Sanz-Sánchez J, et al. Single or dual antiplatelet therapy after transcatheter aortic valve implantation. A meta-analysis of randomized controlled trials. *REC Interv Cardiol.* 2021. **https://doi.org/10.24875/RECICE.M21000210**

SUPPLEMENTARY DATA

Search strategy

(Antiplatelet[All Fields] OR antithrombotic[All Fields] OR ("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) OR ("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields]) OR ("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields]) OR ("ticlopidine"[MeSH Terms] OR "ticlopidine"[All Fields])) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND (transcatheter[All Fields] AND ("aortic valve"[MeSH Terms] OR ("aortic"[All Fields] AND "valve"[All Fields]) OR "aortic valve"[All Fields]))

Table 1 of the supplementary data. Definition of key endpoints

Study	Life-threatening or major bleeding	Myocardial infarction	Stroke
POPular TAVI[1]	**Life-threatening bleeding:**[2] • Fatal bleeding (BARC type 5) OR • Bleeding in a critical organ such as intracranial, intraspinal, intraocular or pericardial requiring pericardiocentesis or intramuscular with compartment syndrome (BARC type 3b, and 3c) OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR • Overt source of bleeding with a drop of hemoglobin levels > 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion > 4 units (BARC type 3b). **Major bleeding:**[2] • Overt bleeding either associated with a drop of hemoglobin levels of, at least, 3.0 g/dL or requiring	**Periprocedural MI (< 72 h after the index procedure):**[1] • New ischemic symptoms (ie, chest pain or shortness of breath) or new ischemic signs (ie, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in, at least, 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormalities) AND • Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of, at least, 1 postoperative sample with peak values exceeding 15x the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further postoperative increase of, at least, 50% is required, AND peak values should exceed the previously stated limit. **Spontaneous MI (> 72 h after the index procedure):** Any of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with, at least, 1 value above the 99th percentile URL	Acute episode of a focal or global neurological deficit with, at least, 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke.[1] Duration of a focal or global neurological deficit > 24 h; OR < 24 h if neuroimaging documents available, a new hemorrhage or infarction; OR neurological deficit resulting in death. No other readily identifiable non-stroke cause for the clinical presentation (ie, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with the designated neurologist. Confirmation of diagnosis by, at least, 1 of the following: • Neurologist or neurosurgical specialist. • Neuroimaging procedure (CT scan or brain MRI); nonetheless, stroke may be diagnosed on clinical grounds alone.

	transfusion of 2 or 3 units of whole blood/RBC or causing hospitalization or permanent injury or requiring surgery AND • Does not meet the criteria for life-threatening or disabling bleeding.	plus the evidence of myocardial ischemia with, at least, 1 of the following: ○ Symptoms of ischemia, ECG changes indicative of new ischemia. [new ST-T changes or new left bundle branch block (LBBB)]. ○ New pathological Q-waves in, at least, 2 contiguous leads. ○ Imaging evidence of a new loss of viable myocardium or new wall motion abnormalities. • Sudden, unexpected cardiac death involving cardiac arrest often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus on the coronary angiography and/or the autopsy or death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. Pathological findings of an acute myocardial infarction.	
ARTE [3]	**Life-threatening bleeding:[2]** • Fatal bleeding (BARC type 5) OR • Bleeding in a critical organ such as intracranial, intraspinal, intraocular or pericardial requiring pericardiocentesis or intramuscular with	**Periprocedural MI (< 72 h after the index procedure):[1]** • New ischemic symptoms (ie, chest pain or shortness of breath) or new ischemic signs (ie, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in, at least, 2 contiguous leads, imaging evidence of new	Acute episode of a focal or global neurological deficit with, at least, 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke.[1] Duration of a focal or global neurological deficit > 24 h; OR < 24 h if neuroimaging documents available, a new

