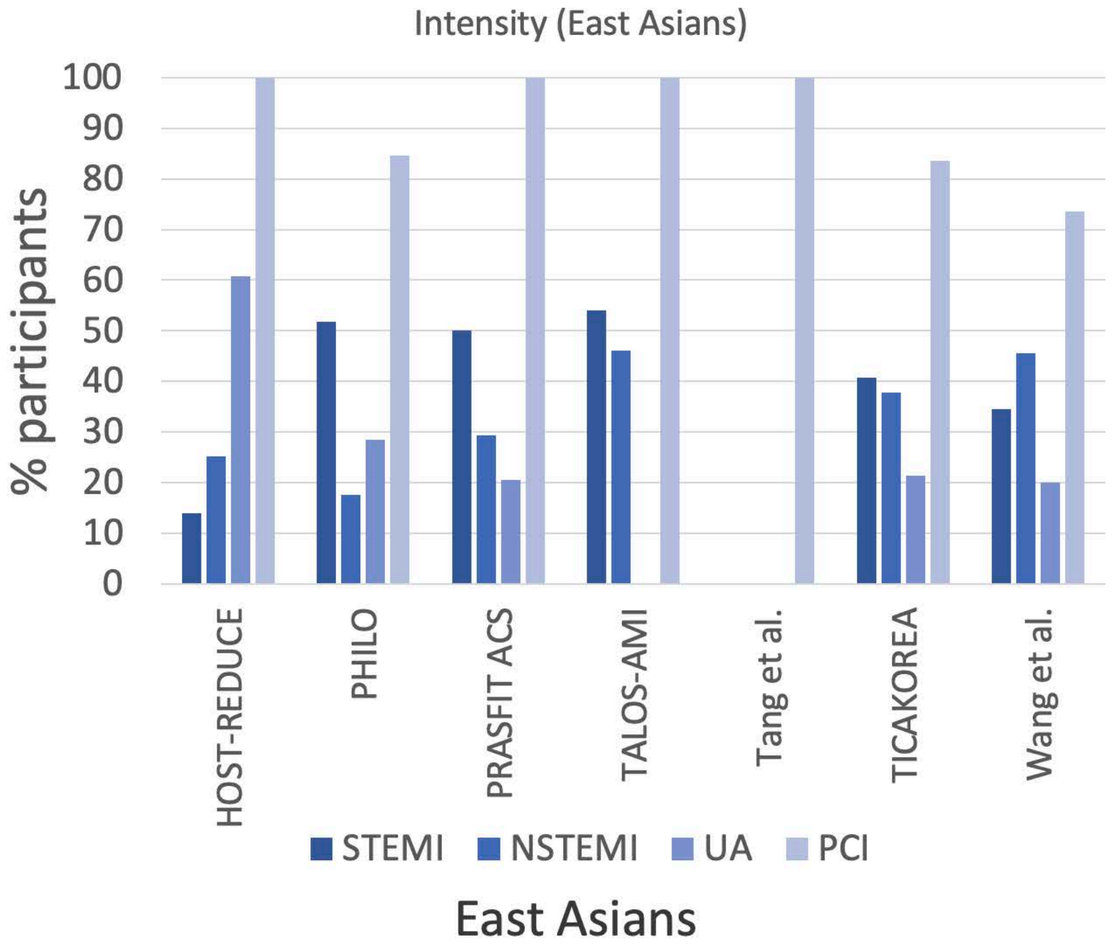


Figure 4.


Intensity (Westerners)
% participants
100
90
80
70
60
50
40
30
20
10
0
Elderly ACS-2
POPular AGE
TOPIC
STEMI
NSTEMI
UA
PCI
Westerners


Intensity (East Asians)
% participants
100
90
80
70
60
50
40
30
20
10
0
HOST-REDUCE
PHILO
PRASFIT ACS
TALOS-AMI
Tang et al.
TICAKOREA
Wang et al.
STEMI
NSTEMI
UA
PCI
East Asians