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Comparison of early and midterm outcomes after transsubclavian/axillary versus transfemoral, transapical, or transaortic transcatheter aortic valve implantation

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ABSTRACT

Background: Outcomes after transsubclavian/transaxillary (TSc/TAx)-transcatheter aortic valve implantation (TAVI) have been unclear.
Objectives: To compare outcomes after TSc/TAx-TAVI versus transfemoral (TF)-TAVI, transapical (TAp)-TAVI, or transaortic (TAo)-TAVI, we performed meta-analysis of currently available studies.
Methods: Studies considered for inclusion met the following criteria: the study population was patients undergoing TAVI; patients were assigned to TSc/TAx-TAVI and TF-TAVI, TAp-TAVI, or TAo-TAVI; and at least one of postprocedural early (30-day or in-hospital) or late (including early) outcomes was reported. An odds or hazard ratio of each early or late outcome with its 95% confidence interval for TSc/TAx-TAVI versus the other approach was extracted from each individual study and combined in the random-effects model.
Results: Our search identified 15 eligible reports from 12 studies including 10,528 patients. Pooled analysis of early all-cause mortality demonstrated a statistically significant reduction after TSc/TAx-TAVI compared with TAp-TAVI ($P = 0.003$) or TAo-TAVI ($P = 0.03$). Pooled analysis of early pacemaker implantation demonstrated a statistically significant increase after TSc/TAx-TAVI compared with TAp-TAVI ($P = 0.0001$) or TAo-TAVI ($P < 0.00001$). Pooled analysis of midterm all-cause mortality demonstrated a statistically significant increase after TSc/TAx-TAVI compared with TF-TAVI ($P = 0.007$).
Conclusions: Early all-cause mortality was lower after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, early pacemaker implantation was more frequent after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, and midterm all-cause mortality was higher after TSc/TAx-TAVI than TF-TAVI.

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Introduction

In transcatheter aortic valve implantation (TAVI), the transfemoral (TF) approach has been the most commonly used with the lowest incidence of postprocedural complications.[1] Due to concomitant peripheral artery disease such as unpassable stenosis, severe tortuosity, or small calibers of the iliofemoral arteries, however, 10%–15% of patients are unable to undergo TF-TAVI.[2] Alternative approaches include transsubclavian (synonym for transaxillary) (TSc/TAx), transapical (TAp), transaortic (TAo), transcarotid, and transcaval. The TAp access is the unique antegrade approach and may offer simple wiring and marvelous controllability.[3] The TAo approach may be more controllable and advantageous to accurate implantation depth.[4] The transcarotid (especially, left transcarotid) approach may be coaxially aligned to the ascending aorta and optimally position the transcatheter valve.[5] Transcaval access is a new approach to attain fully percutaneous TAVI in patients with the inadequate TF access.[6] The subclavian/axillary artery, the minimum luminal diameter of which is commonly >5.0 mm even in case of the <5.0-mm iliofemoral artery, is less atherosclerotic and sinuous than the iliofemoral artery, and the TSc/TAx approach is a fully percutaneous access as well as the transcaval approach.[7] Because limited data for the comparison of TSc/TAx-TAVI and other approaches have been available to date, outcomes

Abbreviations: TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TSc/TAx, transsubclavian (synonym for transaxillary)

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Table 1
Patient characteristics

Study	Design	Approach		Device (%) CoreValve		SAPIEN		Patient number	Age (years)	Men (%)	DM (%)
Adamo 2015[10]	Single-center retrospective observational study	TSc/TAx		3rd generation	100	0		32	82±6	43.8	25.0
		Percutaneous	TF	3rd generation	100	0		170	83±7	61.8	27.6
		Surgical	TF	3rd generation	100	0		76	83±7	55.3	28.9
		TAo		3rd generation	100	0		44	83±6	61.4	34.1
		P value		N/A				–	0.937	0.252	0.538
Ciuca 2016[11]	Multi-center prospective registry	TSc/TAx		58.3		40.0		60	80±6	58.3	33.3
		TAp		98.6		1.4		142	82±6	43.7	23.9
		P value		<0.001				–	0.14	0.04	0.12
Codner 2018[12,*]	Single-center retrospective observational study	TSc/TAx		Evolut R	90.9	SAPIEN 3	9.1	11	84±5.1	18.2	27.3
		TAp		Evolut R	0	SAPIEN 3	100	11	84±4.5	54.5	0.0
		TAo		Evolut R	18.2	SAPIEN 3	81.8	11	83±4.3	63.6	9.1
		Suprasternal		Evolut R	54.5	SAPIEN 3	45.5	11	81±6.2	45.5	45.5
		P value		N/A				–	0.15	0.30	0.03
CoreValve US (Gleason) 2018[13,*]	Post-hoc study from randomized controlled trial	TSc/TAx		100		0		202	80.8 ± 8.1	63.9	43.1
		TF		100		0		202	80.2 ± 9.7	58.9	43.1
		P value		N/A				–	0.506	0.307	>0.999
FRANCE (Eltchaninoff) 2011[14]	Multi-center prospective registry	TSc/TAx	CoreValve	100		0		12	75.5 ± 11.0	50.0	8.3
		TF	SAPIEN	0		100		95	83.2 ± 7.3	56.8	25.3
		TF	CoreValve	100		0		66	82.5 ± 5.9	48.5	33.3
		TAp	SAPIEN	0		100		71	82.1 ± 7.3	64.8	25.4
FRANCE-2 (Gilard) 2012[15,†]	Multi-center prospective registry	TSc/Tax		CoreValve, 33.1; SAPIEN, 66.9 (in all patients)				184	82.2 ± 6.7	71.2	N/A
		TF						2361	83.0 ± 7.2	47.4	
		TAp						567	81.5 ± 7.4	58.6	
		P value		N/A				–	<0.001	<0.001	
FRANCE-2 (Gilard) 2016[16,‡]	Multi-center prospective registry	TSc/TAx/TF/TAp		66.3		33.7		4187	82.8	50.7	25.4
Italian CoreValve (Fiorina) 2017[17]	Multi-center prospective registry	TSc/TAx		100		0		147	83±5	49.0	N/A
		TAo		100		0		95	82±6	46.3	
		P value		N/A				–	0.7	0.7	
Italian CoreValve (Petronio) 2010[18,¶]	Multi-center prospective registry	TSc/TAx		3rd generation	100	0		54	83 (80–86)	66.7	20.4
		TF		3rd generation	100	0		460	83 (78–86)	41.3	27.4
		P value		N/A				–	0.24	0.0004	0.27
Italian CoreValve (Petronio) 2012[19,*,§]	Multi-center prospective registry	TSc/TAx		100		0		141	83.0 (78.9–87.0)	61.0	N/A
		TF		100		0		141	83.0 (78.6–86.1)	57.4	
		P value		N/A				–	0.25	0.54	
Muensterer 2013[20]	Single-center retrospective observational study	TSc/TAx		100		0		40	79.5 ± 8.5	57.5	N/A
		TF		100		0		301	80.2 ± 7.0	44.9	
		P value		N/A				–	0.455	0.132	
Saia 2013[21]	Single-center prospective registry	TSc/TAx/TF/TAp		CoreValve and SAPIEN/SAPIEN XT, 100 and 0 (TSc/TAx), 81.8 and 18.2 (TF), 0 and 100 (TAp)				102	83.7 ± 5.3	39.2	22.5
Taramasso 2011[22]	Single-center retrospective observational study	TSc/TAx		3rd generation	84.2	15.8		19	79.7 ± 5.5	73.7	26.3

(*continued on next page*)

Table 1 (*Continued*)

