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ΠΜΣ «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική
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Perform a meta-analysis of randomized control trials (RCTs) for anticoagulant and antiplatelet treatment in Transcatheter Aortic Valve Replacement (TAVR) published from 2011 to 2020

Μετα-ανάλυση τυχαιοποιημένων μελετών που αφορούν την αντιπηκτική και αντιαιμοπεταλιακή αγωγή σε ασθενείς που υποβάλλονται σε διαδερμική αντικατάσταση της αορτικής βαλβίδος.

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Perform a meta-analysis of randomized control trials (RCTs) for anticoagulant and antiplatelet treatment in Transcatheter Aortic Valve Replacement (TAVR) published from 2011 to 2020

Abstract

INTRODUCTION Antithrombotic and antiplatelet treatment in post-TAVR patients is a controversial issue.

AIM The purpose of this meta-analysis is to investigate the current strategy of antithrombotic and antiplatelet treatment in patients undergoing TAVR with or without previous indication for oral anticoagulation (OAC).

METHODS Only randomized control (RCTs) trials were included and quantitative meta-analysis was performed only for patients without indication for OAC, due to lack of RCTs in patients with indication for OAC. Thus, we assessed the efficacy and safety of single antiplatelet (SAPT) treatment versus dual antiplatelet treatment (DAPT). We used a meta-analytic method with Mantel-Hænszel to calculate the odds ratio (OR) and 95% confidence interval (C.I).

RESULTS Our analysis included four studies with a total of 1086 patients (541 SAPT and 545 DAPT). Life-threatening bleeding was similar between SAPT and DAPT while patients receiving SAPT had fewer major bleeding events than patients receiving DAPT, OR=0.40 , 95% C.I [0.21, 0.75]. Major stroke , myocardial infarction and mortality was also comparable between the two groups while the combine outcome of mortality, life- threatening and major bleeding found to be more often in patients receiving DAPT ,OR=0.65 ,95% C.I [0.46-0.91].

CONCLUSION To sum up, SAPT provided better safety without adding incremental risk in efficacy compared to DAPT.

Περίληψη

ΕΙΣΑΓΩΓΗ Η αντιπηκτική και αντιαιμοπεταλιακή στρατηγική μετά την διαδερμική αντικατάσταση της αορτικής βαλβίδας αποτελεί ζήτημα υπό διερεύνηση

ΣΤΟΧΟΙ Ο στόχος της εν λόγο μέτα-ανάλυσης είναι να συνθέσει και να εκτιμήσει την τρέχουσα αντιπηκτική και αντιαιμοπεταλιακή στρατηγική σε ασθενείς που υποβάλλονται σε διαδερμική αντικατάσταση της αορτικής βαλβίδας. Περιλαμβάνοντας τόσο αυτούς με προηγούμενη ένδειξη για αντιπηκτική αγωγή αλλά και αυτούς χωρίς πρωτύτερη ένδειξη αντιπηκτικής αγωγής. Βασικός γνώμονας της μελέτης ήταν να συμπεριλάβει μόνο τυχαιοποιημένες μελέτες. Ως εκ τούτου ποσοτική μέτα-ανάλυση έγινε μόνο σε ασθενείς χωρίς πρωτύτερη ένδειξη αντιπηκτικής αγωγής διότι μόλις μία τυχαιοποιημένη μελέτη βρέθηκε που να αφορά ασθενείς με προηγούμενη ένδειξη αντιπηκτικής αγωγής.

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ΜΕΘΟΔΟΛΟΓΙΑ Εκτιμήσαμε την αποτελεσματικότητα και την ασφάλεια της μονής και της διπλής αντιαιμοπεταλιακής αγωγής. Χρησιμοποιώντας την μετα-αναλυτική μέθοδο των Mantel-Hænszel υπολογίσαμε τα odds ratio (OR) και τα 95% διαστήματα εμπιστοσύνης (δ.ε).

