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SYSTEMATIC REVIEW AND META-ANALYSIS

Aspirin Alone Versus Dual Antiplatelet Therapy After Transcatheter Aortic Valve Implantation: A Systematic Review and Patient-Level Meta-Analysis

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BACKGROUND: In patients undergoing transcatheter aortic valve implantation without an indication for oral anticoagulation, it is unclear whether single or dual antiplatelet therapy (DAPT) is necessary to minimize both the bleeding and thromboembolic risk. In this patient-level meta-analysis, we further investigate the effect of aspirin alone compared with DAPT for preventing both thromboembolic and bleeding events after transcatheter aortic valve implantation.

METHODS AND RESULTS: We conducted a systematic review of all available randomized controlled trials comparing aspirin with DAPT. In total, 1086 patients were included across 4 eligible trials. The primary outcomes were the composite of all-cause mortality, major or life-threatening bleeding, stroke or myocardial infarction (first composite outcome), and the same composite excluding bleeding (second composite outcome), both tested at 30 days and 3 months. The first composite outcome occurred significantly less in the aspirin-alone group at 30 days (10.3% versus 14.7%, odds ratio [OR], 0.67; 95% CI, 0.46–0.97, *P*=0.034) and 3 months (11.0% versus 16.5%, hazard ratio [HR], 0.66; 95% CI, 0.47–0.94, *P*=0.02), compared with the DAPT group. The second composite outcome occurred in 5.5% and 6.6% at 30 days (OR, 0.83; 95% CI, 0.50–1.38, *P*=0.47) and in 6.9% and 8.5% at 3 months in the aspirin-alone group compared with the DAPT group (HR, 0.82; 95% CI, 0.52–1.29, *P*=0.39), respectively.

CONCLUSIONS: In patients without an indication for oral anticoagulation undergoing transcatheter aortic valve implantation, aspirin alone significantly reduced the composite of thromboembolic and bleeding events, and does not increase the composite of thromboembolic events after transcatheter aortic valve implantation, compared with DAPT.

Key Words: aspirin ■ dual antiplatelet therapy ■ transcatheter aortic valve implantation

Since its introduction, transcatheter aortic valve implantation (TAVI) has evolved as the alternative treatment for surgery in patients with severe symptomatic aortic valve stenosis.[1–6] Newer device technologies and better implantation techniques have largely improved the outcomes of TAVI over the past years. One aspect that has not been sufficiently investigated yet is the optimal antithrombotic treatment after TAVI. What we do know is that both bleeding and thromboembolic risk are high in patients undergoing TAVI. However, the optimal antithrombotic strategy to minimize both these risks is unknown in patients without a long-term indication for oral anticoagulation after TAVI. The latest guidelines recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for the first 3

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CLINICAL PERSPECTIVE

What Is New?

- This is the first individual patient-level meta-analysis including all 4 available randomized clinical trials investigating single antiplatelet therapy versus dual antiplatelet therapy for the first 3 months after transcatheter aortic valve implantation in patients without an indication for oral anticoagulation.

What Are the Clinical Implications?

- Aspirin alone significantly reduced the composite of bleeding and thrombotic events after transcatheter aortic valve implantation compared with dual antiplatelet therapy.
- Aspirin alone does not increase the composite of thromboembolic events at 30 days and 3 months after transcatheter aortic valve implantation compared with dual antiplatelet therapy.
- This meta-analysis provides additional knowledge regarding the optimal antithrombotic treatment after transcatheter aortic valve implantation.

Nonstandard Abbreviations and Acronyms

ARTE	Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation
DATP	dual antiplatelet therapy
POPular TAVI	Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation
SAT-TAVI	Single Antiplatelet Therapy for TAVI
TAVI	transcatheter aortic valve implantation
VARC-2	Valve Academic Research Consortium-2

to 6 months, followed by aspirin alone lifelong.[7,8] Small underpowered randomized trials suggested that aspirin alone after TAVI reduced the incidence of bleeding, and did not increase thromboembolic events compared with DAPT.[9–11] The recently published POPular TAVI cohort A (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial in patients without a long-term indication for oral anticoagulation after TAVI confirmed a lower incidence of bleeding and no increase of thromboembolic events with aspirin alone compared with DAPT.[12] The POPular TAVI trial was powered for bleeding events and a composite end point including bleeding and thromboembolic events but not for thromboembolic events alone. In order to increase statistical power, we performed a pooled individual patient-level meta-analysis from randomized clinical trials, to further evaluate the efficacy of aspirin alone compared with DAPT for preventing both thromboembolic and bleeding events after TAVI in patients without an indication for oral anticoagulation.

METHODS

The data that support the findings of this study are available from Dr. J.M. ten Berg (jurtenberg@gmail.com) upon reasonable request.

Search Strategy

A systematic review of the published data on antithrombotic therapy after TAVI in patients without an established indication for oral anticoagulation was conducted, in accordance with the guidance and reporting items specified in the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13] A literature search in the electronic databases PubMed, EMBASE, and Cochrane was last performed on September 1, 2020. Additionally, conference proceedings and abstracts, Clinicaltrials.gov, and the bibliography of review articles, meta-analyses, or original studies identified by the literature search were screened for other eligible studies. The search included the following terms: “TAVI,” “TAVR,” “transcatheter aortic valve implantation,” “transcatheter aortic valve replacement,” “antiplatelet therapy,” “single antiplatelet therapy,” “dual antiplatelet therapy,” “SAPT,” “DAPT,” “aspirin,” “clopidogrel,” “antiplatelet,” and “antithrombotic therapy” (Complete search is provided in Data S1). Only prospective, randomized clinical trials were selected for inclusion in this meta-analysis; other study designs were excluded. Ultimately, 4 prospective randomized clinical trials investigating aspirin alone compared with aspirin with clopidogrel after TAVI were included in the meta-analysis: (1) the POPular TAVI trial; (2) the ARTE (Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation) trial; (3) the SAT-TAVI (Single Antiplatelet Therapy for TAVI) trial; and (4) the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial from Ussia et al.[9–12] Access to the anonymized patient-level data of all eligible trials was granted by the principal investigator of each trial. Data on baseline characteristics, procedural characteristic, and outcomes were verified using the original

publications, and pooled into 1 single database. Two independent reviewers (J.B. and V.J.N.) assessed the risk of bias for all included trials using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (available in Tables S1 through S4).[14] All included trials were approved by the local ethics committee and institutional review board of each participating center and all patients provided written informed consent.

Definitions and End Points

The primary outcome of this meta-analysis was the composite of all-cause mortality, stroke, or myocardial infarction at 30 days and 3 months. The co-primary outcome was the composite of all-cause mortality, major or life-threatening bleeding, and stroke or myocardial infarction at 30 days and 3 months. The secondary outcomes were all-cause mortality, cardiovascular mortality, major or life-threatening bleeding, stroke and myocardial infarction at 30 days and 3 months. All outcomes were defined according to the VARC-2 (Valve Academic Research Consortium-2).[15]

Data Analysis

The databases with individual patient-level data of the 4 trials were combined into 1 pooled database. Data on the outcomes at 30 days were available for all included trials, the outcomes at 3 months including time-to-event information were available for the POPular TAVI trial, the ARTE trial, and the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial.[9,11,12] For this meta-analysis, the outcomes were analyzed using a 2-step approach. First, the relative risk measures (ie, odds ratios or hazard ratios) and their standard errors for the association of aspirin alone versus aspirin plus clopidogrel were obtained for the primary and secondary outcomes. Second, these estimates were pooled using inverse variance–based fixed-effect meta-analysis. Estimates of random-effect meta-analysis were also depicted in the forest plots. Between-study variance was estimated by Restricted Maximum Likelihood approach. Heterogeneity among studies was estimated by χ^2 test and the I^2 statistics. For the primary outcomes, time-to-event data at 3 months of follow-up were available in 3 studies (POPular TAVI, ARTE, and Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation), hence cumulative incidence graphs for aspirin monotherapy versus aspirin plus clopidogrel were constructed. The pooled hazard ratios shown on the cumulative incidence plots were obtained from stratified Cox-regression models with the individual studies serving as the strata variable, which is similar to the 2-stage fixed-effect meta-analysis.

