Original Article

Single or dual antiplatelet therapy after transcatheter aortic valve replacement: an updated systemic review and meta-analysis

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Background: Although current guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel as an antiplatelet strategy after transcatheter aortic valve replacement (TAVR), it is not based on clinical evidence. Here we aim to review updated evidence systemically and assess safety and efficacy of the two antiplatelet regimens.

Methods: PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to retrieve studies involving single antiplatelet therapy (SAPT) versus DAPT after TAVR. We screened the records and extracted the data from publications independently. Relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were used to compare the efficacy and safety of SAPT with that of DAPT in fixed-effects model with Mantel-Haenszel method. The quality of evidence was assessed by the scoring system, GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

Results: A total of 2,489 patients from 8 studies were enrolled in this meta-analysis. Compared with DAPT, SAPT was associated with a lower all-cause mortality (RR =0.57; 95% CI, 0.36–0.89; P=0.014) and major/life-threatening bleeding (RR =0.62; 95% CI, 0.50–0.76; P=0.000) in 30 days. Furthermore, there was no significant difference found between SAPT and DAPT group in terms of 30-day stroke (RR =0.85; 95% CI, 0.45–1.63; P=0.631) and death beyond 3 months (RR =0.96; 95% CI, 0.81–1.15; P=0.664).

Conclusions: This meta-analysis suggests that compared with DAPT, SAPT after TAVR is more likely to lead to a decline of 30-day mortality along with the reduced risk of bleeding and no increased risk of stroke. However, more clinical data and evidence from randomized controlled trials are warranted to clarify the optimal post-TAVR antiplatelet strategy.

Keywords: Transcatheter aortic valve replacement (TAVR); antiplatelet therapy; aspirin; clopidogrel; P2Y12 receptor antagonist

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Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as an essential therapeutic strategy for patients with severe, symptomatic aortic valve stenosis, especially for those with contraindications as well as a high risk of surgical aortic valve replacement (1). Despite the high success rate of TAVR, two common complications following TAVR, stroke and bleeding, deserve more attention with the widespread application of this procedure. The PARTNER 2A and SURTAVI trials showed that, in patients with intermediate surgical risks, the incidence rates of cerebral ischemia and major bleeding within 30 days after TAVR were about 5% and 10%, respectively (2,3).

Currently, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is the most commonly used post-TAVR antiplatelet regimen in clinical studies. The 2014 AHA/ACC guidelines (4) recommended the application of DAPT for 6 months after TAVR in patients with no indication for anticoagulants (class IIb, level of the evidence C) and this recommendation was retained in the updated edition of 2017 (1). Nevertheless, the recommendation is not based on the results of large randomized trials. On the other hand, Aryal *et al.* and Gandhi *et al.* suggested that the effect of single antiplatelet therapy (SAPT) would be noninferior to DAPT and the application of SAPT was even more likely to reduce the risk of hemorrhage (5,6). However, previous meta-analyses are, for the most part, inadequate to identify the differences between two groups due to small sample sizes. Therefore, we conducted a refined meta-analysis of the recent randomized and observational studies to acquire a better understanding of the safety and efficacy of the two post-TAVR antiplatelet therapies.

Methods

This systemic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement recommended by the Cochrane Collaboration (7).

Search strategy and selection criteria

PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to retrieve relevant studies published from inception to Feb 19, 2018. There is no language restriction in our search. We used a combination of MeSH/Emtree and entry terms of TAVR, platelet aggregation inhibitors, clopidogrel, aspirin, prasugrel, ticagrelor and antiplatelet as search keywords to locate relevant entries. The details of search strategy is shown in Supplementary Data. Manual search was also performed to identify additional publications from the reference lists of related reviews and meta-analyses.

Study selection

The inclusion criteria were as follows: (I) randomized controlled or observational studies, (II) patients undergoing TAVR, (III) direct comparison between SAPT and DAPT after TAVR. Studies were excluded if they were duplicates, conference abstracts or rather missing the outcomes of interest. Two of the researchers screened the electronic records and retrieved publications independently and any discrepancy was resolved through discussing and reading the full text of the article. If necessary, a final reviewer resolved the disagreement.

The safety and efficacy of the two regimens was compared for 30-day outcomes and mortality beyond 3 months. The primary outcome in the current study was 30-day death, while the secondary outcomes are 30-day stroke (major and minor), life-threatening or major bleeding, spontaneous myocardial infarction (MI), as defined by Valve Academic Research Consortium (VARC)-2 (8). The death beyond 3 months was also considered as another secondary outcome.

Data extraction and quality assessment

Two of the investigators extracted the characteristics and data from the retrieved studies independently. We used Cochrane Collaboration tool (by Review Manager 5.3) and Newcastle-Ottawa scale (9) to assess the risk of bias for randomized controlled trials (RCTs) and observational studies, respectively. The quality of evidence was assessed by the scoring system, GRADE (Grading of Recommendations Assessment, Development and Evaluation). The software, GRADEprofiler 3.6, was involved in implementing the scoring system of the evidence

Statistical analysis

This meta-analysis was performed using Stata 12.0 (Stata Corporation, College Station, TX, USA). A fixed-effects model with Mantel-Haenszel method was used to pool data and synthesize the quantitative analysis when the heterogeneity is not evident. Cochran Q test and I^2 statistic were used to assess the heterogeneity. Significant heterogeneity is identified when the P value is less than 0.1 or I^2 is more than 50%. Relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were used to compare the efficacy and safety of SAPT with that of DAPT with two-tailed P value (defined statistical significance when $P<0.05$). Furthermore, a subgroup analysis was conducted to evaluate the results from different types of studies. The publication bias of the primary outcome was investigated by visual estimation of funnel plots.