ΑΠΟΤΕΛΕΣΜΑΤΑ Η μελέτη συμπεριέλαβε 1086 ασθενείς (541 SAPT and 545 DAPT). Η απειλητική για την ζωή αιμορραγία ήταν όμοια κατανεμημένη μεταξύ των δύο θεραπειών ενώ η μεγάλη αιμορραγία φάνηκε ότι ήταν συχνότερη κατά στατιστικά σημαντικό τρόπο στους ασθενείς που ελάμβαναν διπλή αντιαιμοπεταλιακή αγωγή OR=0.40 ,95% C.I [0.21,0.75]. Το ισχαιμικό αγγειακό εγκεφαλικό επεισόδιο το έμφραγμα του μυοκαρδίου και η θνητότητα δεν διέφεραν μεταξύ των δύο θεραπειών ενώ το σύνθετο καταληκτικό σημείο που περιλαμβάνει την μεγάλη αιμορραγία σε συγκερασμό με την απειλητική για την ζωή αιμορραγία και την θνητότητα αποδείχτηκε κατά στατιστικά σημαντικό τρόπο πιο συχνό σε ασθενείς που ελάμβαναν διπλή αντιαιμοπεταλιακή αγωγή OR=0.65 ,95% C.I [0.46-0.91].

ΣΥΜΠΕΡΑΣΜΑΤΑ Εν κατακλείδι η απλή αντιαιμοπεταλιακή αγωγή ήταν πιο ασφαλής χωρίς ωστόσο να υστερεί στην αποτελεσματικότητα σε σχέση με την διπλή αντιαιμοπεταλιακή αγωγή.

Introduction

Transcatheter aortic valve replacement (TAVR) is widely accepted as an alternative to surgical valve replacement for the treatment of severe aortic stenosis. In elderly patients with high operative risk, who are unsuitable for surgical aortic valve replacement, TAVR is the therapy of choice [1][2]. In patients with moderate to high surgical risk TAVR it is considered to be a reasonable alternative [2][3] , while non-inferiority has recently proved in published trials for low risk patients [4][5].

Despite the improvement in the efficacy and safety of the procedure over the years, the prevalence of thromboembolic and bleeding complications after TAVR remains, affecting morbidity and mortality. The optimal strategy of anti-thrombotic treatment remains controversial because current guidelines are based on consensus of experts and small randomized control trials. European guidelines recommend for the first 3-6 months the use of DAPT with aspirin and clopidogrel, followed by lifelong single antiplatelet therapy (SAPT) as the strategy for patients without indication for oral anticoagulation (OAC), whilst SAPT monotherapy may be considered for patients with high bleeding risk. On the other hand US guidelines advocate DAPT with clopidogrel for the first 6 months in addition to lifelong aspirin, whilst OAC with a vitamin K antagonist (VKA) is recommended for at least 3 months after TAVR for low risk of bleeding patients in order to diminish the risk of valve thrombosis. Both guidelines agree in proposing lifelong OAC for patients with other indication for OAC, and additional antiplatelet therapy in these patients is under discussion. [6][7]

Previous studies and meta-analysis have addressed this topic, however the low cohort number of randomized controlled studies and the observational design of the majority of

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the studies , create a difficult condition making it unable to draw safe conclusions. Therefore we performed an up-dated meta-analysis using only the randomized control trials, to address this clinically important issue.

Methods and materials

Data source and strategy

We conduct a systematic literature search using PUBMED, EMBASE and ClinicalTrials.gov from 2011 to 2020, searching for randomized control trials. The search term was; aortic valve AND (percutaneous OR transcatheter OR transluminal OR transarterial OR transapical OR transaortic OR transcarotid OR transaxillary OR transsubclavian OR transiliac OR transfemoral OR transiliofemoral OR "Transcatheter Aortic Valve Replacement"[Mesh]) AND ("Platelet Aggregation Inhibitors"[Mesh] OR antiplatelet OR antithrombotic OR aspirin OR clopidogrel OR ticagrelor). Conference abstracts were excluded and only peer-reviewed publish-data in scientific journals were included. Firstly, we screened the title and the abstract of the results in order to find out if they contain relevant data or not. Then we download the full version of the screened articles and we reviewed them. After that, we used the inclusion and exclusion criteria to decide which manuscripts will be included in our meta-analysis. We also screened the references in every manuscript to investigate for relevant articles.

Inclusion and exclusion criteria

Inclusion criteria were 1: randomized clinical trials investigating the antithrombotic treatment in patients after TAVR 2: at least one of the clinical outcome reported and absolute number in both arms were available for extraction. 3: Clinical outcomes were reports according to the Valve Academic Research Consortium criteria [8]

Exclusion criteria 1: observational studies.