Prespecified subgroup analyses of the primary outcomes at 30 days and 3 months were performed, which included sex, age (≥80 versus <80), renal failure (estimated glomerular filtration rate ≤60 versus >60), body mass index (≥25 versus <25), approach (transfemoral versus other), and prior stroke. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using R version 3.3.3. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Selection

We identified 402 reports with our search. After removal of duplicates, 302 studies were screened for eligibility, after screening for title and abstract 292 studies were excluded (ie, not topic of interest N=219, review or meta-analysis N=73), and after full text screening 10 additional studies were excluded because of a nonrandomized design. The 4 remaining trials were included in this meta-analysis (Figure 1). The included trials were (1) the POPular TAVI trial, N=665; (2) the ARTE trial, N=222; (3) the SAT-TAVI trial, N=120; and (4) the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial, N=79.[9–12] All trials randomly assigned patients in a 1:1 ratio, and in the 2 multicenter trials (POPular TAVI and ARTE) randomization was also stratified by participating center. Both the SAT-TAVI trial and Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial did not describe the randomization tool used for randomization. Patients were all analyzed according to the intention-to-treat principle and clinical outcomes were prespecified in the trial protocols and (except for the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial) adjudicated by an independent blinded clinical end point committee. The risk of bias was considered low for the 3 largest trials and unclear for the smallest trial (Tables S1 through S4).

Study Characteristics

All patients were considered suitable for TAVI, as determined by a dedicated heart team of each center. The main trials' exclusion criteria included a long-term indication for oral anticoagulation, previous coronary artery stenting requiring dual antiplatelet therapy at the time of TAVI, major bleeding within 3 months before TAVI, cerebrovascular accident or transient ischemic accident in the past 6 months, and an allergy or intolerance to aspirin or clopidogrel (or ticlopidine, only for the SAT-TAVI trial). During the procedure, unfractionated heparin was administered with an aimed activated clotting time of >250 seconds.

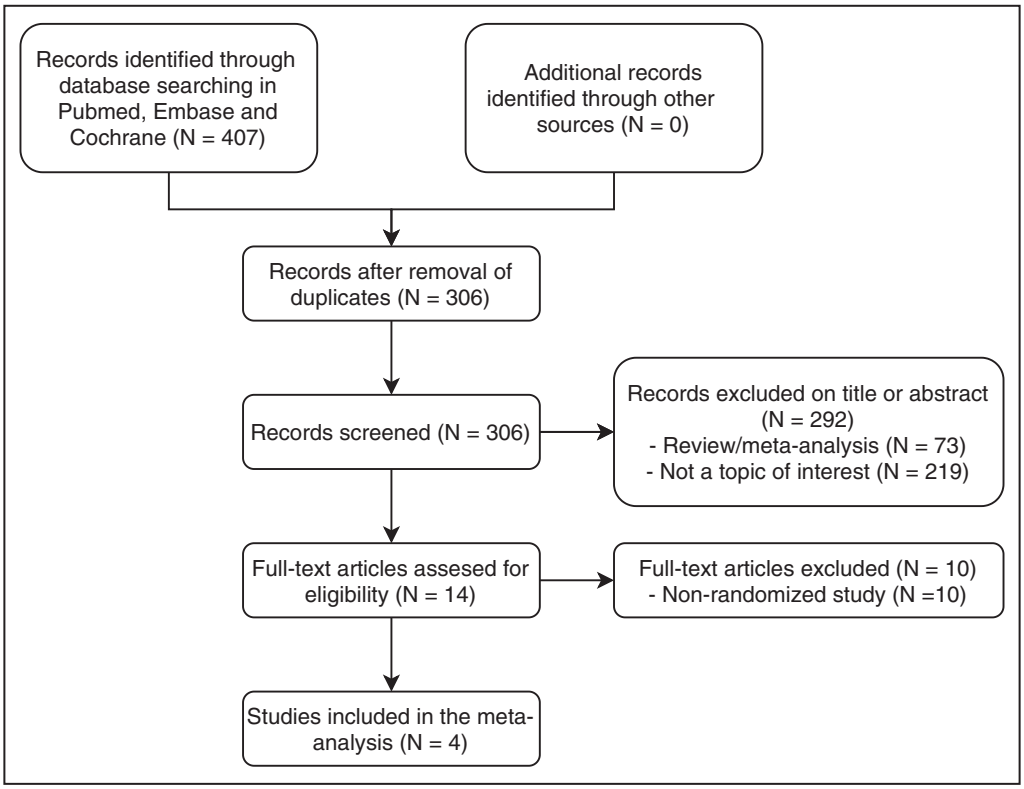

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.
The PRISMA flowchart. N denotes the number of published articles found.

The aspirin-alone group received aspirin at a dose of 80 to 160 mg daily for the entire trial duration. In patients not on aspirin before TAVI, aspirin was initiated within 24 hours before the TAVI procedure. Patients randomized to DAPT received aspirin at a dose of 80 to 160 mg daily with clopidogrel at a dose of 75 mg daily (or ticlopidine 500 mg twice daily) for 3 to 6 months, followed by aspirin alone (80–160 mg daily) for the entire trial duration. Aspirin was initiated within 1 day before TAVI, in patients not already on aspirin therapy. An initial loading dose of 300 mg of clopidogrel was administered within 24 hours before TAVI in patients undergoing transfemoral TAVI and within 24 hours after TAVI in those with a nontransfemoral approach, followed by 75 mg daily for 3 to 6 months, except for the SAT-TAVI trial where it was started directly after the procedure in all patients.[10]

Baseline and Procedural Characteristics

A total of 1086 randomized patients across the 4 included randomized trials were included in this meta-analysis. Of the included patients, 542 were randomized to aspirin alone and 544 to DAPT (or ticlopidine) after TAVI. The pooled baseline characteristics and the distribution of all characteristics for each separate trial are shown in Table 1, including missing data notification of each characteristic. The pooled mean age was 79.9±6.8 years and 49.7% of the patients were women. The median Society of Thoracic Surgeons score was lower in the POPular TAVI trial, compared with the other trials (2.5% versus 4.5% and 5.1%). Procedural characteristics are shown in Table S5. Most TAVI procedures were performed using the transfemoral approach (86.9%) with a balloon-expandable device (59.8%).