Study	Design	Approach	Device (%) CoreValve		SAPIEN	Patient number	Age (years)	Men (%)	DM (%)
		TF	3rd generation	44.3	55.7	140	79.8 ± 6.5	53.6	18.6
		TAp	3rd generation	0	100	16	78.2 ± 6.7	31.3	25.0
		P value	N/A			–	0.6	0.01	0.7
UK CoreValve (Moynagh) 2011[23]	Multi-center prospective registry	TSc/TAx	100		0	35	80.6 ± 4.9	N/A	N/A
		TF	100		0	253	81.7 ± 6.4		
		P value	N/A			–	0.33		
UK TAVI (Fröhlich) 2015[24]	Multi-center prospective registry	TSc/TAx	98.9		1.1	188	83 (78–86)	65.4	23.9
		TF	57.5		41.1	2828	83 (77–87)	51.3	22.2
		TAp	98.9		0.4	761	82 (77–86)	55.8	21.9
		TAo	36.2		63.8	185	84 (77–88)	48.6	21.1
		P value	N/A			–	0.18	<0.0001	0.8

Study	Approach		CAD (%)	Prior cardiac surgery (%)		Stroke (%)		COPD (%)		CKD (%)		PAD (%)		Logistic EuroSCORE (%)	STS PROM (%)
Adamo 2015[10]	TSc/TAx		53.1	CABG	12.5	N/A		15.6		GFR <30 mL/min	40.6	65.6		26 (20–33)	8.3 (5.6–14)
	Percutaneous	TF	43.5		17.6			13.5			17.6	11.2		18 (11–27)	6.7 (4.7–11.2)
	Surgical	TF	42.1		9.2			9.2			25.0	21.1		19 (12–28)	6.0 (4.4–9.1)
	TAo		54.5		22.7			6.8			27.3	70.5		27 (18–33)	8.6 (4.9–11.2)
	P value		0.571		0.194			0.528			0.025	<0.001		<0.001	0.174
Ciuca 2016[11]	TSc/TAx		N/A	28.3		N/A		40.0		61.7		Arteriopathy	31.7	26.7 ± 14.9	8.9 ± 7.5
	TAp			22.5				26.8		59.2			43.7	22.4 ± 12.2	9.5 ± 8.0
	P value			0.24				0.05		0.43			0.07	0.03	0.67
Codner 2018[12,*]	TSc/TAx		N/A	CABG	18.2	Stroke/TIA	18.2	N/A		N/A		45.5		N/A	7.6 ± 2.1
	TAp				72.7		45.5					36.4			9.0 ± 3.7
	TAo				27.3		9.1					36.4			8.5 ± 3.8
	Suprasternal				27.3		18.2					45.5			8.3 ± 3.8
	P value				0.05		0.31					1.00			0.41
CoreValve US (Gleason) 2018[13,*]	TSc/TAx		81.7	33.7		9.9		66.3		Stage 4/5	11.9	60.4		20.7 ± 14.3	9.7 ± 5.9
	TF		83.7	27.7		10.4		68.3			9.4	57.9		19.4 ± 15.0	9.8 ± 5.5
	P value		0.599	0.196		0.869		0.671			0.420	0.613		0.377	0.845
FRANCE (Eltchaninoff) 2011[14]	TSc/TAx	CoreValve	50.0	CABG	33.3	8.3		N/A		N/A		N/A		24.6 ± 14.5	21.0 ± 17.2
	TF	SAPIEN	35.8		24.2	8.4								25.6 ± 11.3	17.4 ± 11.3
	TF	CoreValve	42.4		22.7	12.1								24.7 ± 11.2	21.3 ± 14.6
	TAp	SAPIEN	46.5		28.2	8.5								26.8 ± 11.6	18.4 ± 12.1
FRANCE-2 (Gilard) 2012[15,†]	TSc/Tax		58.4	CABG	24.2	CVD	11.2	35.4		N/A		41.6		20.3 ± 15.2	16.6 ± 13.4
	TF		44.4		15.2		9.6	25.3				12.5		21.2 ± 14.7	14.5 ± 11.9
	TAp		59.4		30.0		11.0	22.7				48.1		24.8 ± 14.7	15.1 ± 13.8
	P value		<0.001		<0.001		0.50	0.003				<0.001		<0.001	0.15
FRANCE-2 (Gilard) 2016[16,‡]	TSc/TAx/TF/TAp		47.7	CABG	17.6	CVD	10.0	24.5		N/A		20.1		21.7	N/A
Italian CoreValve (Fiorina) 2017[17]	TSc/TAx		61.2	15.0		N/A		N/A		N/A		N/A		15 (5–26)	6 (4–12)
	TAo		68.4	26.3										27 (16–39)	10 (5–14)
	P value		0.07	0.023										<0.001	0.005
Italian CoreValve (Petronio) 2010[18,¶]	TSc/TAx		64.8	CABG	14.8	CVA	14.8	Severe	31.5	N/A		55.6		25.3 (15.1–36.6)	N/A
	TF		48.7		16.5		7.0		21.3			15.0		19.4 (12.5–29.8)	
	P value		0.03		0.75		0.06		0.09			<0.0001		0.03	
Italian CoreValve (Petronio) 2012[19,*,§]	TSc/TAx		58.9	N/A		12.8		N/A		Creatinine >2 mg/dl	13.5	85.1		23.7 (15.8–33.6)	N/A
	TF		48.9			9.2					8.5	20.6		23.3 (13.5–32.7)	
	P value		0.09			0.34					0.24	<0.0001		0.32	
Muensterer 2013[20]	TSc/TAx		60.0	15.0		17.5		RD	25.0	N/A		42.5		21.5 ± 12.2	6.6 ± 5.6
	TF		52.2	16.3		11.0			20.3			14.0		19.2 ± 12.8	5.9 ± 4.1
	P value		0.401	0.858		0.321			0.534			<0.001		0.594	0.347

(*continued on next page*)

Table 1 (*Continued*)

Study	Approach	CAD (%)	Prior cardiac surgery (%)	Stroke (%)	COPD (%)	CKD (%)	PAD (%)	Logistic EuroSCORE (%)	STS PROM (%)
Saia 2013[21]	TSc/TAx/TF/TAp	50.0	20.6	4.9	25.5	87.3	11.8	22.6 ± 12.4	8.2 ± 4.1
Taramasso 2011[22]	TSc/TAx	N/A	N/A	CVD 15.8	57.9	36.8	63.2	28.6 ± 14.3	22.3 ± 13.2
	TF			15.0	35.7	28.6	18.6	26.7 ± 15.8	20.6 ± 12.0
	TAp			50.0	37.5	31.3	62.5	33.6 ± 23.2	28.3 ± 15.7
	P value			0.003	0.1	0.7	<0.0001	0.3	0.7
UK CoreValve (Moynagh) 2011[23]	TSc/TAx	74.3	N/A	N/A	40.0	N/A	74.3	25.0 ± 14.7	N/A
	TF	58.5			18.6		21.3	19.1 ± 12.3	
	P value	0.09			0.007		<0.0001	0.02	
UK TAVI (Fröhlich) 2015[24]	TSc/TAx	50.0	33.5	ND 18.6	27.7	N/A	N/A	22 (14–34)	N/A
	TF	40.8	29.3	14.5	26.1			17 (11–26)	
	TAp	53.4	42.6	16.7	26.3			20 (14–31)	
	TAo	47.6	23.8	15.1	38.4			21.2 (15–33)	
	P value	<0.0001	<0.0001	0.42	0.01			<0.0001	

Age, logistic EuroSCORE, and STS PROM are expressed as mean ± standard deviation or median (interquartile range).

* Propensity-score matching.

† 184 TSc/TAx patients were included. 30-day all-cause/cardiovascular mortality and 1-year outcomes were available. 30-day all-cause/cardiovascular mortality and 1-year outcomes except for all-cause mortality were extracted for the present meta-analysis. For the present meta-analysis, 3-year all-cause mortality was extracted from FRANCE-2 (Gilard) 2016[10].

‡ 242 TSc/TAx patients were included. 3-year all-cause mortality were available and extracted for the present meta-analysis.

¶ 54 TSc/TAx patients were included. 30-day and 6-month outcomes were available. 6-month outcomes (except for all-cause/cardiovascular mortality) were extracted for the present meta-analysis. For the present meta-analysis, 30-day outcomes and 2-year all-cause/cardiovascular mortality were extracted from Italian CoreValve (Petronio) 2012[13].

§ 141 TSc/TAx patients were included. 30-day outcomes and 2-year all-cause/cardiovascular mortality were available and extracted for the present meta-analysis.CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cerebrovascular disease; DM, diabetes mellitus; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FRANCE, FRench Aortic National CoreValve and Edwards; GFR, glomerular filtration rate; N/A, not available; ND, neurological disease; PAD, peripheral artery disease; RD, Respiratory disease; STS PROM, Society of Thoracic Surgeons Predicted Risk Of Mortality; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TAx, transaxillary; TF, transfemoral; TIA, transient ischemic attack; TSc, transsubclavian.

after TSc/TAx-TAVI remain unclear. A recent meta-analysis by Amat-Santos et al[8] included a few studies of TSc/TAx-TAVI versus TF-TAVI. The purpose of the present study was to compare outcomes, i.e. early or late all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, major bleeding complications, acute kidney injury, vascular complications, and pacemaker implantation, after TSc/TAx-TAVI versus TF-TAVI, TAp-TAVI, or TAo-TAVI by means of meta-analysis of currently available studies.

Methods

All studies comparing outcomes after TSc/TAx-TAVI versus TF-TAVI, TAp-TAVI, or TAo-TAVI were identified using a 2-level search strategy. First, databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched through May 2018 using Web-based search engines (PubMed and OVID). Search terms included *transaxillary, trans-axillary, transsubclavian, trans-subclavian, transubclavian, axillary*, or *subclavian*; and "*aortic valve implantation*" or "*aortic valve replacement*." 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.

Studies considered for inclusion met the following criteria: the study population was patients undergoing TAVI; patients were assigned to TSc/TAx-TAVI and TF-TAVI, TAp-TAVI, or TAo-TAVI; and at least one of postprocedural early (30-day or in-hospital) or late (including early) outcomes (including all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, major bleeding complications, acute kidney injury, vascular complications, and pacemaker implantation) was reported. We excluded studies not reporting both the incidence of the above-mentioned outcomes after TSc/TAx-TAVI and that after at least one of TF-TAVI, TAp-TAVI, and TAo-TAVI. Appropriateness of a study to be included in the meta-analysis was adjudicated by 2 researchers (HT, TK) and verified independently by a third investigator (TA). Disagreements were resolved by consensus. We evaluated the quality of the studies using the RoBANS [Risk of Bias Assessment Tool for Nonrandomized Studies][9] and assessed risk of bias ranging from low to unclear in accordance with 6 components. An odds or hazard ratio of each early or late outcome with its 95% confidence interval for TSc/TAx-TAVI versus the other approach was extracted from each individual study. If possible, an adjusted rather than unadjusted odds/hazard ratio was preferentially extracted.

Study-specific estimates were combined using inverse variance-weighted averages of logarithmic odds/hazard ratios in the random-effects model according to the comparison of TSc/TAx-TAVI versus TF-TAVI, TSc/TAx-TAVI versus TAp-TAVI, and TSc/TAx-TAVI versus TAo-TAVI. When only <3 odds/hazard ratios were available, we did not combine them. All analyses were conducted using Review Manager version 5.3 (available from http://tech.cochrane.org/revman).

Results

Our search identified 15 eligible reports[10–24] from 12 studies including 10,528 patients (TSc/TAx-TAVI, 965; TF-TAVI, 7468; TAp-TAVI, 1760; TAo-TAVI, 335) (Table 1). No randomized controlled trials and only 3 propensity score matched studies[12,13,19] were included. The quality (risk of bias) of the studies was summarized in Supplemental Fig. S1. In most of studies, Society of Thoracic Surgeons Predicted Risk of Mortality was equivalent among the TSc/TAx-TAVI, TAp-TAVI, and TAo-TAVI groups, and peripheral arterial disease was more frequent in the TSc/TAx-TAVI than TF-TAVI group. Early (30-day/in-hospital) and late (6-month to 3-year [considered as mid-term]) outcomes were summarized in Supplemental Tables S1 and S2, respectively. In Tables 2 and 3, odds/hazard ratios for early (30-

Table 2
Odds ratios [95% confidence interval] for early outcomes

Study	Comparison (TSc/TAx vs)	Early outcomes							
		All-cause mortality	Cardiovascular mortality	Myocardial infarction	Stroke	Major bleeding complications	Acute kidney injury	Vascular complications	Pacemaker implantation
Adamo 2015[10]	TF/TAo	1.07 [0.24, 4.86]	N/A	1.26 [0.06, 25.01]	1.30 [0.16, 10.95]	4.77 [0.84, 27.12]	0.59 [0.08, 4.63]	0.58 [0.03, 10.42]	1.19 [0.43, 3.28]
	TF	1.19 [0.26, 5.55]		1.50 [0.07, 32.04]	1.29 [0.15, 11.08]	4.03 [0.71, 22.96]	0.63 [0.08, 5.01]	0.49 [0.03, 8.81]	1.15 [0.42, 3.20]
	TAo	0.67 [0.11, 3.88]		0.45 [0.02, 11.31]	1.39 [0.08, 23.04]	7.30 [0.34, 157.33]	0.44 [0.04, 4.44]	N/A	1.44 [0.38, 5.48]
Ciuca 2016[11]	TAp	0.18 [0.02, 1.45]	N/A	0.94 [0.18, 5.01]	2.41 [0.33, 17.55]	0.11 [0.03, 0.47]*	0.72 [0.38, 1.36]	0.51 [0.11, 2.43]	6.09 [2.44, 15.20]*
Codner 2018[12]	TAp/TAo	2.10 [0.12, 37.12]	N/A	N/A	N/A	N/A	N/A	N/A	2.22 [0.27, 18.37]
	TAp	1.00 [0.05, 18.30]							2.22 [0.17, 28.86]
	TAo	3.29 [0.12, 89.81]							2.22 [0.17, 28.86]
CoreValve US (Gleason) 2018[13]	TF	0.91 [0.39, 2.12]	0.91 [0.39, 2.12]	1.51 [0.25, 9.12]	1.92 [0.75, 4.91]	1.30 [0.83, 2.04]	0.66 [0.36, 1.20]	1.16 [0.62, 2.16]	0.67 [0.42, 1.08]
FRANCE (Eltchaninoff) 2011[14]	TF/TAp	0.61 [0.08, 4.91]	N/A	N/A	0.94 [0.05, 17.11]	N/A	N/A	1.32 [0.16, 10.88]	2.64 [0.67, 10.38]
	TF	0.72 [0.09, 5.93]			0.82 [0.04, 15.28]			1.24 [0.15, 10.50]	2.11 [0.53, 8.39]
	TAp	0.45 [0.05, 3.80]			1.11 [0.05, 24.57]			1.52 [0.16, 14.92]	5.58 [1.07, 29.09]*
FRANCE-2 (Gilard) 2012[15]	TF/TAp	1.15 [0.70, 1.88]	1.27 [0.74, 2.20]	N/A	N/A	N/A	N/A	N/A	N/A
	TF	1.32 [0.80, 2.16]	1.50 [0.86, 2.61]						
	TAp	0.73 [0.43, 1.25]	0.76 [0.42, 1.38]						
FRANCE-2 (Gilard) 2016[16]	TF/TAp	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	TF								
	TAp								
Italian CoreValve (Fiorina) 2017[17]	TAo	0.55 [0.20, 1.48]	0.41 [0.11, 1.51]	N/A	1.30 [0.12, 14.50]	1.61 [0.81, 3.21]	0.50 [0.28, 0.88]*	2.83 [1.03, 7.83]*	2.95 [1.43, 6.10]*
Italian CoreValve (Petronio) 2010[18]	TF	N/E	N/E	N/E	N/E	N/E	N/E	N/E	N/E
Italian CoreValve (Petronio) 2012[19]	TF	0.88 [0.33, 2.36]	1.15 [0.41, 3.27]	N/A	1.00 [0.20, 5.04]	1.29 [0.79, 2.12]	0.40 [0.15, 1.08]	0.62 [0.23, 1.64]	1.00 [0.58, 1.72]
Muensterer 2013[20]	TF	0.64 [0.14, 2.81]	N/A	N/A	0.57 [0.07, 4.46]	N/A	0.82 [0.24, 2.85]	N/A	0.66 [0.29, 1.48]
Saia 2013[21]	TF/TAp	0.62 [0.03, 11.94]	N/A	2.39 [0.09, 61.85]	1.42 [0.06, 31.23]	N/A	N/A	N/A	N/A
	TF	0.56 [0.03, 10.98]		1.75 [0.07, 45.38]	1.03 [0.05, 22.82]				
	TAp	0.63 [0.02, 16.54]		N/A	N/A				
Taramasso 2011[22]	TF/TAp	2.11 [0.22, 19.93]	2.11 [0.22, 19.93]	N/A	2.83 [0.28, 28.70]	N/A	N/A	0.14 [0.01, 2.37]	0.34 [0.04, 2.66]
	TF	3.83 [0.33, 44.43]	3.83 [0.33, 44.43]		2.54 [0.25, 25.71]			0.12 [0.01, 2.09]	0.35 [0.04, 2.81]
	TAp	0.39 [0.03, 4.74]	0.39 [0.03, 4.74]		2.68 [0.10, 70.30]			N/A	0.24 [0.02, 2.58]
UK CoreValve (Moynagh) 2011[23]	TF	0.27 [0.02, 4.70]	N/A	N/A	0.65 [0.08, 5.17]	N/A	N/A	0.27 [0.04, 2.04]	N/A
UK TAVI (Fröhlich) 2015[24]	TF/TAp/TAo	0.45 [0.18, 1.11]	N/A	N/A	1.48 [0.64, 3.45]	N/A	N/A	0.75 [0.27, 2.04]	2.41 [1.69, 3.44]*
	TF	0.61 [0.25, 1.51]			1.57 [0.67, 3.70]			0.61 [0.22, 1.66]	2.01 [1.41, 2.88]*
	TAp	0.23 [0.09, 0.58]*			1.06 [0.42, 2.64]			5.49 [1.22, 24.75]*	5.80 [3.61, 9.32]*
	TAo	0.31 [0.11, 0.87]*			6.07 [0.72, 50.89]			0.65 [0.18, 2.34]	3.92 [2.03, 7.58]*
Total	**TF/TAp/TAo**	**0.83 [0.62, 1.13]**	**1.07 [0.72, 1.58]**	**1.28 [0.44, 3.72]**	**1.44 [0.89, 2.31]**	**1.15 [0.62, 2.15]**	**0.60 [0.44, 0.81]***	**0.92 [0.57, 1.46]**	**1.51 [0.91, 2.53]**
	TF	**1.00 [0.72, 1.39]**	**1.31 [0.86, 1.98]**	**1.55 [0.38, 6.28]**	**1.40 [0.85, 2.31]**	**1.35 [0.97, 1.87]**	**0.61 [0.38, 0.97]***	**0.79 [0.52, 1.23]**	**1.05 [0.65, 1.68]**
	TAp	**0.52 [0.34, 0.80]***	**0.74 [0.41, 1.31]**	**0.94 [0.18, 5.01]**	**1.27 [0.58, 2.76]**	**0.11 [0.03, 0.47]***	**0.72 [0.38, 1.36]**	**1.65 [0.36, 7.67]**	**4.22 [2.02, 8.83]***
	TAo	**0.48 [0.25, 0.92]***	**0.41 [0.11, 1.51]**	**0.45 [0.02, 11.31]**	**2.54 [0.63, 10.18]**	**1.73 [0.88, 3.39]**	**0.49 [0.28, 0.86]***	**1.43 [0.34, 6.05]**	**3.08 [1.96, 4.84]***
CoreValve subtoal (number of studies)	**TF**	**0.83 [0.49, 1.39]** (6)	**1.00 [0.52, 1.93]** (2)	**1.51 [0.32, 7.11]** (2)	**1.25 [0.65, 2.42]** (6)	**1.35 [0.97, 1.87]** (3)	**0.61 [0.38, 0.97]*** (4)	**0.89 [0.55, 1.45]** (5)	**0.81 [0.60, 1.09]** (5)
	TAo	**0.58 [0.24, 1.36]** (2)	**N/A**	**N/A**	**1.33 [0.21, 8.33]** (2)	**N/A**	**N/A**	**N/A**	**2.51 [1.33, 4.74]*** (2)

* Statistically significant ($P < 0.05$).FRANCE, FRench Aortic National CoreValve and Edwards; N/A, not available; N/E, not extracted; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TAx, transaxillary; TF, transfemoral; TSc, transsubclavian.

Table 3
Odds ratios [95% confidence interval] for late outcomes

Study	Comparison (TSc/TAx vs)	Late outcomes							
		All-cause mortality	Cardiovascular mortality	Myocardial infarction	Stroke	Major bleeding complications	Acute kidney injury	Vascular complications	Pacemaker implantation
Adamo 2015[10]	TF/TAo	1.68 [0.71, 3.96]	N/A	N/A	3.65 [0.92, 14.51]	N/A	N/A	N/A	N/A
	TF	1.72 [0.72, 4.09]			3.53 [0.87, 14.41]				
	TAo	1.50 [0.50, 4.54]			4.45 [0.44, 44.88]				
Ciuca 2016[11]	TAp	Adjusted HR, 1.1 [0.6, 1.9]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Codner 2018[12]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CoreValve US (Gleason) 2018[13]	TF	0.92 [0.58, 1.46]	0.94 [0.57, 1.54]	1.68 [0.40, 7.14]	1.39 [0.68, 2.86]	1.31 [0.85, 2.03]	0.66 [0.36, 1.20]	1.10 [0.60, 2.04]	0.67 [0.43, 1.06]
FRANCE (Eltchaninoff) 2011[14]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FRANCE-2 (Gilard) 2012[15]	TF/TAp	N/E	1.02 [0.63, 1.67]	3.26 [1.34, 7.93]*	1.91 [1.05, 3.46]*	1.76 [0.75, 4.15]	N/A	1.12 [0.69, 1.81]	1.96 [1.39, 2.77]*
	TF		1.17 [0.71, 1.92]	3.95 [1.56, 9.95]*	1.99 [1.09, 3.63]*	2.18 [0.91, 5.24]		0.95 [0.59, 1.54]	1.91 [1.35, 2.71]*
	TAp		0.66 [0.39, 1.12]	1.88 [0.67, 5.24]	1.65 [0.83, 3.29]	0.97 [0.38, 2.47]		3.34 [1.75, 6.35]*	2.18 [1.45, 3.29]*
FRANCE-2 (Gilard) 2016[16]	TF/TAp	1.78 [1.37, 2.31]*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	TF	Adjusted HR, 1.50 [1.22, 1.85]*							
	TAp	Adjusted HR, 1.17 [0.91, 1.51]							
Italian CoreValve (Fiorina) 2017[17]	TAo	1.19 [0.58, 2.42]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Italian CoreValve (Petronio) 2010[18]	TF	N/E	N/E	1.32 [0.07, 26.14]	1.05 [0.13, 8.60]	0.78 [0.10, 6.22]	N/A	N/A	N/A
Italian CoreValve (Petronio) 2012[19]	TF	HR, 0.93 [0.57, 1.52]	HR, 1.01 [0.48, 2.12]	N/A	N/A	N/A	N/A	N/A	N/A
Muensterer 2013[20]	TF	HR, 1.49 [0.75, 2.97]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Saia 2013[21]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Taramasso 2011[22]	TF/TAp	N/A	0.56 [0.07, 4.54]	N/A	N/A	N/A	N/A	N/A	N/A
	TF	HR, 2.73 [0.47, 15.76]	0.72 [0.09, 5.98]						
	TAp	HR, 0.60 [0.09, 4.01]	0.17 [0.02, 1.68]						
UK CoreValve (Moynagh) 2011[23]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UK TAVI (Fröhlich) 2015[24]	TF/TAp/TAo	1.09 [0.74, 1.60]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	TF	HR, 1.22 [0.88, 1.70]							
	TAp	HR, 0.70 [0.48, 1.03]†							
	TAo	HR, 0.79 [0.50, 1.24]‡							
Total	**TF/TAp/TAo**	**1.24 [0.99, 1.54]**	**0.97 [0.71, 1.33]**	**2.60 [1.25, 5.42]***	**1.78 [1.16, 2.72]***	**1.37 [0.93, 2.00]**	**0.66 [0.36, 1.20]**	**1.11 [0.76, 1.62]**	**1.16 [0.41, 3.31]**
	TF	**1.28 [1.07, 1.54]***	**1.03 [0.75, 1.41]**	**2.92 [1.37, 6.20]***	**1.80 [1.17, 2.77]***	**1.42 [0.97, 2.08]**	**0.66 [0.36, 1.20]**	**1.01 [0.69, 1.47]**	**1.15 [0.41, 3.19]**
	TAp	**0.96 [0.70, 1.31]**	**0.54 [0.20, 1.42]**	**1.88 [0.67, 5.24]**	**1.65 [0.83, 3.29]**	**0.97 [0.38, 2.47]**	**N/A**	**3.34 [1.75, 6.35]***	**2.18 [1.45, 3.29]***
	TAo	**0.94 [0.65, 1.35]**	**N/A**	**N/A**	**4.45 [0.44, 44.88]**	**N/A**	**N/A**	**N/A**	**N/A**
CoreValve subtoal (number of studies)	**TF**	**1.07 [0.81, 1.43]** (4)	**0.96 [0.64, 1.45]** (2)	**1.61 [0.44, 5.90]** (2)	**1.62 [0.88, 3.00]** (3)	**1.28 [0.84, 1.97]** (2)	**N/A**	**N/A**	**N/A**
	TAo	**1.27 [0.70, 2.31]** (2)	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**

* Statistically significant ($P < 0.05$).
† Calculated form the HR for TAx versus TF and the HR for TAp versus TF.
‡ Calculated form the HR for TAx versus TF and the HR for TAo versus TF.FRANCE, FRench Aortic National CoreValve and Edwards; HR, hazard ratio; N/A, not available; N/E, not extracted; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TAx, transaxillary; TF, transfemoral; TSc, transsubclavian.

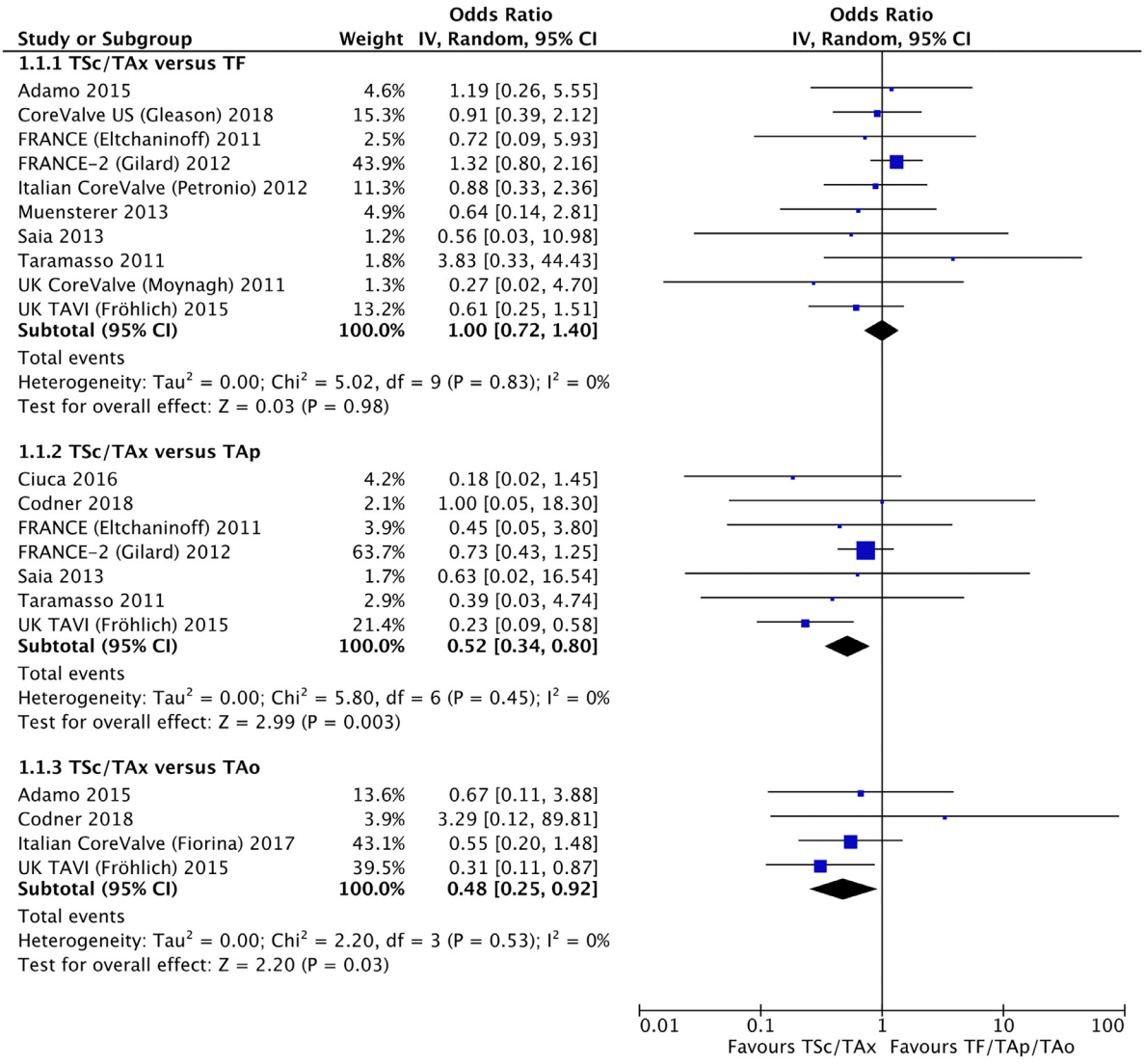

Fig. 1. Forrest plot of early all-cause mortality. CI, confidence interval; FRANCE, FRench Aortic National CoreValve and Edwards; IV, inverse variance; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TSc/TAx, transsubclavian/transaxillary; TF, transfemoral.

day/in-hospital) and late (midterm) outcomes were summarized, respectively. Only 3 adjusted hazard ratios for all-cause mortality from 2 studies[11,16] were available (Table 3).

Results of meta-analysis were summarized in Tables 2 and 3. Pooled analysis of early all-cause mortality demonstrated no statistically significant difference between TSc/TAx-TAVI and TF-TAVI (Fig. 1-1.1.1), but a statistically significant reduction after TSc/TAx-TAVI compared with TAp-TAVI (odds ratio, 0.52; $P = 0.003$; Fig. 1-1.1.2) or TAo-TAVI (odds ratio, 0.48; $P = 0.03$; Fig. 1-1.1.3). There was no statistically significant difference in early cardio(vascular) mortality (Supplemental Fig. S2), myocardial infarction (Supplemental Fig. S3), stroke (Supplemental Fig. S4), major bleeding complications (Supplemental Fig. S5), and vascular complications (Supplemental Fig. S6) among the groups, but a statistically significant reduction in early acute kidney injury after TSc/TAx-TAVI compared with TF-TAVI (odds ratio, 0.61; $P = 0.03$; Supplemental Fig. S7). Pooled analysis of early pacemaker implantation demonstrated no statistically significant difference between TSc/TAx-TAVI and TF-TAVI (Fig. 2-1.8.1), but a statistically significant increase after TSc/TAx-TAVI compared with TAp-TAVI (odds ratio, 4.22; $P = 0.0001$; Fig. 2-1.8.2) or TAo-TAVI (odds ratio, 3.08; $P < 0.00001$; Fig. 2-1.8.3).

Pooled analysis of midterm all-cause mortality demonstrated a statistically significant increase after TSc/TAx-TAVI compared with TF-TAVI (odds ratio, 1.28; $P = 0.007$; Fig. 3-2.1.1), but no statistically significant difference between TSc/TAx-TAVI and TAo-TAVI (Fig. 3-2.1.2) or between TSc/TAx-TAVI and TAo-TAVI (Fig. 3-2.1.3). There was no statistically significant difference in midterm cardio(vascular) mortality (Supplemental Fig. S8) and major bleeding complications (Supplemental Fig. S9) between TSc/TAx-TAVI and TF-TAVI. Pooled analysis demonstrated a statistically significant increase in midterm myocardial infarction (odds ratio, 2.92; $P = 0.005$; Fig. 4) and stroke (odds ratio, 1.80; $P = 0.007$; Fig. 5) after TSc/TAx-TAVI compared with TF-TAVI.

Discussion

Key findings of the present meta-analysis were the following (Tables 2 and 3). Early (30-day/in-hospital) all-cause mortality was lower after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, but equivalent between TSc/TAx-TAVI and TF-TAVI. In contrast, early pacemaker implantation was more frequent after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, but equivalent between TSc/TAx-TAVI and TF-TAVI.

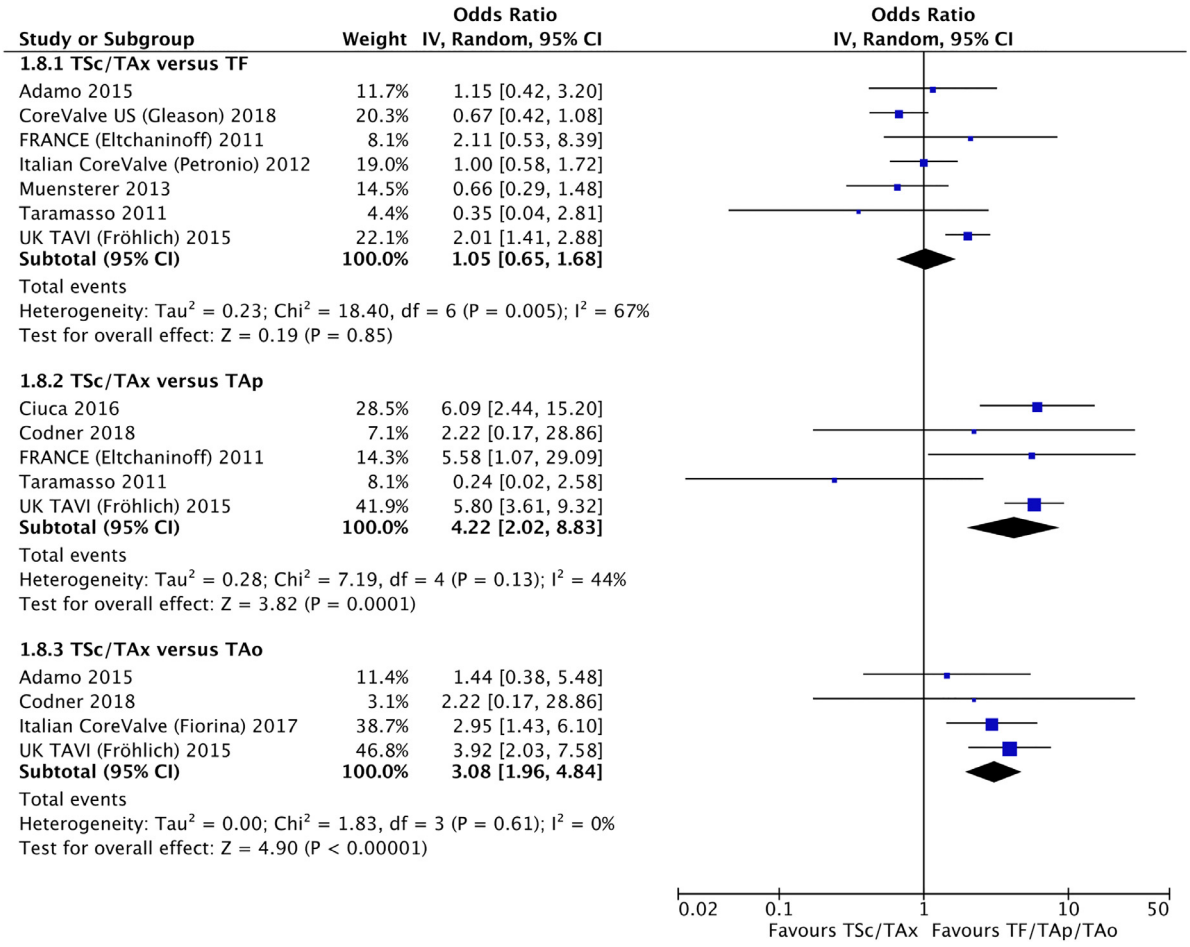

Fig. 2. Forrest plot of early pacemaker implantation. CI, confidence interval; FRANCE, FRench Aortic National CoreValve and Edwards; IV, inverse variance; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TSc/TAx, transsubclavian/transaxillary; TF, transfemoral.

Whereas, midterm (6-month to 3-year) all-cause mortality was higher after TSc/TAx-TAVI than TF-TAVI, but equivalent among TSc/TAx-TAVI, TAp-TAVI, and TAo-TAVI.