Outcomes

We divide outcomes on safety and efficacy endpoints. In the leg of safety, life threatening-bleeding, major bleeding, the composite endpoint of major bleeding and life threatening bleeding, major vascular complications were concluded. In the leg in efficacy, major stroke myocardial infarction (MI) and 3 to 6 months mortality were concluded.

Statistical analysis

Absolute event numbers were either directly extracted or calculated. Mantel-Hænszel methods were used to calculate the pooled estimates of odds ratio (OR) and 95% confidence intervals (95% C.I). I^2 statistic is used to assess the heterogeneity of the pooled estimate and was considered significant when either I^2 >50% or P for heterogeneity <0.10. When significant heterogenity were found Random-effects model was used and fixed effect model was applied when there was no significant heterogeneity. We also visually evaluate publication bias. If an asymmetry was observed, publication bias was quantitatively assessed

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with Egger's Test. Meta analysis were performed with Review Manager 5.4 . A p-value of 0.05 was considered significant.

RESULTS

Summary of included studies

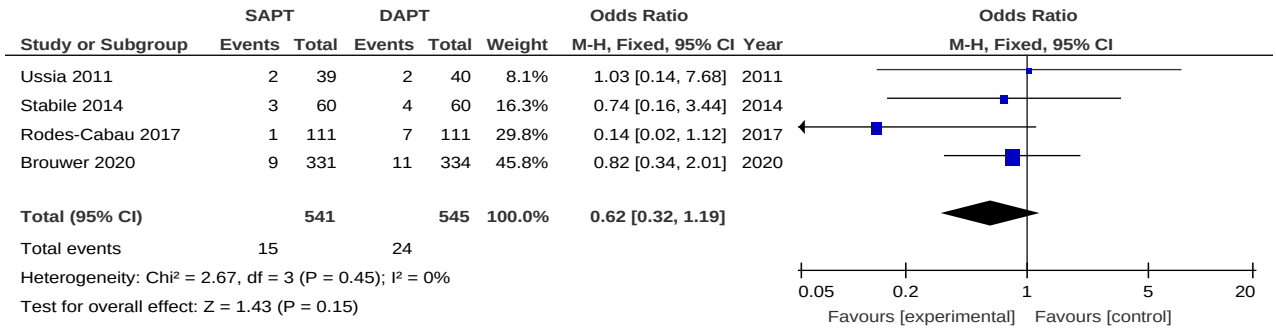
A total of six randomized control studies were identified. For patients with indication for oral anticoagulation one randomized control trial was found [9] comparing OAC alone vs OAC plus clopidogrel. In patients without indication for oral anticoagulation five randomized control studies were found , one of them were comparing patients receiving rivaroxaban and aspirin vs DAPT [10]. Four of the studies were comparing SAPT vs DAPT and were included in quantitative meta-analysis.

A total of 1086 patients (541 SAPT and 545 DAPT) were included. Publication bias was not assessed because the included studies were less than 10. Characteristics of the included studies are summarized in Tables 1 and 2. The median follow –up was 5.5 months .In one study the follow up was only for 30 days when 3 months, 6 months and 1 year were the follow up for the other studies.

Safety endpoints

The incidence of life-threatening bleeding was similar in SAPT compared to DAPT [2.8% vs 4.4%, OR 0.62 C.I 0.32-1.19]. Significant difference was observed in major bleeding (2.58% vs 6.23%, OR 0.40 C.I 0.21-0.75]. As a result there was also significant difference in the composite outcome of life threatening bleeding and major bleeding [5.36% vs 10.64%, OR 0.47 C.I. 0.3-0.75]. Major vascular complication found also to be similar [5.58% vs 6.91%, OR 0.80 C.I 0.46-1.39] between the two regimens.