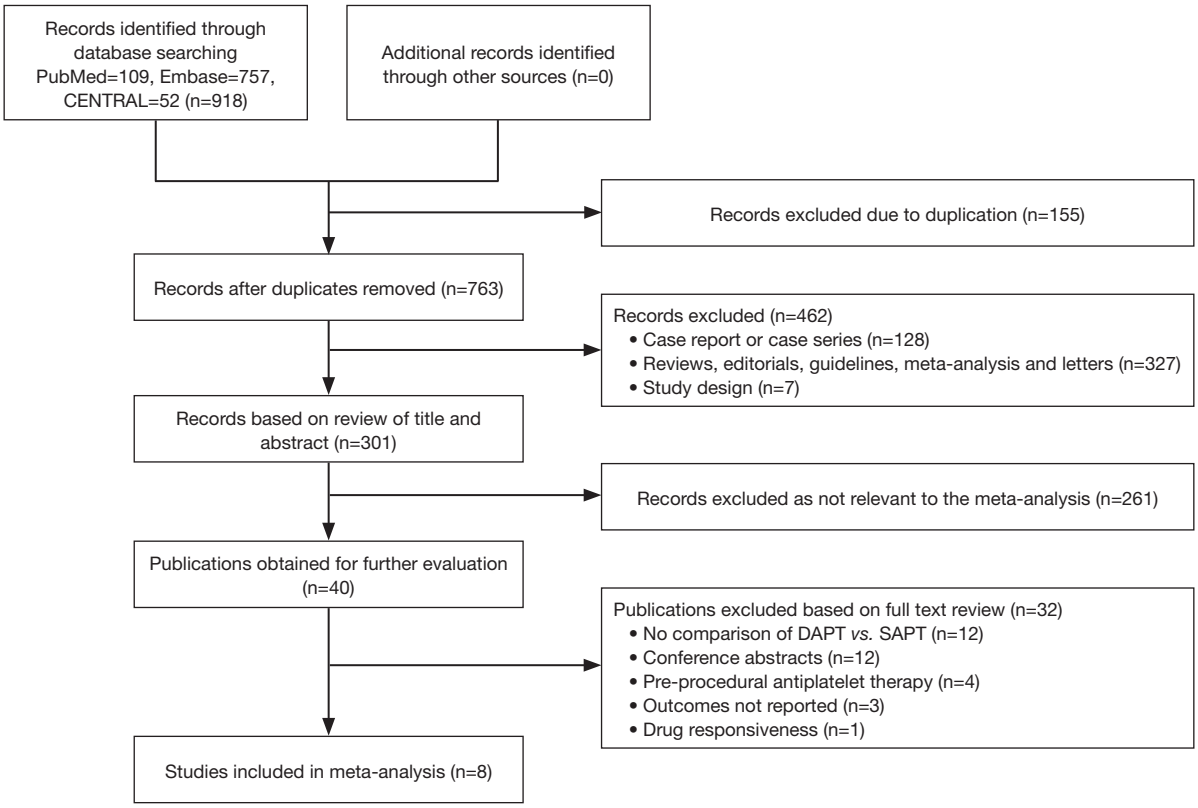

Figure 1 Flow diagram of search and study selection. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

Results

Characteristics of included studies

As shown in the *Figure 1*, we screened 918 records based on title or abstract and there were eight studies (10-17) which met the inclusion criteria defined in the current study and were thus included in our final analysis: three RCTs and five observational studies. Furthermore, out of the five observational studies, three studies (12,14,15) are propensity score matching (PSM) analyses. Overall, using data after PSM, our meta-analysis included a total of 2,489 patients (1,149 on SAPT, 1,340 on DAPT). The characteristics of the eight studies are described in *Table 1* and the clinical features of the patients are listed in *Table 2*. The inclusion and exclusion criteria of the included studies are shown in *Table S1*.

The main access of TAVR used in studies was transfemoral approach, in addition to other approaches including apex, aorta, subclavian, carotid and iliac arteries. The duration of DAPT in these studies mostly ranged from 3 to 6 months, consistent with the recommendation of current guidelines, while 1 month of clopidogrel and aspirin was scheduled in a PSM study (12). Moreover, thienopyridine such as ticlopidine was used in two studies (13,15). SAPT with lifelong low-dose acetylsalicylic acid (ASA) was adopted in three studies, whereas some other studies used ASA for 6 months (11,16,17).

The duration of follow-up in most studies was 30 days. In a retrospective analysis of registry, the median follow-up was 45.0±14.0 months (14). The 30-day outcomes were documented in six studies (10-14,17), whereas 3 studies (10,11,13) provided data at 6 months, and 1 study (17) at 90 days. Two studies (15,16) only reported the 1-year outcomes.

All-cause mortality

Six trials (10-14,17) reported the data on all-cause mortality at 30 days. As shown in *Figure 2*, SAPT lead to a significant decline compared with DAPT in terms of overall effect (RR =0.57; 95% CI, 0.36–0.89; P=0.014). There was no significant difference between the two strategies in RCTs

