Single versus Dual Antiplatelet Therapy after Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

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Keywords

Transcatheter aortic valve implantation · Dual antiplatelet therapy · Single antiplatelet therapy · Meta-analysis

Abstract

Objectives: Although dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is currently recommended in patients after transcatheter aortic valve implantation (TAVI), this practice is not supported by sufficient evidence. This study was performed to compare DAPT to single antiplatelet therapy (SAPT). **Methods:** An electronic search was completed of PubMed, Embase, Ovid Medline, Web of Science, and Cochrane Central Register of Controlled Trials. Studies comparing DAPT versus SAPT in patients undergoing TAVI were included. **Results:** Seven studies incorporating 1,445 patients were eligible for the present meta-analysis. There were no significant differences on 30-day all-cause mortality (OR 1.19, 95% CI 0.63–2.25, $p = 0.593$), 6-month all-cause mortality (OR 1.11, 95% CI 0.49–2.53, $p = 0.796$), or 1-year all-cause mortality (OR 1.19, 95% CI 0.63–2.25, $p = 0.593$). DAPT was associated with an increased risk for 30-day (OR 2.91, 95% CI 1.85–4.58, $p < 0.01$), 6-month (OR 2.54, 95% CI 1.26–5.10, $p < 0.001$), and 1-year major and lethal bleeding (OR 2.65, 95%

CI 1.04–6.77, $p = 0.041$) based on 896, 337, and 583 patients, respectively, compared to SAPT. **Conclusion:** Compared to SAPT, DAPT was not shown to be superior in reducing thrombotic events, but presented an increased risk of major/life-threatening bleeding. More randomized controlled trials are needed to provide further evidence. © 2018 S. Karger AG, Basel

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries [1]. Aortic valve replacement is an effective therapy for severe AS [2]. Surgical aortic valve replacement (SAVR) leads to good long-term survival and the improvement of symptoms, with a low perioperative risk [2–4]. However, a study showed that 33% of elderly patients with severe, symptomatic AS were denied surgery because of older age and LV dysfunction [5]. Transcatheter aortic valve implantation (TAVI) has emerged as an alternative choice for high-risk and

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Fig. 1. Study flow chart of the search strategy.

inoperable patients with severe AS [6–8]. For intermediate-risk patients with severe AS, TAVI is an alternative choice depending on the patients' procedural risks and preferences [8–10]. TAVI has been shown to be noninferior to SAVR, with reduced kidney injury, atrial fibrillation, and major adverse cardiovascular events in TAVI patients [9–12].

In some studies involving patients undergoing TAVI who had valve thrombosis assessed by computed tomography, the incidence of valve thrombosis varied from 7 to 40% [13, 14]. Preventing ischemic events is very important, as this can decrease the risk of atrial fibrillation and device embolization. Therefore, antithrombotic agents are commonly used during and after TAVI. However, due to a lack of evidence, the guidelines do not provide accurate recommendations. For patients without comorbidities, clopidogrel (75 mg daily) is recommended for the first 6 months after TAVI in addition to life-long aspirin (75–100 mg daily) [8].

Although dual antiplatelet therapy (DAPT) decreases the risk of thrombotic events, DAPT increases the risk of bleeding compared to single antiplatelet therapy (SAPT) [15]. How to balance the risk of ischemic events and bleeding is still unclear. Some studies have compared the clinical outcomes of DAPT versus SAPT. As presented here, we summarized the relevant research of DAPT versus SAPT with a systematic review and meta-analysis.

Methods

Search Strategy

We performed the study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. The PubMed, Embase, Ovid Medline, Web of Science, and Cochrane Central Register of Controlled Trials online databases were searched from inception to May 2017 using terms relating to TAVI (transcatheter, percutaneous, aortic valve replacement, aortic valve implantation, TAVI, TAVR) and treatment (antithrombotic, antiplatelet, platelet aggregation inhibitors, aspirin, acetylsalicylic acid, acid acetylsalicylic, 2-(acetyloxy)benzoic acid, clopidogrel, prasugrel, ticagrelor, P2Y antagonist, P2Y receptor antagonist) as key words and Mesh terms. The reference lists of pertinent articles were also screened manually for potentially relevant citations. Two investigators performed the article searches independently, with any disagreement resolved by a third author.

Inclusion and Exclusion Criteria

In this meta-analysis, we accepted the articles that met the following criteria: (1) population-based studies, (2) randomized controlled trials (RCTs) or observational studies, (3) patients with AS who underwent TAVI, (4) comparison of DAPT with SAPT after TAVI, (5) reported early (30 days or in-hospital) or late (≥ 6 months including early) adverse events (death, bleeding, stroke, etc.). We excluded the following articles: (1) fewer than 20 patients, (2) published duplicate trials, (3) comparison of DAPT with SAPT before TAVI, (4) comparison of DAPT with an oral anticoagulant versus SAPT with an oral anticoagulant, (5) no reporting of the clinical outcomes, (6) articles published in a language other than English. If reported data were duplicated, we only enrolled data from the latest report.