	compartment syndrome (BARC type 3b and 3c) OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR • Overt source of bleeding with drop of hemoglobin levels > 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion > 4 units (BARC type 3b). **Major bleeding:**[2] • Overt bleeding either associated with a drop of hemoglobin levels of, at least, 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC or causing hospitalization or permanent injury or requiring surgery AND • Does not meet the criteria for life-threatening or disabling bleeding.	loss of viable myocardium or new wall motion abnormalities) AND • Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of, at least, 1 postoperative sample with peak values exceeding 15x the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further increase of, at least, 50% after the procedure is required AND peak values should exceed the previously stated limit. **Spontaneous MI (> 72 h after the index procedure):** Any of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with, at least, 1 value above the 99th percentile URL plus evidence of myocardial ischemia with, at least, 1 of the following: ○ Symptoms of ischemia, ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]. ○ New pathological Q-waves in, at least, 2 contiguous leads. ○ Imaging evidence of a new loss of viable myocardium or new wall motion abnormalities. • Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and	hemorrhage or infarction; OR neurological deficit resulting in death. No other readily identifiable non-stroke cause for the clinical presentation (ie, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with the designated neurologist. Confirmation of diagnosis by, at least 1, of the following: • Neurologist or neurosurgical specialist. • Neuroimaging procedure (CT scan or brain MRI); nonetheless, stroke may be diagnosed on clinical grounds alone.

		accompanied by presumably new ST-segment elevation or new LBBB, and/ or evidence of fresh thrombus on the coronary angiography and/or the autopsy or death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.	
SAT-TAVI[4]	**Life-threatening or disabling bleeding**[5] Fatal bleeding OR Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular or pericardial requiring pericardiocentesis or intramuscular with compartment syndrome OR Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR Overt source of bleeding with drop of hemoglobin levels ≥ 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units. **Major bleeding:**[5] Overt bleeding either associated with a drop of hemoglobin levels of, at least, 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC AND Does not meet the criteria for life-threatening or disabling bleeding.	**Periprocedural MI**[2] (≤ 72 h after the index procedure) • New ischemic symptoms (ie, chest pain or shortness of breath) or new ischemic signs (ie, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability or imaging evidence of new loss of viable myocardium or new wall motion abnormalities), AND • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of 2 or more postoperative samples taken between 6 h to 8 h apart with a 20% increase in the second sample, and peak values exceeding 10x the 99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in, at least, 2 contiguous leads. **Spontaneous MI:** (> 72 h after the index procedure) Any of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with, at	Rapid onset of a focal or global neurological deficit with, at least, 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke.[2] Duration of a focal or global neurological deficit ≥ 24 h; OR < 24 h if therapeutic intervention(s) performed (ie, thrombolytic therapy or intracranial angioplasty); OR neuroimaging documents available, a new hemorrhage or infarction; OR neurological deficit resulting in death. No other readily identifiable non-stroke cause for the clinical presentation (ie, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of diagnosis by, at least, 1 of the following: • Neurology or neurosurgical specialist. • Neuroimaging procedure (MRI or CT scan or cerebral angiography).

		least, 1 value above the 99th percentile URL plus evidence of myocardial ischemia with, at least, 1 of the following: ○ ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]. ○ New pathological Q waves in, at least, 2 contiguous leads. ○ Imaging evidence of new loss of viable myocardium or new wall motion abnormalities. • Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus on the coronary angiography and/or the autopsy or death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.	• Lumbar puncture (ie, spinal fluid analysis diagnostic of intracranial hemorrhage).
Ussia et al[6]	**Life-threatening or disabling bleeding:[5]** Fatal bleeding OR Bleeding in a critical area or organ such as intracranial, intraspinal, intraocular or pericardial requiring pericardiocentesis or intramuscular with compartment syndrome OR	**Periprocedural MI[2]** (≤ 72 h after the index procedure) • New ischemic symptoms (ie, chest pain or shortness of breath) or new ischemic signs (ie, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability or imaging evidence of new loss of viable myocardium or new wall motion abnormalities), AND	Rapid onset of a focal or global neurological deficit with, at least, 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke.[2] Duration of a focal or global neurological deficit ≥ 24 h; OR < 24 h if therapeutic intervention(s) performed (ie,

	Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR Overt source of bleeding with a drop of hemoglobin levels ≥ 5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 units. **Major bleeding:**[5] Overt bleeding either associated with a drop of hemoglobin levels of, at least, 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC AND Does not meet the criteria for life-threatening or disabling bleeding.	• Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of 2 or more postoperative samples taken between 6 h to 8 h apart with a 20% increase in the second sample and peak values exceeding 10x the 99th percentile upper reference limit (URL) or 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads. **Spontaneous MI** (> 72 h after the index procedure) Any of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with, at least, 1 value exceeding the 99th percentile URL plus evidence of myocardial ischemia with, at least, 1 of the following: o ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]. o New pathological Q waves in, at least, 2 contiguous leads. o Imaging evidence of new loss of viable myocardium or new wall motion abnormalities. • Sudden, unexpected cardiac death involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB, and/or evidence of fresh thrombus on the coronary	thrombolytic therapy or intracranial angioplasty); OR neuroimaging documents available, a new hemorrhage or infarction; OR the neurological deficit resulting in death. No other readily identifiable non-stroke cause for the clinical presentation (ie, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of the diagnosis by, at least, 1 of the following: • Neurology or neurosurgical specialist. • Neuroimaging procedure (MRI or CT scan or cerebral angiography). • Lumbar puncture (ie, spinal fluid analysis diagnostic of intracranial hemorrhage).

