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The dawn of aspirin free strategy after short term dual antiplatelet for percutaneous coronary intervention: meta-analysis of randomized controlled trials

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Abstract

There is still a debate about the safety and efficacy of an aspirin free strategy after percutaneous coronary intervention (PCI). Hence, we performed a meta-analysis comparing aspirin free strategy to dual antiplatlets therapy (DAPT). Randomized trials (RCTs) comparing aspirin free strategy to DAPT in patients who received PCI were included. The primary outcome of interest was bleeding, defined per the Bleeding Academic Research Consortium (BARC). Secondary outcomes included major adverse cardiovascular and cerebrovascular events (MACE); defined as all-cause mortality, myocardial infarction or stroke, the individual component of MACE and stent thrombosis. A total of 4 RCTs with 29,089 patients were included. There was significant reduction in BARC 2,3 or 5 bleeding events in patients who were treated with aspirin free strategy versus DAPT (HR 0.61, 95% CI 0.39−, p = 0.03, I^2 = 89%). Moreover, although there was a trend of reduced major bleeding (BARC 3 or 5) outcomes in the aspirin free strategy group compared to the DAPT group, this did not achieve statistical significance (HR 0.63, 95% CI 0.37–1.06, p = 0.08, I^2 = 795). Additionally, there was no difference between the aspirin free strategy and DAPT in term of MACE (HR 0.92, 95% CI 0.82–1.03, p = 0.13, I^2 = 0%), all-cause mortality (HR 0.89, 95% CI 0.77–1.04, p = 0.15, I^2 = 0%), MI (HR 0.89, 95% CI 0.74–1.08, p = 0.24, I^2 = 0%), stroke (HR 1.13, 95% CI 0.65–1.99, p = 0.66, I^2 = 60%) or stent thrombosis (HR 0.1.01, 95% CI 0.83–1.22, p = 0.93, I^2 = 0%). Aspirin free strategy is as effective as DAPT in reducing MACE with better safety profile in term of bleeding.

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Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

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Keywords

Coronary artery disease; Percutaneous intervention; Aspirin; P2Y12 inhibitors

Background

The optimal duration and regimen for dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) using drug-eluting stents (DES) has been a changing paradigm. The most recent US guidelines prefer DAPT following DES placement for at least 12 months in acute coronary syndrome and 6 months in stable ischemic heart disease [1]. This was based on randomized controlled trials (RCTs) that continued aspirin indefinitely and shortened $P2Y_{12}$ inhibitor duration.

The model that aspirin must be continued with early discontinuation of the $P2Y_{12}$ inhibitor has been recently challenged. Prior to the FDA approval of clopidogrel in 1997, aspirin was one of the few medications that showed survival benefit in acute management and secondary prevention of ischemic heart disease [2–4]. Until recent years, compelling trial data questioning the efficacy of the aspirin as part of DAPT relative to its increased bleeding risk only existed for stroke patients [5]. In the meantime, more potent $P2Y_{12}$ inhibitors and new-generation drug-eluting stents have been developed giving more confidence in the safety of $P2Y_{12}$ inhibitor monotherapy.

Currently, the hypothesis of shortening DAPT after PCI by dropping aspirin and continuation of P2Y12 inhibitors (Aspirin free strategy) to decrease bleeding events has been tested in multiple trials. The aim of the present study was to assess the efficacy and safety of this novel strategy by performing a meta-analysis including the most recent RCTs.

Methods

Search strategy

We searched PubMed/MEDLINE, Embase, and Cochrane databases from inception through September 30, 2019 for RCTs comparing aspirin free strategy to DAPT. We utilized the “related articles” function in PubMed to find relevant articles which were missed by the initial search. In addition, reference lists of included studies were hand searched to further locate relevant articles that were missed by the primary search. Our search and meta-analysis were conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMAP) Statement 2015 [6]. The protocol of this study has been registered at the International prospective register of systematic reviews (PROSPERO) database. Titles and abstracts of the studies which were retrieved by the initial search were screened by two authors (K.O and B.K). The full texts of relevant articles were reviewed to determine if the study met the inclusion criteria. Any discrepancies were resolved by a third author (M.O).

