Editorial

Antithrombotic treatment following transcatheter valve replacement: current considerations

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Provenance: This is an invited Editorial commissioned by the Section Editor Hai-Long Dai (Department of Cardiology, Yan'an Affiliated Hospital of Kunming Medical University, Kunming, China).

Comment on: Rodés-Cabau J, Masson JB, Welsh RC, *et al.* Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. JACC Cardiovasc Interv 2017;10:1357-65.

Submitted Sep 28, 2017. Accepted for publication Oct 01, 2017.
doi: 10.21037/jtd.2017.10.34
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.34

Transcatheter aortic valve implantation (TAVI) or transcatheter aortic valve replacement (TAVR) has been established as a vital alternative to surgical aortic valve replacement (AVR) for intermediate and high surgical risk patients. TAVR has been demonstrated to be either non inferior or even superior to AVR regarding annual all-cause mortality in high risk operable patients, with the implantation of Edwards Sapien valve (ESV) and in Medtronic CoreValve Revalving System (CRS) respectively (1,2). Also, TAVR has been proven superior to optimal medical treatment concerning 1 year all-cause mortality in patients with severe aortic stenosis who cannot undergo surgery (3). Despite the advanced age, comorbidities and fragile status of patients undergoing TAVR, the procedure is currently correlated with a high success rate. However, major ischemic and bleeding events can further complicate the procedure, impairing survival. Therefore, the recommendation of the most appropriate antithrombotic treatment in this high-risk population balancing the risk/benefit ratio is rendered of major clinical importance.

Four large randomized clinical trials PARTNER A and B (1,3), CUSPT (2) and CHOICE (4) with comparable baseline characteristics but higher mean logistic EuroSCORE, STS score and previous stroke incidence in PARTNER trials (*Table 1*), constitute the cornerstone studies reflecting ischemic and bleeding complications under dual antiplatelet therapy (DAPT) for the first 3–6 months and single indefinitely. Placement of Aortic Transcatheter Valves (PARTNER) trial A and B compared TAVI to surgical AVR and medical treatment respectively, administrating 75–100 mg aspirin indefinitely and combined with clopidogrel for the first 6 months.

The Medtronic CoreValve U. S. Pivotal Trial (CUSPT) and The Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve *vs.* Edwards SAPIEN XT (CHOICE) trial compared TAVI versus SAVR and a balloon versus self-expandable TAVI respectively, recommending low to normal dose aspirin indefinitely (81–325 or 100 mg) and clopidogrel for 3 months (2,4). As described in *Table 1*, 30-day all-cause mortality rates were comparable ranging from 3.3% to 5.1%, while 1-year all-cause mortality was increased to PARTNER trials compared to CUSPT (24.2% and 30.7% versus 14.2% respectively). Thromboembolic events as myocardial infarction and stroke at 30 days demonstrated no significant differences varying between 0–0.8% and 2.6–6.7%, respectively, whereas 30-day major vascular access related complications were significant decreased in CUSPT compared to PARTNER A, B and CHOICE trials (5.9% versus 11%, 16.2% and 12.8–14%, respectively). However, major bleeding rates at 30 days presented an increase in CUSPT compared to PARTNER

Table 1 Randomized clinical trials referring to antiplatelet therapy pre- and post-TAVI and respective outcomes

