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Antithrombotic strategies after transcatheter aortic valve implantation: Insights from a network meta-analysis

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Objectives: We aimed to investigate the efficacy and safety of different antithrombotic strategies in patients undergoing transcatheter aortic valve implantation (TAVI) using network meta-analyses.

Background: Meta-analyses comparing single antiplatelet therapy (SAPT) vs. dual antiplatelet therapy (DAPT), ± oral anticoagulant (OAC) was conducted to determine the appropriate post TAVI antithrombotic regimen. However, there was limited direct comparisons across the different therapeutic strategies.

Methods: MEDLINE and EMBASE were searched through December 2018 to investigate the efficacy and safety of different antithrombotic strategies (SAPT, DAPT, OAC, OAC + SAPT, and OAC + DAPT) in patients undergoing TAVI. The main outcome were all-cause mortality, major or life-threatening bleeding events, and stroke.

Results: Our search identified 3 randomized controlled trials and 10 nonrandomized studies, a total of 20,548 patients who underwent TAVI. All OACs were vitamin K antagonists. There was no significant difference on mortality except that OAC + DAPT had significantly higher rates of mortality compared with others ($p < .05$, $I^2 = 0\%$). SAPT had significantly lower rates of bleeding compared with DAPT, OAC +SAPT, and OAC+DAPT (hazard ratio [HR]: 0.59 [0.46-0.77], $p < .001$, HR: 0.58 [0.34-0.99], $p = .045$, HR: 0.41 [0.18-0.93], $p = .033$, respectively, $I^2 = 0\%$). There was no significant difference on stroke among all antithrombotic strategies.

Conclusion: Patients who underwent TAVI had similar all-cause mortality rates among different antithrombotic strategies except OAC+DAPT. Patients on SAPT had significantly lower bleeding risk than those on DAPT, OAC + SAPT, and OAC + DAPT. Our results suggest SAPT is the preferred regimen when there is no indication for DAPT or OAC. When DAPT or OAC is indicated, DAPT + OAC should be avoided.

Abbreviations: CI, confidential interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; NOAC, novel oral anticoagulant; OAC, oral anticoagulant; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonist.

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KEYWORDS
anticoagulant, antiplatelet, antithrombotic, network meta-analysis, transcatheter aortic valve implantation

1 | INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established treatment for severe aortic stenosis, especially for patients with intermediate or high surgical risk.[1,2] The current guidelines recommend dual antiplatelet therapy (DAPT) for 6 months after TAVI and anticoagulation with a vitamin K antagonist (VKA) for 3 months to prevent valve thrombosis, but both are Class IIb recommendations.[3] Recently, a prospective randomized trial (GALILEO), comparing rivaroxaban plus aspirin versus DAPT study was stopped early for increased risk of thromboembolic event, all cause death, and bleeding in the rivaroxaban plus aspirin arm.[4,5] Previous meta-analyses assessed the safety and efficacy of single antiplatelet therapy (SAPT) versus DAPT, ± oral anticoagulation (OAC) therapy, and showed mixed results.[6,7] A comprehensive analysis with a network meta-analysis could compare different antithrombotic strategies and provides valuable insights into this important and common clinical question since the current evidence which supports the guidelines is limited.[3,8] The aim of this study was to investigate the risk and benefit of different antithrombotic regimens for patients undergoing TAVI.

2 | METHODS

All the studies investigating the impact of antithrombotic strategy on survival, bleeding event, and stroke after TAVI were identified using a 2-level search strategy. First, databases including MEDLINE and EMBASE were searched through December 29th, 2018 using Web-based search engines by a medical librarian with expertise in conducting searches for systematic reviews (Figure 1). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Search terms included transcatheter aortic valve implantation or transcatheter aortic valve replacement, or TAVI or TAVR; single antiplatelet therapy or SAPT or dual antiplatelet therapy or DAPT or antiplatelet; anticoagulation or anticoagulant or antithrombotic or vitamin K antagonist or VKA or Coumadin or Warfarin or novel oral anticoagulant or NOAC or direct oral anticoagulant or DOAC or Dabigatran or Apixaban or Rivaroxaban or Edoxaban. Two independent and blinded authors (T.K. and H.T.) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria. When a consensus was not reached between the two authors, a third author (K.H.), who is an expert in the field of TAVI,[9] was consulted to reach a decision. There was no language restriction. Reference lists of included studies for meta-analysis were reviewed to minimize missing relevant studies. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[10]