Inclusion criteria and study outcomes

To be included in the current analysis, the study had to (1) include patients with coronary artery disease (2) patients received PCI for stable coronary artery disease or acute coronary syndrome (ACS). (3) the study is an RCT comparing aspirin free therapy to the standard of care (DAPT for 12 month). (4) at least 12 months of follow up data is available. (5) the trial reported the primary outcome of interest. The primary outcome of interest was bleeding, defined as per the Bleeding Academic Research Consortium Criteria (BARC). We did two separate analysis for major or minor bleeding (BARC 2, 3 or 5) and for major bleeding (BARC 3 or 5). Secondary outcomes included major adverse cardiovascular events (MACE) (defined as all-cause mortality, myocardial infarction or stroke), the individual component of MACE, stent thrombosis (definite or probable as per the Academic Research Consortium Criteria).

Quality assessment

The Cochrane Collaboration tool for assessing the quality of RCTs, the risk of bias summary for the included trials is shown in the online supplement (eFigure-1).

Statistical analysis

We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) using a random-effects model. Heterogeneity was assessed using I^2 statistic. Publication bias was evaluated by funnel plot analysis for the primary outcome. Subgroup analyses was performed based on the duration of initial DAPT therapy in the Aspirin free strategy group (3 months versus 1 month). We did not perform meta-regression analysis due to the low number of the included studies. [7] Statistical significance was set at 5%. All analyses were conducted using RevMan version 5.3 Windows (Cochrane Collaboration, Oxford, UK).

Results

The initial database search retrieved 214 articles. These were screened for eligibility by reading the title and abstract of the study. A total of 14 articles were then screened using the predetermined inclusions criteria to assess eligibility. Details of the study selection process are reported following the PRISMA-P guidelines (Fig. 1). A total of 4 RCTs were finally included; with 29,089 patients (Aspirin Free Strategy = 14,530, DAPT = 14,559), 24% female, mean follow-up 15 ± 5.5 months, mean age of 66 ± 2 years were included in the current meta-analysis. Detailed baseline characteristics of the included studies are shown in (Table 1).

There was significant reduction in BARC 2,3 or 5 bleeding events in patients who were treated with aspirin free strategy versus DAPT (HR 0.61, 95% CI 0.39−, p = 0.03, I^2 = 89%). This persisted in the subgroup analysis based on the initial duration of DAPT in the Aspirin free strategy (3 months versus 1 months, p for interaction 0.94) (Fig. 2). Moreover, although there was a trend of reduced major bleeding (BARC 3 or 5) outcomes in the Aspirin free strategy group compared to the DAPT group, this did not achieve statistical significance (HR 0.63, 95% CI 0.37–1.06, p = 0.08, I^2 = 795). The subgroup analysis based on the duration of

DAPT in the Aspirin free strategy, did not show any effect of 3 months vs 1-month group on the outcomes (p for interaction = 0.98) (Fig. 3).

Additionally, there was no difference between the Aspirin free strategy and DAPT in term of MACE (HR 0.92, 95% CI 0.82–1.03, p = 0.13, I^2 = 0%), all-cause mortality (HR 0.89, 95% CI 0.77–1.04, p = 0.15, I^2 = 0%), MI (HR 0.89, 95% CI 0.74–1.08, p = 0.24, I^2 = 0%), stroke (HR 1.13, 95% CI 0.65–1.99, p = 0.66, I^2 = 60%) or stent thrombosis (HR 0.1.01, 95% CI 0.83–1.22, p = 0.93, I^2 = 0%) (Fig. 4). Moreover, the subgroup analysis based on the initial duration of DAPT in the Aspirin free strategy did not show any difference in MACE between stopping Aspirin at 3 months versus 1 month (p for interaction = 0.229) (Fig. 2).

Discussion

In the current comprehensive meta-analysis comparing aspirin free strategy to DAPT following PCI, we observed several key findings. First, the aspirin free strategy significantly decreased the risk of serious bleeding events and trended toward a significant reduction in major bleeding events. Second, the analysis showed non-inferiority with efficacy outcomes including MACE, all-cause mortality, MI, stroke, and, most notably, stent thrombosis. Third, non-inferiority in MACE was seen in both 1-month and 3-month analyses.