		angiography and/or the autopsy or death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.	

Table 2 of the supplementary data. Risk of bias assessment for the trials included

Study	Publication date	Bias from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Outcome measurement bias	Selection bias of the reported result	Overall bias
POPular TAVI[1]	2020	Low	Low	Low	Low	Low	Low
ARTE[3]	2017	Low	Low	Low	Low	Low	Low
SAT-TAVI[4]	2013	Some concerns	Low	Low	Low	Low	Some concerns
Ussia et al[6]	2011	Some concerns	Low	Low	Some concerns	Low	Some concerns

Table 3 of the supplementary data. Pooled analysis based on a fixed-effects and random-effects model for the clinical endpoints

Endpoint	OR	95%CI	*P*	RR	95%CI	*P*	RR	95%CI	*P*
	Fixed effects			Fixed effects			Random effects		
Life-threatening or major bleeding	0.43	0.27-0.69	.001	0.46	0.30-0.72	.001	0.46	0.30-0.72	.001
All-cause mortality	1.01	0.61-1.66	.97	1.01	0.63-1.61	.97	1.02	0.63-1.63	.94
Myocardial infarction	0.47	0.17-1.32	.16	0.48	0.17-1.32	.15	0.50	0.18-1.40	.189
Stroke	0.97	0.54-1.74	.91	0.97	0.55-1.69	.91	0.98	0.55-1.73	.94
Any bleeding	0.50	0.36-0.70	< .001	0.57	0.44-0.75	< .001	0.58	0.44-0.76	< .001

95%CI, 95% confidence interval; OR, odds ratio; RR, relative risk**.**

Table 4 of the supplementary data. Leave-one-out sensitivity analysis for the primary composite endpoint

Study omitted	OR	95%CI
POPular-TAVI[1]	0.41	0.19-0.90
ARTE[3]	0.47	0.28-0.78
SAT-TAVI[4]	0.44	0.27-0.73
Ussia et al[6]	0.41	0.25-0.68

95%CI, 95% confidence interval; OR, odds ratio.

Figure 1 of the supplementary data. Funnel plot for life-threatening or major bleeding. OR, odds ratio; SE, standard error.