Randomized clinical trials	PARTNER A (1)	PARTNER B (3)	CUSPT (2)	CHOICE (4)
Characteristics				
Sample size	348	179	394	221 (238*)
Age (years)	83.6±6.8	83.1±8.6	83.2±7.1	80.75
Male (%)	57.8	45.8	53.6	35.65
Logistic EuroSCORE	29.3±16.5	26.4±17.2	17.6±13.0	21.8
STS score	11.8±3.3	11.2±5.8	7.3±3.0 (STS-PROM)	5.9
NYHA III/IV (%)	94.3	92.2	85.8	61/19.9
Coronary artery disease (%)	74.9	67.6	75.4	63.05
Cerebral vascular disease (%)	29.3	27.4	12.9	19.9
Peripheral vascular disease (%)	43	30.3	41.7	17.4
AF (%)	40.8	32.9	41**	29.05
Pulmonary hypertension (%)	42.4	42.4	NA	NA
AVA (cm^2)	0.7±0.2	0.6±0.2	0.72±0.23	0.7
Mean aortic valve gradient (mmHg)	42.7±14.6	44.5±15.7	48.27±15.31	43.15
Moderate/severe MR (%)	19.8	22.2	NA	36.15
Antiplatelet therapy pre TAVI				
Aspirin (mg)	75–100	75–100	81–325	100
Clopidogrel (mg)	300	300	300	NA
Antiplatelet post TAVI				
Aspirin/duration	75–100 mg lifelong	75–100 mg lifelong	81–325 mg/3 months	100 mg lifelong
Clopidogrel/duration	75 mg/6 months	75 mg/6 months	75 mg/3 months	75 mg/3 months
Transfemoral (%)	70	100	82	100
Transapical or other[#] (%)	30	0	18[#]	0
CRS: Medtronic CoreValve Revalving System (%)	0	0	100	50
ESV: Edwards Sapien valve (%)	100	100	0	50
Outcomes: 30-day and 1-year				
30-day all-cause mortality (%)	3.4	5	3.3	4.1[$]/5.1[&]
30-day cardiovascular mortality (%)	3.2	4.5	3.1	4.1[$]/4.3[&]
1-year all-cause mortality (%)	24.2	30.7	14.2	NA
1-year cardiovascular mortality (%)	14.3	19.6	10.4	NA
Myocardial infarction at 30 days (%)	0	0	0.8	0.8[$]/0[&]
Myocardial infarction at 1 year (%)	0.4	0.6	1.9	NA
Stroke at 30 days (%)	4.7	6.7	4.9	5.8[$]/2.6[&]
Stroke at 1 year (%)	6	10	8.8	NA

Table 1 (*continued*)

Table 1 (*continued*)

Randomized clinical trials	PARTNER A (1)	PARTNER B (3)	CUSPT (2)	CHOICE (4)
Major vascular access site related complication at 30 days (%)	11	16.2	5.9	14[$]/12.8[&]
Major bleeding at 30 days (%)	9.3	16.8	28.1	19[$]/14.5[&]
Major bleeding at 1 year (%)	14.7	22.3	29.5	NA
Life threatening bleeding at 30 days (%)	NA	NA	13.6	8.3[$]/12[&]
Life threatening bleeding at 1 year (%)	NA	NA	16.6	NA
New onset AF at 30 days (%)	8.6	0.6	11.7[##]	NA
New onset AF at 1 year (%)	12.1	0.6	15.9[##]	NA
New pacemaker implantation at 30 days (%)	3.8	3.4	19.8	17.3[$]/37.6[&]
New pacemaker implantation at 1 year (%)	5.7	4.5	22.3	NA

*, patients included in secondary analysis/30-day follow up; **, prior AF of aflutter; [#], other non-iliofemoral or transapical; [##], new or worsening AF; [$], refers to balloon expandable Edwards Sapien valve; [&], refers to self-expandable valve Medtronic CoreValve. NA, not available; TAVI, transcatheter aortic valve implantation.

A, B and CHOICE trials (28.1% versus 9.3%, 16.8% and 14.5–19%).

There are also six VARC reporting registries with a great variance in sample size, baseline characteristics, mean logistic EuroSCORE, previous stroke and coronary artery disease history, as described in *Table 2* (5-10). Regarding the antiplatelet therapy, low dose aspirin 75–100 mg recommended indefinitely, while clopidogrel duration varied mainly between 1 and 6 months. In these registries, all-cause mortality at 30 days reported between a range of 2.1–16% and stroke incidence between 1–6%. Transfemoral access is reported in the majority of procedures presenting a variance in major vascular access site related complications (VASC) at 30 days between 2.9–10.7%. In addition, major bleeding rates at 30 days revealed significant differences (1–20.9%).