To date, this is the only comprehensive meta-analysis of studies testing aspirin free strategy versus DAPT in patients who received PCI. The included studies have only been published within the past 2 years as this hypothesis has been introduced only recently. Due to early studies showing mortality benefit in ischemic heart disease, aspirin therapy quickly became standard of care even before the advent of PCI. Though notably increased bleeding risk was seen, the ischemic benefit far outweighed this drawback. In 2001, the Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation (CURE) trial showed DAPT, with the addition of clopidogrel to aspirin, in ACS lowered ischemic events at 1 year but increased major bleeding by a lesser extent [8]. This benefit was subsequently seen in post PCI patients leading to current DAPT guidelines [2]. The observation of poor clopidogrel response and incidence of in-stent thrombosis in a substantial portion of patients, led to the development of the more-potent oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor [9, 10]. Along with aspirin in DAPT, these newer drugs decreased ischemic events in high-risk patients but at the expense of more major bleeding events [11, 12]. At that point in time, monotherapy with $P2Y_{12}$ inhibitors had not been studied in ACS or post PCI patients. Interestingly, the Aspirin and clopidogrel compared with clopidogrel along after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH) trial found that in post stroke patients clopidogrel monotherapy was noninferior to DAPT in regards to major adverse cardiovascular and cerebrovascular events (MACE) but led to significantly less major and life-threatening bleeding [2, 5].

The first large trial to test the hypothesis of $P2Y_{12}$ inhibitor monotherapy in patients who received PCI was GLOBAL-LEADERS published in 2018 [13]. The trial randomized 15,968 patients into either a DAPT with ticagrelor for 1 month followed by ticagrelor monotherapy for 23 months arm versus a standard DAPT with clopidogrel or ticagrelor for 12 months followed by aspirin monotherapy for 12 months arm. The results were

inconsistent with the other three trials analyzed as they did not show a benefit for $P2Y_{12}$ inhibitor monotherapy in terms of hemodynamically significant bleeding. Interestingly, as GLOBAL-LEADERS was designed as a superiority trial and had the closest trend toward benefit for $P2Y_{12}$ inhibitor monotherapy with clinical outcomes including MACE (P = 0.056) [13, 14].

We subdivided the analyses by duration of initial DAPT in the aspirin free strategy. SMART-CHOICE and TWILIGHT included 3-month DAPT arms while GLOBAL-LEADERS and STOPDAPT-2 tested 1-month arms. Against intuitive thought, it appeared as the 3-month trials demonstrated a reduced risk of both hemodynamically significant and major bleeding while the 1-month trials did not. However, the statistical test of subgroup interaction was non-significant (p for interaction = 0.98) and hence this should be interpreted with caution. We believe that this result reflect the difference between trials in term of designs and inclusions criteria, for example in TWILIGHT patients were randomized following an event-free initial 3 months of DAPT, so patients who developed any bleeding of ischemic events in the event free period were excluded from randomization [15]. Moreover, a highlight of TWILIGHT was their inclusion of high-risk ischemic and bleeding patients. Patients had to have at least one high-risk clinical as well as angiographic feature to be eligible. Similarly, the TICO trial is currently randomizing ACS patients after 3 months of DAPT with ticagrelor to standard of care versus ticagrelor monotherapy for 9 months and will supply additional data to this regimen [16].

Future directions with this paradigm will be to assess monotherapy with prasugrel following a shorter duration of DAPT. While multiple RCTs show efficacy for both ticagrelor and prasugrel following PCI compared to clopidogrel in DAPT, the Prospective Randomized Trial of Ticagrelor Versus Prasugrel in Patients with Acute Coronary Syndrome—Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 5) trial displayed superiority of Prasugrel in MACE with comparable bleeding outcomes [11, 12, 17]. Our study has several limitations which need to be acknowledged. First, this was a study level meta-analysis and consequently it lacked patients level data. Second, there was variation in the studies protocols and designs which contributed to the heterogeneity among the studies, GLOBAL-LEADERS and STOPDAPT-2 primarily looked at efficacy outcomes of MACE whiles TWILIGHT was designed to assess bleeding risk with MACE as secondary outcome. Furthermore, TWILIGHT was the only double-blinded study while the other three were open-label. Another limitation to our study is the paucity of adherence data with each medication regimen. Ticagrelor is a twice a day medication while aspirin and clopidogrel are both only daily. This dosing variable was thought to be a significant factor in the results of ISAR-REACT 5. Even with these limitations, our data offers a comprehensive analysis of current randomized trials testing $P2Y_{12}$ inhibitor monotherapy regimens.