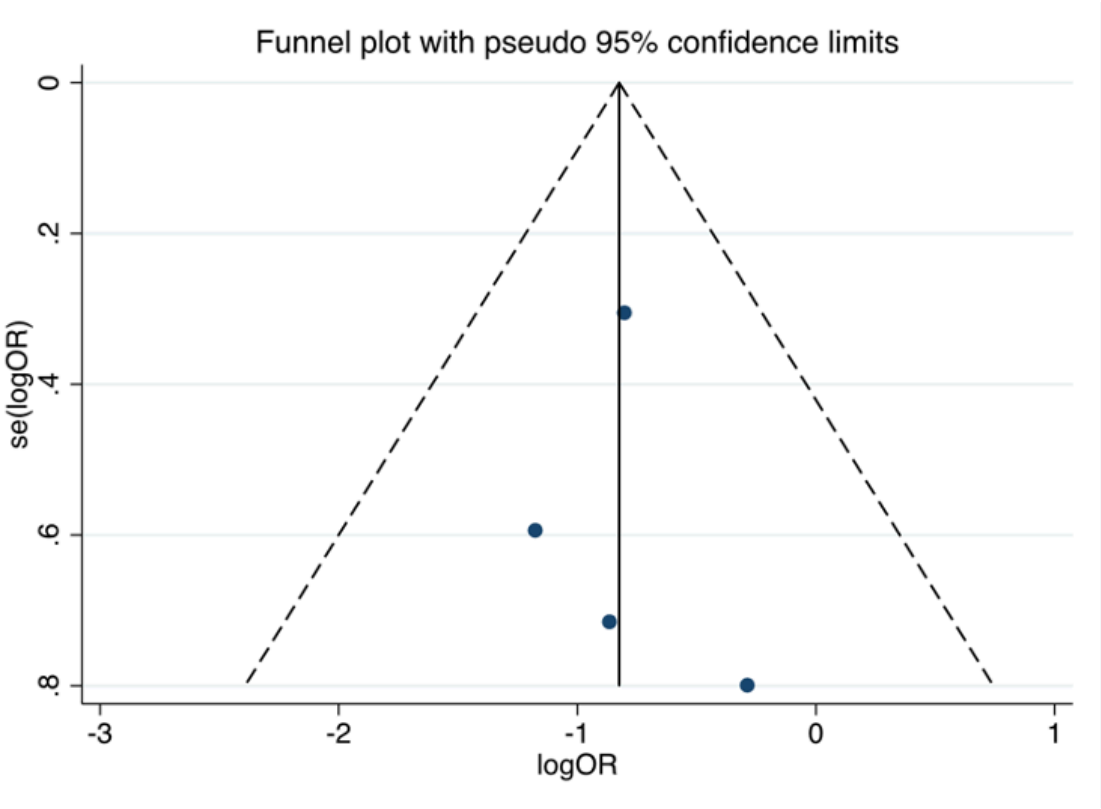


Figure 2 of the supplementary data. Funnel plot for all-cause mortality. OR, odds ratio; SE, standard error.

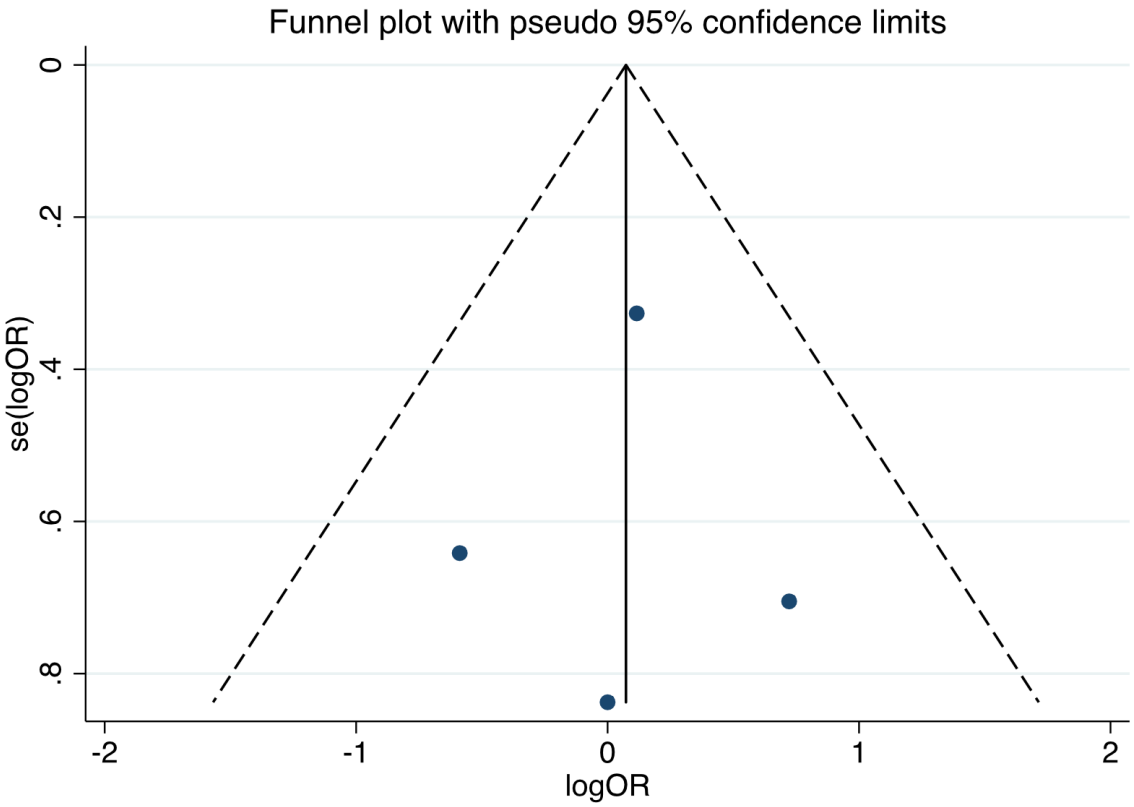


Figure 3 of the supplementary data. Funnel plot for myocardial infarction. OR, odds ratio; SE, standard error.