In most of the studies included in the present meta-analysis, Society of Thoracic Surgeons Predicted Risk of Mortality was equivalent among the TSc/TAx-TAVI, TAp-TAVI, and TAo-TAVI groups (Table 1). Far less procedural invasiveness of TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI may simply bring about lower early all-cause mortality demonstrated in the present meta-analysis (odds ratio for TSc/TAx-TAVI versus TAp-TAVI, 0.52; $P = 0.003$; odds ratio for TSc/TAx-TAVI versus TAo-TAVI, 0.48; $P = 0.03$; Table 2; Fig. 1-1.1.2/3). This hypothesis may be strengthened by the finding that early all-cause mortality is lower after TF-TAVI (less invasive as well as TSc/TAx-TAVI) than TAp-TAVI. A recent meta-analysis by Zhao et al[25] of 14 studies (including a total of 5718 patients) demonstrated that early all-cause mortality was significantly lower after TF-TAVI than TAp-TAVI (7.5% versus 11.6%; odds ratio, 0.57). Differences between patients in different TAVI-approach groups (selection bias), however, should be concerned. In a meta-analysis by Liu et al[26] of 9 studies with no significant difference in logistic EuroSCORE between the TF-TAVI and TAp-TAVI groups (including a total of 1123 patients), early all-cause mortality was equivalent (9.2% versus11.4%; $P = 0.14$). In contrast, our previous meta-analysis[27] of odds ratios adjusting for potential confounders from 18 studies (including a total of 6606 patients) demonstrated that early all-cause mortality was significantly higher after TAp-TAVI than TF-TAVI (odds ratio, 1.61; $P = 0.0009$). To confirm the present findings, a randomized controlled trial of TSc/TAx-TAVI versus TAp-TAVI or TAo-TAVI should be conducted.

More frequent early pacemaker implantation after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI demonstrated in the present meta-analysis (odds ratio for TSc/TAx-TAVI versus TAp-TAVI, 4.22; $P = 0.0001$; odds ratio for TSc/TAx-TAVI versus TAo-TAVI, 3.08; $P < 0.00001$; Table 2; Fig. 2-1.8.2/3) may be explicated by the predominant use of CoreValve in TSc/TAx-TAVI. In a study by Ciuca et al,[11] the incidence of atrioventricular (AV) block with the necessity of new pacemaker implantation was more frequent in the TSc/TAx group (27.1% versus 5.6%, $P < 0.001$), which was clearly device-related rather than access-related (29.5% in patients receiving CoreValve versus 7.1% in patients receiving SAPIEN, $P < 0.001$). Fröhlich et al[24] also demonstrated, in their study from the UK TAVI registry, that the higher rate of postprocedural pacemaker implantation after TSc/TAx-TAVI (22.9%) than TAp-TAVI (4.9%) or TAo-TAVI (7.0%) was associated with predominantly using CoreValve in TSc/TAx-TAVI (98.9%) compared with TAp-TAVI (0.4%) or TAo-TAVI (36.2%). On the basis of a meta-analysis by Siontis et al[28] of data derived from 9 studies (including a total of 5131 patients), implantation of CoreValve was associated with a 2.5-fold increased risk of permanent pacemaker implantation compared with SAPIEN (risk ratio, 2.54; $P < 0.01$). Self-expandable valve design and deeper valve implantation (into the left ventricular outflow tract) likely contribute to an increase in the risk of AV block with CoreValve,[28] which may bring about more injury to the AV node and left bundle branches retarded due to the self-

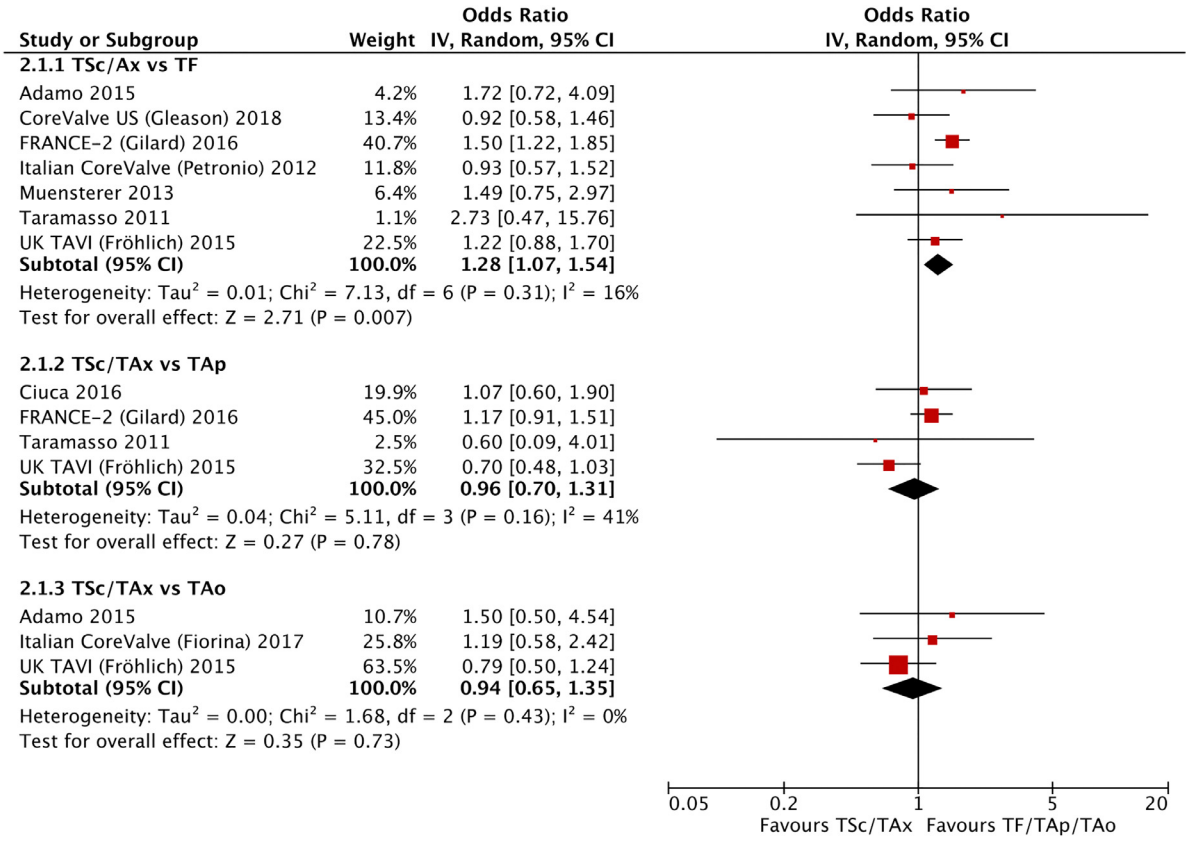

Fig. 3. Forrest plot of midterm all-cause mortality. CI, confidence interval; FRANCE, FRench Aortic National CoreValve and Edwards; IV, inverse variance; TAo, transaortic; TAp, transapical; TAVI, transcatheter aortic valve implantation; TSc/TAx, transsubclavian/transaxillary; TF, transfemoral.

expandable prosthetic nature and subsequent tissue edema.[29] However, Fiorina et al[17] demonstrated, in their study exclusively using CoreValve (from the Italian CoreValve registry), that the incidence of new permanent pacemaker implantation in the TAx group was higher compared to the TAo group (27.9% versus 11.6%; $P = 0.017$) even in multivariable analysis (odds ratio, 3.697; $P = 0.017$), which may not appropriately explicated. Further investigations would be required.