Conclusion

In this up-to-date meta-analysis of trial data, shortened DAPT regimens followed by $P2Y_{12}$ inhibitor monotherapy significantly decreased the risk of serious bleeding events and trended toward a significant reduction in major bleeding events while showing no difference in

MACE. More trials are needed to further detail beneficial treatment regimens and to target certain risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- There is still a debate about the safety and efficacy of an aspirin free strategy after percutaneous coronary intervention (PCI).
- A meta-analysis of four randomized controlled trials with 29,089 patients, comparing aspirin free strategy to standard of care was conducted.
- There was significant reduction in BARC 2,3 or 5 bleeding events in patients who were treated with aspirin free strategy versus standard of care.
- There was no difference between the aspirin free strategy and standard of care in term of ischemic outcomes.

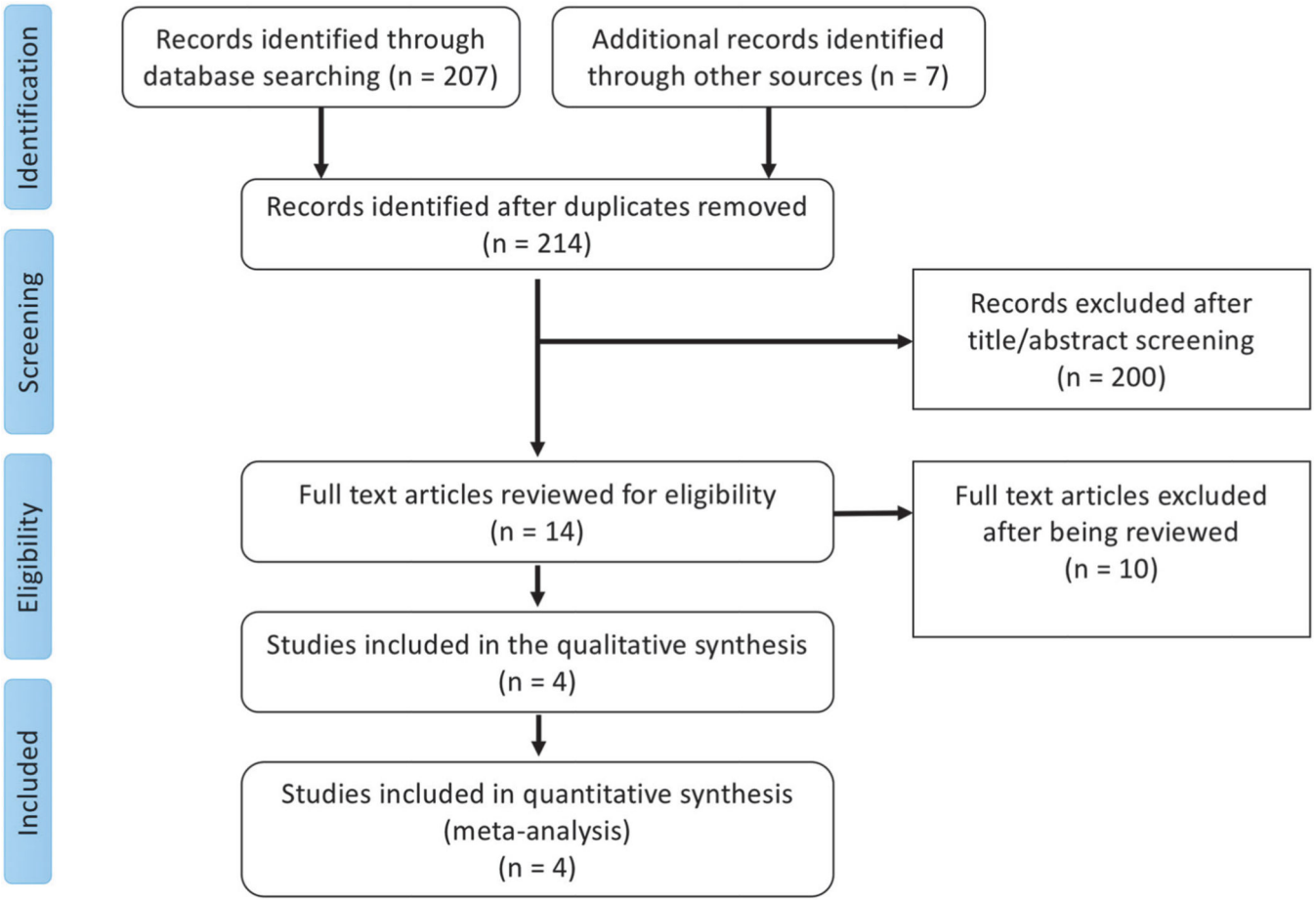

Fig. 1.
The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

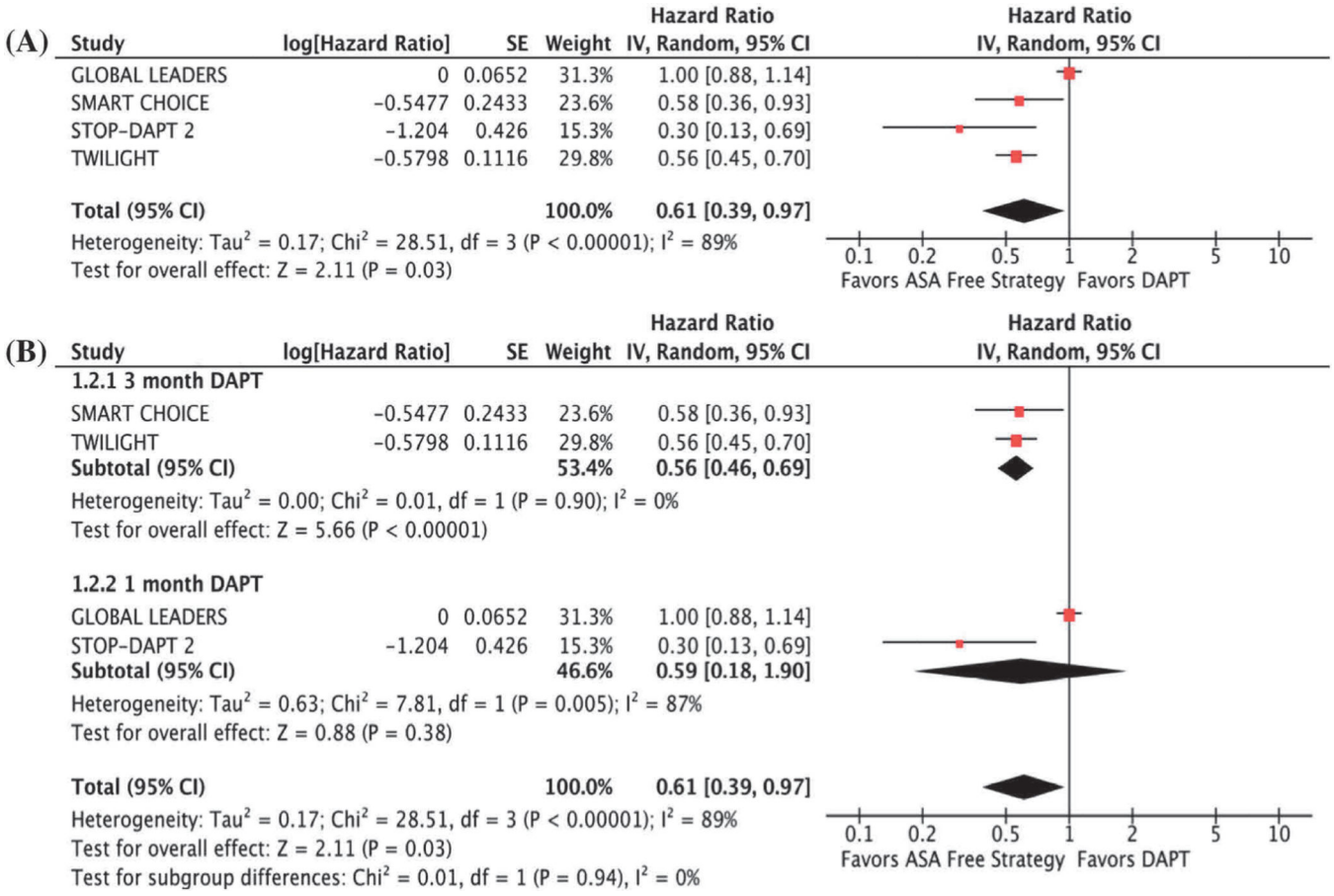

Fig. 2.

a Forest plot comparing BARC 2, 3 or 5 bleeding between the Aspirin free strategy and dual antiplatelet therapy (DAPT). **b** Subgroup analysis based on the duration of the initial DAPT therapy in the Aspirin free strategy comparing 3 months versus 1 month