Primary and Secondary Outcomes at 30 Days

The composite of all-cause mortality, major or life-threatening bleeding, stroke, and myocardial infarction at 30 days occurred in 10.3% of patients in the aspirin-alone group and 14.7% of patients in the DAPT group (odds ratio [OR], 0.67; 95% CI, 0.46–0.97, *P*=0.034). The second primary composite outcome, including all-cause mortality, stroke, or myocardial infarction, occurred in 5.5% of patients receiving aspirin alone and in 6.6% of patients receiving DAPT (OR, 0.83; 95% CI, 0.50–1.38, *P*=0.47) at 30 days (Table 2 and Figure 2).[9–12] Major bleeding and the combination of major or life-threatening bleeding occurred less in the aspirin-alone group, compared with the DAPT group (2.4% versus 5.9%, 95% OR, 0.40; CI,

Table 1. Baseline Characteristics*

Characteristics	Ussia et al[9] (N=79)	SAT-TAVI[10] (N=120)	ARTE[11] (N=222)	POPular TAVI[12] (N=665)	Overall (N=1086)
Randomization group, n (%)					
Aspirin alone	39 (49.4)	61 (50.8)	111 (50.0)	331 (49.8)	542 (49.9)
Aspirin with clopidogrel	40 (50.6)	59 (49.2)	111 (50.0)	334 (50.2)	544 (50.1)
Age, y	80.8±5.1	80.2±5.3	79.3±9.0	80.0±6.3	79.9±6.8
Female sex, n (%)	43 (54.4)	80 (66.7)	93 (41.9)	324 (48.7)	540 (49.7)
NYHA class III or IV, n (%)	60 (75.9)	115 (95.8)	120 (54.1)	432 (65.0)	727 (67.4)
Body mass index†	26.1±4.2	27.1±4.2	28.3±7.1	27.0±4.7	27.2±5.2
Society of Thoracic Surgeons risk score‡	4.5 [1.5–12.9]	NA	5.1 [0.6–31.0]	2.5 [0.7–32.5]	3.1 [0.6–32.5]
Hypertension, n (%)	66 (83.5)	114 (95.0)	173 (77.9)	498 (74.9)	851 (78.4)
Diabetes mellitus, n (%)	21 (26.6)	34 (28.3)	77 (34.7)	163 (24.5)	295 (27.2)
Previous myocardial infarction, n (%)	11 (13.9)	NA	46 (20.7)	59 (8.9)	116 (10.7)
Peripheral artery disease, n (%)	7 (8.9)	NA	50 (22.5)	115 (17.3)	172 (15.8)
Previous cerebrovascular disorder, n (%)	6 (7.6)	NA	21 (9.5)	74 (11.1)	101 (9.3)
Chronic renal impairment, n (%)§	11 (13.9)	42 (35.0)	114 (51.4)	354 (53.2)	521 (47.1)
Previous coronary-artery bypass grafting, n (%)	6 (7.6)	0 (0)	94 (42.3)	115 (18.9)	226 (20.8)
Left ventricular ejection fraction, n (%)					
>50%	48 (60.8)	67 (55.8)	160 (72.1)	489 (73.5)	764 (70.3)
30%–50%	26 (32.9)	45 (37.5)	46 (20.7)	139 (20.9)	256 (23.6)
≤30%	5 (6.3)	8 (6.7)	16 (7.2)	37 (5.6)	66 (6.1)

ARTE indicates Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation; NA, not available; NYHA, New York Heart Association; POPular TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; SAT-TAVI, Single Antiplatelet Therapy for TAVI; and TAVI, transcatheter aortic-valve implantation.

*Plus–minus values are means±SD. Median are depicted with corresponding interquartile range.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

‡Society of Thoracic Surgeons risk scores range from 0% to 100%, with higher scores indicating a higher risk of death after cardiac surgery.

§Chronic renal impairment is defined as estimated glomerular filtration rate of <60 mL/1.73 m^2.

0.21–0.78, *P*=0.007, and 5.4% versus 10.1%, 95% OR, 0.51; CI, 0.32–0.82, *P*=0.005, respectively) (Table 2 and Figures S1 and S2). The individual incidences of life-threatening bleeding (3.0% versus 4.2%, 95% OR, 0.76; CI, 0.39–1.51, *P*=0.44), stroke (2.8% versus 3.5%, 95% OR, 0.79; CI 0.39–1.60, *P*=0.51), myocardial infarction (0.7% versus 1.5%, 95% OR, 1.35; CI, 0.30–6.08, *P*=0.70), death (2.6% versus 3.1%, 95% OR, 0.82; CI, 0.40–1.72, *P*=0.61) and cardiovascular death (2.4% versus 3.1%, 95% OR, 0.76; CI, 0.36–1.61, *P*=0.47) were numerically lower in the aspirin-alone group but not statistically different (Table 2 and Figures S3 through S7). Results of the prespecified subgroup analyses for both primary outcomes are shown in Figures S8 and S9, which did not show any evidence for effect-modification according to sex, age, body mass index, renal function, TAVI approach, and history of stroke.

Primary and Secondary Outcomes at 3 Months

Three-month follow-up was only available for the POPular TAVI trial, the ARTE trial, and the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial, which comprised a total of 966 patients: 481 randomized to aspirin alone and 485 patients to DAPT. At 3 months, a first primary composite outcome event was observed in 11.0% of patients receiving aspirin alone and in 16.5% of patients receiving DAPT (hazard ratio [HR], 0.66; 95% CI, 0.47–0.94, *P*=0.02). A second primary composite outcome event was observed in 6.9% of patients in the aspirin-alone group and in 8.5% of patients in the DAPT group (HR, 0.82; 95% CI, 0.52–1.29, *P*=0.39) (Table 3, Figure 3, and Figure S10). The incidences of the secondary outcomes are listed in Table 3. Both major bleeding and the combination of major or life-threatening bleeding were significantly less frequent in the aspirin-alone group, compared with the DAPT group (2.3% versus 6.4%, 95% OR, 0.35; CI, 0.17–0.71, *P*=0.004, and 4.8% versus 10.5%, 95% OR, 0.43; 95% CI, 0.26–0.72, *P*=0.001, respectively) (Figures S11 and S12). As for the 30-day outcomes, the individual incidences of life-threatening bleeding (2.5% versus 4.1%, 95% OR, 0.67; CI, 0.31–1.44, *P*=0.30), stroke (3.1% versus 3.9%, 95% OR, 0.80; CI, 0.39–1.61, *P*=0.52), myocardial infarction (0.8% versus 1.9%, 95% OR, 1.01; CI, 0.25–4.07, *P*=0.99), death (3.7%

Table 2. Primary and Secondary Outcomes at 30 Days

Outcomes at 30 d	Aspirin (N=542) No. (%)	Dual Antiplatelet Therapy (N=544) No. (%)	OR (95% CI)	*P* Value
Primary outcomes				
Composite of all-cause mortality, major and life-threatening bleeding, stroke, or myocardial infarction	56 (10.3)	80 (14.7)	0.67 (0.46–0.97)	0.034
Composite of all-cause mortality, stroke, or myocardial infarction	30 (5.5)	36 (6.6)	0.83 (0.50–1.38)	0.47
Secondary outcomes				
Major bleeding	13 (2.4)	32 (5.9)	0.40 (0.21–0.78)	0.007
Life-threatening or disabling bleeding	16 (3.0)	23 (4.2)	0.76 (0.39–1.51)	0.44
Major, life-threatening, or disabling bleeding	29 (5.4)	55 (10.1)	0.51 (0.32–0.82)	0.005
Stroke	15 (2.8)	19 (3.5)	0.79 (0.39–1.60)	0.51
Myocardial infarction	4 (0.7)	8 (1.5)	1.35 (0.30–6.08)	0.70
Death from any cause	14 (2.6)	17 (3.1)	0.82 (0.40–1.72)	0.61
Death from cardiovascular cause	13 (2.4)	17 (3.1)	0.76 (0.36–1.61)	0.47

OR indicates odds ratio.

versus 4.3%, 95% OR, 0.86; CI, 0.44–1.66, *P*=0.65), and cardiovascular death (3.3% versus 4.1.%, 95% OR, 0.80; CI, 0.40–1.59, *P*=0.52) at 3 months were numerically lower in the aspirin-alone group as compared with the DAPT group, but these differences were not statistically significant (Figures S13 through S17). The results of the prespecified subgroups are shown in Figures S18 and S19. Heterogeneity between the included trials in treatment effects was low for all primary and secondary outcomes (I^2<25%).