Notably, additional five studies have compared directly the ischemic and bleeding endpoints of single versus DAPT post TAVI. The rationale of DAPT in TAVI patients consists in the ischemic event prevention, especially stroke, periprocedurally as well as in the first month post the procedure. The ARTE, SAT-TAVI and Ussia *et al.* randomized trials demonstrated the lack of any beneficial impact of DAPT (aspirin and clopidogrel) on the stroke prevention post TAVR (11-13). Interestingly, ARTE trial (11) randomized 222 patients to aspirin versus aspirin plus clopidogrel following TAVR and revealed no significant difference in the 30- and 90-day stroke rate (0.9% versus 2.7% in aspirin versus DAPT groups), except a general tendency toward a lower incidence of mortality, myocardial infarction and stroke of aspirin alone, as described in *Table 3*. Similarly, SAT-TAVI trial (12) randomized 120 patients undergoing TAVR to aspirin versus aspirin and clopidogrel and showed no difference in 30-day major stroke rate (1.7% in both groups). Ussia *et al.* (13) reported a 30-day stroke rate of 5% in aspirin versus 3% in DAPT group, in a total population of 79 patients following TAVR with the CoreValve system. In accordance with these results, two recent meta-analyses reported similar cerebrovascular event rates in TAVR patients receiving aspirin versus DAPT (16,17). Overall, SAT-TAVI (12) and Ussia *et al.* (13) trials, presented no significant differences in both 30-day ischemic (mortality, myocardial infarction, stroke) and bleeding events between aspirin monotherapy and DAPT, except the lower rate of cumulative major and minor VASC complications in aspirin versus DAPT treated patients (5% versus 13.3%, $P<0.05$) in the SAT-TAVI trial.

Durand *et al.* (14) compared prospectively two antiplatelet therapy strategies, using single (aspirin or clopidogrel) versus DAPT (aspirin and clopidogrel) in 362 consecutive patients that enrolled in the FRANCE 2 TAVI registry. Similar to the previous mentioned studies (11-13), the mortality and thromboembolic event rates demonstrated no difference between single and dual antiplatelet treated groups. In accordance with SAT-TAVI trial, overall vascular complications were significantly reduced in single

Table 2 Registries referring to antiplatelet therapy post TAVI and the corresponding outcomes