LIFE-THREATENING BLEEDING



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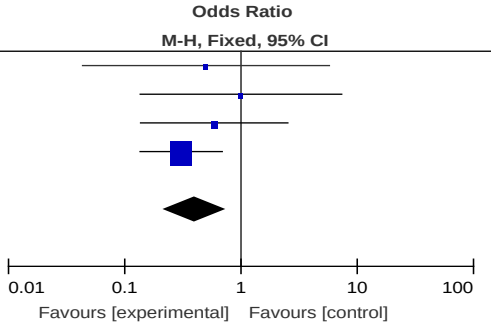
MAJOR BLEEDING

Study or Subgroup	SAPT Events	SAPT Total	DAPT Events	DAPT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Ussia 2011	1	39	2	40	5.8%	0.50 [0.04, 5.75]	2011
Stabile 2014	2	60	2	60	5.9%	1.00 [0.14, 7.34]	2014
Rodes-Cabau 2017	3	111	5	111	14.7%	0.59 [0.14, 2.53]	2017
Brouwer 2020	8	331	25	334	73.6%	0.31 [0.14, 0.69]	2020
Total (95% CI)		**541**		**545**	**100.0%**	**0.40 [0.21, 0.75]**	
Total events	14		34				

Heterogeneity: Chi² = 1.53, df = 3 (P = 0.67); I² = 0%

Test for overall effect: Z = 2.84 (P = 0.005)

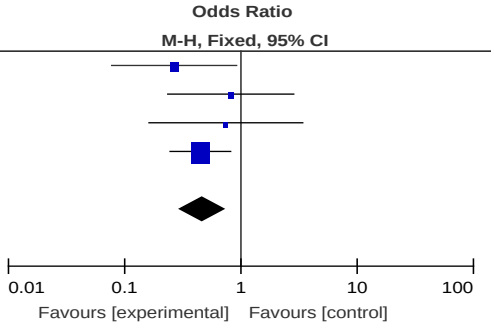


LIFE-THREATENING BLEEDING AND MAJOR BLEEDING

Study or Subgroup	SAPT Events	SAPT Total	DAPT Events	DAPT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Ussia 2011	4	39	12	40	19.7%	0.27 [0.08, 0.92]	2011
Stabile 2014	5	60	6	60	10.2%	0.82 [0.24, 2.84]	2014
Rodes-Cabau 2017	3	111	4	111	7.2%	0.74 [0.16, 3.40]	2017
Brouwer 2020	17	331	36	334	62.9%	0.45 [0.25, 0.82]	2020
Total (95% CI)		**541**		**545**	**100.0%**	**0.47 [0.30, 0.75]**	
Total events	29		58				

Heterogeneity: Chi² = 1.94, df = 3 (P = 0.58); I² = 0%

Test for overall effect: Z = 3.17 (P = 0.002)

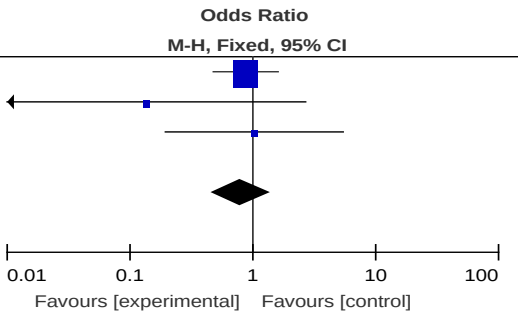


MAJOR VASCULAR COMPLICATION

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Brouwer 2020	21	331	24	334	78.3%	0.88 [0.48, 1.60]
Stabile 2014	0	60	3	60	12.1%	0.14 [0.01, 2.69]
Ussia 2011	3	39	3	40	9.6%	1.03 [0.19, 5.43]
Total (95% CI)		**430**		**434**	**100.0%**	**0.80 [0.46, 1.39]**
Total events	24		30			

Heterogeneity: Chi² = 1.53, df = 2 (P = 0.47); I² = 0%

Test for overall effect: Z = 0.80 (P = 0.43)



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Efficacy endpoints

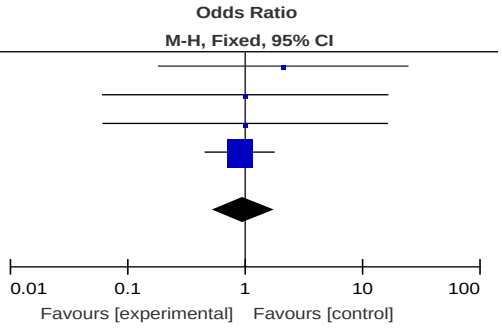
Major stroke was similarly observed in SAPT and DAPT [3.88% vs 4.03% OR 0.96 C.I. 0.52-1.78]. Myocardial infarction was only reported in three studies and no significant difference was observed [1.8% vs 1.57% OR 1.05 C.I:0.35-3.18]. No difference was reported in three to six months mortality [6.09% vs 6.05% OR 1.01 C.I 0.61-1.66]. However the composite outcome of mortality, life-threatening bleeding and major bleeding found to be more often in patients receiving DAPT than patients receiving SAPT [11.46% vs 16.69%, OR 0.65 C.I 0.46-0.92]