Higher midterm all-cause mortality after TSc/TAx-TAVI than TF-TAVI (despite equivalent early all-cause mortality) demonstrated in the present meta-analysis (odds ratio, 1.28; $P = 0.007$; Table 3; Fig. 3-2.1.1) may be partially explicated by more frequent midterm myocardial infarction and stroke after the former than the latter. More frequent midterm myocardial infarction (odds ratio, 2.92, $P = 0.005$; Fig. 4) and stroke (odds ratio, 1.80, $P = 0.007$; Fig. 5) were demonstrated in the present meta-analysis (Table 3). Another explanation may be more frequent baseline peripheral arterial disease in patients undergoing TSc/TAx-TAVI than TF-TAVI. Indeed, in most of the studies included in the present meta-analysis, baseline peripheral arterial disease was more frequent in the TSc/TAx-TAVI than TF-TAVI group (Table 1). Furthermore, peripheral arterial disease is independently associated with higher all-cause mortality after TAVI. After adjustment for baseline characteristics in a study by Fanaroff et al,[30] peripheral arterial disease significantly associated with a higher rate of 1-year all-cause mortality in patients undergoing TF-TAVI (adjusted hazard ratio, 1.14; $P = 0.008$).

Baseline patient comorbidity may affect prognosis of various TAVI approaches. For 645 TAp-TAVI patients surviving ≥30 days in the I-TA [Italian Registry of Trans-Apical Aortic Valve Implantation]

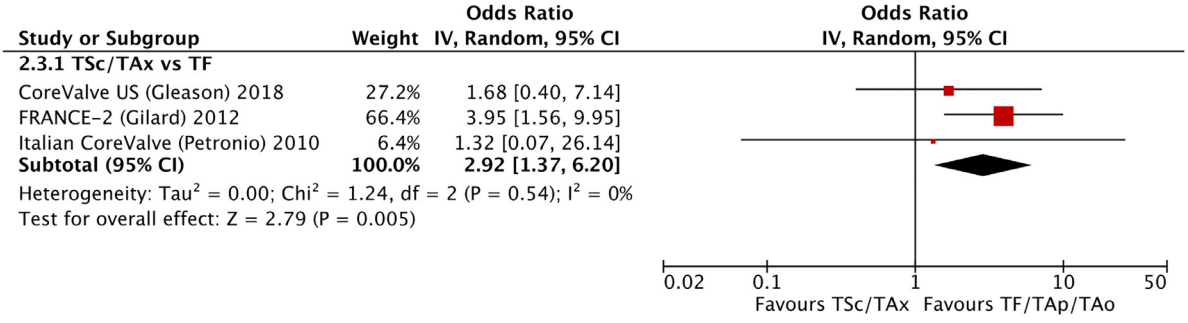

Fig. 4. Forrest plot of midterm myocardial infarction. CI, confidence interval; FRANCE, FRench Aortic National CoreValve and Edwards; IV, inverse variance; TAo, transaortic; TAp, transapical; TSc/TAx, transsubclavian/transaxillary; TF, transfemoral.

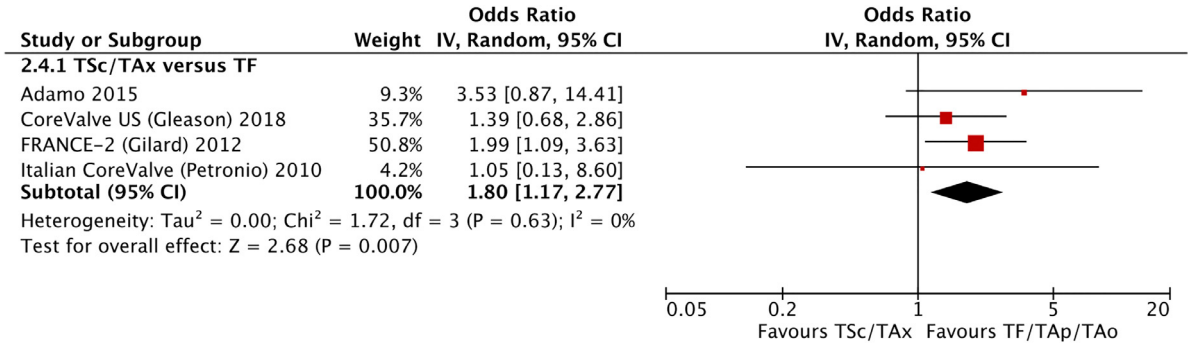

Fig. 5. Forrest plot of midterm stroke. CI, confidence interval; FRANCE, FRench Aortic National CoreValve and Edwards; IV, inverse variance; TAo, transaortic; TAp, transapical; TSc/TAx, transsubclavian/transaxillary; TF, transfemoral.

registry,[31] insulin-dependent diabetes, creatinine ≥2.0 mg/dL or dialysis, preoperative rhythm disorders, and left ventricular ejection fraction <30% independently predicted 1-year mortality. For 253 TAo-TAVI patients in the ROUTE [Registry of the Utilization of the TAo-TAVI approach using the Edwards SAPIEN Valve],[32] renal insufficiency, New York Heart Association class III/IV, and pulmonary disease independently predicted 1-year composite of death, non-fatal myocardial infarction, non-fatal stroke/transient ischemic attack, major vascular complications, life-threatening bleeding, acute kidney injury, or rehospitalization for valve-relate symptoms or worsening congestive heart failure. Furthermore, pulmonary disease independently predicted 1-year mortality.[32] Regrettably, predictors of prognosis after TSc/TAx-TAVI have been never researched to date.

Because TSc/TAx-TAVI enables to treat vast plurality of patients who are not able to undergo TF-TAVI, the TAp and TAo approach for TAVI may be on the decline with advancing experience of the TSc/TAx access. Furthermore, the renunciation of TAp-TAVI may be motivated by worse early and midterm outcomes after TAp-TAVI than after TF-TAVI. Although the present results suggest TSc/TAx-TAVI should be further adopted and diffused, better percutaneous approach of TSc/TAx-TAVI should be facilitated by continuous evolvement of slenderer device-calibers and more effective and secure closure-devices.

The present findings must be interpreted with caution in the context of their limitations. No randomized controlled trials and only 3 propensity score matched studies were included in the present meta-analysis. Among the 6 components of risk of bias[9] for the non-randomized studies included, selection of participants (selection bias), measurement of exposure (performance bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias) were, in general, low risk of bias, whereas confounding variables (selection bias) and blinding of outcome assessments (detection bias) were, on the whole, high risk of bias (Supplemental Fig. S1). Interpreting the results of the present meta-analysis of non-randomized studies must include the following consideration: e.g. attrition is often found and unsatisfactorily reported, assessing interventions and outcomes is unwontedly performed in accordance with standard protocols, and outcomes are uncommonly blinded.[33] For non-randomized studies distinct from randomized controlled trials, analysing adjusted (rather than unadjusted) effect estimates, i.e. attempting to control for confounders, would be appropriate.[33] Only few adjusted hazard ratios for all-cause mortality, however, were available in the studies included in the present meta-analysis. Non-blinding or non-masking of outcome appraisers may increase the risk of detection bias that knowledge of which intervention was performed, rather than the intervention itself, militates against outcome measure.[34] Publication bias favoring TSc/TAx-TAVI due to investigators' interest in each individual study, which may influence the present results, was minimized by exhaustively searching eligible studies.

Conclusion

Early all-cause mortality was lower after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, early pacemaker implantation was more frequent after TSc/TAx-TAVI than TAp-TAVI or TAo-TAVI, and midterm all-cause mortality was higher after TSc/TAx-TAVI than TF-TAVI. These results should be cautiously expounded because of the meta-analysis of non-randomized studies. To determine the present findings, randomized controlled trials of TSc/TAx-TAVI versus TF-TAVI, TAp-TAVI, or TAo-TAVI would be required.

Disclosure

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.04.002.

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