Table 1 Main characteristics of included studies

Study (years)	Type	Primary endpoint	Secondary endpoint
Ussia (10) [2011]	Single-center, RCT	MACCE: composite of death from any cause, MI, major stroke, urgent or emergency conversion to surgery, and LTB	NA
Poliacikova (11) [2013]	Single-center, retrospective	MACCE (combined endpoint of all-cause mortality, ACS or stroke) and NACE (combined endpoint of all-cause mortality, ACS, stroke, or major bleeding	NA
Durand (12) [2014]	Multicenter, prospective	Combination of mortality, major stroke, LTB, MI, and major vascular complications at 30 days	30-day transfusion, any vascular complication, any stroke, any bleeding, AKI, and success rate
Stabile (13) [2014]	Single-center, RCT	30-day mortality	Stroke, bleeding, vascular complication, AKI, valve deterioration
D'Ascenzo (14) [2017]	Multicenter, prospective	Prosthetic heart valve dysfunction (AVA <1.2 cm^2, median gradient >20 mmHg and peak velocity >3m/s, excluding AR	All cause death, cardiovascular death, bleedings, vascular complications and cerebrovascular accidents at 30 days and at follow-up
Ichibori (15) [2017]	Single-center, retrospective	Composite endpoint of all-cause death, nonfatal MI, nonfatal stroke and major bleeding or LTB	NA
Mangieri (16) [2017]	Single-center, retrospective	1-year NACE (composite of all-cause mortality, MI, cerebrovascular events, major bleeding requiring hospitalization and valve thrombosis) and mortality	NA
ARTE (17) [2017]	Multicenter, RCT	Rate of death, MI, stroke or TIA, or major or LTB at 3-month follow-up	Incidence of MI, stroke, major or LTB, and death at 3 months

RCT, randomized controlled trial; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction; LTB, life-threatening bleeding; NA, not available; NACE, net adverse clinical event; ACS, acute coronary syndrome; AKI, acute kidney injury; AVA, aortic valve area; AR, aortic regurgitation; TIA, transient ischemic attack.

(RR =0.83; 95% CI, 0.35–1.94; P=0.662) and observational studies showed significant subtotal effect (RR =0.50; 95% CI, 0.29–0.85; P=0.010).

Seven trials (10,11,13-17) reported the data on all-cause mortality beyond 3 months. As shown in *Figure 3*, the death beyond 3 months is similar for both SAPT and DAPT groups (RR =0.96; 95% CI, 0.81–1.15; P=0.664). In the subgroup analysis, similar results were obtained in RCTs (RR =0.86; 95% CI, 0.41–1.82; P=0.702) and observational studies (RR =0.97; 95% CI, 0.81–1.16; P=0.735).

Stroke

In six studies (10-14,17) involving 1,962 patients, 30-day stroke (major and minor) occurred in 36 patients (1.8%) and no significance was observed (RR =0.85; 95% CI, 0.45–1.63; P=0.631) in either RCTs (RR =1.01; 95% CI, 0.30–3.43; P=0.990) or observational studies (RR =0.80; 95% CI, 0.37–1.72; P=0.567) (*Figure 4*).

Life-threatening or major bleeding

Life-threatening or major bleeding at 30 days was reported in 294 patients (14.9%) by pooling data from the six studies (10-14,17). SAPT showed a benefit over DAPT in reducing the risk of life-threatening or major bleeding (RR =0.62; 95% CI, 0.50–0.76; P=0.000). The consistent results were obtained in observational studies (RR =0.62; 95% CI, 0.50–0.78; P=0.000) whereas no significance was observed in RCTs (RR =0.55; 95% CI, 0.28–1.08; P=0.082) (*Figure 5*).

Myocardial infarction

The 30-day spontaneous MI was documented by five studies (10-13,17). As shown in *Figure S1*, the incidence of MI was not different in SAPT *vs.* DAPT (RR =0.50; 95% CI, 0.14–1.77; P=0.281). Similarly, there was no difference in subgroup analysis for RCTs (RR =0.25; 95% CI, 0.03–2.20; P=0.212) and observational studies (RR =0.85; 95% CI, 0.16–4.44; P=0.843).

Table 2 Clinical features of patients in included studies

Study (year)	Regimens	No.	Age (years)	Male (%)	EuroSCORE (%)	STS score (%)	AF (%)	Diabetes (%)	Previous MI (%)	Mean gradient (mmHg)	AVA (cm^2)
Ussia (10) [2011]	SAPT	39	80±6	16 (41.0)	21±16	7±3	6 (15.0)	8 (20.5)	4 (10.3)	57±18	0.6±0.3
	DAPT	40	81±4	20 (50.0)	23±15	8±5	4 (10.0)	13 (32.5)	7 (17.5)	52±6	0.6±0.2
Poliacikova (11) [2013]	SAPT	91	82±6.9	49 (53.8)	NA	NA	10 (11.0)	16 (17.6)	NA	79.0±24.3	0.71±0.22
	DAPT	58	81.6±6.3	32 (55.2)	NA	NA	16 (27.6)	16 (27.6)	NA	93.8±27.7	0.67±0.17
Durand (12) [2014]	SAPT	164	82.7±6.3	90 (54.9)	20.0±12.4	7.4±6.1	37 (23.0)	40 (24.4)	22 (13.4)	50.1±15.2	0.61±0.16
	DAPT	128	84.6±5.8	50 (39.1)	20.2±11.6	6.9±4.0	45 (35.2)	30 (23.4)	14 (10.9)	48.3±19.5	0.63±0.14
Stabile (13) [2014]	SAPT	60	81.1±4.8	24 (40.0)	25.1±12.0	10.4±6.8	NA	17 (28.3)	NA	63.6±14.1	NA
	DAPT	60	80.2±5.7	16 (26.7)	23.34± 8.15	9.7±5.1	NA	15 (25.0)	NA	59.4±15.4	NA
D'Ascenzo (14) [2017]	SAPT	605	81±4	256 (42.3)	19±13	8±6	54 (10.0)	154 (25.5)	103 (17.0)	NA	NA
	DAPT	605	81±5	269 (44.5)	21±14	8±7	75 (12.0)	159 (26.3)	118 (19.5)	NA	NA
Ichibori (15) [2017]	SAPT	78	83±6	28 (35.9)	24.2±15.6	10.7±7.4	NA	24 (30.8)	NA	50.5±17.0	0.70±0.19
	DAPT	66	84±6	24 (36.4)	25.5±18.5	12.2±12.7	NA	22 (33.3)	NA	56.0±19.0	0.62±0.17
Mangieri (16) [2017]	SAPT	108	84.3±7.1	46 (42.6)	21.3±17.2	7.9±6.7	22 (20.4)	19 (17.6)	13 (12.0)	NA	NA
	DAPT	331	82.9±8.2	117 (35.3)	19.4±13.0	7.2±6.6	54 (16.3)	89 (26.9)	63 (19.0)	NA	NA
ARTE (17) [2017]	SAPT	111	79±9	59 (53.2)	NA	6.4±4.6	NA	36 (32.4)	20 (18.0)	43±15	0.40±0.11
	DAPT	111	79±9	70 (63.1)	NA	6.2±4.4	NA	41 (36.9)	26 (23.4)	43±16	0.42±0.13

