Single Antiplatelet Therapy Versus Dual Antiplatelet Therapy After Transcatheter Aortic Valve Replacement: A Meta-analysis of Randomized Controlled Trials

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Abstract

INTRODUCTION: After transcatheter aortic valve replacement (TAVR), ischemic/embolic complications and bleeding remain important because it correlates with mortality. The optimal antithrombotic regimen after successful TAVR remains unclear. This study compared the efficacy and safety of single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) among post-TAVR patients.

METHODS: Extensive search of PubMed, MEDLINE, Cochrane, and Ovid was done for articles published until November 20, 2020. Studies were limited to randomized controlled trials. Outcome measures include stroke, myocardial infarction (MI), all-cause mortality, and major bleeding. Two reviewers independently reviewed the studies. Results were gathered from published articles, journals, and clinical trials. Studies were critically appraised with regard to methods of minimizing bias. All four studies included received a quality scale for meta-analysis overall score of not less than B. Statistical analysis was done using Review Manager V5.4.

RESULTS: Four randomized controlled trials with 1086 patients were included in this meta-analysis. Overall, the risk of stroke (odds ratio [OR], 0.94 [0.54–1.64]), MI (OR, 0.50 [0.18–1.40]), and overall mortality (OR, 1.01 [0.65–1.57]) did not differ significantly between DAPT and SAPT. There was increased risk of bleeding noted with DAPT, thus favoring SAPT (OR, 0.44 [0.30–0.65]).

CONCLUSION: Among patients who underwent TAVR, DAPT compared with SAPT had similar rates of stroke, MI, and death. Because of lower rates of bleeding, we recommend using single antiplatelet therapy after TAVR.

KEYWORDS: TAVR, TAVI, antiplatelet, single antiplatelet therapy, antithrombotic, DAPT

BACKGROUND

The performance of transcatheter aortic valve replacement (TAVR) has expanded considerably during the past decade. Technological advances and refinement in implantation techniques have resulted in improved procedural outcomes, whereas indications are progressively extending toward lower-risk patients.[1]

Antithrombotic regimen after successful TAVR is of the utmost importance to prevent ischemic events. Not only ischemic, but also bleeding events, in the periprocedural period and months after TAVR remain a relevant concern to be faced with optimized antithrombotic therapy. Moreover, the antiplatelet and anticoagulant pharmacopeia has evolved significantly in recent years with new drugs and multiple possible combinations.[2]

Based on expert consensus, American and European guidelines have recommended the use of a dual antiplatelet therapy (DAPT) in the absence of overwhelming risk of bleeding, considering the bioprosthetic valve would behave similarly to a coronary stent in terms of flow conditions.[3] A DAPT for the first 3 to 6 months has been adopted, with the rationale of protecting device-related thromboembolic events, whereas the endothelialization of the metallic valve frame is ongoing. In patients without an underlying indication for chronic oral anticoagulation (OAC), DAPT consisting of low-dose (75–100 mg once daily) acetylsalicylic acid (ASA) and clopidogrel (75 mg once daily) for 3 to 6 months, followed by lifelong single antiplatelet therapy (SAPT), is generally recommended. Lifelong OAC is recommended for patients with transcatheter implanted bioprostheses, who have other indications for anticoagulation.

The concept of SAPT has been preliminarily evaluated in three relatively small randomized controlled trials (RCTs). A patient-level meta-analysis by Raheja et al[4] of three RCTs[5–7] included a total of 421 patients, and the composite of death, major or life-threatening bleeding, and major vascular complications at 30 days was more frequent with DAPT than SAPT (17.6% vs 10.9%; odds ratio [OR], 1.73; 95% confidence interval [CI], 1.00–2.98; $P = 0.05$).[7] Consistently, the 30-day risk of major or life-threatening bleeding was also increased with DAPT versus SAPT (11.4% vs 5.2%, respectively; OR, 2.24; 95% CI, 1.17–3.31; $P = 0.011$) without difference in the composite of myocardial infarction (MI) or stroke (3.8% vs 3.8%; $P = 0.99$) or death (5.2% vs 3.8%; $P = 0.48$).