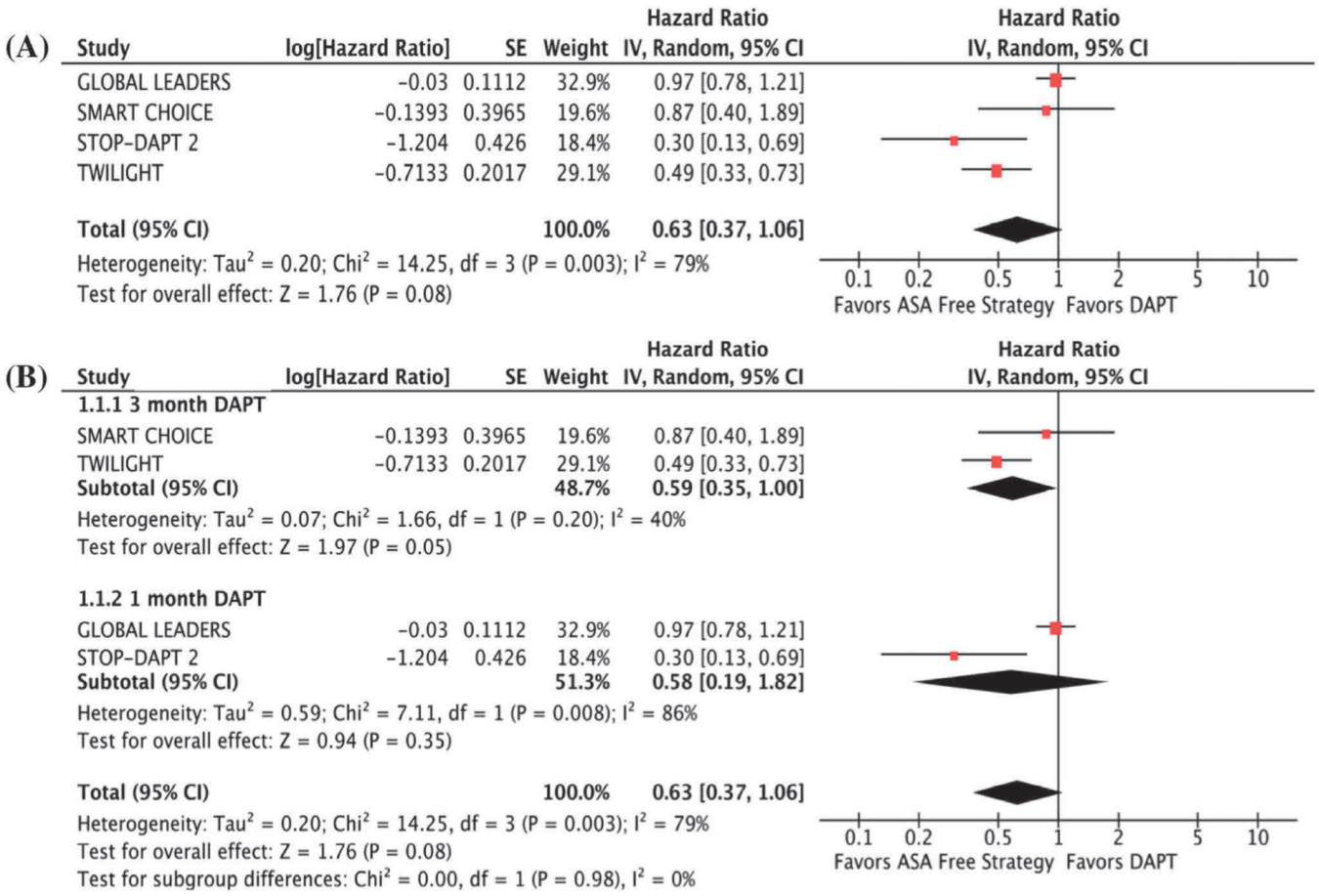

Fig. 3.

a Forest plot comparing BARC 3 or 5 bleeding between the Aspirin free strategy and dual antiplatelet therapy (DAPT). **b** Subgroup analysis based on the duration of the initial DAPT therapy in the Aspirin free strategy comparing 3 months versus 1 month