STS, Society of Thoracic Surgeons; AF, atrial fibrillation; MI, myocardial infarction; AVA, aortic valve area; NA, not available

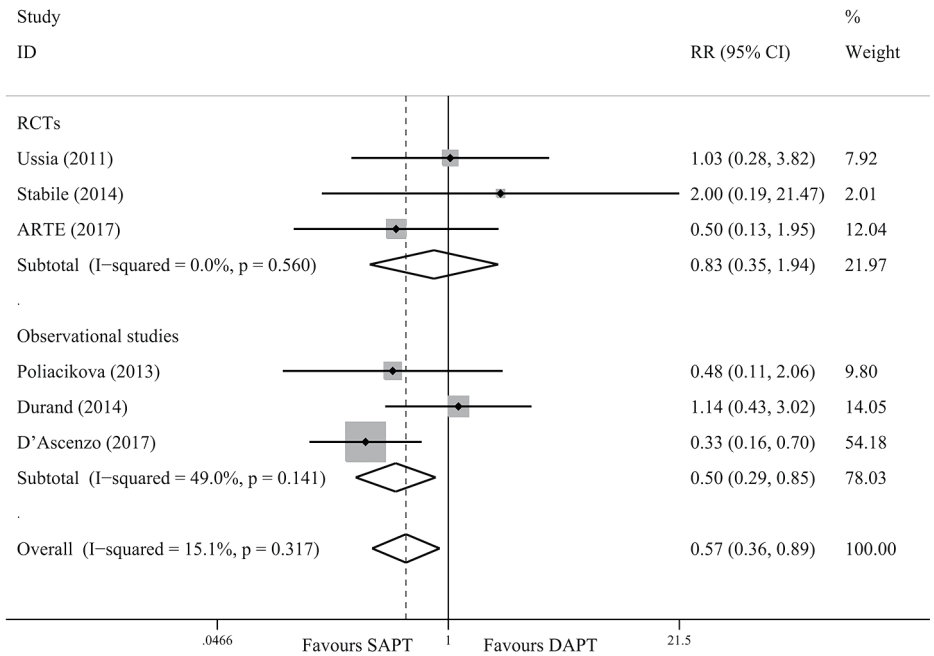

Figure 2 Forest plot for 30-day all-cause mortality. RR, relative risk; RCT, randomized controlled trial.

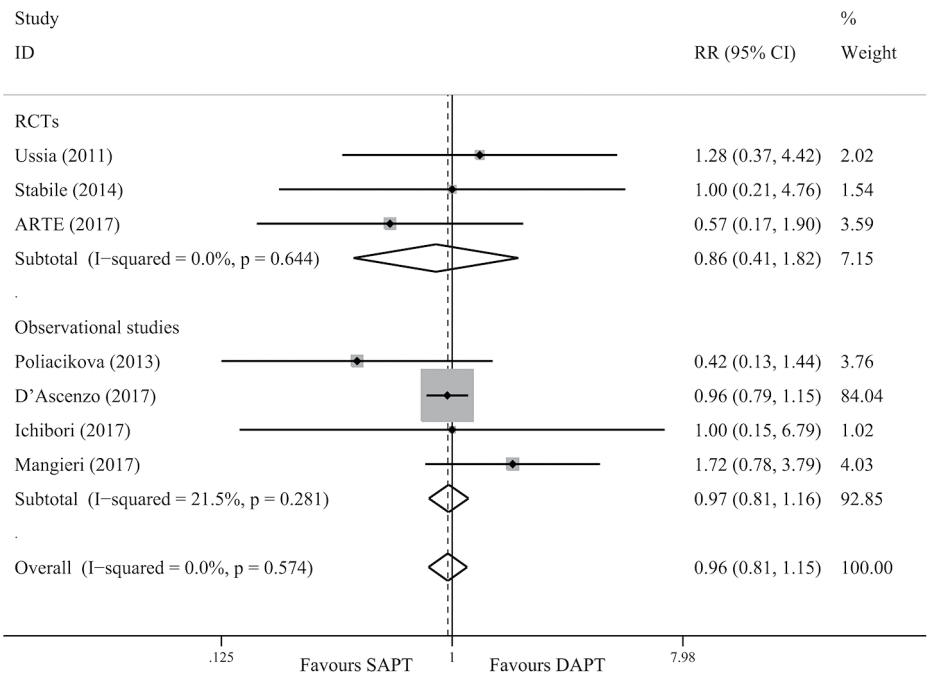

Figure 3 Forest plot for all-cause mortality beyond 3 months. RR, relative risk; RCT, randomized controlled trial.

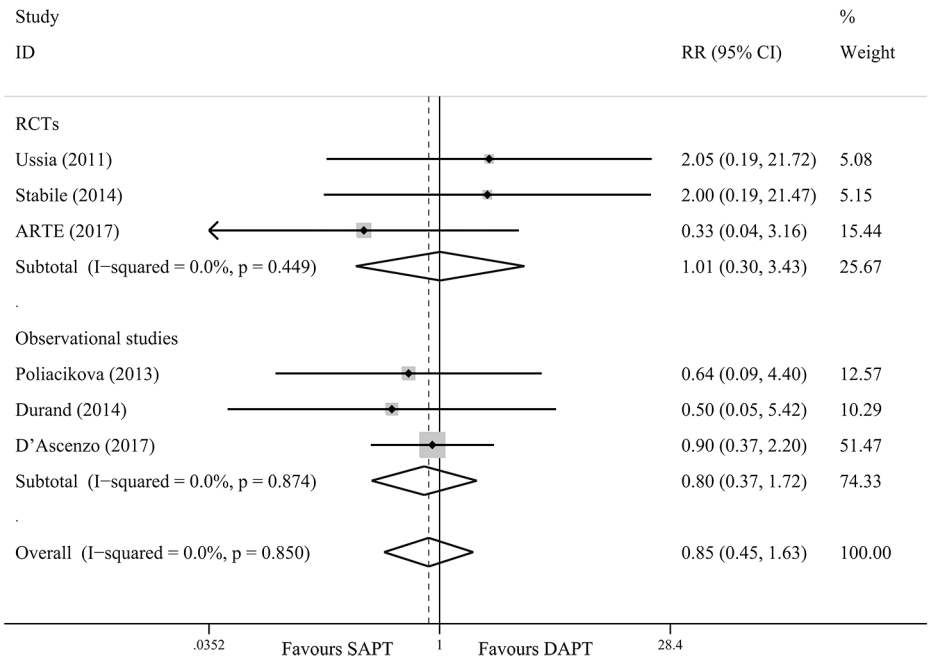

Figure 4 Forest plot for 30-day stroke. RR, relative risk; RCT, randomized controlled trial.

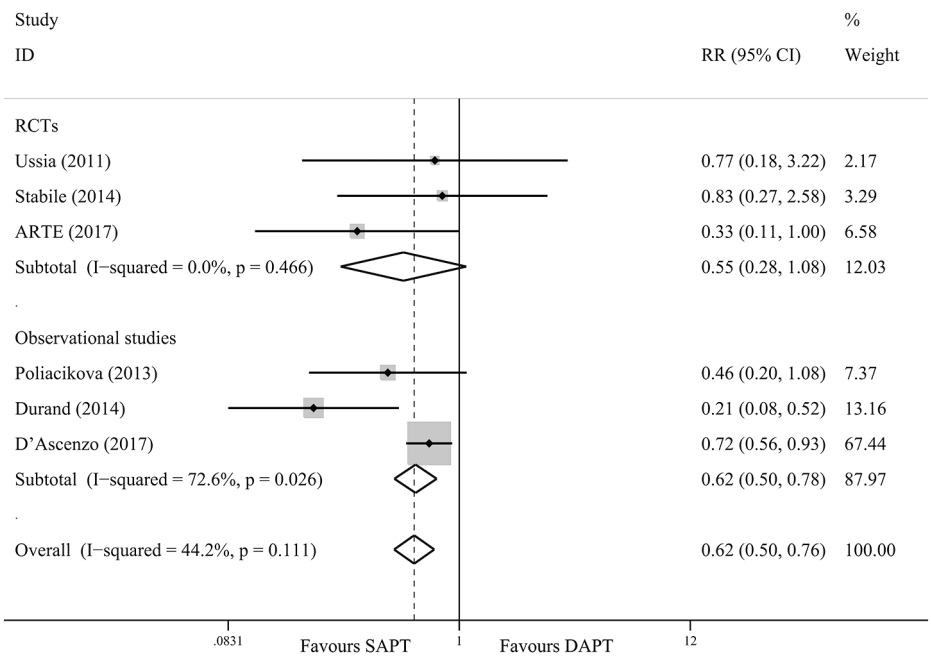

Figure 5 Forest plot for 30-day life-threatening/major bleeding. RR, relative risk; RCT, randomized controlled trial.

Quality assessment

As shown in the *Figure S2*, all RCTs have unclear bias for random sequence generation without giving sufficient messages. And only one trial (17) reported using random block size to conceal treatment allocation. Two of the three trials are open-labeled studies (10,13). For reporting bias, one study (13) did not report all outcomes. Furthermore, the ARTE trial (17) was prematurely stopped after the inclusion of 74% of the planned study population thus it was deemed to have a high risk of other biases. According to the Newcastle-Ottawa scale (*Table S2*), most observational studies were found to be of good quality. The summary of quality assessment for outcomes by GRADE was shown in *Table S3* for both RCTs and observational studies. The level of the evidence for RCTs was downgraded due to the limited number of events. The funnel plots of 30-day mortality were symmetrical by visual estimation thus there was no evident publication bias (*Figure S3*). No significant heterogeneity was observed between studies for each outcome.

Discussion

This meta-analysis of SAPT versus DAPT in the patients undergoing TAVR enrolled 2489 participants from three randomized trials and five observational studies. Our results show that SAPT (*vs.* DAPT) may decrease the incidence of death at 30 days, with a reduced risk of major/life-threatening bleeding. Furthermore, SAPT is noninferior to DAPT in terms of all-cause mortality beyond 3 months. For other secondary outcomes, there is no significant difference between the two regimens with respect to 30-day stroke and spontaneous MI. These data thus suggest that compared with DAPT, SAPT may be used as a safer post-TAVR strategy to improve the prognosis of patients.

Stroke and hemorrhage are two common complications after TAVR. The antiplatelet therapy is a two-edged sword for clinicians to balance the risk of ischemia and bleeding events in the postoperative management of patients. Patients with aortic valve stenosis often have elder age and multiple comorbidities such as atrial fibrillation (AF) or coronary artery disease, which undoubtedly increases the complexity of applying antiplatelet regimens. Although 6-month DAPT is recommended for those people without indication for anticoagulation by current guidelines (1), this recommendation is an empirical strategy.

There is still a controversy about antiplatelet regimens after TAVR. Previous meta-analyses conducted by Aryal *et al.* (5) and Gandhi *et al.* (6) indicated that the effect of SAPT is not inferior to DAPT and there is even a tendency to reduce bleeding events. On the contrary, Verdoia *et al.* (18) supported the use of DAPT for the decreased mortality without increasing the risk of bleeding. To investigate the optimal antiplatelet strategy after TAVR, we therefore performed this updated meta-analysis including ARTE trial (17) and other recent observational studies. We only included the studies which directly compare the two groups, avoiding the interference from anticoagulation. Considering the limited number of RCTs, we also pooled the data from observational studies and performed subgroup analysis to observe the potential impact. Compared with previous meta-analyses, this research retrieved eight studies including more than 2,000 participants. Further, we also assessed the data beyond 3 months and used GRADE approach to evaluate the quality of outcomes, which has not been applied in previous analyses.

Our results show a significant benefit of SAPT over DAPT on all-cause death and bleeding events at 30 days. The decline of all-cause mortality can benefit from the decreased major or life-threatening bleeding events. Meanwhile, there was no significant difference observed in terms of 30-day stroke, MI as well as mortality beyond 3 months during the comparison of SAPT and DAPT. These findings indicated that, compared with the 6-month DAPT recommended in the previous publications, SAPT may be an appropriate strategy after TAVR. However, it is essential to take into account that the sample size is still relatively small and data from large randomized trials are required to evaluate the two strategies. The POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; NCT02247128) cohort A is an ongoing large randomized study designed to assess the 1-year outcome between DAPT and aspirin alone, which will provide further investigation in patients without an indication for oral anticoagulant (OAC).

There are several limitations in our analysis. In the first place, despite the latest trials included, our sample size was relatively small due to a lack of relevant published studies, which would limit the statistical power of this analysis and the ability to observe statistically significant effects. In addition, few published studies reported the clinical outcomes beyond 30 days. As a result, the safety and efficacy of the two regimens in terms of long-term follow-up cannot be well observed. However, it was noted that there was no evident heterogeneity and publication bias in this analysis.

Conclusions

In conclusion, our findings suggest that SAPT after TAVR may have less 30-day mortality than DAPT by means of reducing the incidence of bleeding, with no increased risk of stroke and MI compared with DAPT. Further large-scale randomized controlled studies will elucidate the uncertainty of antiplatelet regimens after TAVR and establish the optimal approach to minimizing ischemic and bleeding risks.

Acknowledgements

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study did not involve any experiment on humans or animals, thus ethical approval was not necessary.

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Supplementary

Search strategy for PubMed, Embase and CENTRAL

PubMed: 109

((("Transcatheter Aortic Valve Replacement"[Mesh]) OR Transcatheter Aortic Valve Implantation[Title/Abstract])) AND (((((("Aspirin"[Mesh]) OR Acetylsalicylic Acid[Title/Abstract]) OR Clopidogrel[Title/Abstract]) OR Prasugrel[Title/Abstract]) OR Ticagrelor[Title/Abstract]) OR Antiplatelet[Title/Abstract]) OR "Platelet Aggregation Inhibitors"[Mesh])

Embase: 757

No.	Query	Results	Date
#3.	#1 AND #2	757	19 Feb 2018
#2.	'antithrombocytic agent'/exp OR 'acetylsalicylic acid'/exp OR 'clopidogrel'/exp OR 'prasugrel'/exp OR 'ticagrelor'/exp OR 'aspirin':ab,ti OR 'clopidogrel':ab,ti OR 'prasugrel':ab,ti OR 'ticagrelor':ab,ti OR 'antiplatelet':ab,ti	333,586	19 Feb 2018
#1.	'transcatheter aortic valve implantation'/exp OR 'transcatheter aortic valve replacement':ti,ab	14,440	19 Feb 2018

CENTRAL: 52

#1 MeSH descriptor: [Transcatheter Aortic Valve Replacement]
#2 MeSH descriptor: [Aspirin]
#3 MeSH descriptor: [Platelet Aggregation Inhibitors]
#4 clopidogrel:ti,ab,kw
#5 Acetylsalicylic Acid:ti,ab,kw
#6 ticagrelor:ti,ab,kw
#7 antiplatelet:ti,ab,kw
#8 prasugrel:ti,ab,kw
#9 Transcatheter Aortic Valve Implantation:ti,ab,kw
#10 #1 OR #9
#11 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#12 #10 AND #11

Table S1 Inclusion and exclusion criteria of studies

Study (year)	Inclusion criteria	Exclusion criteria
Ussia (10) [2011]	(I) Severe symptomatic AS with valve area <1 cm^2; (II) refused for standard AV replacement	(I) Vascular disease that precluded access; (II) severe deformation of the chest; (III) intracardiac thrombus; (IV) unprotected stenosis of the left main coronary artery not amenable to PCI; (V) MI within seven days; (VI) Prosthetic heart valves; (VII) active infection; (VIII) leukopenia (<3,000 white blood cells/mm^3); (IX) coagulopathy; (X) active bleeding; (XI) acute anemia (hemoglobin <9 mg/dL); (XII) aorta could not be fully dilated with a 23-mm aortic valvuloplasty balloon; (XIII) native AV annulus size >24 mm or <19 mm; (XIV) liver cirrhosis; (XV) recurrent PE; (XVI) porcelain aorta; (XVII) respiratory failure; (XVIII) history of radiotherapy to the mediastinum; (XIX) severe connective tissue disease; (XX) previous PCI or ACS requiring DAPT; (XXI) need for OAC; (XXII) allergy or intolerance to study drugs
Poliacikova (11) [2013]	Patients with symptomatic severe AS who underwent TAVI	NA
Durand (12) [2014]	(I) Symptomatic adults with severe AS who were not candidate for surgical AV replacement; (II) AVA <0.8 cm^2, mean AG≥40 mm Hg, or peak aortic jet velocity ≥4.0 m/s; (III) NYHA class II, III or IV	None
Stabile (13) [2014]	(I) Severe AS: Echo-derived AVA <0.8 cm^2 (or AVA index <0.5 cm^2/m^2) and mean AVG >40 mmHg or peak jet velocity >4.0 m/s; (II) cardiac symptoms: NYHA Functional Class ≥II, syncope; (III) high surgical risk: predicted risk of operative mortality ≥15% (determined by site surgeon and cardiologist) or STS score ≥10	(I) Aortic annulus diameter (echo measurement) <18 or >25 mm; (II) aortic dissection or iliac-femoral dimensions or disease precluding safe sheath insertion; (III) untreated CAD requiring revascularization; (IV) Severe AR or MR (>3+) or prosthetic valve (any location); (V) acute MI within 1 month; (VI) Upper GI bleeding within 3 months
D'Ascenzo (14) [2017]	Patients undergoing balloon-expandable TAVI	NA
Ichibori (15) [2017]	Patients who underwent TAVI using balloon-expandable AV	Indications for OAC
Mangieri (16) [2017]	All consecutive patients who underwent TAVI	(I) Patients discharged on anticoagulant therapy (either as monotherapy or with an antiplatelet agent); (II) patients who died during index hospitalization; (III) TAVI patients discharged without any antiplatelet or anticoagulant therapy because of a prohibitive risk of bleeding; (IV) TAVI procedure not performed through a TF route
ARTE (17) [2017]	Patients with clinical indications for TAVR with a balloon-expandable valve	Need for chronic anticoagulation treatment, major bleeding within the 3 months before the TAVR procedure, prior intracranial bleeding, DES implantation within the year before the TAVR procedure, and allergy to clopidogrel and/or aspirin

AS, aortic stenosis; AV, aortic valve; PCI, percutaneous intervention; PE, pulmonary embolism; ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; OAC, oral anticoagulation; TAVI, transcatheter aortic valve implantation; NA, not available; AG, aortic gradient; NYHA, New York Heart Association; AVA, aortic valve area; AVG, aortic valve gradient; CAD, coronary artery disease; AR, aortic regurgitation; MR, mitral regurgitation; GI, gastrointestinal; DES, drug-eluting stent.

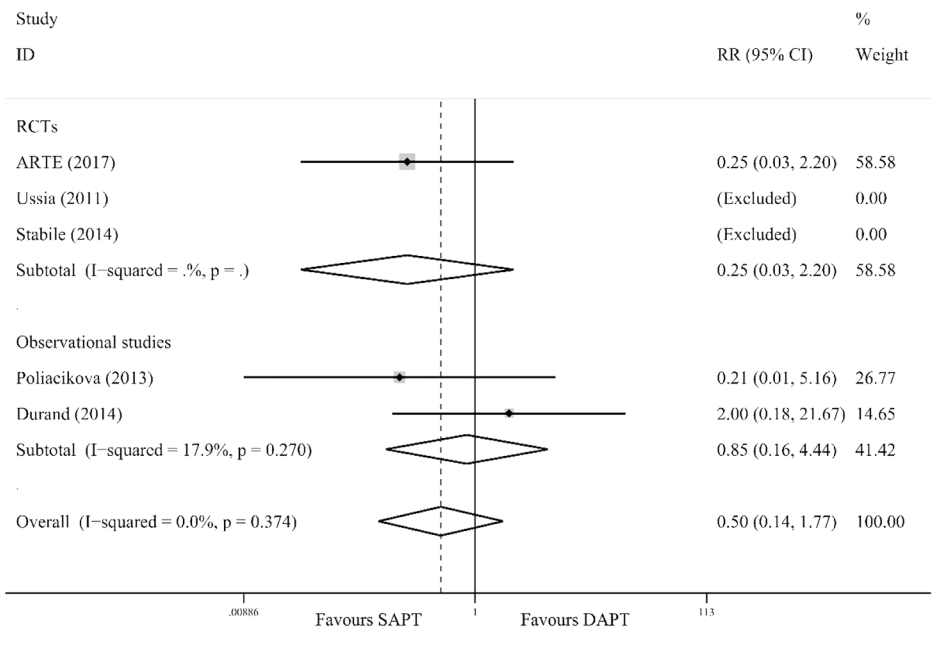

Figure S1 The forest plot for 30-day spontaneous myocardial infarction. RCT, randomized controlled trial; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

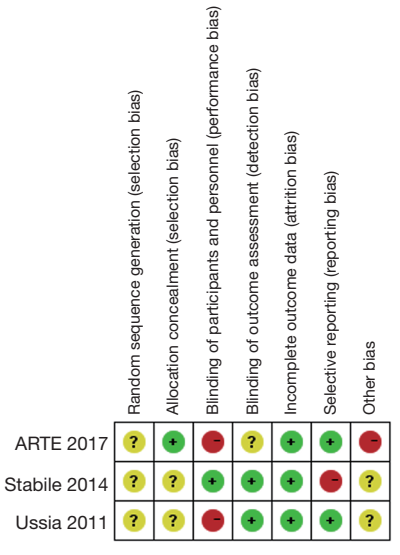

Figure S2 Risk of bias summary of included randomized studies.

Table S2 Results of quality assessment of observational studies by Newcastle-Ottawa scale

Study (first author)	Representativeness of the exposed cohort	Selection of non-exposed cohort†	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts on the basis of design or analysis	Assessment of outcome	Adequacy of duration of follow-up	Completeness of follow-up	Total score
Poliacikova (11)	*	*	*	*	*, –	*	*	*	8
Durand (12)	*	–	*	*	*, –	*	*	*	7
D'Ascenzo (14)	*	–	*	*	*, *	*	*	*	8
Ichibori (15)	*	*	–	*	*, *	*	*	*	8
Mangieri (16)	*	*	–	–	*, –	*	*	–	5

†, a star was awarded if the patients were from the same center; *, a rewarded score by Newcastle-Ottawa scale; –, the item does not get a score.

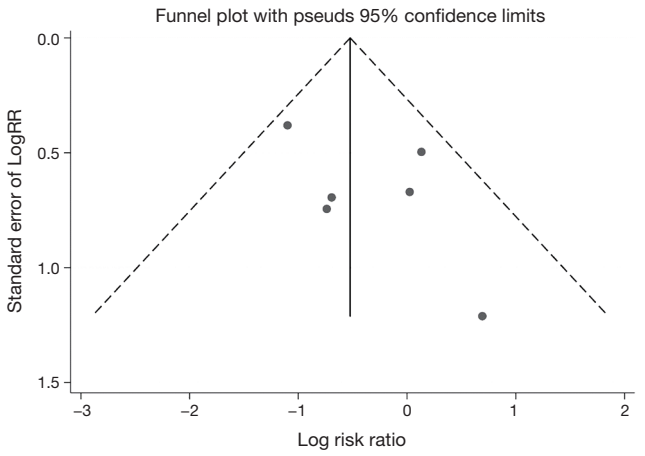

Figure S3 The funnel plot for 30-day mortality.

Table S3 GRADE assessment of the quality of evidence for outcomes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk (DAPT)	Corresponding risk (SAPT)				
30-day mortality-RCT (follow-up: 30 days)	Study population		0.83 (0.35–1.94)	421 (3 studies)	⊕⊕⊕⊖ (moderate[1])	
	52 per 1,000	43 per 1,000 (18 to 101)				
	Low					
	17 per 1,000	14 per 1,000 (6 to 33)				
	High					
	100 per 1,000	83 per 1,000 (35 to 194)				
30-day mortality-nRCT (follow-up: 30 days)	Study population		0.50 (0.29–0.85)	1,541 (3 studies)	⊕⊕⊖⊖ (low)	
	50 per 1,000	25 per 1,000 (15 to 43)				
	Low					
	45 per 1,000	22 per 1,000 (13 to 38)				
	High					
	77 per 1,000	38 per 1,000 (22 to 65)				
Mortality beyond 3 months-RCT (follow-up: >3 months)	Study population		0.86 (0.41–1.82)	421 (3 studies)	⊕⊕⊕⊖ (moderate[1])	
	66 per 1,000	57 per 1,000 (27 to 121)				
	Low					
	50 per 1,000	43 per 1,000 (20 to 91)				
	High					
	100 per 1,000	86 per 1,000 (41 to 182)				
Mortality beyond 3 months-nRCT (follow-up: >3 months)	Study population		0.97 (0.81–1.16)	1,886 (4 studies)	⊕⊕⊖⊖ (low)	
	181 per 1,000	176 per 1,000 (147 to 210)				
	Low					
	48 per 1,000	47 per 1,000 (39 to 56)				
	High					
	177 per 1,000	172 per 1,000 (143 to 205)				
Stroke-RCT (follow-up: 30 days)	Study population		1.01 (0.3–3.43)	421 (3 studies)	⊕⊕⊕⊖ (moderate[1])	
	24 per 1,000	24 per 1,000 (7 to 81)				
	Low					
	17 per 1,000	17 per 1,000 (5 to 58)				
	High					
	27 per 1,000	27 per 1,000 (8 to 93)				
Stroke-nRCT (follow-up: 30 days)	Study population		0.80 (0.37–1.72)	1,541 (3 studies)	⊕⊕⊖⊖ (low)	
	19 per 1,000	15 per 1,000 (7 to 32)				
	Low					
	17 per 1,000	14 per 1,000 (6 to 29)				
	High					
	34 per 1,000	27 per 1,000 (13 to 58)				
Life-threatening/major bleeding-RCT (follow-up: 30 days)	Study population		0.55 (0.28–1.08)	421 (3 studies)	⊕⊕⊕⊖ (moderate[1])	
	104 per 1,000	57 per 1,000 (29 to 113)				
	Low					
	100 per 1,000	55 per 1,000 (28 to 108)				
	High					
	108 per 1,000	59 per 1,000 (30 to 117)				
Life-threatening/major bleeding-nRCT (follow-up: 30 days)	Study population		0.62 (0.5–0.78)	1,541 (3 studies)	⊕⊕⊖⊖ (low)	
	210 per 1,000	130 per 1,000 (105 to 163)				
	Low					
	190 per 1,000	118 per 1,000 (95 to 148)				
	High					
	264 per 1,000	164 per 1,000 (132 to 206)				
Myocardial infarction-RCT (follow-up: 30 days)	Study population		Not estimable	421 (3 studies)	⊕⊕⊕⊖ (moderate[1])	
	19 per 1,000	0 per 1,000 (0 to 0)				
	Low					
	–	–				
	High					
	36 per 1,000	0 per 1,000 (0 to 0)				
Myocardial infarction-nRCT (follow-up: 30 days)	Study population		0.85 (0.16–4.44)	331 (2 studies)	⊕⊕⊖⊖ (low)	
	13 per 1,000	11 per 1,000 (2 to 60)				
	Low					
	11 per 1,000	9 per 1,000 (2 to 49)				
	High					
	17 per 1,000	14 per 1,000 (3 to 75)				

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1], total number of events is less than 300. GRADE Working Group grades of evidence: High quality, further research is very unlikely to change our confidence in the estimate of effect; Moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate. CI: Confidence interval; RR: Risk ratio.