Registries	Gilard *et al.* (5)	Nuis *et al.* (6)	Tchetche *et al.* (7)	Borz *et al.* (8)	Griese *et al.* (9)	Abramowitz *et al.* (10)
Characteristics						
Sample size	3,195	214	943	250	162	249
Age (years)	82.7±7.2	80±8	81±7	83.3±6.5	82±5	83±5
Male (%)	51	50	53.8	46	29.6	39
Logistic EuroSCORE (%)	21.9±14.3	10–22	12.9–28.8	23.1±12.8	16.7±12.5	NA for overall
STS score (%)	14.4±11.9	3.4–7.5	NA	NA	NA	NA
NYHA III/IV (%)	75.9	82	81.1	NA	81.5	NA
Coronary artery disease (%)	47.9	24[y]	45.1	34.8	9.9[g]	57
Cerebral vascular disease (%)	10	23	15.7	NA	8	8.4
Peripheral vascular disease (%)	20.8	21	25	22.1	NA	12
AF (%)	26.6	30	NA	NA	33.3	NA
Pulmonary hypertension (%)	19.6	NA	NA	NA	NA	NA
CRS: Medtronic CoreValve Revalving System (%)	33.1	100	NA	0	18.5	NA
ESV: Edwards Sapien valve (%)	66.9	0	NA	50.8; 49.2 XT Sapien	81.5 XT Sapien	NA
Transfemoral access (%)	74.6	95	84 (9.1 surgical)	76	100	NA
Transapical/other (%)	17.8/7.6	0/5[j]	9.4/6	24	0	NA
Antiplatelet therapy pre-TAVI						
Aspirin (mg)	≤160	80	NA	250 IV	100	NA
Clopidogrel mg loading	300	600	300	300	NA	NA
Antiplatelet therapy post TAVI						
Aspirin/duration	≤160 mg/ lifelong	100 mg/ 6 months	NA/≤6 months	NA	100 mg/ NA	100 mg
Clopidogrel/duration	75 mg/ 1 month	75 mg/ 6 months	75 mg/ ≤6 months	NA	75 mg/NA	75 mg/ 6 months
Outcomes at 30 days and 1 year*						
All-cause mortality 30 days (%)	9.7; (24*)	16[k]/6[m]	7.2	7.6	5.6	a=2.1; b=2.9
Cardiovascular mortality 30 days (%)	7; (14.3*)	NA	6.3	NA	NA	NA
Myocardial infarction at 30 days (%)	NA; (1.2*)	NA	1.59	2	NA	0
Stroke 30 days (%)	3.4; (4.1*)	6	2.6	2.4	NA	a=2.8; b=1
Major vascular access site related complication 30 days (%)	NA; (4.7*)	NA	10.7	6.4	4.3	a=3.5; b=2.9
Major bleeding 30 days (%)	NA; (4.5*)	NA	20.9	9.6	3.7	a=2.1; b=1
Life threatening bleeding 30 days (%)	NA; (1.2*)	NA	13.9	13.2	9.9	NA
New onset AF at 30 days (%)	NA	NA	NA	NA	NA	NA
New pacemaker implantation 30 days (%)	NA; (15.6*)	NA	15.5	6.1	NA	a=24.3; b=22.9

*, 1 year outcome only available in Gilard *et al.* study; [y], previous MI; [k], patients with stroke; [m], patients without stroke; [j], surgical access; [g], previous MI; a, group 1 with aortic stenosis and coronary artery disease; b, group 2 with aortic stenosis. NA, not available; TAVI, transcatheter aortic valve implantation; ESV, Edwards Sapien valve; IV, intravenous.

Table 3 Studies investigating single versus dual antiplatelet therapy post TAVI and their respective outcomes

Studies	ARTE (11)		Durand (14)		SAT-TAVI (12)		Poliacikova (15)		Ussia (13)	
	Asp	DAPT	Asp or clop	DAPT	Aspirin	DAPT[k]	Aspirin	DAPT	Aspirin	DAPT
Characteristics										
Sample size	111	111	164	128	60	60	91	58	39	40
Age (years)	79±9	79±9	82.7±6.3	84.6±5.8	81.1±4.8	80.2±5.7	82±6.9	81.6±6.3	81±4	80±6
Male (%)	53.2	63.1	54.9	39.1	40	33.3	46.2	44.8	41	50
Logistic EuroSCORE (%)	NA	NA	20.0±12.4	20.2±11.6	25.1±12.0	23.34±8.15	NA	NA	21±16	23±15
STS score (%)	6.4±4.6	6.2±4.4	7.4±6.1	6.9±4.0	10.4±6.8	9.7±5.1	NA	NA	7±3	8±5
NYHA III/IV (%)	NA	NA	79.9	77.4	88.3	90	NA	NA	59	65
Coronary artery disease (%)	NA	NA	50	30.5	NA	NA	54.9	63.8	NA	NA
Cerebral vascular disease (%)	NA	NA	7.9	9.4	NA	NA	NA	NA	10	5
Peripheral vascular disease (%)	20	25.2	17.1	7.8	NA	NA	NA	NA	10	8
AF (%)	NA	NA	23	35.2	NA	NA	11	27.6	15	10
Pulmonary Hypertension (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CRS: Medtronic CoreValve Revalving System (%)	0	0	32.9	0	0	0	100	100	100	100
ESV: Edwards Sapien valve (%)	100[y]	100[y]	67.1	100	100 XT Sapien	100 XT Sapien	0	0	0	0
Transfemoral access (%)	65.8	72.1	84.1	76.6	NA	NA	NA	NA	100	95
Transapical/other (%)	18/16.2	16.2/11.7	14.6	23.4	NA	NA	NA	NA	0	0/5
Antiplatelet therapy pre-TAVI										
Aspirin (mg)	80–100	80–100	75[#]	75	75–160	75–160	300 loading	300 loading	100	100
Clopidogrel mg loading	0	300	0	300*	NA	NA	0	300	300	300
Clopidogrel (mg)	0	75	75[#]	75	0	75	0	75	0	75