MAJOR STROKE

	SAPT		DAPT			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Ussia 2011	2	39	1	40	4.5%	2.11 [0.18, 24.24]	2011
Stabile 2014	1	60	1	60	4.7%	1.00 [0.06, 16.37]	2014
Rodes-Cabau 2017	1	111	1	111	4.8%	1.00 [0.06, 16.19]	2017
Brouwer 2020	17	331	19	334	86.0%	0.90 [0.46, 1.76]	2020
Total (95% CI)		**541**		**545**	**100.0%**	**0.96 [0.52, 1.78]**	
Total events	21		22				

Heterogeneity: Chi² = 0.44, df = 3 (P = 0.93); I² = 0%

Test for overall effect: Z = 0.13 (P = 0.90)

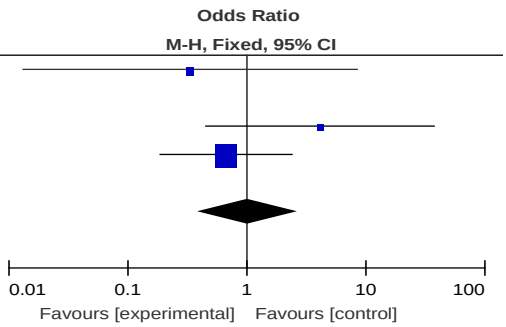


MYOCARDIAL INFARCTION

	Experimental		Control			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**Year**
Ussia 2011	0	39	1	40	17.6%	0.33 [0.01, 8.43]	2011
Stabile 2014	0	60	0	60		Not estimable	2014
Rodes-Cabau 2017	4	111	1	111	11.6%	4.11 [0.45, 37.39]	2017
Brouwer 2020	4	331	6	334	70.9%	0.67 [0.19, 2.39]	2020
Total (95% CI)		**541**		**545**	**100.0%**	**1.01 [0.39, 2.63]**	
Total events	8		8				

Heterogeneity: Chi² = 2.41, df = 2 (P = 0.30); I² = 17%

Test for overall effect: Z = 0.02 (P = 0.99)



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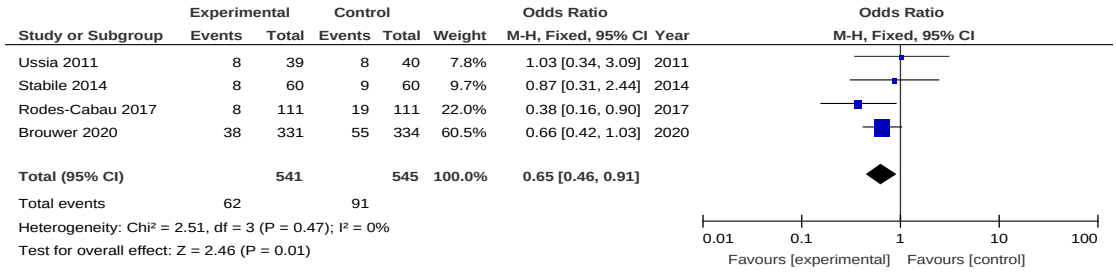
MORTALITY 3 TO 6 MONTHS

Mortality, Life-threatening bleeding and Major bleeding



DISCUSSION

In patients without indication for oral anticoagulation, four randomized control studies comparing SAPT vs DAPT have been meta-analyzed, the main findings were:

1. The safety between two regimens was different, SAPT were safer than DAPT, due to fewer major bleeding events.
2. Efficacy did not differ between the two regimens
3. Mortality during follow up of three to six months did not differ

The combined outcomes of mortality, life-threatening and major bleeding were more often in patients receiving DAPT, making SAPT a safer choice without risking the efficacy in the same time.

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We also found an RCT for patients without indication for oral anti-coagulation, which compares rivaroxaban plus aspirin with patients receiving aspirin plus clopidogrel (DAPT) [10]. This trial terminated prematurely because of safety concerns. Patients receiving rivaroxaban based treatment were associated with higher burden of thrombo-embolic and bleeding events and higher risk of death. To sum up, in terms of treatment strategy for patients without indication for oral anticoagulation, strategy recommending rivaroxaban and aspirin has been rejected as inferior to DAPT.