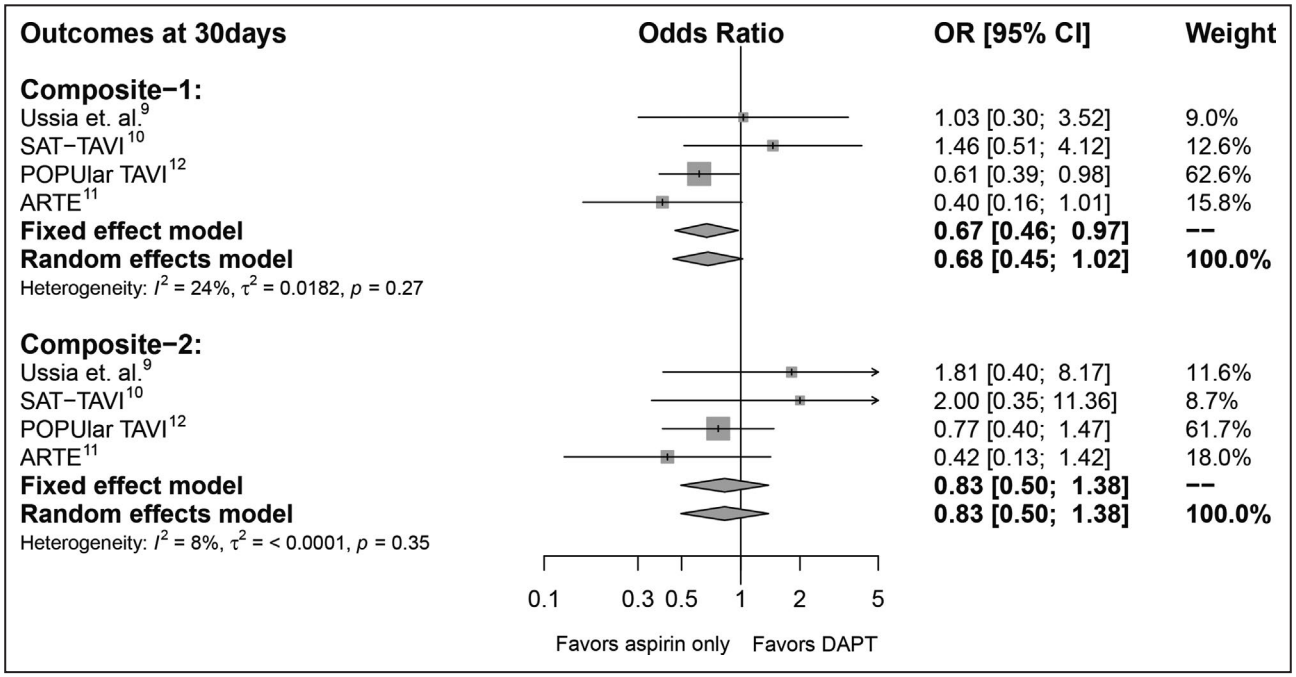

Figure 2. Meta-analysis of the primary outcomes at 30 days.
Meta-analysis of both primary outcomes at 30 days. The first primary outcome was the composite of all-cause mortality, major or life-threatening bleeding, stroke, or myocardial infarction. The second primary outcome was the composite of all-cause mortality, stroke, or myocardial infarction. ARTE indicates Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation; OR, odds ratio; POPular TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; SAT-TAVI, Single Antiplatelet Therapy for TAVI; and TAVI, transcatheter aortic valve implantation.

Table 3. Primary and Secondary Outcomes at 3 Months*

Outcomes at 3 mo	Aspirin (N=481) No. (%)	Dual Antiplatelet Therapy (N=485) No. (%)	HR (95% CI)	OR (95% CI)	*P* Value
Primary outcomes					
Composite of all-cause mortality, major and life-threatening bleeding, stroke, or myocardial infarction	53 (11.0)	80 (16.5)	0.66 (0.47–0.94)	…	0.02
Composite of all-cause mortality, stroke, or myocardial infarction	33 (6.9)	41 (8.5)	0.82 (0.52–1.29)	…	0.39
Secondary outcomes					
Major bleeding	11 (2.3)	31 (6.4)		0.35 (0.17–0.71)	0.004
Life-threatening or disabling bleeding	12 (2.5)	20 (4.1)		0.67 (0.31–1.44)	0.30
Major, life-threatening, or disabling bleeding	23 (4.8)	51 (10.5)		0.43 (0.26–0.72)	0.001
Stroke	15 (3.1)	19 (3.9)		0.80 (0.39–1.61)	0.52
Myocardial infarction	4 (0.8)	9 (1.9)		1.01 (0.25–4.07)	0.99
Death from any cause	18 (3.7)	21 (4.3)		0.86 (0.44–1.66)	0.65
Death from cardiovascular cause	16 (3.3)	20 (4.1)		0.80 (0.40–1.59)	0.52

ARTE indicates Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation; HR, hazard ratio; OR, odds ratio; and POPular TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation.

*Data on the primary and secondary outcomes at 3 months was available only for the POPular TAVI trial, ARTE trial, and Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial (in total 966 patients).

DISCUSSION

In this patient-level meta-analysis of all available prospective randomized trials, we investigated the effect of aspirin alone compared with DAPT after TAVI on thromboembolic and bleeding complications in patients without an indication for oral anticoagulation. In summary, aspirin alone significantly reduced the rate of the composite of major and life-threatening bleeding or thromboembolic events (including all-cause mortality, major and life-threatening bleeding, stroke, or myocardial infarction), compared with DAPT. The difference was caused by a large increase of major and life-threatening bleeding complications in patients receiving DAPT as compared with patients receiving aspirin alone. Moreover, aspirin alone after TAVI was not associated with an increased incidence of the composite of thromboembolic complications (including all-cause mortality, stroke, or myocardial infarction). Also, the individual incidences of all-cause mortality, cardiovascular mortality, stroke, and myocardial infarction outcome were comparable between both groups.

Even decades after its introduction, the ideal antithrombotic strategy following TAVI is not completely determined yet. In order to minimize both the thromboembolic risk and the bleeding risk, an optimal balance in antithrombotic therapy should be pursued. The current guidelines on antithrombotic therapy following TAVI in patients without a long-term indication for oral anticoagulation recommend DAPT with aspirin and clopidogrel for the first 3 to 6 months, followed by aspirin alone.[7,8] However, these statements rely on expert consensus, rather than prospective randomized evidence. Antiplatelet therapy in addition to aspirin is considered to reduce the risk of thromboembolic complications in the first period after TAVI, as was observed in patients undergoing coronary artery stenting.[16] After this initial period, the thromboembolic risk is thought to return to that of the general elderly population and therefore does not need strong antithrombotic therapy.[17]

Obviously, initiation of dual antiplatelet therapy comes at the cost of an increased risk for bleeding, especially for patients undergoing TAVI. The general TAVI population is considered to be at higher risk for bleeding than patients undergoing coronary artery stenting, because of their advanced age and the presence of more comorbidities such as renal disease and previous bleeding. Previously randomized trials independently showed significantly lower incidences of bleeding events in patients receiving aspirin alone as compared with DAPT after TAVI.[9–11] In this meta-analysis, we observed lower rates of major and life-threatening bleeding in patients on aspirin alone compared with patients on DAPT.

More interesting is whether an aspirin-alone strategy is effective enough in preventing thromboembolic complications as compared with DAPT. Of all thromboembolic complications, stroke is most prevalent, occurring in up to 8% within the first 30 days.[3–6,18–20] Studies investigating cerebral protection devices showed that a large amount of debris was scattered during the procedure, potentially causing stroke in

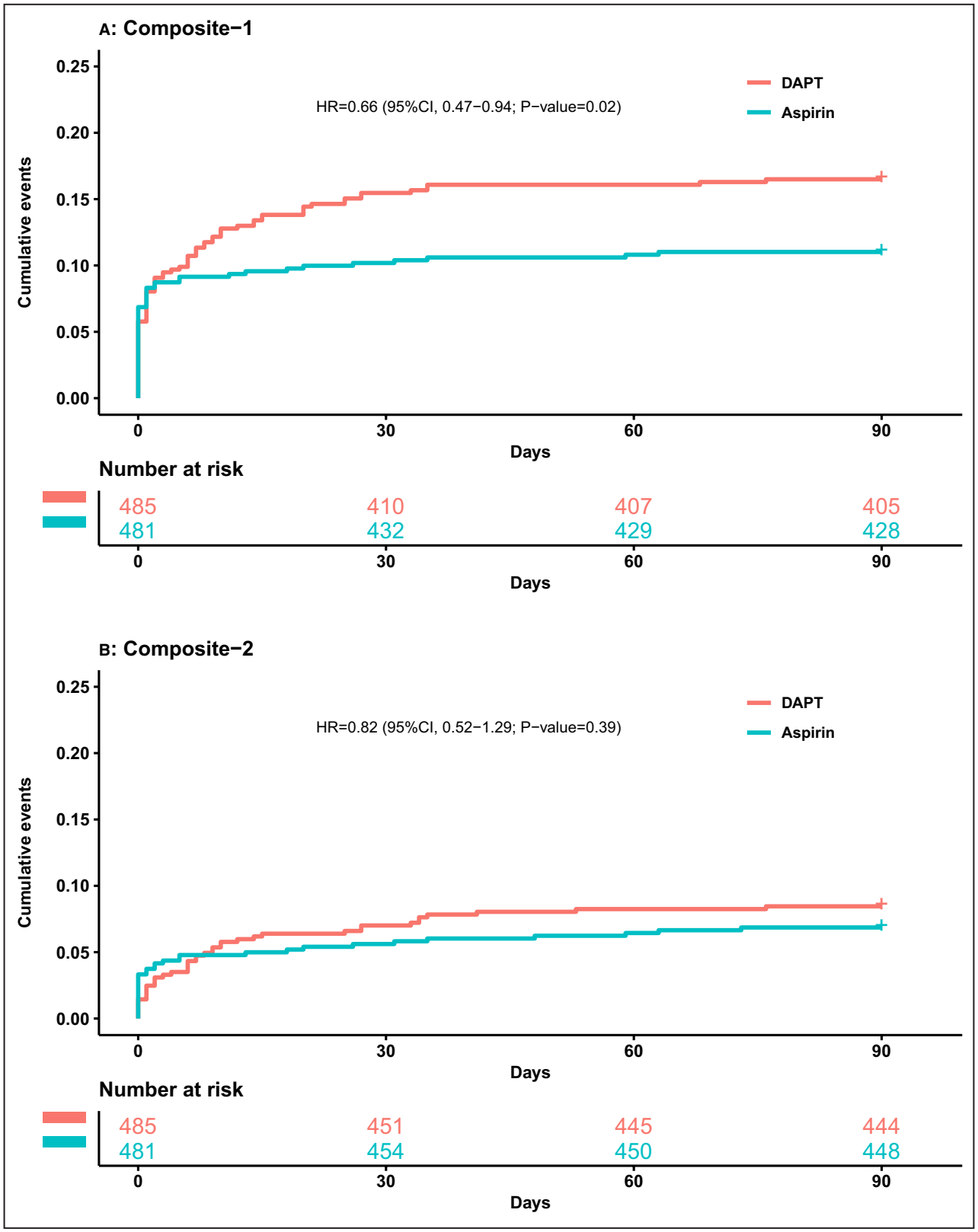

Figure 3. The primary composite outcomes at 3 months.
Cumulative incidence of the primary composite outcomes at 3 months. The first primary composite outcome (ie, all-cause mortality, major or life-threatening bleeding, stroke, or myocardial infarction) is shown in (**A**). The second primary composite outcome (ie, all-cause mortality, stroke, or myocardial infarction) is shown in (**B**). DAPT indicates dual antiplatelet therapy; and HR, hazard ratio.

the periprocedural period.[21,22] This debris contained acute thrombus, valve and artery wall tissue or calcification, and even foreign materials. In the subacute period (30 days to 3 months), other risk factors for stroke play a role such as existing or new-onset atrial arrhythmias, incomplete stent frame endothelialization, and valve thrombosis (prosthetic or native valve thrombosis).[23–25] Based on these findings, the guidelines recommend DAPT in the early period after TAVI. On the other hand, several previously published observational and randomized studies observed no increase of thromboembolic complications, such as stroke, in patients receiving aspirin without additional antiplatelet therapy.[9–11,26–31]

Whether an aspirin-alone strategy is sufficiently effective in preventing thromboembolic complications compared with DAPT is not known. All available trials were underpowered to answer this question. In this meta-analysis we pooled all available randomized trials on a patient-level, in order to amplify the statistical power and provide a broader insight in the efficacy of aspirin alone after TAVI. In the current study, we also observed no benefit of DAPT compared to aspirin alone after TAVI in preventing thromboembolic complications such as stroke at 30 days and at 3 months. In fact, the composite of thromboembolic complications and its individual components were comparable between both groups. None of the individual components showed a hint of an increased occurrence with aspirin alone. Based on our results, we consider aspirin alone the optimal antithrombotic treatment after TAVI rather than DAPT, in patients without a long-term indication for oral anticoagulation and who do not require DAPT at the time of TAVI (eg, recent coronary artery stenting). On the other hand, the ongoing indication shift towards lower-risk patients and a broader patient population undergoing TAVI might require a more patient-tailored antithrombotic strategy, balancing the thrombotic and bleeding risk in the individual patient, instead of standardized treatments.

Our trial has several limitations. First, all included trials were open label and investigators were not blinded for treatment allocation, possible leading to a high risk for performance bias. Second, there was some heterogeneity regarding baseline characteristics between the included trials; however, the results of the included trials were all in the same direction. Third, the POPular TAVI trial was the largest trial and mainly responsible for the results of this meta-analysis. On the other hand, the results of the smaller trials regarding both primary outcomes were in the same direction as in the POPular TAVI trial. Fourth, despite the fact that we included all available prospective randomized trials, this meta-analysis remains relatively underpowered for the thromboembolic composite outcome. Last, the 3-month follow-up was only available for the POPular TAVI trial, ARTE trial, and Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation trial.

In this patient-level meta-analysis of randomized trials investigating aspirin alone as compared with aspirin with clopidogrel after TAVI in patients without a chronic indication for oral anticoagulation, aspirin alone was associated with a significant reduction of the composite of major and life-threatening bleeding or thromboembolic events (including all-cause mortality, major and life-threatening bleeding, stroke, or myocardial infarction), and major or life-threatening bleeding, compared with DAPT at 30 days and 3 months. Furthermore, aspirin alone, compared with DAPT, did not increase the incidence of the composite of thromboembolic events (all-cause mortality, stroke, or myocardial infarction) at 30 days and 3 months.

ARTICLE INFORMATION

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None.

Supplementary Material

Data S1
Tables S1–S5
Figures S1–S19

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Supplemental Material

Data S1.

Supplemental Methods: Search Strategy in Pubmed and EMBASE

Pubmed search on 01-Sept-2020

((Transcatheter aortic valve implantation) OR (transcatheter aortic valve replacement) OR (TAVI) OR (TAVR)) AND ((Aspirin) OR (clopidogrel) OR (SAPT) OR (single antiplatelet) OR (dual antiplatelet) OR (antithrombotic) OR (antiplatelet) OR (antiplatelet therapy) OR (DAPT))

((Transcatheter aortic valve implantation) OR (transcatheter aortic valve replacement) OR (TAVI) OR (TAVR)) AND ((Aspirin) OR (clopidogrel) OR (SAPT[text word]) OR (single antiplatelet) OR (dual antiplatelet) OR (antithrombotic) OR (antiplatelet) OR (antiplatelet therapy) OR (DAPT))

(((((("transcatheter aortic valve replacement"[MeSH Terms] OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "replacement"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields]) OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "implantation"[All Fields])) OR "transcatheter aortic valve implantation"[All Fields]) OR (("transcatheter aortic valve replacement"[MeSH Terms] OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "replacement"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields])) OR "TAVI"[All Fields]) OR "TAVR"[All Fields]) AND ((((((((((("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) OR "aspirins"[All Fields]) OR "aspirin s"[All Fields]) OR "aspirine"[All Fields]) OR (("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields]) OR "clopidogrel s"[All Fields])) OR "SAPT"[Text Word]) OR (((((("single person"[MeSH Terms] OR ("single"[All Fields] AND "person"[All Fields])) OR "single person"[All Fields]) OR "single"[All Fields]) OR "singles"[All Fields]) AND ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields]))) OR ("dual"[All Fields] AND ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields]))) OR ("antithrombotic"[All Fields] OR "antithrombotics"[All Fields])) OR ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields])) OR (("antiplatelet"[All Fields] OR "antiplatelets"[All Fields]) AND ((((((("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR "therapies"[All Fields]) OR "therapy"[MeSH Subheading]) OR "therapy"[All Fields]) OR "therapy s"[All Fields]) OR "therapys"[All Fields]))) OR (("2 deoxythymidylyl 3 5 2 deoxyadenosine"[Supplementary Concept] OR "2 deoxythymidylyl 3 5 2 deoxyadenosine"[All Fields]) OR "dapt"[All Fields]))

EMBASE search on 01-Sept-2020:

('transcatheter aortic valve implantation'/exp/mj OR 'tavi'/mj OR tavr OR (transcatheter AND aortic AND 'valve'/mj AND 'replacement'/mj)) AND ('clopidogrel'/exp/mj OR 'aspirin'/exp/mj OR 'dual antiplatelet therapy'/mj OR 'single antiplatelet therapy'/mj OR 'antithrombotic therapy'/mj)

Table S1. The Cochrane Risk of Bias Tool of the POPular TAVI Trial(12)

Bias domain	Source of bias	Support for judgement	Review authors' judgement
Selection bias	Random sequence generation	Patients were randomly assigned in a ratio of 1:1 with the use of electronic web-based computer system, stratified according to center.	Low risk of bias (+)
	Allocation concealment	Patients were randomly assigned in a ratio of 1:1 with the use of electronic web-based computer system, stratified according to center.	Low risk of bias (+)
Performance bias	Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Patients and personnel were not blinded to the assigned treatment.	High risk of bias (-)
Detection bias	Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	All events were analyzed and adjudicated by an independent clinical evaluation committee.	Low risk of bias (+)
Attrition bias	Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	All patients were included in the analysis according to the groups to which they were originally assigned (modified intention-to-treat analysis). 25 patients were excluded before the TAVI procedure.	Low risk of bias (+)
Reporting bias	Selective reporting	The reported primary and secondary endpoints were pre-specified. Some additions analyses were performed post hoc.	Low risk of bias (+)

Table S2. The Cochrane Risk of Bias Tool of the ARTE Trial(11)

Bias domain	Source of bias	Support for judgement	Review authors' judgement
Selection bias	Random sequence generation	Patients were randomly assigned in a ratio of 1:1 with the use of random block sizes to conceal treatment allocation from the patients, and randomization was stratified according to center.	Low risk of bias (+)
	Allocation concealment	Patients were randomly assigned in a ratio of 1:1 with the use of random block sizes to conceal treatment allocation from the patients, and randomization was stratified according to center.	Low risk of bias (+)
Performance bias	Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Patients and personnel were not blinded to the assigned treatment.	High risk of bias (-)
Detection bias	Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	All events were analyzed and adjudicated by an independent clinical evaluation committee.	Low risk of bias (+)
Attrition bias	Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	All patients were included in the analysis according to the groups to which they were originally assigned (modified intention-to-treat analysis).	Low risk of bias (+)
Reporting bias	Selective reporting	The reported primary and secondary endpoints were pre-specified.	Low risk of bias (+)

Table S3. The Cochrane Risk of Bias Tool of the SAT-TAVI Trial(10)

Bias domain	Source of bias	Support for judgement	Review authors' judgement
Selection bias	Random sequence generation	Patients were randomly assigned in a ratio of 1:1. The treating physician was blinded for the randomization. The used randomization tool had not been described.	Unclear risk of bias (?)
	Allocation concealment	Patients were randomly assigned in a ratio of 1:1. The treating physician was blinded for the randomization. The used randomization tool had not been described	Low risk of bias (-)
Performance bias	Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Patients and personnel were not blinded to the assigned treatment after randomization.	High risk of bias (-)
Detection bias	Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	All events were analyzed and adjudicated by an independent clinical evaluation committee.	Low risk of bias (+)
Attrition bias	Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	All patients were included in the analysis according to the groups to which they were originally assigned (intention-to-treat analysis).	Low risk of bias (+)
Reporting bias	Selective reporting	The reported primary and secondary endpoints were pre-specified.	Low risk of bias (+)

Table S4. The Cochrane Risk of Bias Tool of the Dual Antiplatelet Therapy Versus Aspirin Alone in Patients Undergoing Transcatheter Aortic Valve Implantation Trial(9)

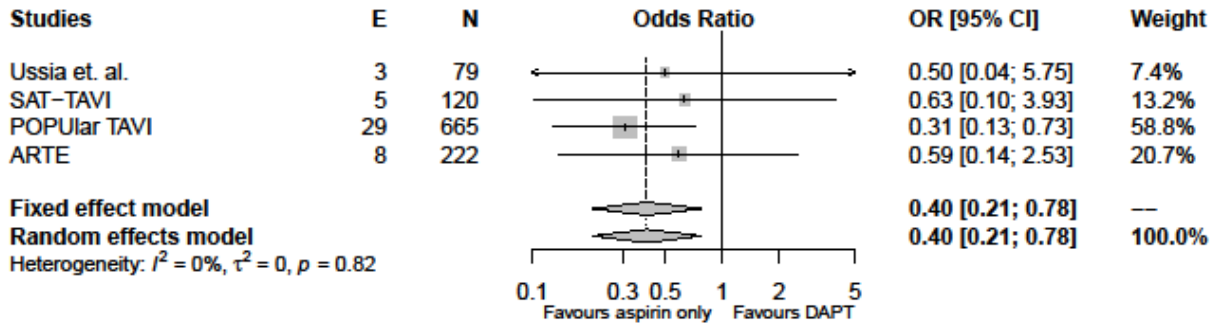
Bias domain	Source of bias	Support for judgement	Review authors' judgement
Selection bias	Random sequence generation	Patients were randomly assigned in a ratio of 1:1. The treating physician was blinded for the randomization. The used randomization tool had not been described.	Unclear risk of bias (?)
	Allocation concealment	Patients were randomly assigned in a ratio of 1:1. The used randomization tool had not been described	Unclear risk of bias (?)
Performance bias	Blinding of participants and personnel. Assessments should be made for each main outcome (or class of outcomes).	Patients and personnel were not blinded to the assigned treatment after randomization.	High risk of bias (-)
Detection bias	Blinding of outcome assessment. Assessments should be made for each main outcome (or class of outcomes).	It is unclear if reported event were adjudicated by an independent blinded clinical endpoint committee	Unclear risk of bias (?)
Attrition bias	Incomplete outcome data. Assessments should be made for each main outcome (or class of outcomes).	All patients were included in the analysis according to the groups to which they were originally assigned (intention-to-treat analysis).	Low risk of bias (+)
Reporting bias	Selective reporting	The reported primary and secondary endpoints were pre-specified.	Low risk of bias (+)