Because of bleeding risks and related mortality implications, doubts have emerged with respect to the risk/benefit assessment of combination antithrombotic regimens after TAVR, and the evaluation of simplified single agent regimens has emerged as a meaningful target for clinical investigation.

RESEARCH QUESTION

Among patients who underwent TAVR, is DAPT better than SAPT in preventing stroke, MI, and mortality without causing significant bleeding risk?

OBJECTIVES

The objective of this study is to perform a meta-analysis of RCTs in the determination of the effectiveness and safety of SAPT versus DAPT following TAVR in terms of prevention of stroke, MI, and all-cause mortality, without causing significant life-threatening bleeding events.

METHODS OF REVIEW

Criteria for Considering Studies in the Review

Types of Studies

The meta-analysis was limited to RCTs. There was no restriction on language of reporting or on time period. Published and unpublished randomized clinical trials were included whether it is single-blinded, double-blinded, or unblinded. Nonhuman studies were excluded.

Types of Participants

Subjects included in the studies were analyzed according to the following inclusion criteria: adult patients older than 70 years, not candidates for surgical aortic valve replacement; undergoing TAVR, mean age, sex, previous stroke or transient ischemic attack, hypertension, diabetes mellitus, previous MI, heart failure, and echocardiographic findings. Development of adverse cardiovascular events during follow-up was documented.

Types of Interventions

The intervention is SAPT versus DAPT for the first 3 months following TAVR.

Types of Outcome Measures

1. Primary outcome

   Primary outcome measure in this study is the development of thromboembolic events, which were defined in the included trials as stroke and MI.

2. Secondary outcome

   Secondary outcome measures include all-cause mortality and major bleeding. Major bleeding was defined as being life-threatening and/or requiring blood transfusion, as well as any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury.

Search Methods

Electronic Searches

We identified three references through electronic searches of PubMed, Cochrane Library, and MEDLINE up to October 20, 2020. We also looked into reference list of articles. Free texts were used for the following terms: "transcatheter aortic valve replacement," "transcatheter aortic valve implantation," and "antiplatelet." A total of 20 articles were identified, and four articles were included in the meta-analysis (Figure 1).

Data Collection and Analysis

Selection of Studies and Inclusion and Exclusion Criteria

Electronic literature search for RCTs involving patients receiving SAPT compared with DAPT in the first 3 months following

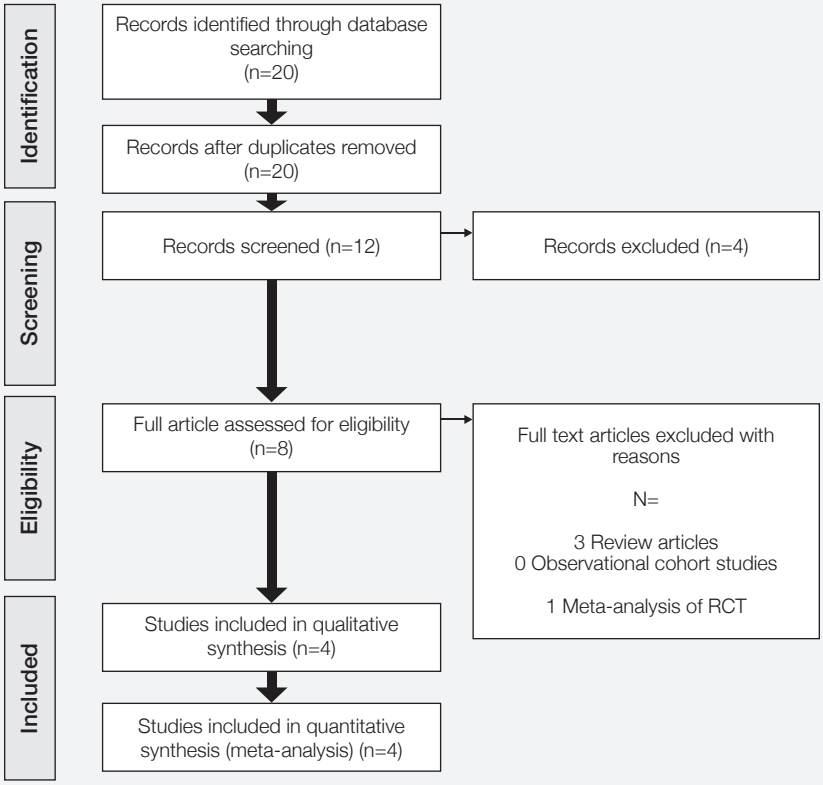

Figure 1. Trial selection process. RCT, randomized controlled trial

TAVR was performed. Studies were excluded if (1) studies were nonrandomized, nonprospective, and/or observational studies; (2) patients with previous percutaneous coronary intervention or MI requiring DAPT, need for direct OAC, with bleeding diathesis; (3) absence of aforementioned clinical outcomes; and (4) duplicate studies.

Data Extraction and Management

Eight articles were considered for inclusion in the meta-analysis. All studies were carefully analyzed, discussed, and appraised by two independent reviewers. After application of initial eligibility criteria, four articles were excluded. The remaining four articles were all RCTs and were subjected to critical appraisal and quality assessment using a validated and objective quality assessment criterion for controlled interventional studies (quality assessment tool from Cochrane Collaboration). Studies were included if there was an agreement between the two reviewers. Disagreements and discrepancies of each quality assessment were settled among the reviewers through a third reviewer.

Data in the studies were obtained and tabulated (Table 2) independently by the study authors. This included the number of patients, the particular drug interventions given, age, sex, and follow-up duration.

Assessment of Risk of Bias in Included Studies

Studies included are all RCTs. Each study was critically appraised with regard to methods of minimizing selection bias, performance bias, exclusion bias, and detection bias using Cochrane's risk-of-bias tool for meta-analysis. Two reviewers independently appraised each journal, and discrepancies among the assessment of risk of biases were settled through a third independent reviewer. All three studies included received a quality scale for meta-analysis overall score of B. The quality assessment and risk of bias of the included studies are summarized in Table 1.

All trials included were open-label. Randomization was done adequately in the four studies. The baseline characteristics of study participants were well balanced in the four trials.

Measures of Treatment Effect

The incidence of thromboembolic events, all-cause mortality, and major bleeding in the SAPT and DAPT groups was recorded. The OR and the 95% CI were calculated using Review Manager V5.4.

Unit of Analysis Issues

The primary outcome measure used was the occurrence of thromboembolic events.

Assessment of Heterogeneity

Data were assessed for heterogeneity. Quantitative syntheses of data were performed if clinical heterogeneity was negligible. Clinical heterogeneity may be caused by differences in study populations, interventions, or definition of endpoints.

Table 1. Quality Assessment and Risk of Bias

Study	Method	Randomization	Allocation Concealment	Baseline Characteristics	Blinding	ITT	Adequacy of F/U	QA	Remarks
Ussia et al,[5] 2011	Randomized, open-label trial	Met "We designed a randomized, open-label, single-center study with blinded assessment of the study end points."	Not stated	Met Baseline characteristics were similar. Under Table 1	Not met Open-label study design	Met	Met	B	Limitations include open-label study and small sample size
Stabile et al,[6] 2014	Randomized, open-label trial	Met "…Out of these 120 patients, who met inclusion/exclusion study criteria and gave informed consent, were randomized."	Not stated	Met Baseline characteristics were similar. Under Table 1	Not met Open-label study design	Met	No dropouts	B	Limitations include open-label study and small sample size
Rodes-Cabau et al,[7] 2017	Randomized, open-label trial	Met "Patients were randomized (1:1) the day before the TAVR procedure to receive aspirin…"	Met "Random block sizes were used to conceal treatment allocation from the patients, and randomization was stratified by clinical center."	Met Baseline characteristics were similar. Under Table 1	Not met Open-label study design	Met	No dropouts	B	Limitations include open-label study and small sample size
Brouwer et al,[8] 2020	Randomized, open-label trial	Met "Patients were randomly assigned at least 1 day and no more than 90 days before TAVI, in a 1:1 ratio…"	Met "Randomization was performed by an electronic Web response system, with stratification according to center."	Met Baseline characteristics were similar. Under Table 1	Not met Open-label study design	Met	No dropouts	B	Limitations include open-label study

F/U=follow-up; ITT=intention to treat; QA=quality assessment.

Heterogeneity was analyzed using a χ^2 test on n – 1 degrees of freedom, with an α of 0.05 used for statistical significance and with the I^2 test. I^2 values greater than 25%, 50%, and 75% were considered evidence of low, moderate, and high levels of statistical heterogeneity, respectively. If substantial statistical heterogeneity was noted ($I^2 > 50\%$), the reviewers performed statistical analyses to explore the influence of statistical models on effect size and the influence of each study by excluding one study at a time to assess the robustness of results. Sensitivity and subgroup analyses were performed to assess the robustness of the results and to statistically compare subgroups, respectively.

Characteristics of the Studies Included

Assessment of Reporting Bias

The four RCTs included were all published studies. The test for funnel plot asymmetry was not done because fewer than 10 studies were included in our meta-analysis.

1. Ussia et al,[5] 2011

Methods	Single-center, RCT
Participants	79 patients (39 SAPT, 40 DAPT)
Interventions	300-mg loading dose of clopidogrel on the day before TAVI followed by a 3-month maintenance daily dose of 75 mg clopidogrel plus aspirin 100 mg lifelong (DAPT group) or aspirin 100 mg alone (ASA group)
Outcomes	Primary outcome: major adverse cardiac and cerebrovascular event: composite of death from any cause, MI, major stroke, urgent or emergency conversion to surgery, and life-threatening bleed (LTB) Secondary outcome: NA
Notes	Allocation concealment: Blinding: open-label study Intention to treat: Dropout:

2. Stabile et al,[6] 2014

Methods	Single-center, RCT
Participants	120 patients (60 SAPT, 60 DAPT)
Interventions	DAPT group (aspirin and clopidogrel 75 mg every day or ticlopidine 500 mg twice a day) or ASA group (aspirin only).
Outcomes	Primary outcome: 30-day mortality Secondary outcome: 30-day bleeding and major adverse cardiac and cerebrovascular event; 6-month valve failures and neurologic events
Notes	Allocation concealment: Blinding: blinded with respect to dabigatran dose but unblinded adjusted-dose warfarin Intention to treat: met Dropout: none

3. Rodes-Cabau et al,[7] 2017

Methods	Multicenter, RCT
Participants	222 patients (111 SAPT, 111 DAPT)
Interventions	Aspirin or ASA (80–100 mg/d) or aspirin or ASA (80–100 mg/d) plus clopidogrel (75 mg/d) following the TAVR procedure
Outcomes	Primary outcome: death, MI, stroke or transient ischemic attack, or major or LTB at 3 months Secondary outcome: Incidence of MI, ischemic stroke, major or LTB, and death at 3 months
Notes	Allocation concealment: Blinding: open-label study Intention to treat: Dropout: none

4. Brouwer et al,[8] 2020

Methods	Multicenter, RCT
Participants	665 patients (331 SAPT, 334 DAPT)
Interventions	Aspirin alone or aspirin plus clopidogrel for 3 months after TAVI
Outcomes	Primary outcome: bleeding (including minor, major, and life-threatening or disabling bleeding) and non–procedure-related bleeding over a period of 12 months Secondary outcome: composite of bleeding or thromboembolic events and consisted of death from cardiovascular causes, non–procedure-related bleeding, stroke from any cause, or MI. The other secondary outcome was a composite of death from cardiovascular causes, ischemic stroke, or MI; this outcome differed from the first secondary outcome by excluding non–procedure-related bleeding
Notes	Allocation concealment: Blinding: open-label study Intention to treat: Dropout: none

Table 2. Characteristics of Patients in the Included Trials

Study	nSAPT/DAPT	Interventions	Mean Age, y SAPT/DAPT	Female, n (%)	Follow-up Duration, mo
Ussia et al,[5] 2011	39 / 40	3 mo DAPT vs ASA	80 ± 6/81 ± 4	54%	6 mo
Stabile et al,[6] 2014	60/60	6 mo DAPT vs ASA	81.1 ± 4.8/80.2 ± 5.7	67%	1 mo
Rodes-Cabau et al,[7] 2017	111/111	3 mo DAPT vs ASA	79.9 ± 9/79.9 ± 9	42%	3 mo
Brouwer et al,[8] 2020	331/334	12 mo DAPT vs ASA	80.4 ± 6.2/79.5 ± 6.4	49%	12 mo

RESULTS

Search Results

Electronic literature searches initially yielded a total of 20 studies (Figure 1). Eight articles were duplicates and were excluded. Thereafter, a total of eight studies were excluded on a title basis and/or abstract review. Eight articles were assessed in full text, of which the following were excluded on the following basis: three studies were review articles, and one was meta-analysis of an RCT. With thorough review of study eligibility, the remaining four RCTs were included in the meta-analysis.

Patient Characteristics

A total of 1086 patients were included in the final analysis from the four RCTs. The study by Ussia et al[5] involved 79 patients, with 54% female and follow-up duration of 6 months. The study by Stabile et al[6] involved 120 participants composed of 67% female, with follow-up duration of only 1 month. The study by Rodes-Cabau et al[7] comprised 120 participants, 42% of whom were female, with follow-up duration of 3 months. Lastly, the latest study by Brouwer et al[8] was composed of 665 participants, 49% of whom were female, with follow-up duration of 12 months (Table 2).

Analysis of Thromboembolic Events

There were 23 stroke events (4.3%) that occurred in the SAPT group versus 25 (4.6%) in the DAPT group. However, pooled analysis done (Figure 2) showed no statistically significant benefit of anticoagulation using DAPT over SAPT in the prevention of stroke with an OR of 0.94 (95% CI, 0.54–1.64; $P = 0.67$). Using random-effects model, the studies were found to have low heterogeneity with an I^2 of 0.

There were 5 (1.0%) myocardial infarction events that occurred in the SAPT versus 11 (2%) in the DAPT group. However, pooled analysis done (Figure 3) showed no statistically significant benefit of anticoagulation using DAPT over SAPT in the prevention of myocardial infarction with an odds ratio of 0.50 (95% CI, 0.18–1.40; $P = 0.16$). Using random-effects model, the studies were found to have low heterogeneity with an I^2 of 0.

Analysis of All-Cause Mortality

There was no statistically significant difference in terms of mortality benefit of using DAPT versus SAPT with an OR of 1.01 (95% CI, 0.65–1.57; $P = 0.70$; Figure 4). The studies were found to have low heterogeneity with an I^2 of 0.

Safety Profile

Pooled analysis for the four studies (Figure 5) showed higher incidence of major bleeding in the DAPT versus the antiplatelet group, which was statistically significant with an OR of 0.44 (95% CI, 0.30–0.65; $P = 0.61$). Using the random-effects model, the studies were found to have low heterogeneity with an I^2 of 0.

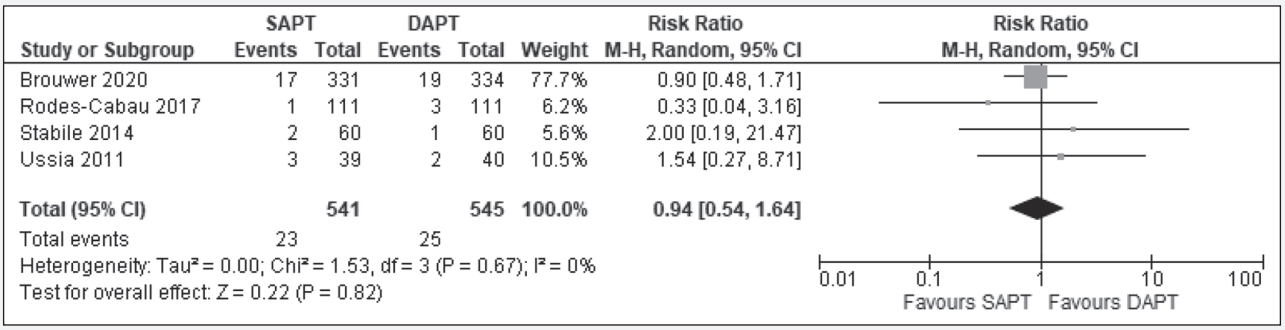

Figure 2. Forest plot showing pooled incidence of stroke after transcatheter aortic valve replacement using single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) using random-effects model with 95% confidence interval (CI)

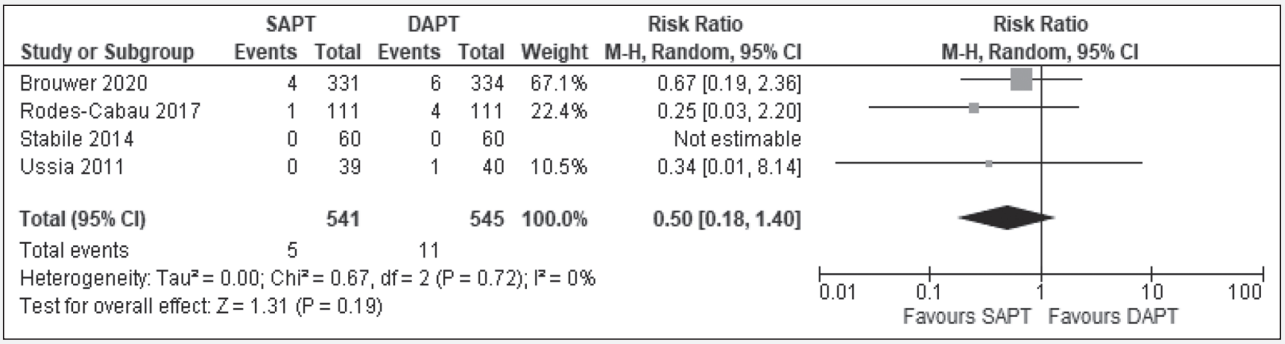

Figure 3. Forest plot showing pooled incidence of myocardial infarction after transcatheter aortic valve replacement using single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) using random-effects model with 95% confidence interval (CI)

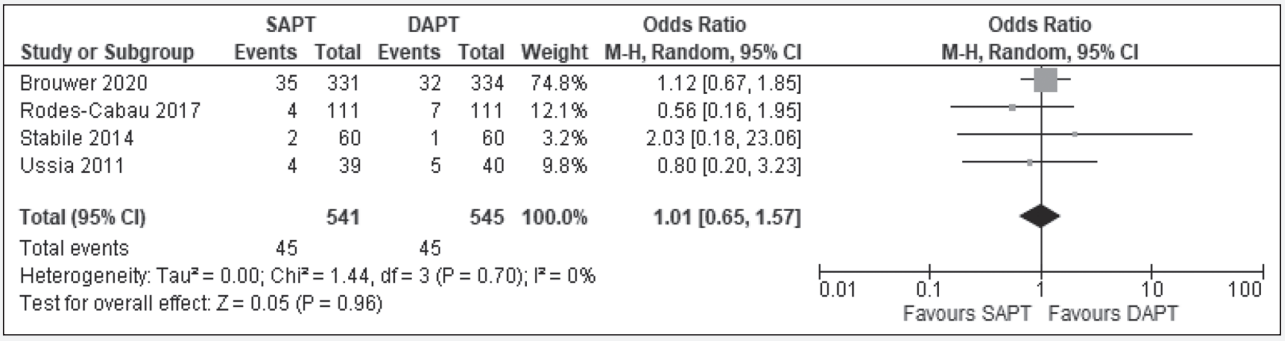

Figure 4. Forest plot showing pooled incidence of all-cause mortality transcatheter aortic valve replacement using single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) using random-effects model with 95% confidence interval (CI)