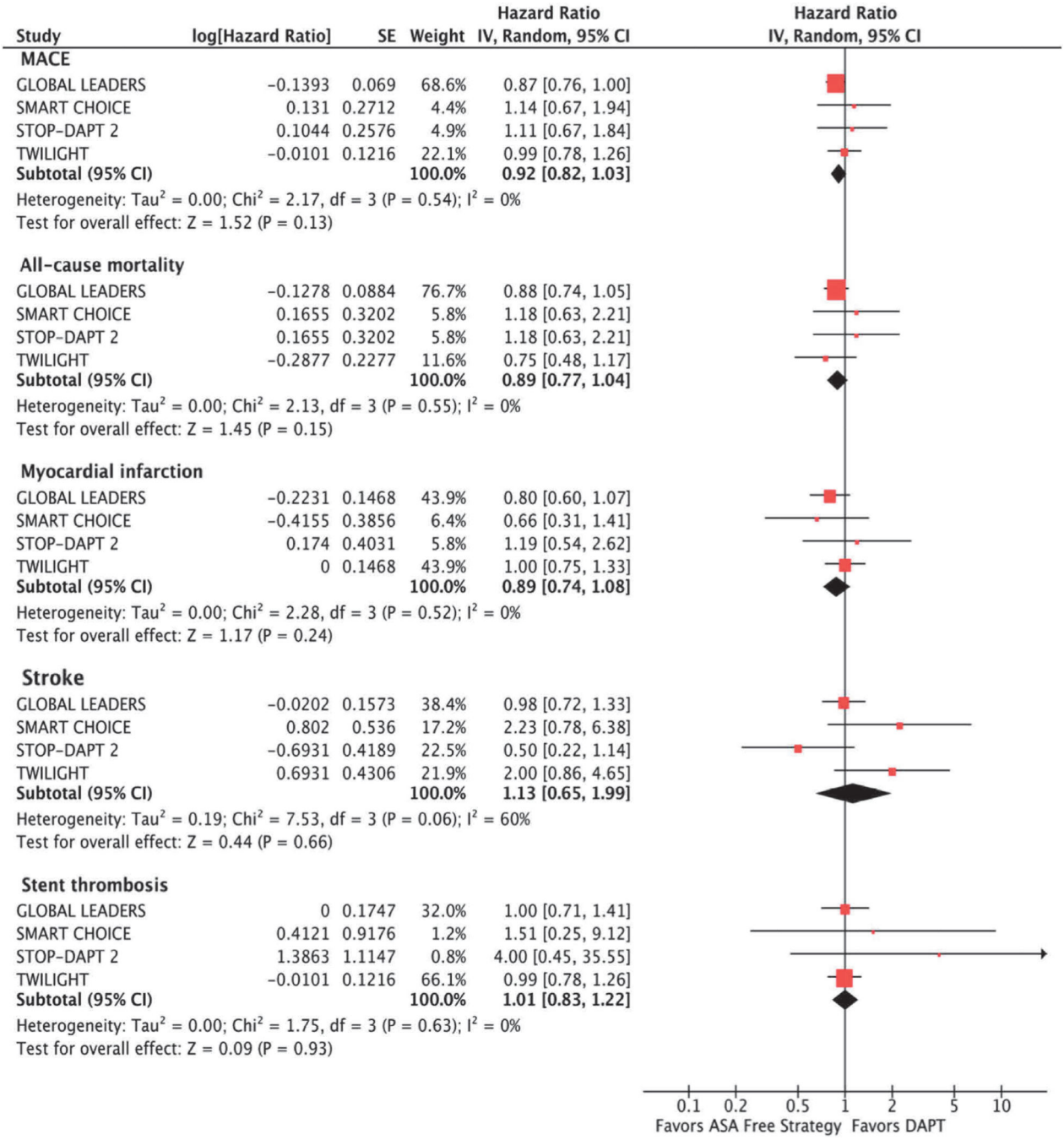

Fig. 4.