Table 1. Baseline characteristics of the included studies

Study type	Ichihori [15], 2017	Rodés-Cabau [27], 2017	Mangieri [22], 2017	Durand [23], 2014	Polackkova [24], 2013	Stabile [25], 2011	Ussia [26], 2011
Study type	Retrospective study	RCT	Retrospective study	Prospective study	Prospective study	Randomized trial	Randomized trial
Enrollment date/ location	October 2009 to January 2015/Japan Osaka Univ. Hospital, single center	NA/9 centers in Canada, Europe, and South America	January 2009 to May 2015/Italy, single center	January 2010 to December 2011/France, 3 tertiary centers	December 2007 to June 2012/UK, single center, Sussex Cardiac Centre	May 2009 to August 2010/Italy, single center	May 2009 to August 2010/Italy, single center
Inclusion	NA	Patients with clinical indications for TAVR with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve	NA	1. Patients with symptomatic severe AS who were not candidates for surgical AV replacement because of coexisting illness 2. AVA <0.8 cm ² , mean aortic gradient ≥40 mm Hg or a peak aortic jet velocity ≥4.0 m/s 3. NYHA functional class II, III, or IV	All patients who underwent TAVI	1. Severe AS: echo-derived AVA <0.8 cm ² or AVA index <0.5 cm ² /m ² and mean AVG >40 mm Hg or peak jet velocity >4.0 m/s 2. Cardiac symptoms: NYHA functional class ≥II, syncope 3. High surgical risk: predicted risk of operative mortality ≥15% (determined by site surgeon and cardiologists) or STS score ≥10	1. Severe symptomatic AS with AVA <1 cm ² 2. Refused for standard AV replacement
Exclusion	Patients who had indications for oral anticoagulant therapy before TAVI	1. Need for chronic anticoagulation treatment 2. Major bleeding within the 3 months before the TAVR procedure 3. Prior intracranial bleeding, drug eluting stent implantation within the year before the TAVR procedure 4. Allergy to clopidogrel and/or aspirin	1. Patients discharged on anticoagulant therapy (either as monotherapy or with an antiplatelet agent) 2. Patients who died during index hospitalization (8 deaths occurred during the procedure, 4 patients died for noncardiac reasons, and the remaining 22 were in-hospital deaths) due to a cardiovascular origin 3. Patients who underwent TAVI who were discharged without any antiplatelet/anticoagulant therapy because of a prohibitive risk of bleeding 4. TAVI procedure not performed through a transfemoral route	All patients included in the registry	NA	1. Aortic annulus diameter (echo measurement) <18 mm or >25 mm 2. Aortic dissection or iliac-femoral dimensions or disease precluding safe sheath insertion 3. Untreated coronary artery disease requiring revascularization 4. Severe aortic regurgitation or mitral regurgitation (>3+) or prosthetic valve (any location) 5. Acute MI within 1 month 6. Upper gastrointestinal bleeding within 3 months 7. Cerebrovascular accident or TIA within 6 months 8. Any cardiac procedure, other than balloon aortic valvuloplasty, within 1 month or within 6 months for drug eluting stent 9. Indication for oral anticoagulation therapy (i.e., atrial fibrillation) 10. Aspirin intolerance/allergy 11. Thienopyridine intolerance/allergy	1. Vascular disease that precluded access 2. Severe deformation of the chest 3. Intracardiac thrombus 4. Unprotected stenosis of the left main coronary artery not amenable to PCI 5. MI within 7 days 6. Prosthetic heart valve 7. Active infection 8. Leukopenia 9. Coagulopathy 10. Active bleeding 11. Acute anemia (Hb <9 mg/dL) 12. Aorta could not be fully dilated with a 23-mm aortic valvuloplasty balloon 13. Aortic annulus size <19 mm or >24 mm 14. Liver cirrhosis 15. Recurrent pulmonary embolism 16. Porcelain aorta 17. Respiratory failure 18. History of radiotherapy to mediastinum 19. Severe connective tissue disease 20. Previous PCI or MI requiring DAPT 21. Need for oral anticoagulation therapy 22. Allergy or intolerance to study drugs
Medicine use: DAPT group	Lifelong low-dose aspirin 100 mg daily for 6 months Ticlopidine 200 mg or clopidogrel 75 mg daily for 6 months	Aspirin or acetylsalicylic acid (80–100 mg/day) for at least 6 months, plus clopidogrel (75 mg/day) for 3 months	ASA (75/100/150 mg/day) clopidogrel (75 mg/day) within 3–6 months	1. ASA 75 mg/day 2. Clopidogrel 300 mg loading then 75 mg/day; duration 1–6 months	1. ASA 75 mg/day 2. Clopidogrel 300 mg loading then 75 mg/day; duration 6 months	1. ASA 80 mg/day 2. Clopidogrel 75 mg/day or ticlopidine 500 mg BID; duration 6 months	1. ASA 10.0 mg/day 2. Clopidogrel 300 mg loading then 75 mg/day; duration 3 months
Medicine use: SAPI group	Lifelong low-dose aspirin 100 mg daily for 6 months	Aspirin or acetylsalicylic acid (80–100 mg/day) for at least 6 months	Either ASA or clopidogrel for 3–6 months	ASA 75 mg/day or clopidogrel 75 mg/day (without clopidogrel loading dose), duration 1–6 months	ASA 300 mg loading then ASA 75 mg/day; duration 6 months	ASA 75–160 mg/day; duration 6 months	ASA 100 mg/day; duration 3 months
TAVI device	SAPIEN or SAPIEN XT	SAPIEN XT or SAPIEN 3 valve	SAPIEN XT or SAPIEN 3 valve	1. SAPIEN; transfemoral or transapical route 2. CoreValve (Medtronic) transfemoral or subclavian route	CoreValve	SAPIEN	CoreValve
Follow-up, months	1, 6, and 12	1, 3, and 12	12	1, 6	1, 6	1, 6	1, 6
Combined/composite endpoint/ primary endpoint	All-cause death, nonfatal myocardial infarction, nonfatal stroke, and major or life-threatening bleeding complications	Rate of death, MI, ischemic stroke or TIA, or major or life-threatening bleeding at 3-month follow-up	NACE: composite of all-cause mortality, myocardial infarction, cerebrovascular events, major bleeding requiring hospitalization, and valve thrombosis	Combination of 30-day mortality, major stroke, life-threatening bleeding, MI, and major vascular complications at 30 days	MACE: all-cause mortality, ACE or stroke NACE: combined endpoint all-cause mortality, ACE, stroke, or major bleeding	Primary endpoint not specified: cardiovascular death, major vascular complications, minor vascular stroke, acute MI, all-cause mortality, life-threatening or disabling bleeding, acute kidney injury	Composite of death from any cause, MI, major stroke, urgent or emergency conversion to surgery, and life-threatening bleeding
Secondary outcome	NA	The incidence of MI, ischemic stroke, major or life-threatening bleeding, and death at 3 months	NA	30-day transfusion, any vascular complications, any stroke, any bleeding, acute kidney injury, and success rates	NA	NA	NA

RCT, randomized controlled trials; NA, not available; TAVR, transcatheter aortic valve replacement; TAVI, transcatheter aortic valve implantation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; ASA, acetylsalicylic acid; Hb, hemoglobin; NYHA, New York Heart Association; MI, myocardial infarction; TIA, transient ischemic attack; DAPT, dual antiplatelet therapy; SAPI, single antiplatelet therapy; NACE, net adverse clinical and cerebrovascular event; ACE, acute coronary event; BID, twice daily.

Data Extraction

Two investigators extracted the data independently from the eligible studies, with disagreements resolved by a third author. The name of the first author, year of publication, study type, inclusion and exclusion criteria, duration of follow-up, and patients' baseline data were recorded, as well as factors such as overall mortality, myocardial infarction (MI), bleeding and complications, vascular complications, stroke, etc.

Quality Assessment

The quality of the relevant articles was assessed by 2 authors. For RCTs, we used the Cochrane Collaboration Risk of Bias Tool to evaluate six bias domains [17]. For case control and cohort studies, we used the Newcastle-Ottawa Quality Assessment Scale to assess quality [18]. Studies were evaluated on the following three aspects: selection, comparability, and exposure/outcome. Studies with a score of 7 or higher were considered high quality. Any disagreements were resolved through consulting a third author.

Outcomes

The primary endpoints for this study were early (30 days or in-hospital) or late (≥ 6 months, including early) all-cause mortality, which can reflect the net effect of thrombotic and bleeding events. The secondary endpoints were MI, valve thrombosis, stroke (major, minor), and transient ischemic attack (TIA), bleeding (lethal, major, minor), and early (30 days or in-hospital) or late (≥ 6 months, including early) vascular complications (major). All clinical events were defined according to the Valve Academic Research Consortium-2 (VARC-2) [19].

Statistical Analysis

Pooled odds ratios (OR) were acquired using STATA version 12 (StataCorp, College Station, TX, USA) [20]. A two-sided p value < 0.05 was considered to be the level of statistically significant difference. The Q and I^2 statistics were calculated to evaluate statistical heterogeneity among the trials. If I^2 statistics showed $p < 0.10$ and $I^2 > 50\%$, a random-effects model was used to estimate the pooled OR [21]. Funnel plots and the Egger regression asymmetry test were conducted to assess publication bias.

Results

Search Results

The process of study selection is illustrated in Figure 1. Our search strategy yielded 1,202 articles, 359 of which were duplicated articles. A total of 70 full-text articles remained after screening the titles and abstracts. Finally, a total of 7 articles incorporating 1,445 patients were included in the present study after removing review articles, meta-analyses, and irrelevant articles [15, 22–27].

Characteristics of the Included Articles

Of the 7 included articles, 3 were RCTs [25–27] and the others were observational articles [16, 22–24]. The mean age was 82.1 years, and 55.6% of the patients were

women. A total of 794 patients were treated with aspirin plus clopidogrel (or ticlopidine) as the DAPT group, and 651 patients were treated with aspirin or clopidogrel as the SAPT group. Four studies completed a 6-month follow-up [23–16], 2 studies completed 12-month follow-up periods [15, 22], and 1 study was prematurely stopped [27], reporting the 30-day and 3-month outcomes. Five of the included studies used SAPIEN devices [15, 22–23, 25, 27], while the other 2 used CoreValve devices [24, 26]. Detailed characteristics of the articles and patient baseline data are provided in Tables 1 and 2.

Quality Assessment

The quality assessment of the RCTs using the Cochrane Collaboration Risk of Bias Tool is presented in Table 3, and the assessment of observational studies using the Newcastle-Ottawa Quality Assessment Scale is shown in Table 4. Four observational studies included in our meta-analysis were considered to be high quality (with scores of 8, 8, 8, and 7).

All-Cause Mortality

On the basis of 5 studies incorporating 752 patients, the incidence of 30-day all-cause mortality was found in 22 out of 360 (6.1%) patients in the DAPT group, and in 20 out of 391 (5.1%) in the SAPT group. DAPT had a similar risk for 30-day all-cause mortality, with an OR of 1.19 (95% CI 0.63–2.25, $p = 0.593$, $I^2 = 0\%$; Fig. 2).

The all-cause mortality rates at 6 months and 1 year were similar. No significant differences for 6-month all-cause mortality were noted, with an OR of 1.11 (95% CI 0.49–2.53, $p = 0.796$, $I^2 = 0\%$; Table 5). Compared to SAPT, DAPT had a similar risk for 1-year all-cause mortality, with an OR of 0.78 (95% CI 0.38–1.57, $p = 0.486$, $I^2 = 36.9\%$; Table 5).

Stroke (Major, Minor) and TIA

Four studies involving 632 patients reported the incidence of 30-day stroke (major, minor, and TIA). In the DAPT group, the incidence of stroke was 2.8% (9/300). In the SAPT group, the incidence was 2.6% (8/332). There was no significant difference between the 2 groups (OR 1.22, 95% CI 0.45–3.33, $p = 0.698$, $I^2 = 0\%$; Fig. 3).

The outcomes at 6 months and 1 year between DAPT and SAPT were similar. No significant differences in the incidence of 6-month stroke (major, minor, and TIA) were observed (OR 0.81, 95% CI 0.21–3.10, $p = 0.753$, $I^2 = 0\%$; Table 5). Also, DAPT showed a similar incidence for 1-year stroke (major, minor, and TIA; OR 1.58, 95% CI 0.59–4.28, $p = 0.364$, $I^2 = 0\%$; Table 5).

Table 2. Baseline characteristics of the included patients

	Ichibori [15], 2017		Rodés-Cabau [27], 2017		Mangieri [22], 2017		Durand [23], 2014		Poliacikova [24], 2013		Stabile [24], 2011		Ussia [26], 2011	
	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT
Patients, <i>n</i>	66	78	111	111	331	108	128	164	58	91	60	60	40	39
Mean age, years	84±6	83±6	79±9	79±9	82.9±8.2	84.3±7.1	84.6±5.8	82.7±6.3	81.6±6.3	82±6.9	81.1±4.8	80.2±5.7	80±6	81±4
Female	42 (63.6)	50 (64.1)	41 (36.9)	52 (46.9)	214 (64.6)	62 (57.4)	78 (60.9)	74 (45.1)	36 (44.8)	42 (46.2)	36 (60)	44 (73.3)	20 (50)	23 (59)
Chronic renal failure (GFR <60 mL/min or creatinine >200 μmol/L)	eGFR (1.73 mL/min/m ²) 42.1±22.5	GFR <60 mL/min 70 (63.1)	70 (63.1)	eGFR 46 (42.5)	<60 mL/min/m ² 114 (34.4)		11 (8.6)	12 (7.3)	3 (5.2)	5 (5.5)	NA	NA	6 (15)	5 (13)
Diabetes	22 (33.3)	24 (30.8)	41 (36.9)	36 (32.7)	89 (26.8)	19 (17.5)	30 (23.4)	40 (24.4)	16 (27.6)	16 (17.6)	15 (25)	17 (28.3)	13 (33)	8 (21)
Dyslipidemia	47 (71.2)	59 (75.6)	NA	NA	168 (50.7)	63 (58.3)	97 (59.1)	55 (43)	NA	NA	NA	NA	NA	NA
Hypertension	NA	86 (77.5)	87 (79.8)	NA	260 (78.5)	91 (84.2)	90 (70.3)	116 (70.7)	NA	NA	57 (95)	57 (95)	35 (88)	31 (80)
CAD	35 (53.0)	29 (37.2)	NA	NA	NA	NA	82 (50)	39 (30.5)	37 (63.8)	50 (54.9)	NA	NA	NA	NA
Previous MI	NA	26 (23.4)	20 (18.4)	63 (19)	13 (12)	14 (10.9)	22 (13.4)	NA	NA	NA	NA	NA	7 (18)	4 (10)
Previous CABG	10 (15.2)	39 (12.8)	42 (35.1)	70 (38.5)	20 (21.1)	20 (18.5)	10 (7.8)	30 (18.3)	17 (29.3)	19 (20.9)	NA	NA	2 (5)	4 (10)
Previous stroke	13 (19.7)	22 (28.2)	NA	NA	NA	NA	12 (9.4)	13 (7.9)	NA	NA	NA	NA	2 (5)	4 (10)
Previous PCI	25 (37.9)	11 (14.1)	NA	NA	NA	NA	NA	NA	16 (27.6)	20 (22.0)	13 (21.3)	14 (23.3)	12 (30)	9 (23)
Atrial fibrillation	NA	NA	NA	NA	54 (16.2)	22 (10.1)	45 (35.2)	37 (23)	16 (27.6)	10 (11)	NA	NA	4 (10)	6 (15)
Pacemaker	NA	NA	NA	NA	18 (5.4)	9 (8.3)	10 (7.8)	18 (11)	NA	NA	NA	NA	4 (10)	1 (3)
Baseline aspirin	NA	NA	NA	NA	169 (51)	52 (48)	46 (35.9)	92 (56.1)	NA	NA	60	60	NA	NA
Baseline clopidogrel	NA	NA	NA	NA	73 (22)	12 (11.1)	8 (6.3)	13 (7.9)	NA	NA	NA	NA	NA	NA
Baseline warfarin	NA	NA	NA	NA	16 (4.8)	2 (1.8)	42 (32.8)	46 (28)	NA	NA	NA	NA	NA	NA
EuroScore, %	Logistic 25.5±18.5	24.2±15.6	NA	NA	Logistic 19.4±13	21.3±17.2	20.2±11.6	20.0±12.4	NA	NA	23.34±8.15	25.1±12.0	23±15	21±16
STS score, %	12.2±12.7	10.7±7.4	6.2±4.4	6.4±4.6	7.2±6.6	7.9±6.7	7.4±6.1	6.9±4.0	NA	NA	9.7±5.1	10.4±6.8	8±5	7±3
EF (mean ± SD)	NA	NA	55±12	54±13	52.6±12.9	51.6±13.4	60.5±14.0	54.4±13.6	NA	NA	52.4±14.4	51.3±11.0	51±12	54±8

Table 2 (continued)

	Ichihori [15], 2017		Rodés-Cabau [27], 2017		Mangieri [22], 2017		Durand [23], 2014		Polićkova [24], 2013		Stabile [24], 2011		Ussia [26], 2011	
	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT
EF <30%	EF <50% 13 (14.1) (19.7)	11 (14.1)	NA	NA	NA	NA	2 (1.2)	0 (0)	EF <50% 10 (15.4) (17.2)	14 (15.4)	7 (11.6)	8 (13)	NA	NA
PAP mean, mm Hg	NA	NA	NA	NA	39.9±13	39.3±13	Pulmonary artery systolic pressure 44.6±14.1	44.1±12.8	Peak gradient 79.0±24.3	93.8±27.7	53.64±13.54	51.3±12.1	NA	NA
Mean gradient, mm Hg	56.0±19.0	50.5±17.0	43±16	43±15	NA	NA	48.3±19.5	50.1±15.2	NA	NA	59.4±15.4	63.6±14.1	52±6	57±18
Mean aortic valve area, cm ²	0.62±0.17	0.70±0.19	Indexed AVA 0.42±0.13	0.40±0.11	NA	NA	0.63±0.14	0.61±0.16	0.67±0.17	0.71±0.22	NA	NA	0.6±0.2	0.6±0.3
Preoperative AR ≥mild	49 (74.2)	63 (80.7)	55 (49.5)	56 (50.5)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NYHA class II	III or IV 44 (66.7)	37 (47.4)	NA	NA	III or IV 181 (54.6)	53 (48.1)	III or IV 99 (77.4)	131 (79.9)	NA	NA	6 (10.0) 35 (58.3) 19 (31.7)	7 (11.7) 32 (53.3) 21 (35)	III or IV 23 (59) 26 (65)	23 (59)
Device success	62 (93.9)	76 (97.4)	101 (90.9)	94 (86.2)	NA	NA	122 (95.3)	159 (97)	55 (94.8)	90 (98.9)	60 (100)	60 (100)	38 (95)	36 (92)
Access	Trans-apical 29 (43.9)	Trans-apical 42 (53.9)	Femoral 80 (72.1) Transapical 18 (16.2) Transaortic 10 (9.0) Transcarotid 3 (2.7)	Femoral 73 (65.8) Transapical 20 (18.0) Transaortic 14 (12.6) Transcarotid 4 (3.6)	Femoral access 331 (100)	Femoral access 108 (100)	Trans-femoral 98 (76.6) Trans-apical 30 (23.4) Subclavian 0	Trans-femoral 138 (84.1) Trans-apical 24 (14.6) Subclavian 2 (1.2)	NA	NA	NA	NA	Trans-femoral 38 (95) Trans-sub-clavian 2 (5)	Trans-femoral 39 (100) Trans-sub-clavian 0
SAPIEN device	20 mm 5 (7.6)	20 mm 0 (0.0)	NA	NA	NA	NA	60 (46.9)	60 (54.5)	NA	NA	34 (56.7)	34 (56.7)	NA	NA
23 mm	23 mm 48 (61.5)	23 mm 48 (61.5)	NA	NA	NA	NA	68 (53.1)	44 (40)	NA	NA	23 (43.3)	26 (43.3)	NA	NA
26 mm	26 mm 45 (68.2)	26 mm 30 (38.5)	NA	NA	NA	NA	0	6 (3.5)	NA	NA	0	0	NA	NA
29 mm	29 mm 16 (24.2)	29 mm 16 (24.2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CoreValve device	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
26 mm	26 mm 29 mm 31 mm	26 mm 29 mm 31 mm	NA	NA	NA	NA	16 (29.6) 35 (64.8) 3 (5.6)	0	NA	NA	23 (56) 17 (43) 0	34 (56.7) 26 (43.3) 0	23 (56) 17 (43) 0	12 (31) 27 (69) 0
Conversion to open surgery	0 (0.0)	2 (2.6)	2 (1.8)	3 (2.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Values in parentheses are percentages. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; GFR, glomerular filtration rate; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; EF, ejection fraction; PAP, pulmonary artery pressure; AR, aortic regurgitation; NYHA, New York Heart Association; NA, not available.

Table 3. Quality assessment of RCTs through the Cochrane Collaboration Risk of Bias Tool

	Rodés–Cabau [27], 2017	Stabile [25], 2011	Ussia [26], 2011
Random sequence generation (selection bias)	Low risk	Unclear risk	Unclear risk
Allocation concealment (selection bias)	Low risk	Unclear risk	Unclear risk
Blinding of participants and researchers (performance bias)	High risk	Unclear risk	High risk
Blinding of outcome assessment (detection bias)	High risk	Unclear risk	Low risk
Incomplete outcome data (attrition bias)	High risk	Low risk	Low risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk
Other bias	Unclear risk	Unclear risk	Unclear risk

Table 4. Assessment of observational studies through the Newcastle-Ottawa Quality Assessment Scale

	Durand [23], 2014	Poliacikova [24], 2013	Mangieri [22], 2017	Ichibori [15], 2017
<i>Selection</i>				
Representativeness of exposed cohort	1	1	1	1
Selection of nonexposed cohort	1	1	1	1
Ascertainment of exposure	1	1	1	1
Outcome of interest absent at start of study	1	1	1	1
<i>Comparability</i>				
On the basis of the design or analysis	2	1	2	2
<i>Outcome</i>				
Assessment of outcome	0	0	0	0
Follow-up long enough for outcomes to occur	1	1	1	1
Adequacy of follow-up	1	1	1	1
Total score	8	7	8	8

Table 5. Summary of clinical outcomes (DAPT vs. SAPT)

Outcomes	OR	95% CI	I^2 , %	p value
30-day major stroke	0.99	0.27–3.70	0	0.99
30-day minor stroke	1.34	0.30–6.01	0	0.71
30-day TIA	0.59	0.08–4.53	0	0.61
30-day major and minor stroke	1.16	0.39–3.50	0	0.79
6-month all-cause mortality	1.11	0.49–2.53	0	0.80
1-year all-cause mortality	0.78	0.39–1.58	36.9	0.49
6-month major and lethal bleeding	2.54	1.26–5.10	0	0.009
1-year major and lethal bleeding	2.65	1.04–6.77	0	0.04

DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.

Furthermore, the stroke incidence (major, minor, and TIA) of the periprocedural period was consistent with the other periods (OR 0.73, 95% CI 0.30–1.78, $p = 0.484$, $I^2 = 0\%$; Table 5).

Stroke can be divided into major stroke, minor stroke, and TIA. Compared to SAPT, DAPT showed a similar risk across each of these stroke categories. The detailed statistics are presented in Table 5.

Fig. 2. DAPT versus SAPT for 30-day all-cause mortality.

Fig. 3. DAPT versus SAPT for 30-day stroke (major, minor, and TIA).

Myocardial Infarction

Five studies including 752 patients reported the occurrence of 30-day MI. The occurrence rates of 30-day MI in the DAPT and SAPT groups were low, at 0.14% (5/360) versus 1.0% (4/392). No significant discrepancies in the occurrences of 30-day MI were revealed (OR 1.35, 95% CI 0.38–4.82, $p = 0.763$, $I^2 = 0\%$; Fig. 4).

Bleeding

In 6 studies involving 896 patients, 30-day major and lethal bleeding occurred in 60 of 426 (16.2%) patients in the DAPT group and in 30 of 470 (6.4%) patients in the SAPT group. DAPT had an increased risk for 30-day major and lethal bleeding (OR 2.80, 95% CI 1.75–4.48, $p < 0.001$, $I^2 = 2.4\%$; Fig. 5).

Compared to SAPT, DAPT was associated with an increased risk for 6-month major and lethal bleeding (OR

Fig. 4. DAPT versus SAPT for 30-day MI.

Fig. 5. DAPT versus SAPT for 30-day major and lethal bleeding.

2.54, 95% CI 1.26–5.10, $p < 0.01$, $I^2 = 0\%$; Table 5). Patients in the DAPT group had a significantly increased risk of 1-year major and lethal bleeding (OR 2.65, 95% CI 1.04–6.77, $p = 0.041$, $I^2 = 0\%$; Table 5). Also, DAPT had a trend towards increased risk for periprocedural major and lethal bleeding (OR 1.95, 95% CI 0.95–4.01, $p = 0.069$, $I^2 = 0\%$; Table 5).

Three studies including 381 patients reported the incidence of 30-day minor bleeding. In contrast to 30-day major and lethal bleeding, no significant differences in the incidence of 30-day minor bleeding were found (OR 1.01, 95% CI 0.41–2.49, $p = 0.985$, $I^2 = 0\%$; Fig. 6).

Fig. 6. DAPT versus SAPT for 30-day minor bleeding.

Fig. 7. DAPT versus SAPT for 30-day major vascular complications.

Vascular Complications (Major)

Based on 4 studies incorporating 530 patients, the incidence of 30-day major vascular complications was found to be 22 cases out of 249 (8.8%) in the DAPT group and in 14 out of 281 (5.0%) in the SAPT group. DAPT had a trend towards increased risk for 30-day major vascular complications but did not reach statistical significance (OR 1.74, 95% CI 0.87–3.48, $p = 0.117$, $I^2 = 0\%$; Fig. 7).

Discussion

In our meta-analysis, we pooled all available studies to compare the outcome of two antiplatelet therapies. The major findings of the present meta-analysis are as follows. (1) There were no significant differences in 30-day, 6-month, and 1-year all-cause mortality between the DAPT and SAPT groups. (2) Regarding ischemic events such as MI and stroke, no significant differences between

the 2 groups were found. (3) Concerning bleeding events, we found that DAPT was associated with a 2.9-fold higher risk of 30-day major and lethal bleeding, 2.5-fold higher risk of 6-month major and lethal bleeding, and 2.7-fold higher risk of 1-year major and lethal bleeding. DAPT had a trend towards increased risk for periprocedural major and lethal bleeding. No significant differences in the incidence of 30-day minor bleeding were found. (4) Compared to SAPT, DAPT had a similar risk of 30-day major vascular complications.

We conducted a subgroup analysis between randomized studies and observational studies. No differences in 30-day major and lethal bleeding, all-cause mortality, stroke (major, minor, and TIA) between the 2 study types were noted. In the randomized studies, there was a trend towards increased risk for 30-day MI in the DAPT group, which was different from the observational studies. In our included studies, some patients used Corevalve devices (self-expandable valve), while some patients used SAPI-

EN or SAPIEN XT devices (balloon-expandable valve). We excluded 1 study because no detailed information was provided. We found that balloon-expandable valves had a similar risk for 30-day major and lethal bleeding, all-cause mortality, and stroke (major, minor, and TIA) compared to self-expandable valves, while discrepancy in 30-day MI between the two kinds of valve was found. Durand et al. [23], Poliacikova et al. [24], and Ussia et al. [26] gave their patients taking clopidogrel a 300-mg preload. According to the subgroup analysis, we found that using a clopidogrel preload had a similar risk for 30-day major and lethal bleeding, all-cause mortality, and stroke (major, minor, and TIA), but not for 30-day MI. In our included articles, 2 reported that no 30-day MI occurred, which may have affected the outcome of different subgroups.

ARTE (aspirin versus aspirin + clopidogrel following TAVI), a latest RCT, may provide powerful information [27]. In this study, patients treated with DAPT had significantly increased risks for 30-day and 3-month major and life-threatening bleeding. However, no significant discrepancies in the incidence of MI and stroke were found. Czerwińska-Jelonkiewicz et al. [28] found that aspirin after TAVI significantly reduced the risk of vascular complications and bleeding with no adverse impact on efficacy endpoints in comparison to other strategies. Sterling et al. [29] revealed a trend towards an increased incidence of major/life-threatening bleeding when comparing DAPT to SAPT, with similar rates of stroke and death. One study also discovered that after TAVI with a balloon-expandable prosthesis, SAPT significantly reduced the rates of major vascular complications and major bleeding without having an impact on valve function [30]. Other studies also revealed similar outcomes [31–33]. Therefore, SAPT may be a beneficial option for patients after TAVI, which is also supported by our findings.

Patients undergoing TAVI are usually elderly and may have comorbidities, meaning they may have more clinical symptoms. We considered some mild clinical symptoms, such as minor stroke, TIA, and minor bleeding, which are easily ignored. Compared to SAPT, DAPT had similar risks for these mild clinical symptoms.

In comparison with the studies by Gandhi et al. [34] and Aryal et al. [35], we found some further information, as follows: (1) no discrepancies in the incidence of 30-day minor stroke, TIA, minor bleeding, major vascular complications, 6-month and 1-year clinical outcomes were revealed; (2) the study type, valve, and use of a clopidogrel preload had little effect on 30-day stroke (major, minor,

and TIA), all-cause mortality, and major and lethal bleeding, but did impact on 30-day MI.

The current recommendations are based on the few studies that have reported the clinical outcomes of DAPT after TAVI [3], which were empirically determined. TAVI patients are generally old and in a poor condition, which may lead to more dangerous events. The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines did not recommend antiplatelet therapy for the TAVI [2]. The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommended 75 mg of clopidogrel daily for the first 6 months after TAVI in addition to life-long aspirin, 75–100 mg daily (class-recommendation, evidence level C) [3, 8].

Some studies found that patients undergoing TAVI had valve thrombosis, characterized by reduced leaflet motion, increased mean pressure gradients, and imaging abnormalities [13, 14, 36–38]. These studies demonstrated that oral anticoagulants have a protective effect. Compared to surgical valves, valve thrombosis occurred more commonly in transcatheter valves [37]. Some factors may be considered responsible for valve thrombosis, such as inadequate antiplatelet therapy, patients' hypercoagulability, atrial fibrillation, endothelial injury produced by balloon predilation, and valve malposition, etc. [13, 36–38]. Thus, we should evaluate the condition of patients and their valve function to decide whether oral anticoagulants are needed. According to the guidelines, for patients with a low risk of bleeding, anticoagulation with a vitamin K antagonist (VKA) is recommended for at least 3 months with an international normalized ratio of 2.5 [8]. Patients with valve thrombosis or atrial fibrillation may need anticoagulation with VKA therapy. Abdul-Jawad et al. [39] revealed that for patients with VKA therapy, concomitant antiplatelet therapy had no significant difference on stroke or death, while significantly increasing the incidence of major and lethal bleeding. However, the clinical outcomes remain unclear. Banerjee et al. [40] conducted a meta-analysis, finding little evidence of outcomes of patients on anticoagulation after TAVI. There is a need for wider collection of anticoagulation data.

Strokes or TIA are common complications of TAVI. The occurrence of clinical stroke after TAVI averages about 3% [41]. Patients undergoing TAVI may have a high risk for strokes associated with atrial fibrillation. Chakravarty et al. [37] found that subclinical leaflet thrombosis may be associated with an increased occurrence of stroke or TIA. The occurrence of stroke may lead to a bad prognosis. However, nowadays antithrombotic

therapies are not provided accurately. DAPT are recommended empirically, but the efficacy and safety still need further testing.

Bleeding complications are also commonly seen. Major bleeding complications are associated with high mortality and a poor prognosis [42]. The cause of bleeding may be mechanical. Catheters may damage access sites and arteries, which could lead to internal bleeding and vascular complications [41]. Also, patients may have some related diseases, such as arterial calcification, anemia, or gastrointestinal diseases, etc. [43]. Some studies found that patients treated with clopidogrel showed a wide variability in platelet reactivity (PLTR) [44]. One study demonstrated that TAVI-related bleeding occurred during the procedure or in the early postprocedural period, and premedication with clopidogrel enhanced response to clopidogrel early after TAVI, and a significant periprocedural drop in clopidogrel PLTR are considered to increase the risk of TAVI-related bleeding [45]. Hence, PLTR may affect bleeding and ischemic events. Furthermore, patients undergoing TAVI are generally treated with DAPT, which may increase the risk of bleeding. Antiplatelet therapy is necessarily to decrease the risk of ischemic events, meaning bleeding is sometimes inevitable. Bleeding is acceptable, but the most important thing is that it should be controlled well. If bleeding risks becoming lethal, the therapy should be adjusted. How to balance ischemic and bleeding events is still unclear, with further research being needed.

Our meta-analysis reported early (30 days, periprocedure) and late (6 months, 1 year) ischemic and bleeding events. The results provide clinical doctors with the different outcomes of 2 therapies, and open further areas of study for antiplatelet therapy following TAVI. Our study suggests that, when compared to SAPT, DAPT had significantly increased risks for 30-day, 6-month, and 1-year major and lethal bleeding. However, there were no significant differences in MI, stroke, all-cause mortality, minor bleeding, and vascular complications (major) between DAPT and SAPT. SAPT may be a beneficial option. Thus, the efficacy and safety of SAPT requires further research. Regarding patients with comorbidities, the antithrombotic therapy after TAVI also needs more research. One study designed to try to solve these problems is investigating antiplatelet therapy for patients undergoing TAVI (POPular-TAVI, NCT02247128). The POPular-TAVI trial is a multicenter open-label RCT which aims to compare the 1-year safety endpoint and net clinical benefit endpoint between aspirin and clopidogrel (cohort A), aspirin monotherapy (cohort A), oral anticoagulation

and clopidogrel (cohort B), and oral anticoagulation monotherapy (cohort B). It is anticipated that the results of this trial will provide additional information.

Limitations

There are several limitations to our study. Firstly, 7 studies including 1,445 patients were enrolled, which is a small number, meaning the efficacy and safety cannot be evaluated with sufficient power. TAVI is a new procedure that is unavailable or limited in many hospitals. Secondly, considering that only 2 or 3 studies reported late (≥ 6 months including early) clinical outcomes, it was not possible to meaningfully evaluate the mid-term outcomes of the 2 therapies. Thirdly, the procedural approaches reported were different, which may have influenced the clinical outcomes. When the included studies did not report the detailed relevant information, we were unable to perform a subgroup analysis. Lastly, because the patients with atrial fibrillation need oral anticoagulation, we excluded these patients. Although these patients represent a large proportion of those undergoing TAVI, the antithrombotic therapy for these patients is still unclear. It is hoped that the POPular-TAVI trial will offer additional information.

Conclusion

Compared to SAPT, DAPT appeared to have a similar incidence of MI, stroke, and all-cause mortality, but higher risk for early and mid-term major and lethal bleeding. SAPT may be a beneficial option for patients after TAVI. Further large-scale RCTs are needed to enhance the evidence for antithrombotic strategies in patients undergoing TAVI.

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