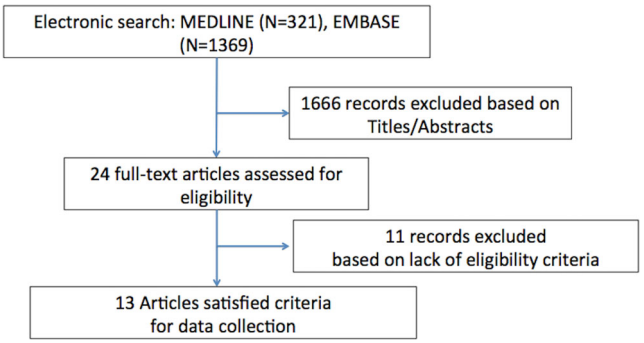

FIGURE 1 Study selection

Studies included met the following criteria: the study was peer-reviewed by journals, the design was a comparative study of patients with different antithrombotic strategies; SAPT, DAPT, oral anticoagulant (OAC), OACSAPT (OAC plus SAPT), Triple (OAC plus DAPT), the study had at least one of all cause mortality, major bleeding and/or life-threatening bleeding, and stroke, with a follow-up period of minimum 3 months. All endpoints need to be defined with Valve Academic Research Consortium or Valve Academic Research Consortium-2.[11,12]

For each study, data regarding events number was abstracted. If propensity score matching analysis was performed, we used data from the propensity score matched cohort. If adjusted hazard ratios (HRs) were reported, we used adjusted hazard ratios. We performed network meta-analysis using "netmeta" 3.3.2 package (R Foundation for Statistical Computing, Vienna, Austria).[13] Within the framework, I^2 and the Q statistics, which represents the proportion of total variation in study estimates that is due to heterogeneity, were used to quantify heterogeneity.[14,15] The I^2 statistic represents the proportion of variability that is not attributable to chance. I^2 values over 50% indicate substantial heterogeneity. The Q statistics is the sum of a statistic for heterogeneity, and a statistic for inconsistency, which represents the variability of treatment effect between direct and indirect comparisons at the meta-analytic level.[16] We used the random-effects model for the analysis. The treatments were ranked using the P-score, which

TABLE 1 Baseline characteristics

			Study design	Patient number					Age					Men				
Study	Ref. no	f/u duration		SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple
Sherwood et al	8	1 year	Multicenter registry	3,148	13,546				84 [78–88]	84 [78–88]				50.4%	51.8%			
Varshney et al	18	2 year	Single center retrospective				88	20				81 ± 7.9	80.9 ± 6.3				60.2%	60%
D'Ascenzo et al	19	45 months	Multicenter registry PS matching	605	605	105	105		81 ± 4	81 ± 5	81 ± 5	82 ± 6		37%	38%	42%	39%	
Rodes-Cabau et al	20	3 months	Multicenter, RCT	111	111				79 ± 9	79 ± 9				53.2%	63.1%			
Holy et al	21	6 months	Single center retrospective		315	199				80.4 ± 7	80.6 ± 5.7				42.4%	46%		
Gesis et al	22	6 months	Single center retrospective			77	41	49			83.6 ± 4.7	82.7 ± 4.8	82.3 ± 6.0			40.3%	41.5%	53.1%
Abdul-Jaward et al	23	13 months	Multicenter registry			101	463	57			n/a	n/a	n/a			n/a	n/a	n/a
Stabile et al	24	6 months	Single center, RCT	60	60				81.1 ± 4.8	80.2 ± 5.7				40.0%	33.3%			
Poliacikova et al	25	6 months	Single center retrospective	59	55	18			82 ± 6.9	81.6 ± 6.3	80.3 ± 4.5			46.2%	44.8%	54.5%		
Figini et al	26	11 months	Single center retrospective		300		43			79 ± 8		80 ± 6			52%		49%	
Ussia et al	27	6 months	Single center, RCT	39	40				81 ± 4	80 ± 6				41%	50%			
Vavuranakis et al	28	23.4 months	Single center retrospective, PS matching		20		20			80.6 ± 3.7		80.2 ± 5.4			20%		20%	
Ichibori et al	29	12 months	Multicenter registry, PS matching	44	44				84 ± 6	84 ± 5				35.9%	36.4%			

Abbreviations: DAPT, dual antiplatelet therapy; OAC, oral anticoagulant, OACSAPT, oral anticoagulant plus single antiplatelet therapy; PS, propensity score; RCT, randomized controlled trial; SAPT, single antiplatelet therapy; Triple, oral anticoagulant plus dual antiplatelet therapy.

TABLE 2 Baseline characteristics

	Coronary artery disease					Cerebrovascular disease					Peripheral artery disease					Atrial fibrillation				
Study	SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple
Sherwood et al	53.3%	64.6%				9.8%	10.2%				22.3%	25.2%				n/a	n/a			
Varshney et al				n/a	n/a				18.2%	20%				21.6%	30%				81.8%	70%
D'Ascenzo et al						7.0%	8.0%	27%	29%		37%	36%	38%	41%		10%	12%	60%	63%	
Rodes-Cabau et al	n/a	n/a				n/a	n/a				20.0%	25.2%				n/a	n/a			
Holy et al		68.5%	63.6%				n/a	n/a				14.6%	16.2%				10.5%	69.2%		
Gesis et al			n/a	n/a	n/a			11.7%	17.1%	18.4%			n/a	n/a	n/a			93.5%	100%	91.8%
Abdul-Jaward et al			n/a	n/a	n/a			n/a	n/a	n/a			n/a	n/a	n/a			n/a	n/a	n/a
Stabile et al	n/a	n/a				n/a	n/a				n/a	n/a				n/a	n/a			
Poliacikova et al	54.9%	63.8%	45.5%			n/a	n/a	n/a			n/a	n/a	n/a			11%	27.6%	90.9%		
Figini et al		46%		26%			16%		5.0%			31%		26%			n/a		n/a	
Ussia et al	n/a	n/a				10%	5.0%				10%	8.0%				n/a	n/a			
Vavuranakis et al		60%		35%			5.0%		5.0%			n/a		n/a			0.0%		100%	
Ichibori et al	38.6%	45.5%				27.3%	20.5%				n/a	n/a				n/a	n/a			

Abbreviations: DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; OACSAPT, oral anticoagulant plus single antiplatelet therapy; SAPT, single antiplatelet therapy; Triple, oral anticoagulant plus dual antiplatelet therapy.

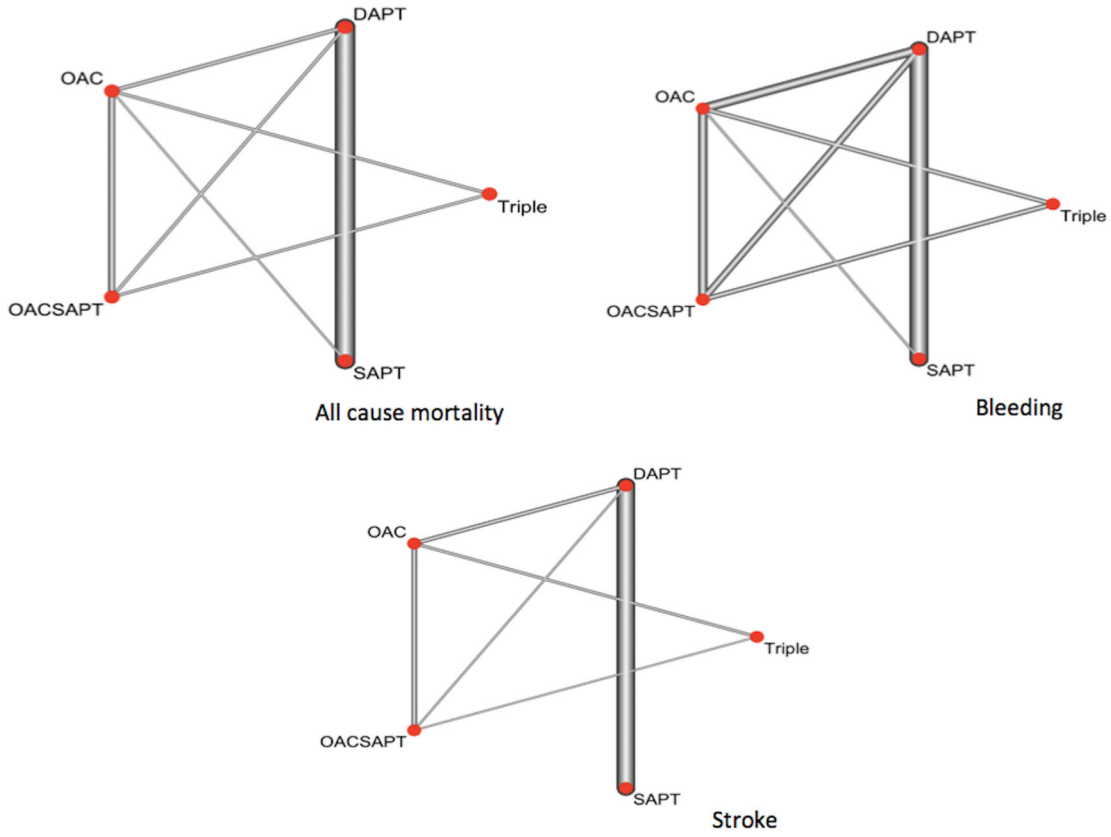

FIGURE 2 Antithrombotic strategies in the network. The width of connecting lines between antithrombotic strategies reflects the number of studies available for each comparison

was considered 100% when a treatment was certain to be the best and 0% when a treatment was certain to be the worst.[17]

As sensitivity analyses, we conducted analyses (a) excluding the largest study (*N* = 16,694, 81.2%) from the main analysis,[8] (b) limiting to randomized controlled trials and propensity score matched analyses, (c) comparing short term follow up period ≤1 year and long term follow up period ≥1 year.

3 | RESULTS

Our search identified 13 eligible studies,[8,18–29] enrolling a total of 20,548 TAVI patients, which included eight studies investigating patients on OAC (*N* = 1,386, 6.7%). There were 3 randomized controlled trials, 3 propensity score matched analyses, and 7 retrospective cohort studies (including four studies with adjusted HR). Patients' baseline characteristics are summarized in Tables 1 and 2. Studies using OAC (OAC, OACSAPT, and Triple) had higher percentages of patients with atrial fibrillation. All OACs were VKA and all P2Y12 inhibitors were clopidogrel. The characteristics of the network are shown in Figure 2. Briefly, 18, 16, and 11 armed comparisons were used for survival, bleeding, and stroke, respectively. Each study endpoint is shown in Table 3.

Figure 3 shows a network meta-analysis for all cause mortality. There were no significant heterogeneity (I^2 = 0%, p = .91), and inconsistency (p = .97). P-scores were 89.7% (DAPT), 73.6% (SAPT), 51.4% (OAC + SAPT), 35.2% (OAC), and 0.03% (Triple). There was no significant difference in mortality among SAPT, DAPT, OAC, and OACSAPT but Triple had significantly higher rates of mortality compared with other antithrombotic strategies (p < .05 for all comparisons).

Figure 4 shows a network meta-analysis for major and/or life-threatening bleeding events. There was no significant heterogeneity (I^2 = 0%, p = .71), and inconsistency (p = .27). P-scores were 93.7% (SAPT), 77.3% (OAC), 35.3% (DAPT), 33.9% (OACSAPT), and 9.8% (Triple). SAPT had significantly lower rates of bleeding compared with DAPT, OAC + SAPT, and Triple (HR [95% confidence interval or CI]: 0.59 [0.46–0.77], p < .001, HR [95% CI]: 0.58 [0.34–0.99], p = .045, HR [95% CI]: 0.41 [0.18–0.93], p = .033, respectively).

Figure 5 shows a network meta-analysis for stroke. There was no significant heterogeneity (I^2 = 0%, p = .72), and inconsistency (p = .78). P-scores were 64.6% (OAC), 62.9% (SAPT), 58.0% (OACSAPT), 47.1% (DAPT), and 17.3% (Triple). There was no significant difference on stroke among all antithrombotic strategies.

The sensitivity analysis excluding the largest study[8] showed similar results of all-cause mortality, bleeding, and stroke from the main analysis (Supplemental figures 1–3). The second sensitivity analysis limiting to 3 randomized controlled trials and 3 propensity score matched analyses (no data of Triple therapy, and network meta-analysis regarding stroke could not be performed due to a few studies

TABLE 3 Outcomes of all studies

	Death					Major bleeding and/or life threatening bleeding						Stroke						Myocardial infarction				
Study	SAPT	DAPT	OAC	OACSAPT	Triple	Definition	SAPT	DAPT	OAC	OACSAPT	Triple	Definition	SAPT	DAPT	OAC	OACSAPT	Triple	SAPT	DAPT	OAC	OACSAPT	Triple
Sherwood et al	12.6%	10.6%				Major[b]	2.3%	2.5%				Infarction	3.5%	3.4%				1.8%	2.1%			
Varshney et al				32%	61%	Major[b]				18%	29%	Infarction/hemorrhagic				n/a	n/a				n/a	n/a
D'Ascenzo et al	26%	27%	37.1%	34.3%		Major[b]	1.6%	4.0%	2.9%	4.8%		Infarction/hemorrhagic	0.7%	1.5%	2.9%	3.8%		n/a	n/a	n/a	n/a	
Rodes-Cabau et al	3.6%	6.3%				Major or LTB[b]	3.6%	10.8%				Infarction	0.9%	2.7%				0.9%	3.6%			
Holy et al		7.9%	12.0%			Major or LTB[b]		17.5%	16.5%			Infarction/hemorrhagic		4.4%	4.0%				1.6%	0.5%		
Gesis et al			6.5%	12.2%	22.5%	Major or LTB[b]			0.0%	7.3%	8.2%	Infarction/hemorrhagic			0%	2.4%	8.2%			n/a	n/a	n/a
Abdul-Jaward et al			22.8%	19.2%	19.3%	Major or LTB[b]			14.9%	25.0%	17.5%	Ischemic			5.0%	5.2%	7.0%			0.0%	2.8%	5.3%
Stabile et al	5.0%	5.0%					n/a	n/a					n/a	n/a				n/a	n/a			
Poliacikova et al	6.8%	10.9%	11.1%			Major or LTB[a]	8.5%	18.2%	5.6%			Infarction/hemorrhagic	3.4%	3.6%	0.0%			0.0%	1.8%	0.0%		
Figini et al		15.5%		16.3%		Major[a]		33.1%		25.6%		Ischemic		2.7%		2.4%			2.0%		2.4%	
Ussia et al	13%	10%				Major[a]	3.0%	5.0%				Infarction/hemorrhagic	5.0%	3.0%				0.0%	3.0%			
Vavuranakis et al		15%		20%		Major[a]		20%		10%		Infarction/hemorrhagic		n/a		n/a			n/a		n/a	
Ichibori et al	n/a	n/a				Major[b]	4.6%	18.2%					n/a	n/a				n/a	n/a			

Abbreviations: DAPT, dual antiplatelet therapy; LTB, life threatening bleeding; OAC, oral anticoagulant; OACSAPT, oral anticoagulant plus single antiplatelet therapy; SAPT, single antiplatelet therapy; Triple, oral anticoagulant plus dual antiplatelet therapy.

[a]Definition of VARC (Valve Academic Research Consortium) criteria.

[b]Definition of VARC (Valve Academic Research Consortium)-2 criteria.

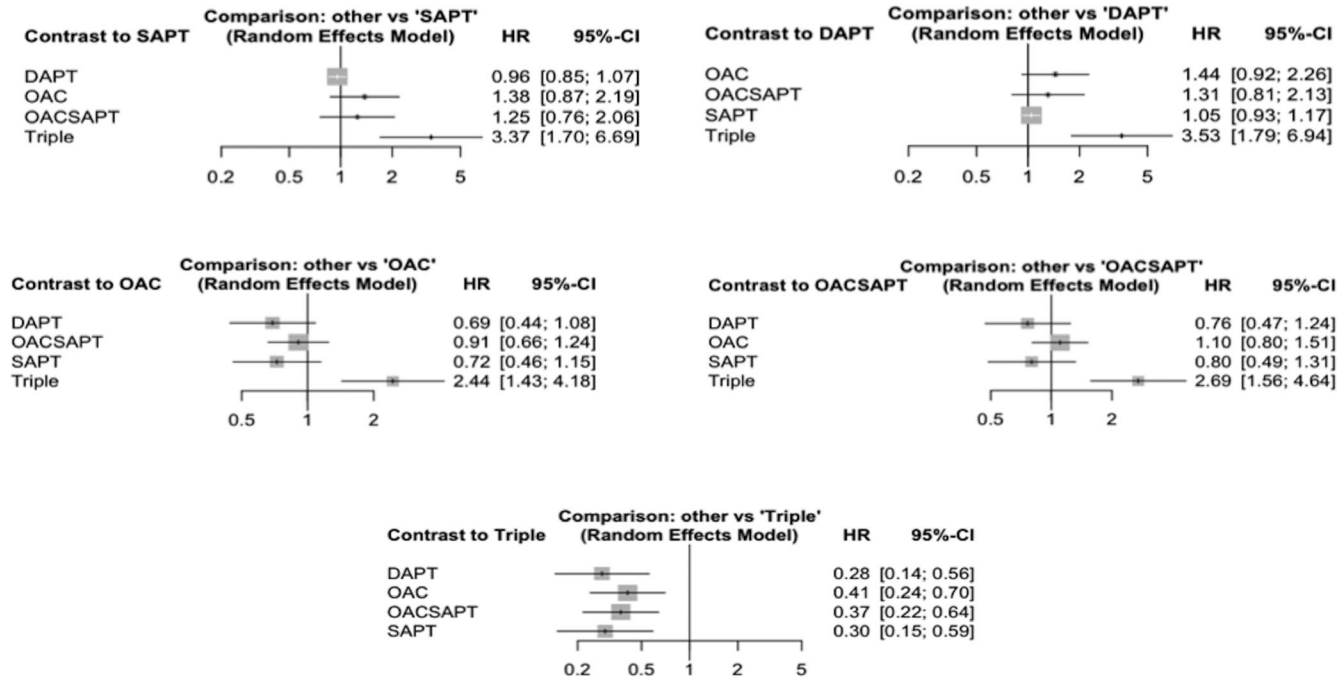

FIGURE 3 Forest plots among treatments for mortality (random-effects model)

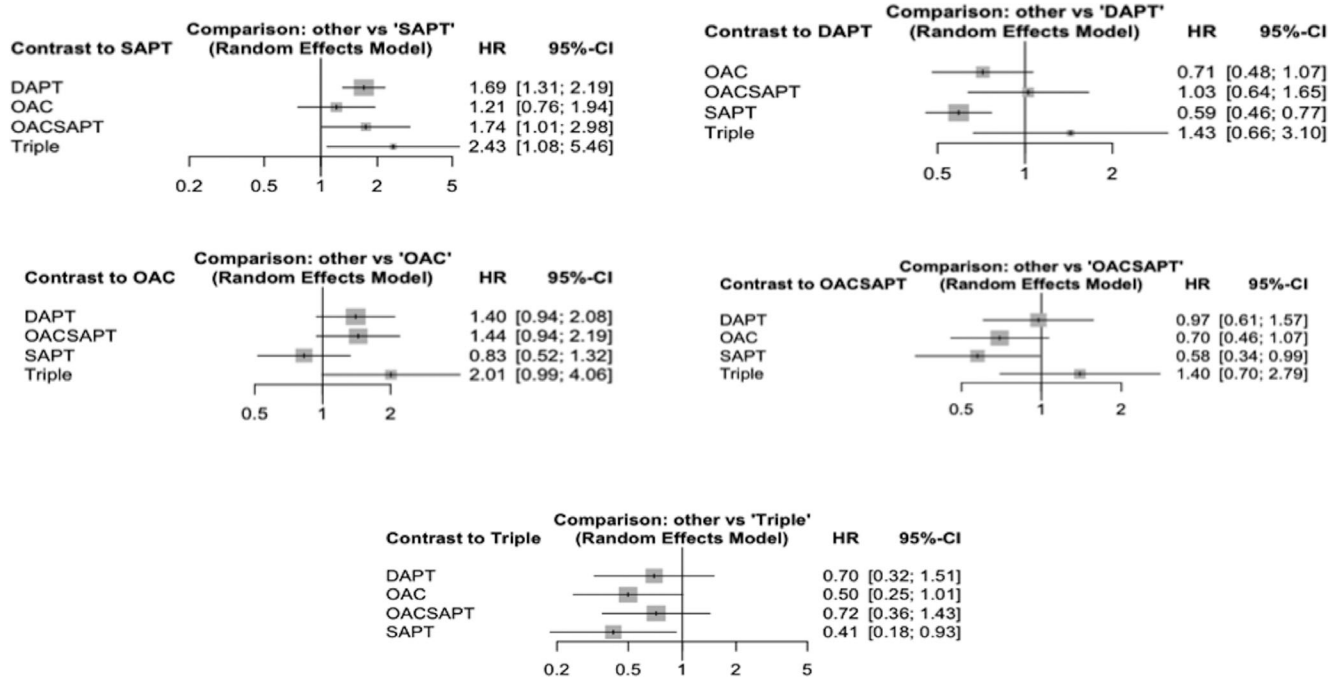

FIGURE 4 Forest plots among treatments for bleeding (random-effects model)

available) showed no survival differences among antithrombotic strategies and SAPT had significantly lower rates of bleeding compared with DAPT (Supplemental figures 4, 5). The third sensitivity analysis with short term follow up period ≤1 year (nine studies) showed no different outcomes in all-cause mortality and stroke from the main analysis. SAPT had significantly lower rates of bleeding compared with DAPT (Supplemental figures 6–8). The sensitivity analysis with long term follow up period ≥1 year (nine studies) showed Triple had significantly higher mortality than OAC and OACSAPT, and SAPT had significantly lower rates of bleeding compared with DAPT, and OAC had significantly lower rates of bleeding compared with OACSAPT and Triple (Supplemental figures 9-11).

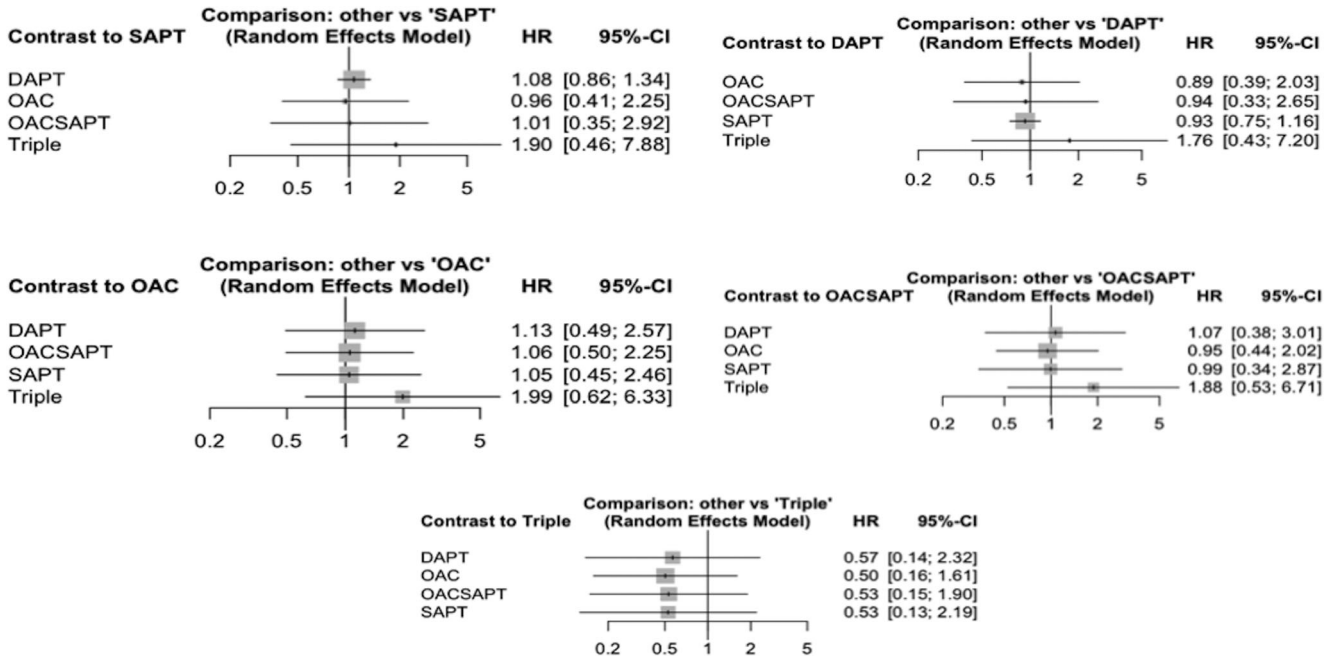

FIGURE 5 Forest plots among treatments for stroke (random-effects model)

4 | DISCUSSION

Our study showed that there was no significant difference in mortality among SAPT, DAPT, OAC, and OAC + SAPT. Triple had significantly higher rates of mortality compared with other antithrombotic strategies. SAPT had significantly lower rates of bleeding compared with DAPT, OACSAPT, and Triple. There was no significant difference on stroke among all antithrombotic strategies, but OAC had the favorable outcome on stroke according to P-score. Our study will provide better antithrombotic strategies for patients who undergo TAVI.

Previous meta-analyses showed mixed results.[6,7,30,31] Some meta-analyses showed higher bleeding rates with DAPT than SAPT, but similar mortality.[6,30] Another meta-analysis showed lower rates of bleeding with regimens including VKA than without.[7] In our network meta-analyses, we included 13 studies, which is the largest compared to other meta-analyses, and we showed no significant difference in mortality among SAPT, DAPT, OAC, and OAC + SAPT. Top three ranks in favorable outcomes on survival were DAPT, SAPT, and OAC. SAPT had significantly lower rates of bleeding compared with DAPT, OACSAPT, and Triple. Our network meta-analyses has the advantages to assess outcomes of regimens including OAC with direct and indirect comparisons because only a small proportion of people were treated with OAC (6.2%), with minimal heterogeneity. GALILEO trial comparing Rivaroxaban plus aspirin and DAPT study was stopped early for increased risk of thromboembolic event, all cause death, and primary bleeding.[4,5] Although ATLANTIS trial comparing Apixaban to current standard of care after TAVI will find out the best antithrombotic strategy,[32] we might suggest that SAPT is the preferred regimen when there is no indication for DAPT or OAC post-TAVI because of low bleeding rates. When DAPT or OAC is indicated, Triple should be avoided or duration should be minimized to avoid bleeding events. We might also suggest OAC can be an option more than a year after TAVI since sensitivity analysis limiting studies with long term follow up period ≥1 year showed OAC had significantly lower rates of bleeding compared with OACSAPT and Triple if OAC is indicated.

The rate of stroke was similar across different treatment regimens, but OAC had the favorable outcome on stroke according to P-score. Given the different pharmacological mechanism between VKA and novel oral anticoagulant (NOAC), the effect of thromboembolic prevention after TAVI could be different between these OACs. Previous data showed NOAC had higher bleeding and thromboembolic events than VKA in mechanical valve recipients.[33] Another study suggested that VKA was more effective in suppressing coagulation activation because it inhibits the activation of both tissue factor-induced coagulation inhibiting factor VII and contact induced coagulation pathway by inhibiting factor IX, factor X, and thrombin in the common pathway.[34] These factors may explain the favorable trends of stroke in OAC and OACSAPT arms compared with DAPT, which is different from the GALILEO trial.[5]

Our results showed that Triple had the worst outcomes on survival, bleeding, and stroke according to P-score. TAVI candidates often have history with atrial fibrillation and high stroke risk, and therefore not infrequently have indications of OAC.[1,2] In addition, when new-onset atrial fibrillation occurs, there will be further increase in possible OAC candidates. Because the current guideline recommends DAPT for 6 months post-TAVI, clinicians often have to decide whether to prescribe Triple therapy in these patients. Our study suggests that OACSAPT conferred similar mortality, bleeding, and stroke as compared with DAPT and therefore OACSAPT could be an option in those who may need Triple therapy. Although major adverse

cardiac event rates were not significantly different in DAPT and Triple for patients with atrial fibrillation undergoing percutaneous coronary intervention,[35] we consider that Triple should be avoided if possible and the duration should be minimized for post-TAVI patients when Triple therapy is clinically indicated.

The present analysis has several limitations. First, there were only few available data on anticoagulation therapy after TAVI. Therefore, we included observational studies with consequent selection and ascertainment bias. This may potentially explain the reason for higher mortality with Triple therapy (high percentages of atrial fibrillation) since atrial fibrillation could influence mortality, stroke, and bleeding.[36,37] However, sensitivity analysis restricted to randomized controlled trials and propensity score matched studies showed no different in mortality among SAPT, DAPT, OAC, and OACSAPT. Moreover, our study is the largest meta-analysis to examine the antithrombotic strategy for TAVI patients and we performed a network meta-analysis to provide both direct and indirect comparisons of different antithrombotic strategies.[38] Secondly, we need to address the difference of baseline characteristics on each antithrombotic strategy. In our study, patients on DAPT had more likely to have coronary artery disease,[8] and patients on OAC had higher proportions of atrial fibrillation and prior cerebrovascular disease.[19] Despite using the data of propensity score matched analysis or adjusted HR if available, these confounding factors could not be eliminated, which might affect our results. Finally, since we did not have access to individual patients' data, our data should be interpreted carefully.

5 | CONCLUSION

Patients who underwent TAVI had similar all-cause mortality rate among different antithrombotic strategies except that Triple conferred higher all-cause mortality risk. Patients on SAPT had significantly lower bleeding risk than those on DAPT, OAC + SAPT, and Triple. Our results suggest that SAPT is the preferred regimen when there is no indication for DAPT or OAC post-TAVI. When DAPT or OAC is indicated, Triple should be avoided or duration should be minimized to avoid bleeding events.

DISCLOSURE

Dr Hayashida is a clinical proctor for Edwards Lifescience. Dr Bangalore is an advisory board of Abbott Vascular, Biotronik, Amgen. Dr Bangalore has honoraria from Pfizer, Merck, AstraZeneca.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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