Table S5. Procedural Characteristics

Characteristics	Aspirin alone (N=542)	Aspirin with clopidogrel (N=544)
Approach – no. (%)		
Transfemoral	475 (87.6)	469 (86.2)
Transapical	39 (7.2)	51 (9.4)
Direct aortic	14 (2.6)	10 (1.8)
Transcarotid	12 (2.2)	10 (1.8)
Transsubclavia	2 (0.4)	4 (0.4)
Valve type – no. (%)		
Sapien XT, Edwards Lifesciences	167 (30.8)	169 (31.1)
Sapien 3, Edwards Lifesciences	159 (29.3)	154 (28.3)
Sapien Ultra, Edwards Lifesciences	0 (0)	1 (0.2)
CoreValve, Medtronic	50 (9.2)	50 (9.2)
CoreValve Evolut R, Medtronic	90 (16.6)	85 (15.6)
CoreValve Evolut Pro, Medtronic	37 (6.8)	35 (6.4)
Engager, Medtronic	0 (0)	1 (0.2)
Accurate Neo, Boston Scientific*	15 (2.8)	13 (2.4)
Lotus, Boston Scientific	13 (2.4)	16 (2.9)
JenaValve, JenaValve Technology GmbH	3 (0.6)	8 (1.5)
Portico, St. Jude Medical	5 (0.9)	11 (2.0)
Direct Flow, Direct Flow Medical	3 (0.6)	1 (0.2)
Valve size – no. (%)		
20	1 (0.2)	6 (1.1)
21	1 (0.2)	0 (0)
23	153 (28.2)	127 (23.3)
25	12 (2.2)	15 (2.8)
26	180 (33.2)	207 (38.1)
27	17 (3.1)	21 (3.9)
29	152 (28.0)	138 (25.4)
31	2 (0.4)	4 (0.7)
34	24 (4.4)	26 (4.8)

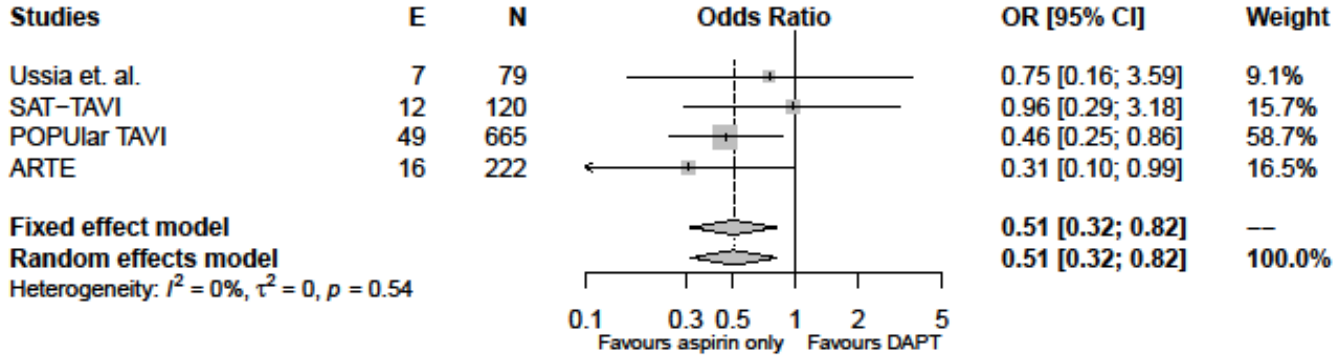
*Accurate Neo size S corresponds with 23mm, M with 25mm, and L with 27mm.

Figure S1. Meta-Analysis of the Secondary Outcome Major Bleeding at 30 Days



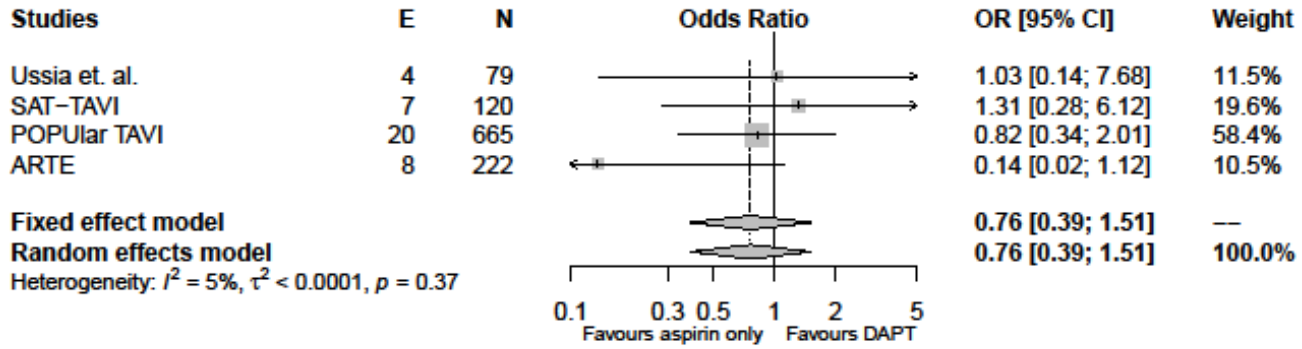
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), and OR = odds ratio.

Figure S2. Meta-Analysis of the Secondary Outcome Major or Life-Threatening Bleeding at 30 Days



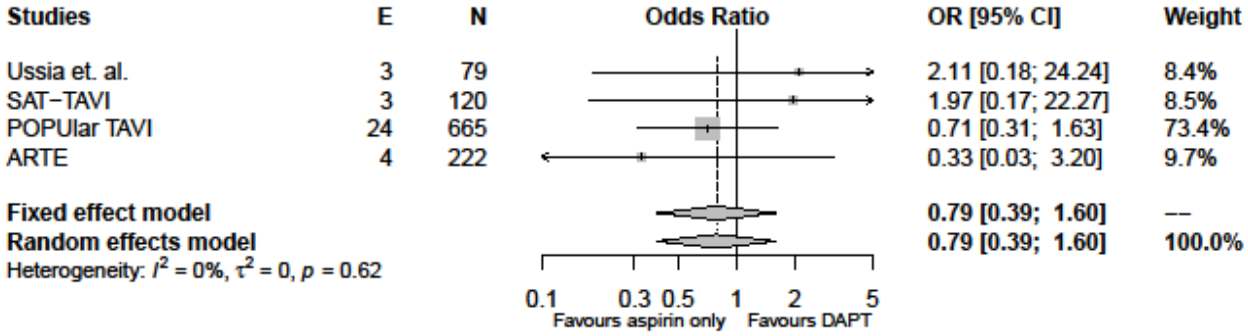
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S3. Meta-Analysis of the Secondary Outcome Life-Threatening Bleeding at 30 Days