Forest plot comparing the ischemic endpoints between the Aspirin free strategy and dual antiplatelet therapy (DAPT)

Table 1

Baseline characteristics of the studies included in the current meta-analysis

Time	TWILIGHT	TWILIGHT	STOP-DAPT-2	STOP-DAPT-2	SMART-CHOICE	SMART-CHOICE	GLOBAL LEADERS	Global LEADERS
Year	2019	2019	2019	2019	2019	2019	2018	2018
Arm	Ticagrelor monotherapy	DAPT	Clopidogrel monotherapy	DAPT	P2Y12 inhibitor monotherapy	DAPT	Ticagrelor monotherapy	DAPT
Number	3555	3564	1500	1509	1495	1498	7980	7988
Follow-up, months	12	12	12	12	12	12	24	24
Age (mean ± standard deviation)	65.2 ± 10.3	65.1 ± 10.4	68.1 ± 10.9	69.1 ± 10.4	64.6 ± 10.7	64.4 ± 10.4	64.5 ± 10.3	66.6 ± 10.3
Female, N (%)	844 (23.8%)	852 (23.9%)	317 (21.1%)	355 (23.5%)	408 (27.3%)	387 (25.8%)	1865 (23.4%)	1849 (23.1%)
HTN, N (%)	2580 (72.6%)	2574 (72.2%)	1105 (73.7%)	1116 (74.0%)	921 (61.6%)	919 (61.3%)	5882 (74.0%)	5883 (73.3%)
DM, N (%)	1319 (37.1%)	1301 (36.5%)	585 (39.0%)	574 (38.0%)	570 (38.2%)	552 (36.8%)	2049 (25.7%)	1989 (24.9%)
HLD, N (%)	2157 (60.7%)	2146 (36.5%)	1116 (74.4%)	1128 (74.8%)	673 (45.1%)	679 (45.5%)	5345 (69.3%)	5423 (70.0%)
Prior PCI, N (%)	1502 (42.3%)	1496 (42.0%)	503 (33.5%)	529 (35.1%)	172 (11.5%)	177 (11.8%)	2609 (32.7%)	2612 (32.7%)
Prior CABG, N (%)	362 (10.2%)	348 (9.8%)	17 (1.1%)	42 (2.8%)			448 (5.6%)	495 (6.2%)
UA, N (%)	1249 (35.1%)	1245 (34.9%)	193 (12.9%)	214 (14.2%)	467 (31.2%)	491 (32.8%)	1004 (12.6%)	1018 (12.7%)
NSTEMI, N (%)	1024 (28.8%)	1096 (30.8%)	81 (5.4%)	99 (6.6%)	239 (16.0%)	230 (15.4%)	1684 (21.1%)	1689 (21.1%)
STEMI, N (%)	Excluded	Excluded	291 (19.4%)	270 (17.9%	164 (11.0%)	150 (10.0%)	1062 (13.3%)	1030 (12.9%)
Stable angina, N (%)	1047 (29.7%)	999 (28.0%)	NA	NA	625 (41.8%)	625 (41.8%)	NA	NA
Angiographic Lesion complexity								
Bifurcation, N (%)	434 (12.2%)	432 (12.1%)	376 (25.1%)	393 (26%)	199 (13.3%)	181 (12.1%)	1251 (12.0%)	1265 (12.1%)
Total occlusion, N (%)	222 (6.2%)	224 (6.3%)	55 (3.7%)	67 (4.4%)	NA	NA	NA	NA
Bypass grafts, N (%)	62 (1.7%)	72 (2.0%)	3 (0.2%)	3 (0.2%)	NA	NA	115 (1.1%)	106 (1.0%)
Total lesion treated	1585	1597	1575	1606	1849	1885	10403	10438
LAD	1993 (56.1%)	2010 (56.4%)	828 (55.2%)	854 (56.6%)	903 (48.8%)	950 (50.4%)	4283 (41.2%)	4383 (42.0%)
LCx	1151 (32.4%)	1146 (32.4%)	268 (17.9%)	305 (20.2%)	399 (21.6%)	376 (19.9%)	2524 (24.3%)	2553 (24.5%
RCA	1243 (35.0%)	1257 (35.2%)	436 (29.1%)	410 (27.2%)	524 (28.3%)	524 (27.8%)	3284 (31.6%)	3206 (30.7%)
Left main	166 (4.7%)	187 (5.2%)	43 (2.9%)	37 (2.5%)	23 (1.2%)	35 (1.9%)	197 (1.9%)	190 (1.8%)
Multivessel PCI	NA	NA	100 (6.7%)	116 (7.7%)	430 (28.8%)	457 (30.5%)	2012 (25.5%)	2001 (25.3%)

ASA aspirin, *HTN* hypertension, *DM* diabetes mellitus, *HLD* hyperlipidemia, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *ACS* acute coronary syndrome, *UA* unstable angina, *LVEF* left ventricular ejection fraction, *LAD* left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery