Dual Antiplatelet Versus Single Antiplatelet in Post–Transcatheter Aortic Valve Implantation/Transcatheter Aortic Valve Replacement for Stroke Prevention: A Systematic Review and Meta-analysis

Ralph Yap, MD | Douglas Bailon, MD | Abigail Louise Te-Rosano, MD
St Luke's Medical Center—Global City, Taguig

Abstract

BACKGROUND: There is ambiguity on antiplatelet therapy for post–transcatheter aortic valve replacement (TAVR) patients for stroke prevention, but dual antiplatelet therapy (DAPT) is routinely started despite lack of data on effectiveness and bleeding safety of DAPT versus single antiplatelet therapy (SAPT). This study aims to determine the effectiveness of DAPT versus SAPT in stroke prevention and assess bleeding safety.

METHODS: A systematic search was done for randomized clinical trials involving DAPT and SAPT in patients who underwent TAVR. The primary outcome was stroke after 1 year of either DAPT and SAPT and life-threatening bleeding. Secondary end points included all-cause mortality. Trials were identified through systematic searches on the following databases (November 2019): Cochrane, MEDLINE, and Google Scholar and ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform. Risk ratio was used for dichotomous outcomes. Heterogeneity among the studies for the meta-analysis was detected using a χ^2 test (0.01 level of significance). Risk-of-bias assessment was done.

RESULTS: There is a lower incidence of stroke in patients on DAPT, but with a higher incidence of life-threatening bleeding and major bleeding. There is also a lower incidence of all-cause mortality in SAPT. The statistical power of this meta-analysis is low due to small population size.

CONCLUSION: Single antiplatelet therapy is comparable to DAPT in preventing stroke with the added benefit of a lower incidence of life-threatening and major bleeding and a lower incidence of all-cause mortality.

KEYWORDS: antiplatelet therapy, bleeding, dual antiplatelet therapy, single antiplatelet therapy, mortality, myocardial infarction, stroke, transcatheter aortic valve replacement, transcatheter aortic valve implantation

BACKGROUND

Description of the Condition

Degenerative, calcific valvular aortic stenosis (AS), caused by an active process of atherosclerosis, calcification, and ossification, is the most common cause of AS in industrialized nations. The prevalence of calcific AS is age-dependent and thus is expected to increase because of demographic aging of the global population. It is well recognized that severe AS carries a poor prognosis if left untreated.[1]

The Intervention and Purpose of the Review

Andersen et al[2] demonstrated the feasibility of transcatheter aortic valve replacement (TAVR) in 1992 using a porcine aortic valve folded into a balloon expandable stent.

The primary advantage of TAVR is that the valve can be deployed percutaneously over the native valve without the need for open-heart surgery; this is a huge step forward for patients who have been refused surgery due to high risk. Since approval of TAVR in the United States, the Society of Thoracic Surgeons/ American College of Cardiology Transcatheter Valve Therapy Registry investigators have reported a procedural success of 92%.[3]

Current consensus recommends a 3- to 6-month dual antiplatelet therapy (DAPT) in patients undergoing transcatheter aortic valve replacement (TAVR) or to continue with oral anticoagulant agents if already indicated before procedure. However, recent studies showed that treatment with aspirin has the same efficacy of DAPT, but it was associated with a significant reduction in major bleeding.[4]

This review aims to determine the effectiveness of single antiplatelet therapy (SAPT) versus DAPT in stroke prevention and assess bleeding safety.

Objectives

This study aims to determine the effectiveness of DAPT versus SAPT in stroke prevention and to assess bleeding safety.

METHODS

Search Strategy

A systematic literature search was conducted through PubMed, EMBASE, ClinicalTrials.gov, and Herdin.ph from its inception to November 15, 2019, for randomized clinical trials only. The search terms were as follows: *TAVI* and *TAVR* and *dual antiplatelet* and *single antiplatelet; TAVI* and *TAVR* and *dual antiplatelet* and *aspirin; transcatheter aortic valve replacement* and *dual antiplatelet* and *single antiplatelet; transcatheter aortic valve implantation* and *dual antiplatelet* and *aspirin; TAVI* and *TAVR* and *dual antiplatelet* and *single antiplatelet; TAVI* and *TAVR* and *dual antiplatelet* and *aspirin* or *ticagrelor* or *clopidogrel*. Only published data in peer-reviewed scientific journals were included, and literature search was limited to articles published in English.

The searched articles were browsed based on its title and study type and whether they contained the needed data. Based on the inclusion/exclusion criteria, studies were sorted and included in the final analysis of the article.

Inclusion and Exclusion Criteria

Article titles, abstracts, and full texts were reviewed if possible. For inclusion, studies had to be randomized controlled trials (RCTs) only involving post-TAVR patients who were on DAPT and SAPT and with some of the clinical outcomes of interest. Exclusion criteria were observational studies, registries, no antiplatelet therapy, and patients taking anticoagulation.

Data Extraction

The information was extracted from the text, tables, and graphs of the full text of the articles. No contact with authors to request further information was made; all the information needed was in full text.

Types of Outcomes

The primary outcome was stroke and all-cause mortality at 30 days and at 6 months and with a secondary outcome of life-threatening bleeding and major bleeding.

Search Methods for Identification of Studies

Search Strategy

Trials were identified through systematic searches of the following bibliographic databases on January 2019: (1) Cochrane Central Register of Controlled Trials (2017 Issue 5) in the Cochrane Library; (2) MEDLINE (Ovid, 1996 to November 2019); (3) EMBASE (Ovid, 1996–2019). The preliminary search strategy for MEDLINE (Ovid) was adapted for use in the other databases. Cochrane sensitivity-maximizing RCT filter was applied to MEDLINE (Ovid), and adaptations of it to the other databases. A search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization International Clinical Trials Registry Platform, and also Herdin.ph database was made.

Data Collection and Analysis

The methods used in this review are in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Figure 1).

This is a summary of the risk-of-bias judgments across different studies for each of the domains listed (Figures 2 and 3). When considering treatment effects, the risk of bias was considered for the studies that contributed to that outcome.

Assessment of Bias in Conducting the Systematic Review

The review of the studies was based on the published protocol of Benstoem (2015) and report of any deviations from it.

Blinding (Performance Bias and Detection Bias)

None of the three studies have double or even triple blinding.

Incomplete Outcome Data (Attrition Bias)

The study by Rodés-Cabau et al[9] was the only study with good follow-up of patients. The study by Ussia et al[11] and Stabile et al[10] did not state dropout rates and patient follow-up. All of the three studies had relatively small sample sizes. Rodés-Cabau

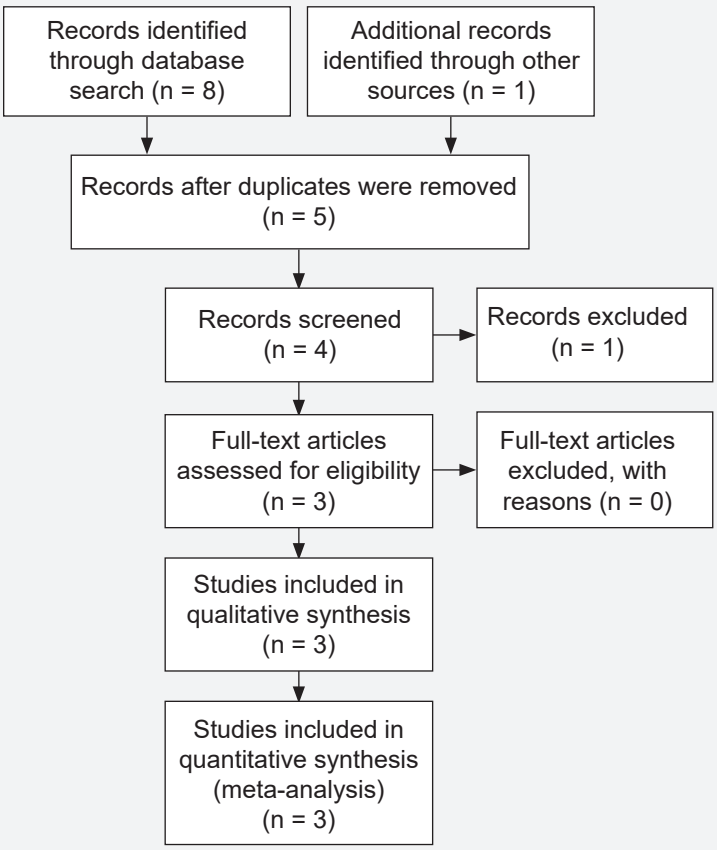

Figure 1. Study flow diagram

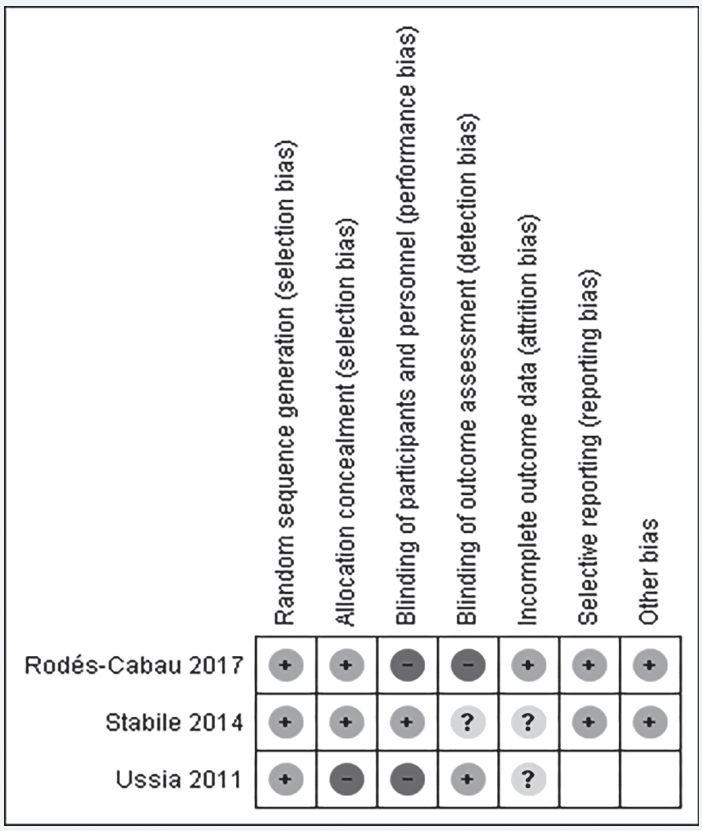

Figure 2. Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each included study.

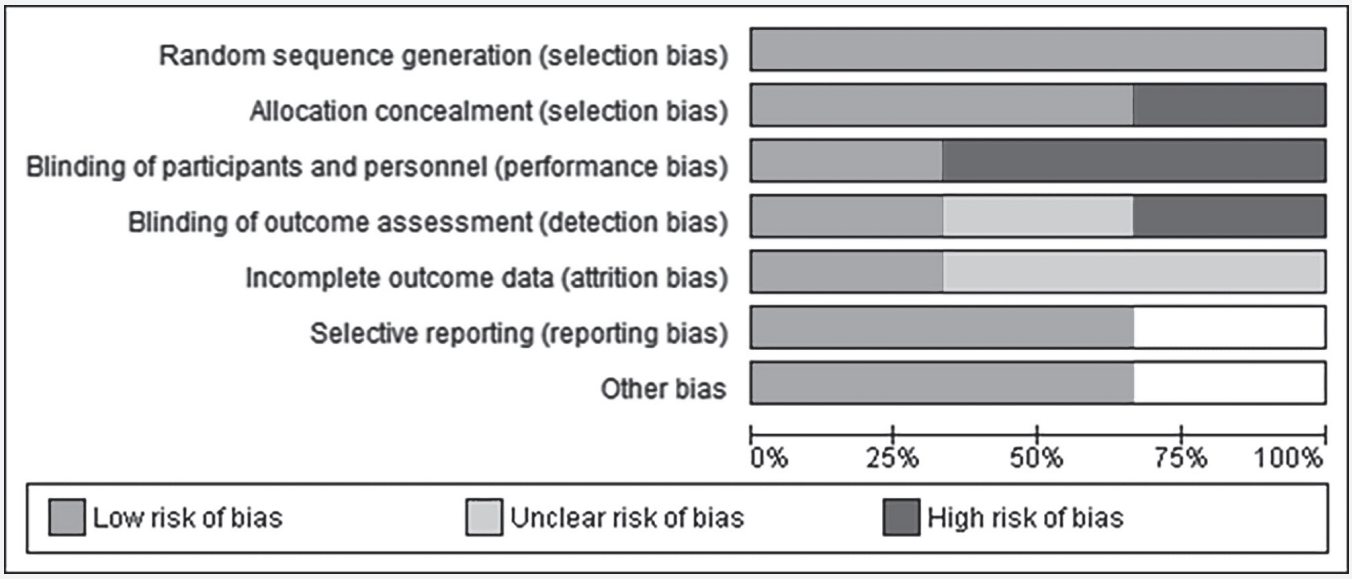

Figure 3. Risk-of-bias graph: review authors' judgments about each risk-of-bias item presented as percentages across all included studies

et al had the most study sample size (N = 111) with each arm, and their enrollment was prematurely stopped because of lack of financial support. Overall, the risk of bias for all of the three studies was high.

Selective Reporting (Reporting Bias)

Only the study by Rodés-Cabau et al[9] reported selective reporting, which decreases the risk of bias. The study by Ussia et al[11] and Stabile et al[10] did not clearly state any selective reporting; thus, it is an unclear risk.

Table 1. Characteristics and Risk of Bias of Included Studies

1. Rodés-Cabau et al,[9] 2017

Methods	Randomized, open-label, multicenter trial
Participants	Clinical indications for TAVR
Intervention	Single antiplatelet vs dual antiplatelet
Outcome	SAPT tended to reduce the occurrence of major adverse events, reducing the risk for major life-threatening events while not increasing the risk for myocardial infarction or stroke

Risk of Bias

Bias	Authors' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Random block sizes were used to conceal treatment allocation from patients
Allocation concealment (selection bias)	Low risk	Random block sizes were used to conceal treatment allocation from patients, and randomization was stratified by clinical center
Blinding of participants and personnel (performance bias)	High risk	Participants were blinded, but it was unclear whether personnel were blinded; open-label study
Blinding of outcome assessment (detection bias)	High risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	Complete patient follow-up
Selective reporting (reporting bias)	Low risk	Stated
Other bias	Unclear risk	Not clearly stated

2. Stabile et al,[10] 2014

Methods	Randomized, open-label
Participants	Clinical indications for TAVR
Intervention	SAPT vs DAPT
Outcome	Increased vascular complications with DAPT vs SAPT No clear benefit of DAPT use in reducing ischemic events

Bias	Authors' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Randomization
Allocation concealment (selection bias)	High risk	Open-label
Blinding of participants and personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias)	Low risk	Blinding of study end points
Incomplete outcome data (attrition bias)	Unclear risk	Not clearly stated
Selective reporting (reporting bias)	Unclear risk	Not clearly stated
Other bias	Unclear risk	Not clearly stated

3. Ussia et al,[11] 2011

Methods	Randomized, open-label, single-center study
Participants	Clinical and anatomic indications for TAVR
Intervention	SAPT vs DAPT
Outcome	No significant benefit of DAPT vs SAPT in reducing ischemic events

Bias	Authors' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Stated
Allocation concealment (selection bias)	High risk	Open-label
Blinding of participants and personnel (performance bias)	High risk	Open-label
Blinding of outcome assessment (detection bias)	Low risk	Blinding of study end points
Incomplete outcome data (attrition bias)	Unclear risk	Not clearly stated
Selective reporting (reporting bias)	Unclear risk	Not clearly stated
Other bias	Unclear risk	Not clearly stated

DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy; TAVR=transcatheter aortic valve replacement.

Table 2. Description of Included Studies

Author (Year)	Rodés-Cabau et al[9] (2017)		Stabile et al[10] (2014)		Ussia et al[11] (2011)	
Study design	Randomized, open-label, multicenter trial		Randomized study, open-label, single center		Randomized, open-label, single center	
Study groups	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT
Study population	111	111	60	60	39	40
Antithrombotic regimen	Randomized the day before TAVR to receive ASA (80–100 mg/d) or ASA (80–100 mg/d) plus clopidogrel (75 mg/d) following TAVI		Randomly assigned to ASA (75–160 mg/d) and clopidogrel (75 mg/d) or ticlopidine 500 mg twice a day or Aspirin (75–160 mg/d) alone		Randomized to receive 300-mg loading dose of clopidogrel on the day before TAVI followed by a 3-mo maintenance daily dose of 75 mg clopidogrel plus aspirin 100 mg lifelong or aspirin 100 mg alone	
Loading regimen	300 mg of clopidogrel—given within 24 h prior to TAV		Not stated		300 mg of clopidogrel was administered on the same day before TAVI	

ASA=acetylsalicylic acid; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy; TAVR=transcatheter aortic valve replacement; TAV=transcatheter aortic valve; TAVI=transcatheter aortic valve implantation; TAVR=transcatheter aortic valve replacement.

Assessment of the Quality of the Evidence

The quality of the strength of evidence was evaluated for our primary outcomes for the comparison of SAPT and DAP with primary outcomes of composite end point (including all-cause mortality, stroke, life-threatening bleeding, and major bleeding), and secondary outcomes include all-cause mortality at 30 days and at 6 months.

Measures of treatment effect were analyzed using dichotomous data as risk ratios with 95% confidence intervals (CIs). For continuous data, mean difference with 95% CI was used for outcomes measured in the same way between trials.

The quality of the evidence was assessed using the GRADE approach. The GRADE approach considers five areas (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome.

Description of Studies

Three RCTs with a total of 421 participants were included. The participants received aspirin plus clopidogrel as the control arm and clopidogrel as the experimental arm. The study by Stabile et al[10] included using either ticlopidine or clopidogrel in the control group. The group with ticlopidine was associated with a higher incidence of vascular bleeding.

Excluded Studies

Included in the literature search was one study by Nijenhuis et al[5] entitled Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular-TAVI); no partial results were available for inclusion in the review. This study is ongoing but not actively recruiting participants. The primary outcome was a safety end point, defined as freedom from all bleeding complications at 1 year after TAVI, and the coprimary outcome was the safety end point defined as freedom from non–procedure-related bleeding complications at 1 year after TAVI. Secondary outcomes included net clinical benefit end point defined as freedom from cardiovascular mortality, myocardial infarction, and stroke at 1 year after TAVI. This study included oral anticoagulants plus either aspirin or clopidogrel and oral anticoagulant alone.[5]

With a study population of 1000 participants, this study can have better statistical power and clinical impact to patients.

Effects of Intervention

Primary Outcome

All-cause mortality at 30 days in SAPT was lower at 3.8% compared with 4.7% in DAPT (odds ratio [OR], 0.8; 95% CI, 0.31–2.08; $P = 0.86$; $I^2 = 0\%$; Figure 4). No significant heterogeneity was observed with the three studies and is not statistically significant ($P = 0.64$), but SAPT has a lower all-cause mortality at 30 days.

All-cause mortality at 3 to 6 months days in SAPT is lower at 5.7% compared with 6.6% in DAPT (OR, 0.86; 95% CI, 0.38–1.90; $P = 0.65$; $I^2 = 0\%$; Figure 5). No significant heterogeneity was observed with the three studies and is not statistically significant ($P = 0.70$), but SAPT has a lower all-cause mortality at 3 to 6 months.

The incidence of stroke in SAPT is higher at 4.7% compared with 1.9% in DAPT (OR, 2.56; 95% CI, 0.79–8.30; $P = 0.12$; $I^2 = 0\%$; Figure 6). No significant heterogeneity was observed

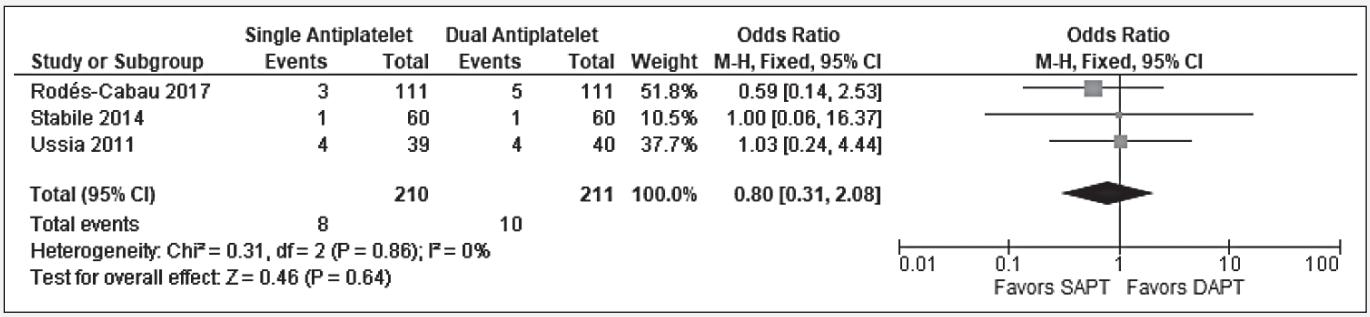

Figure 4. All-cause mortality at 30 days (*CI=confidence interval; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy.*)

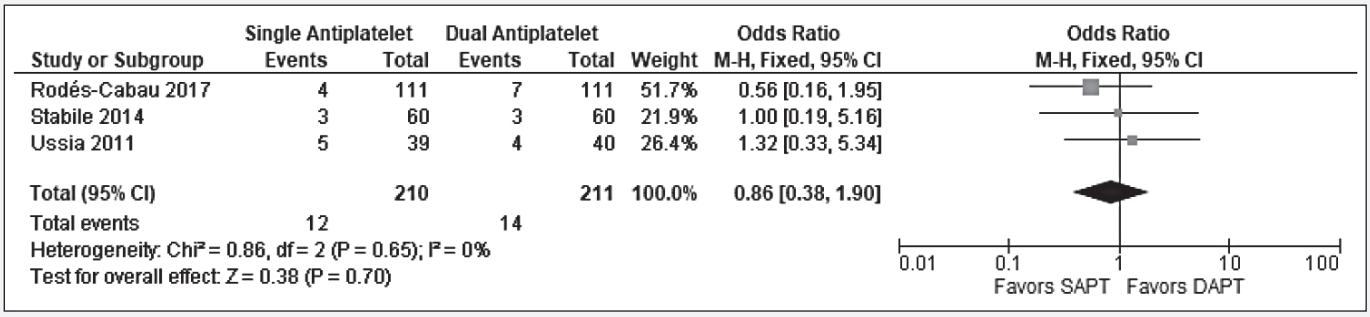

Figure 5. All-cause mortality at 3 to 6 months (*CI=confidence interval; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy.*)

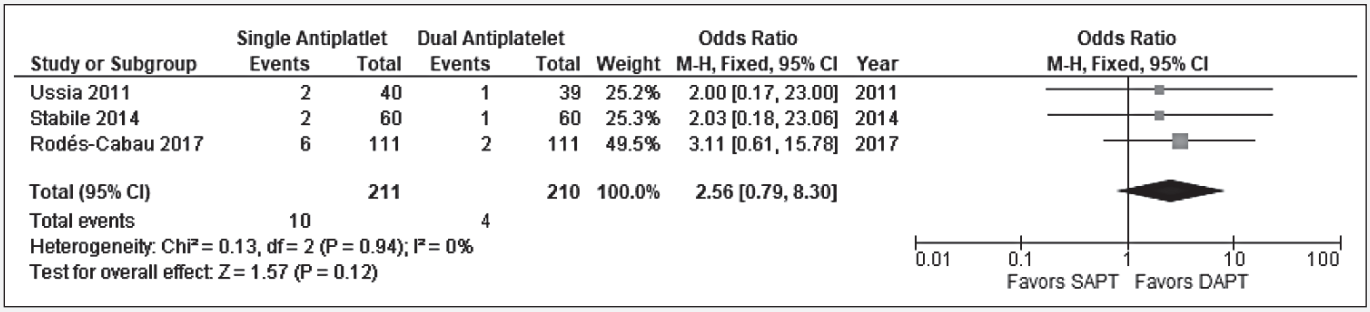

Figure 6. Incidence of stroke (*CI=confidence interval; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy.*)

with the three studies and is not statistically significant but with a lower incidence of stroke in the DAPT group and is not statistically significant (P = 0.12).

The incidence of life-threatening bleeding in SAPT is lower at 2.8% compared with 6.1% in DAPT (OR, 0.44; 95% CI, 0.16–1.19; P = 0.33; I^2 = 0%; Figure 7). No significant heterogeneity was observed with the three studies and is not statistically significant (P = 0.11), but SAPT has a lower incidence of life-threatening bleeding in the SAPT.

The incidence of major bleeding in SAPT is lower at 2.8% compared with 4.2% in DAPT (OR, 0.65; 95% CI, 0.23–1.87; P = 0.88; I^2 = 0%; Figure 8). No significant heterogeneity was observed with the three studies and is not statistically significant (P = 0.43), but SAPT has a lower incidence of major bleeding compared with DAPT.

DISCUSSION

The results show that SAPT was associated with a trend toward lower bleeding complications compared with DAPT and no difference in all-cause mortality at 30 days and at 6 months. Dual antiplatelet therapy is associated with a higher incidence of life-threatening bleeding and major bleeding.

The indication for starting DAPT in post-TAVR patients has been primarily prevention of stroke following months after the procedure. The proposed mechanism of stroke events post-TAVR may explain the lack of benefit of DAPT.[6-8] Almost half of strokes within 30 days post-TAVR occur immediately after or within 24 hours postprocedure and appear to be related mainly to embolic events resulting from mechanical interaction between the transcatheter valve system, the aorta, and the disease aortic valve.[6-8]

Overall Completeness and Applicability of Evidence

All trials have similar inclusion and exclusion criteria, with similar sets of patients and almost similar methodology. All the trials used in this meta-analysis measured important clinical outcomes—stroke, mortality, life-threatening bleeding, and major bleeding. However, all the studies have small sample sizes and cannot be used on their own due to this limitation. With the ongoing study by Nijenhuis et al[5] with more study population, more questions can be answered in the future.

CONCLUSION

All studies had small sample sizes and lack clinical power to make proper recommendations. Although there is a trend toward a lower incidence of bleeding and no difference in mortality rates between SAPT and DAPT, studies with larger sample sizes with proper blinding are needed to ensure quality data and appropriate recommendations can be done.

Implications for Research

Future research in a large, randomized, and triple blinding to decrease the risk of bias is needed to add clinical power to existing data.

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CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

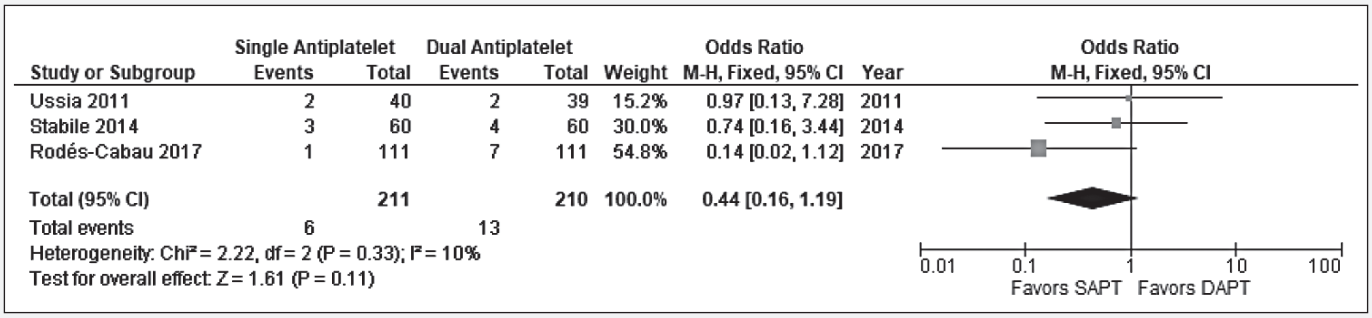

Figure 7. Life-threatening bleeding (*CI=confidence interval; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy.*)

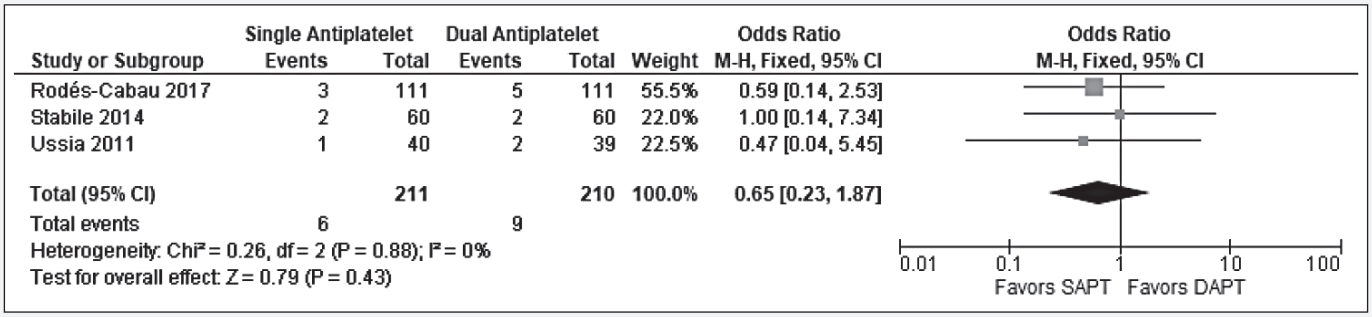

Figure 8. Major bleeding (*CI=confidence interval; DAPT=dual antiplatelet therapy; SAPT=single antiplatelet therapy.*)

REFERENCES:

1. Thaden JJ, Nkomo VT, Enriquez-Sarano, M. The Global Burden of Aortic Stenosis. *Prog Cardiovasc Dis* 2014;56(6):565–571. doi:10.1016/j.pcad.2014.02.006
2. Andersen HR, Knudsen LL, Hasenkam JM. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J* 1992;13(5):704–708. doi:10.1093/oxfordjournals.eurheartj.a060238.
3. Rajput FA, Zeltser R. Aortic valve replacement [updated March 31, 2019]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; January 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537136/.
4. Ferlini M, Mauri S, Rossini R. Dual antiplatelet therapy after TAVR: a drop in the bucket? *Int J Cardiol* 2019;280:46–48. doi:10.1016/j.ijcard.2019.01.069.
5. Nijenhuis VJ, Bennaghmouch N, Hassell M, et al. Rationale and design of POPular-TAVI: antiPlatelet therapy for Patients undergoing Transcatheter Aortic Valve Implantation. *Am Heart J* 2016;173:77–85. doi:10.1016/j.ahj.2015.11.008.
6. Rodés-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol* 2013;62:2349–2359.
7. Nombela-Franco L, Webb JG, de Jaegere PP, et al. Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation* 2012;126:3041–3053.
8. Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation* 2013;127:2194–2201.
9. Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve. *JACC Cardiovasc Interv* 2017(13):1357–1365. doi:10.1016/j.jcin.2017.04.014.
10. Stabile E, Pucciarelli A, Cota L, et al. SAT-TAVI (single antiplatelet therapy for TAVI) study: a pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. *Int J Cardiol* 2014;174(3):624–627. doi:10.1016/j.ijcard.2014.04.170.
11. Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*, 2011;108(12):1772–1776. doi:10.1016/j.amjcard.2011.07.049.