Table 3 (*continued*)

Table 3 (*continued*)

Studies	ARTE (11)		Durand (14)		SAT-TAVI (12)		Poliacikova (15)		Ussia (13)	
	Asp	DAPT	Asp or clop	DAPT	Aspirin	DAPT[k]	Aspirin	DAPT	Aspirin	DAPT
Antiplatelet therapy post TAVI										
Aspirin/duration	80–100/ ≥6 months	80–100/ ≥6 months	75**/ lifelong	75/lifelong	75–160/ lifelong	75–160/ lifelong	75/ 6 months	75/ 6 months	100/ lifelong	100/ lifelong
Clopidogrel/duration	0	75/3 months	75/lifelong	75/1 month	0	75/6 months	0	75/ 6 months	0	75/ 3 months
Outcomes at 30 days										
All-cause mortality 30 days (%)	2.7	5.4	7.9	9.4	NA	NA	3.3	6.9	10	10
Cardiovascular mortality 30 days (%)	NA	NA	NA	NA	3.3	1.7	NA	NA	0	3
Myocardial infarction at 30 days (%)	0.9	3.6	1.2	0.8	0	0	1.1	0	0	0
Stroke 30 days (%)	0.9	2.7	1.2	4.7	3.4	1.7	2.2	3.4	5	3
Major vascular access site related complication 30 days (%)	NA	NA	5.5	10.2	0	5	3.3	5.17	NA	NA
Major bleeding 30 days (%)	2.7	4.5	2.4	13.3	3.3	3.3	NA	NA	3	5
Life threatening bleeding 30 days (%)	0.9	6.3	3.7	12.5	5	6.67	NA	NA	5	5
Minor bleeding 30 days (%)	NA	NA	2.4	9.4	1.7	5	NA	NA	10	8
All bleeding at 30 days	NA	NA	8.5	31.2	10	15	8.8	19	18	18
New onset AF at 30 days (%)	10.8[x]	10.8[x]	NA	NA	NA	NA	NA	NA	NA	NA
New pacemaker implantation 30 days (%)	NA	NA	12.9	3.1	NA	NA	NA	NA	NA	NA

*, 300 mg loading with clopidogrel was given only in transfemoral access; [#], in naive patients aspirin alone (75 mg) was initiated the day before TAVI and followed lifelong. In patients previously treated with aspirin, aspirin alone was continued during and after TAVI. In patients previously treated with clopidogrel, clopidogrel was continued during TAVI without either additional loading dose before TAVI or aspirin administration; **, aspirin or clopidogrel lifelong; [k], patients assigned to DAPT: aspirin and clopidogrel 75 mg or ticlodipine 500 mg twice daily; [y], Sapien 3 or Sapien XT; [x], defined as periprocedural. Asp, Aspirin; clop, Clopidogrel; NA, not available; TAVI, transcatheter aortic valve implantation.