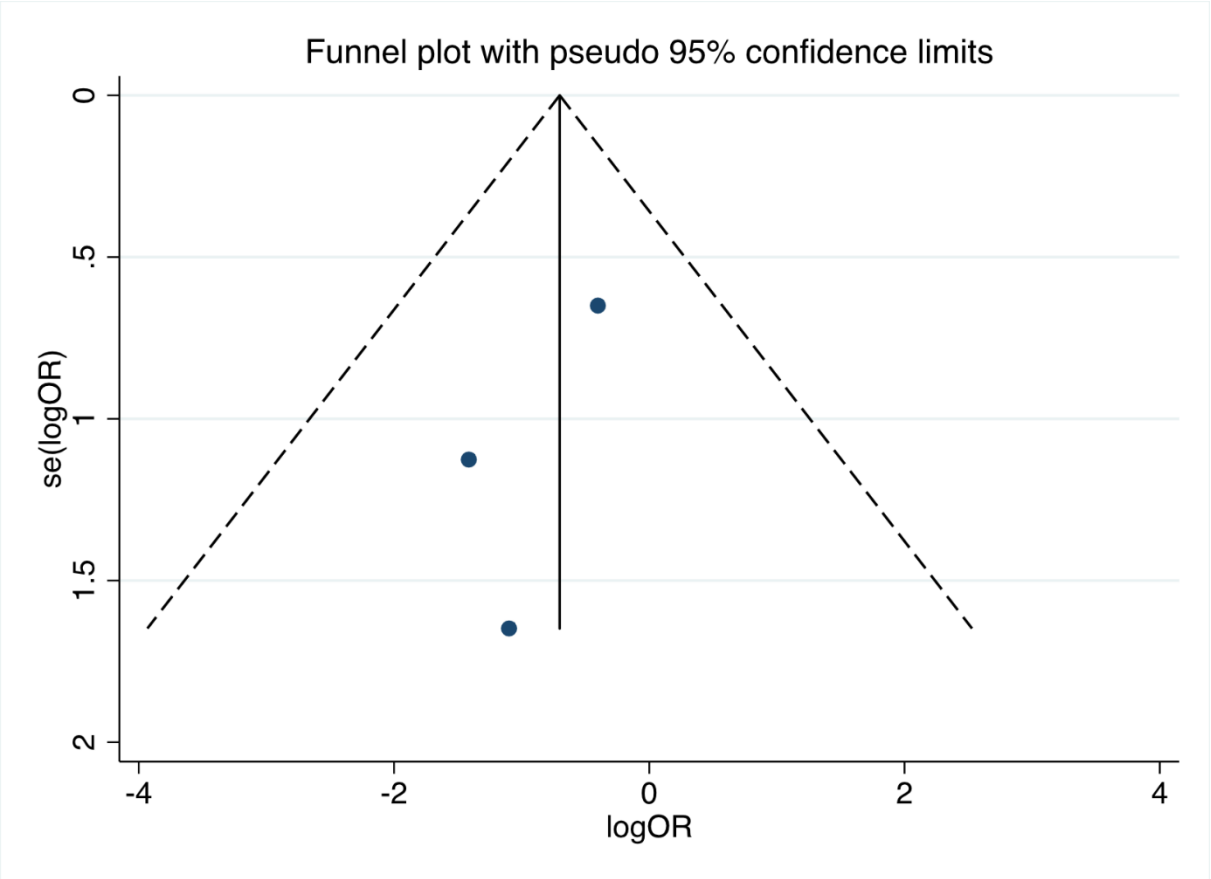


Figure 4 of the supplementary data. Funnel plot for stroke. OR, odds ratio; SE, standard error.