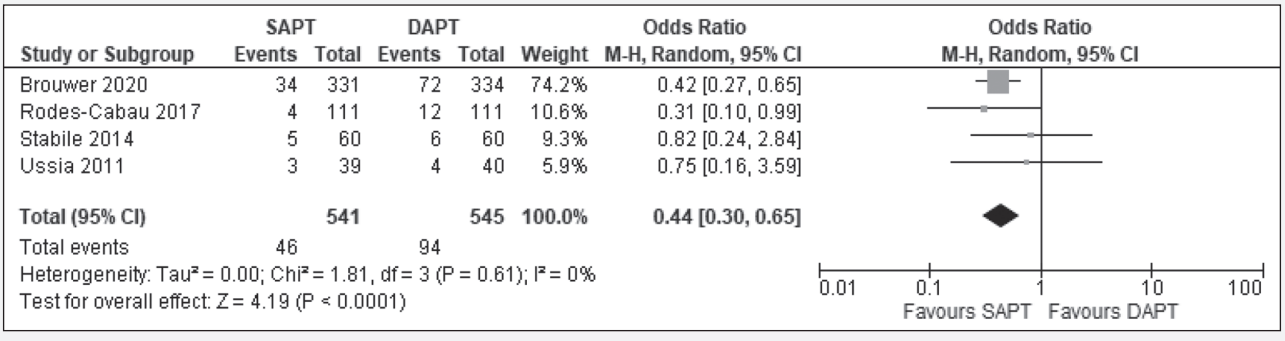

Figure 5. Forest plot showing pooled incidence of major bleeding after TAVR using SAPT versus DAPT using random-effects model with 95% confidence interval

DISCUSSION

In this meta-analysis comparing SAPT versus DAPT among post-TAVR patients, DAPT did not prevent stroke, MI, or mortality when compared with SAPT. Moreover, DAPT was associated with an increased risk of major and life-threatening bleeding as compared with SAPT.

A source of heterogeneity among the studies is the duration of treatment and follow-up, the difference in dosing range of aspirin, and the difference in the secondary antiplatelet used, particularly in the study by Stabile et al, which involved the use of ticlopidine instead of clopidogrel. Longer duration of follow-up in the study by Brouwer et al,[8] which is for 12 months, which involved need for DAPT with aspirin and clopidogrel, entailed a possible higher bleeding risk.

The rationale for post-TAVR antithrombotic therapy stems from potential risk of thromboembolic events after TAVR. While factors related to device implantation such as aorta manipulation and embolization of debris are the likely causative factor for stroke in immediate postintervention period, valve thrombosis has been speculated in the later period. However, in the 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guideline,[9] the recommended antithrombotic therapy after TAVR is vague: with DAPT for the first 3 to 6 months after TAVR with grade of class IIA, and SAPT in the case of high bleeding risk graded as IIB. A recently published trial reported no benefit of DAPT in leaflet thrombosis prevention compared with SAPT; hence, the role of DAPT after TAVR is questionable.

The previous meta-analysis by Raheja et al,[4] which included only 421 participants comparing DAPT and SAPT after TAVR, reported the same conclusion that there is increased bleeding risk and no benefit in stroke prevention with DAPT, which is consistent with our report.

We performed a more comprehensive analysis, which also included the recent study by Brouwer et al,[8] which has a high number of participants included in the study. Our analysis is the largest to date comparing DAPT versus SAPT for individual relevant endpoints.

CONCLUSION

Among patients who underwent TAVR, SAPT compared with DAPT had similar rates of stroke, MI, or all-cause mortality. Moreover, SAPT (aspirin alone) had lower rates of significant bleeding as compared with DAPT.

RECOMMENDATIONS

Our findings strengthen the previous evidence that DAPT after TAVR does not significantly reduce stroke, MI, or mortality compared with SAPT and is associated with a higher risk of significant bleeding. Because of lower rates of major bleeding, we recommend SAPT over DAPT after transcatheter aortic valve replacement.

CONFLICT OF INTEREST

The authors state no conflict of interest. The manuscript has not been supported by any sources of support, including sponsorship and any financial sources.

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