antiplatelet therapy (7.9% versus 19.5%, P=0.003). DAPT treated patients presented a significant increase in minor VASC compared to single aspirin or clopidogrel therapy (9.4% versus 2.4%, P=0.017) and an increased but non-significant frequency in major VASC (10.2% versus 5.5%, P=0.134), respectively. All bleeding, major and life-threatening bleeding, as well as the transfusion rates were significantly elevated in the DAPT versus single antiplatelet therapy (31.2% versus 8.5%, P <0.0001; 13.3% versus 2.4%, P<0.0001; 12.5% versus 3.7%, P=0.005; 25% versus 7.3%, P<0.0001; respectively). Also, Poliacikova *et al.* (15) retrospective study demonstrated an trend towards increased 30-day bleeding rates in DAPT versus aspirin treated patients, not reaching statistical significance (P=0.069 for both in-hospital and 30-day bleeding). The composite of all-cause mortality, acute coronary event, stroke, and all bleeding was significantly increased in DAPT versus aspirin group (in-hospital P=0.01 and 30-day follow up P=0.02), difference driven mainly by bleeding complications as major adverse cardiac and cerebrovascular event rates were similar in two groups. Similarly, ARTE trial revealed that aspirin reduced significantly the risk of composite major and life threatening bleeding compared to DAPT in TAVR patients (3.6% versus 10.8%, P=0.038), without increasing the risk of stroke or myocardial infarction (11). Indeed, ARTE trial confirmed that DAPT is correlated with an increased rate risk of severe bleeding [major or life threatening compared to patients receiving aspirin (11)]. Notably, the majority of bleeding events in DAPT treated patients were correlated with vascular access site complications, whereas a great number of non-access related bleedings such as gastrointestinal bleeding recorded in these patients. In addition, the majority of life threatening bleeding events (88%) were observed in DAPT treated patients, fact that further supports the higher incidence and severity of bleeding complications during dual antiplatelet treatment in consistence with other studies (18,19).

The POPULAR-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial (NCT02247128) is expected to elucidate the impact of aspirin versus DAPT on bleeding events as a single primary outcome in TAVR patients.

Interestingly, bleeding events have been proven to outweigh significantly cerebrovascular events, as major bleedings are correlated with worse outcomes and even increased mortality post TAVR procedures (20-22). Bleeding complications could be attributed to both of the great invasive nature of TAVR as well as the high risk profile and fragility of elderly patients undergoing the procedure. Given these parameters, it is inevitable that DAPT will be related with increased bleeding risk. On the other hand, no beneficial impact of DAPT over single antiplatelet therapy regarding cerebrovascular event prevention has been proven by several TAVR studies (23-26). It is well known that 50% of strokes within the first month post TAVR occur periprocedurally or within 24 hours post procedure, whereas the stroke risk seems to peak within the first 7 days post TAVR (11). Acute strokes stem from embolic events during the mechanical interaction of the transcatheter valve system with the highly calcified native aortic valve, while subacute strokes can be induced by more traditional predisposing factors such as atrial fibrillation. Neither periprocedural embolization nor atrial fibrillation could be prevented by DAPT, rendering further the limited therapeutic potential of DAPT.

Consequently, it is evident that DAPT increases significantly bleeding complications without reducing ischemic events post TAVR. In conclusion, major advances have been accomplished in the field of TAVI. However, ischemic and bleeding complications remain prevalent impairing survival in TAVR patients. Small randomized studies and meta-analyses have demonstrated a lack of benefit of DAPT over single antiplatelet therapy, as DAPT is correlated with increased bleeding events without decreasing thromboembolic complications post TAVR. Further, large scale studies should be performed to elucidate the optimal antithrombotic treatment post TAVR.

Acknowledgements

None.

Footnote

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

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Cite this article as: Koniari I, Kounis NG, Hahalis G. Antithrombotic treatment following transcatheter valve replacement: current considerations. J Thorac Dis 2017;9(11):4251-4259. doi: 10.21037/jtd.2017.10.34