The first 2 RCTS Stabile et al. and Ussia et al. [11] [12] comparing SAPT vs DAPT showed no differences in clinical outcomes between the two treatments. Although, the addition of clopidogrel was associated with a modest increase in the rate of bleedings. Similar results provided also 2 retrospective studies Durand et al, Poliacikova et al and the meta –analysis Gandhi et al [13][14][15]. Gradually the suggestion ,that a treatment with aspirin could be justified against DAPT offering similar survival benefits and a lower hemorrhagic risk, has been established. Previous meta-analysis of Ando et al [16], revealed similar 30 day life threatening and major bleeding between SAPT and DAPT with a strong trend toward more life threatening and bleeding events in the DAPT group. Ando et al, included three randomized control studies comparing DAPT vs SAPT. The addition of recently published RCT, Popular TAVI [17] changed the status of SAPT and DAPT comparison ,providing clearer evidence, leading to our results.

When considering the risk of cerebrovascular ischemic after TAVI, the tendency to enhance antithrombotic treatment is advocated. Nombela et al [18] showed that the increased risk of stroke remains for up to 2 months after the procedure but more than 50% of these events occur in the periprocedural phase, due to valve calcium embolization and the manipulation of catheters into an athiromasic aorta. Two are the proposed mechanisms, the prothrombotic state of the valve leaflet prior to their complete endothilization within the first 3 months and atrial-fibrillation. Fourty per-cent (40%) of patients undergoing TAVI have concomitant atrial fibrillation with a relevant impact on mortality [19][20] . Gallego et al [21] showed that the cessation of anticoagulation reduce the survival of patients with atrial fibrillation when no clear benefit has emerged when associating OAC with antiplatelet agents [22]. The association of antiplatelet agents with OAC has to be weighed against an increased risk of bleeding [23] [24].

In terms of patients with indication for oral anticoagulation, mainly due to concomitant atrial fibrillation , current guidelines suggest lifelong OAC. The last meta-analysis of Liang et al, [25] suggest that Vitamin K antagonist is a better regimen compared to NOACs on decreasing risks in post-TAVI patients. More specifically all cause mortality and life-threatening bleeding were similar between patients receiving NOACs and VKAs, while VKA showed a better protective effect in disabling and non-disabling stroke. The addition of antiplatelet therapy to OAC does not appear to reduce the incidence of thrombo-embolic events and actually increases the risk of major or life-threatening bleeding [26] [27]. Hence, if no other indication of antiplatelet therapy exists (recent percutaneous coronary intervention) current available evidence suggest that OAC alone without concomitant antiplatelet therapy may be the preferred anti thrombotic treatment for TAVR patients with AF.

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CONCLUSION

In patients without indication for oral anticoagulation, after meta-analyzing four randomized control studies, in contrast to current guidelines SAPT found to be safer than DAPT, due to fewer major bleeding events. On the other hand the efficacy of both regimens were similar. In patients with previous indication for oral anticoagulation only one randomized control study were found and we could not include it in our meta-analysis. Ongoing studies will provide additional evidences because the number of TAVR procedures is growing worldwide and it is crucial to determine the optimal antithrombotic treatment.

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Table 1 Summary of demographic and clinical features of included studies

Author (publication year)	Brouwer (2020)		Rodes-Cabau (2017)		Stabile (2014)		Ussia (2011)	
	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT
Age ,years(mean+/-SD)	80.4±6.2	79.5±6.4	79±9	79±9	81.1±4.8	80.2±5.7	81±4	80±6
Male,%	50.5	52.1	53.2	63.1	40.0	33.3	41.0	50.0
Hypertension ,%	73.4	76.3	79.8	77.5	95.0	95.0	79.5	87.5
Diabetes,%	23.6	25.4	32.7	36.9	25	28.3	20.5	32.5
Previous myocardial infarction,%	8.5	9.3	18.4	23.4	NR	NR	10.3	17.5
Previous coronary artery bypass graft,%	18.4	19.5	38.5	35.1	NR	NR	10.3	17.5
Peripheral vascular disease,%	14.2	20.4	20.0	25.2	NR	NR	10.3	7.5
Chronic obstructive pulmonary disease,%	15.7	22.2	30	25.2	NR	NR	10.3	7.5
Chronic renal failure,%	NR	NR	63.1	63.1	NR	NR	12.8	15
Society of Thoracic Surgeon score,%	2.6	2.4	6.4±4.6	6.2±4.4	10.4±6.8	9.7±5.1	7±3	8±5
Mean gradient, mmHg			43±15	43±6	63.6±14.1	59.4±15.4	57±18	52±16
Left ventricular ejection fraction,%	NR	NR	54±13	55±12	NR	NR	51±12	54±8
Aortic valve area, cm^2	NR	NR	0.40±0.11	0.42±0.13	NR	NR	0.6±0.2	0.6±0.3