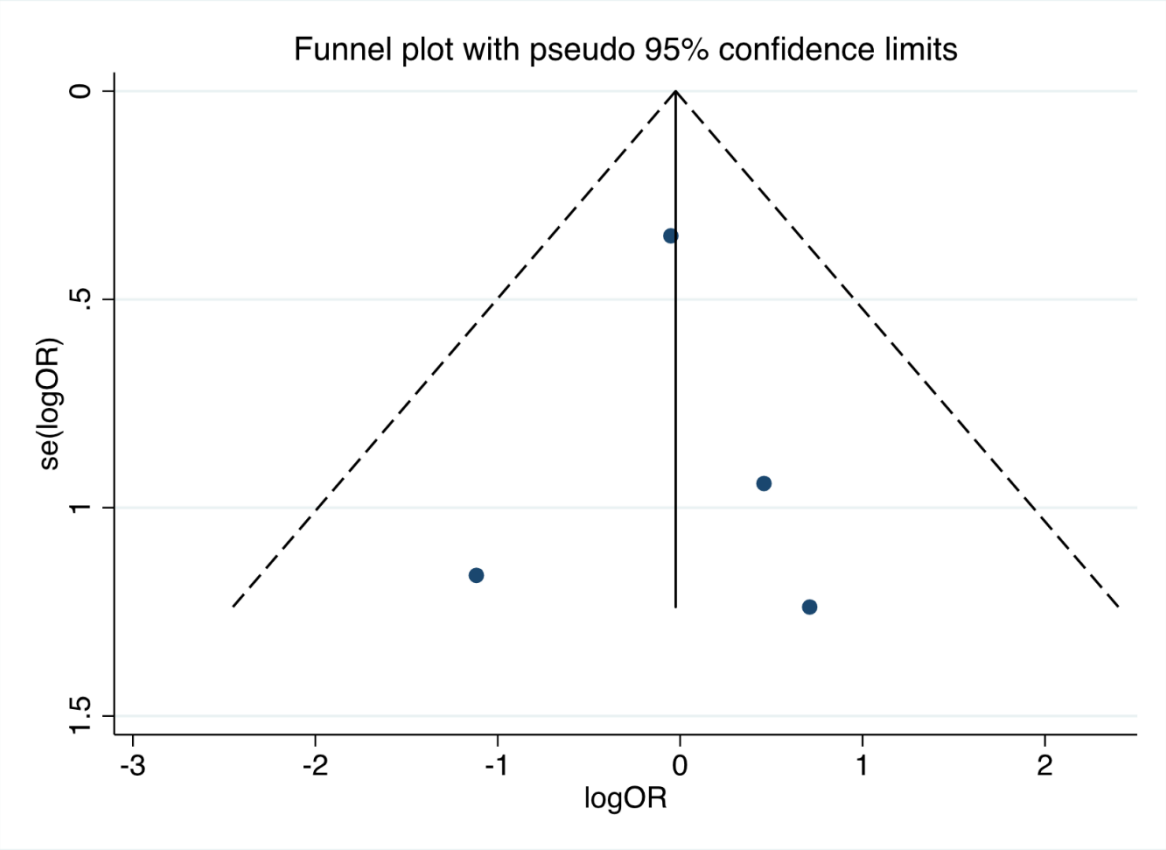
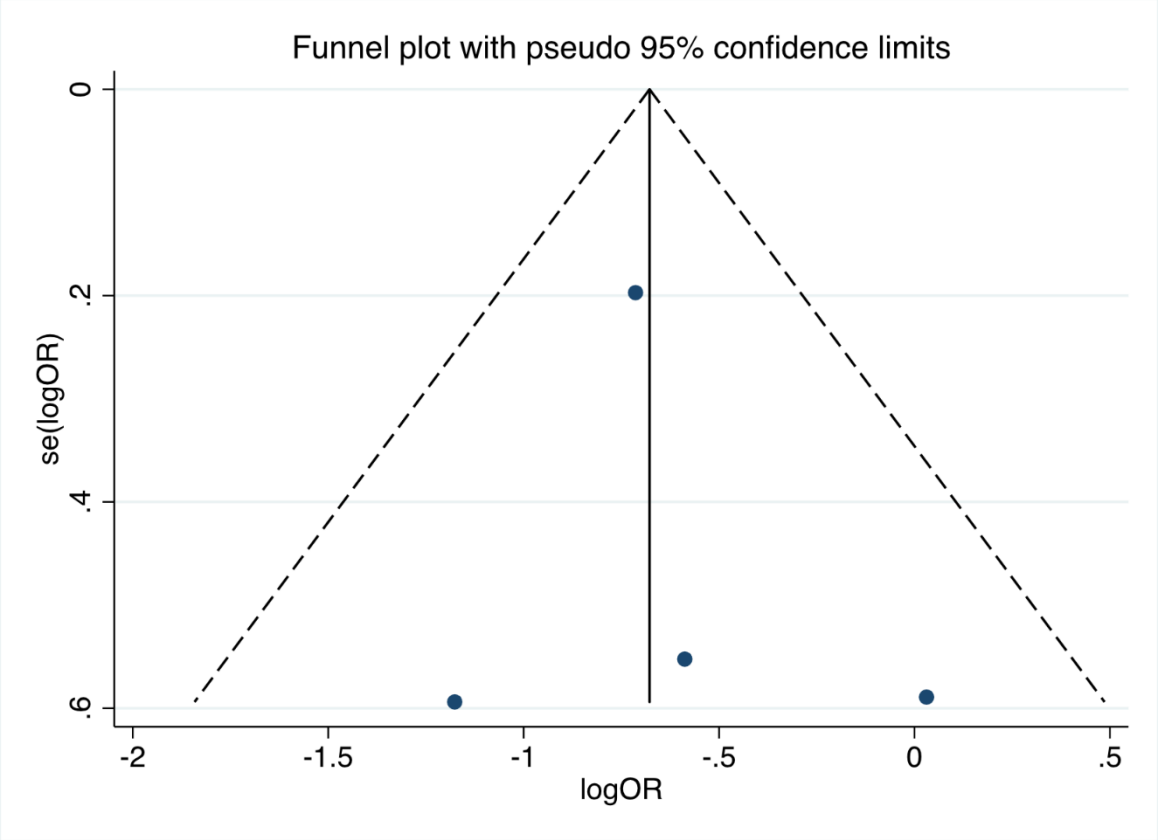


Figure 5 of the supplementary data. Funnel plot for any bleeding. OR, odds ratio; SE, standard error.



REFERENCES OF THE SUPPLEMENTARY DATA

1. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation. *N Engl J Med*. 2020. 83:1447-1457.

2. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33:2403–2418.

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5. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Eur Heart J*. 2011;32:205–217.

6. Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin al1 in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol*. 2011;108:1772–1776.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including (when applicable): background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions, and implications of key findings; systematic review registration number.	2.3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5.6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if, and where it can be accessed to (ie, website), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (ie, PICOS, length of follow-up), and report characteristics (ie, years considered, language, publication status) used as criteria for eligibility giving rationale.	6
Information sources	7	Describe all information sources (ie, databases with dates of coverage, contact with study authors to identify additional studies) used during the search, and date of last search.	6

Search	8	Present the entire electronic search strategy for, at least, 1 database, including all limits used in such a way that it could be repeated.	1, supplementary
Study selection	9	State the process for selecting studies (ie, screening, eligibility, part of a systematic review, and when applicable, of a meta-analysis).	6
Data collection process	10	Describe the method of data extraction from reports (ie, piloted forms, independently, in duplicate), and any processes for obtaining and confirming data from researchers.	6
Data items	11	List and define all variables for which data were sought (ie, PICOS, funding sources), and any assumptions and simplifications made.	6.7
Risk of bias in individual studies	12	Describe the methods used for assessing the risk of bias of individual studies (including specifications of whether this was conducted at study or outcome level), and how this information will be used in data synthesis.	7
Summary measures	13	State the principal summary measures (ie, risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods used for managing data and combining results from the studies. If conducted, include measures of consistency (ie, I^2) for each meta-analysis.	7.8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessments of risk of bias that may impact the cumulative evidence (ie, publication bias, selective reporting within studies).	7.8
Additional analyses	16	Describe methods of additional analyses (ie, sensitivity or subgroup analyses, meta-regression). If conducted, indicate which were prespecified.	7.8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility purposes, and included in the review, with reasons for exclusions at each stage, ideally on a flow diagram.	8
Study characteristics	18	For each study, present the characteristics on which data were extracted (ie, study size, PICOS, follow-up period), and provide citations.	8
Risk of bias within studies	19	Present data on each study risk of bias and, if available, any outcome level assessments (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally on a forest plot.	8.9
Synthesis of results	21	Present results of each meta-analysis conducted, including confidence intervals and measures of consistency.	8.9
Risk of bias across studies	22	Present results of any assessments of risk of bias across the studies (see Item 15).	9

Additional analysis	23	Give results of additional analyses if conducted (ie, sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (ie, healthcare providers, users, and policy makers).	9, 10, 11, 12
Limitations	25	Discuss limitations at study and outcome level (ie, risk of bias), and at review-level (ie, incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe the sources of funding for the systematic review and other support (ie, supply of data), and the role of funders regarding the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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