Table 2 : Summary of included studies for study design, included cohort, intervention regimen, and inclusion/exclusion criteria

Author (publication year)	Brouwer (2020)		Rodes-Cabau (2017)		Stabile (2014)		Ussia (2011)	
	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT	SAPT	DAPT
Study design	Randomized open-label, multi-center trial performed at 17 European sites		Randomized open-label, multi-center trial in Canada Europe and South America		Randomized study		Randomized open-label, single –center trial.	
Cohort ,numbers	331	334	111	111	60	60	39	39
Anti-platelet regimens for both SAPT and DAPT group	Randomized 1 to 90 days before TAVR in a 1:1 ratio to receive		Patients were randomized the day before procedure to		Randomly assigned to aspirin(75 to 160mg/day) and clopidogrel 75mg/day		Randomized to receive 300mg loading dose of clopidogrel on the day before TAVI followed by 3-	

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	aspirin(80-100mg/day) or clopidogrel (75mg/day) with aspirin (75-100mg/day)	receive aspirin (80-100 mg/day) or aspirin (80-100 mg/day) plus clopidogrel (75 mg per day)	or ticlopidine 500mg/ twice daily or aspirin alone	month maintenance daily dose of 75 mg clopidogrel plus aspirin100 mg lifelong or aspirin 100mg alone
Loading of anti-platelet	An initial dose of 300mg of aspirin within one day before TAVR for SAPT group. 300mg of aspirin and clopidogrel within one day before the TAVR for DAPT group.	300mg of clopidogrel was administered within 24-hours prior to transfemoral-TAVR Same dose loading was administeres within 24-hours post non-transfemoral TAVI	Not reported	300mg of clopidogrel was administered on the day before TAVI.
Major inclusion criteria	No indication for oral anticoagulation	1:Patients with clinical indications for TAVI with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve	1:Severe aortic stenosis defined as aortic valve area <0.8cm² (or aortic valve index <0.5cm²/m²) and mean aortic gradient >40mmHg or peak jet velocity >4.0m/s 2:NYHA functional class more than II or syncope 3:High surgical risk	Consecutive patients who meet the clinical and anatomic criteria for TAVR
Major exclusion criteria	1:Implantation of drug eluting stent within 3 months or the implantation of a baremetal stent within 1 month before TAVR	1:Need for chronic anticoagulation 2:Major bleeding within 3 months before TAVR 3:Prior intracranial bleeding 4:Drug-eluting stent implantation within the year before the TAVI 5:Allergy to aspirin and clopidogrel	1:Aortic annulus diameter <18 or >25 2:Aortic dissection or iliac femoreal dimensions or disease precluding safe sheath insertion 3:Untreated coronary artery disease requiring revascularization 4:Severe aortic regurgitation or mitral regurgitation or prosthetic valve (any location) 5:Acute myocardial infarction within 1 months 6:Upper	1:Liver cirrhosis, recurrent pulmonary embolism, porcelain aorta, respiratory failure, history of radiotherapy to the mediastinum and severe connective tissue disease 2:Previous percutaneous coronary intervention or acute coronary syndrome requiring DAPT 3:Need for oral anticoagulation therapy 4:Allergy or intolerance to any of the study drugs

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			gastrointestinal bleeding within 3 months 7:Cerebrovascular accident or transient ischaemic attack within 6 months 8:Any cardiac procedure, other than ballonn valvuloplasty within 1 month or within 6 months for drug eluting stents 9:Indication for oral anticoagulation therapy 10:Aspirin or thienopiridine intolerance/allergy	

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,Äî Comparison of Regimes

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