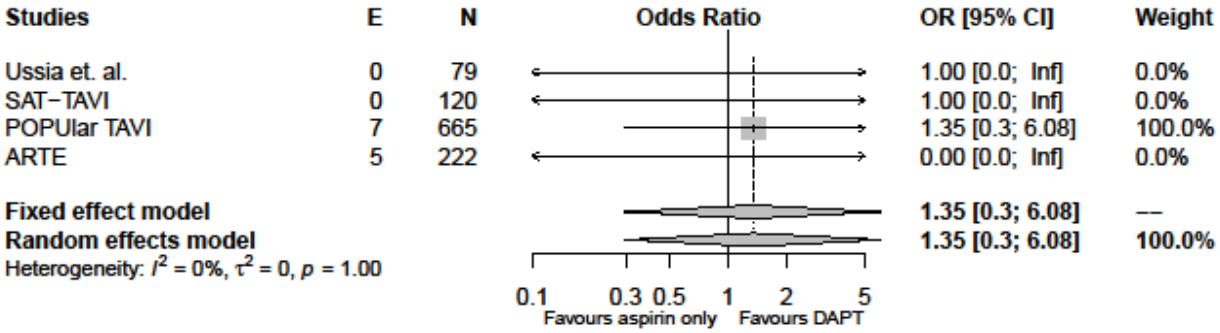
CI = confidence interval, CV = cardiovascular, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S4. Meta-Analysis of the Secondary Outcome Stroke at 30 Days



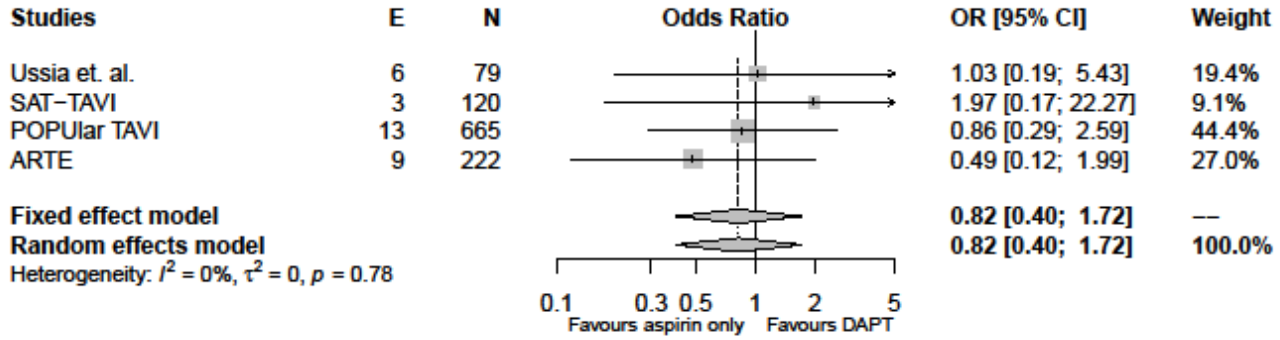
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S5. Meta-Analysis of the Secondary Outcome Myocardial Infarction at 30 Days



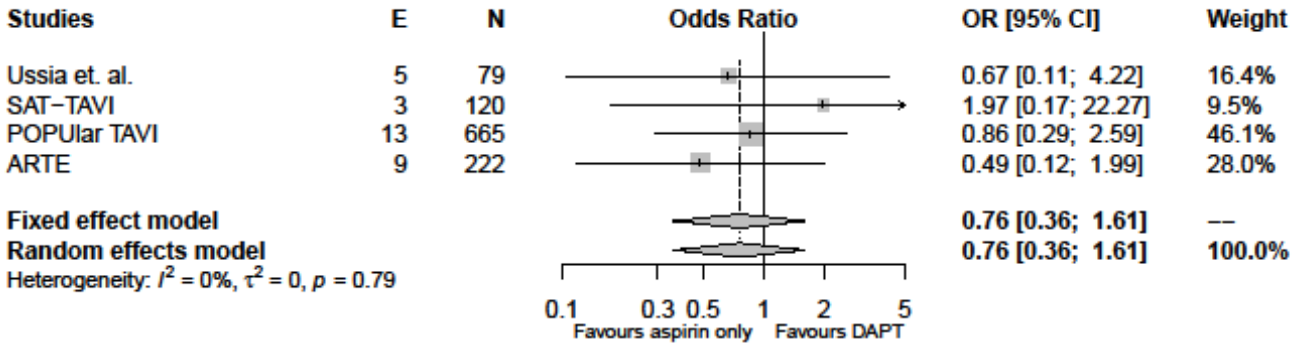
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S6. Meta-Analysis of the Secondary Outcome All-Cause Mortality at 30 Days



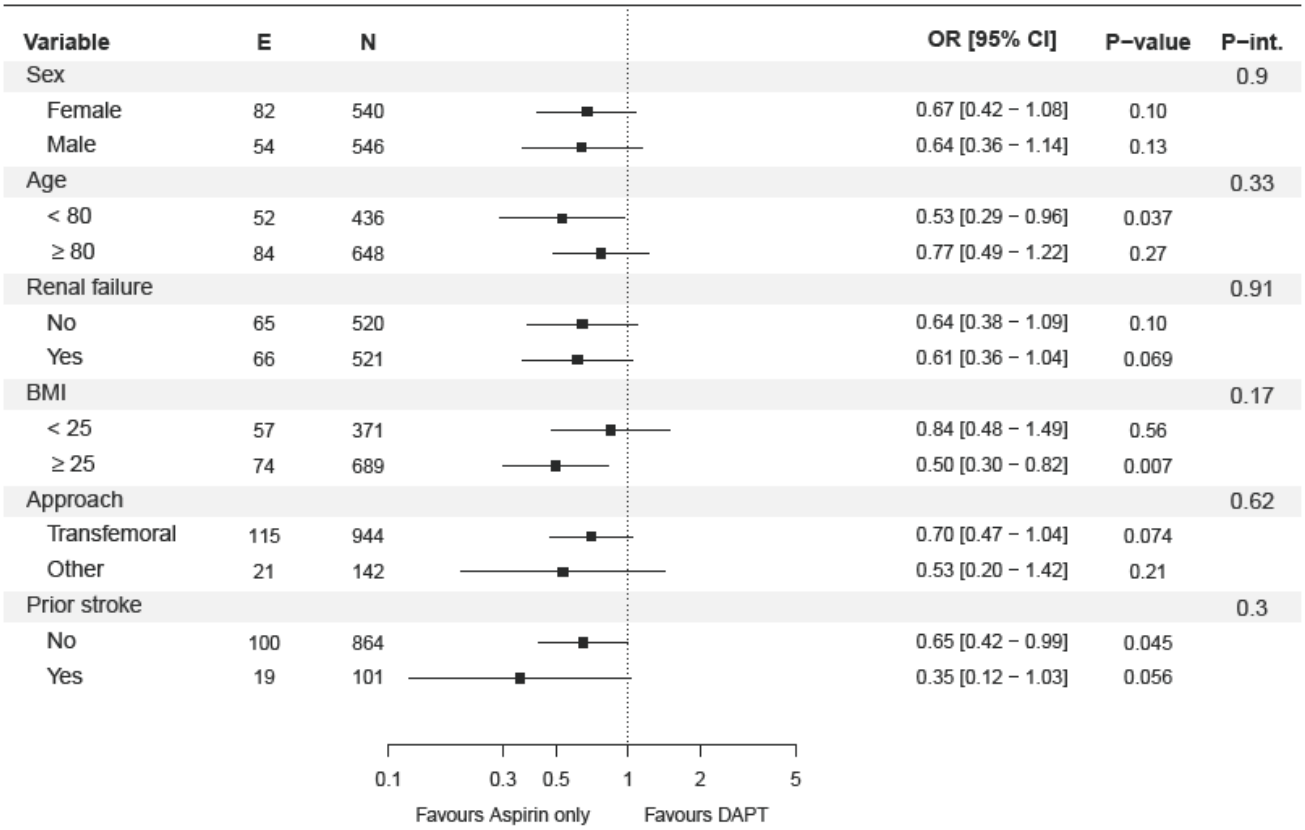
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S7. Meta-Analysis of the Secondary Outcome Cardiovascular Mortality at 30 Days



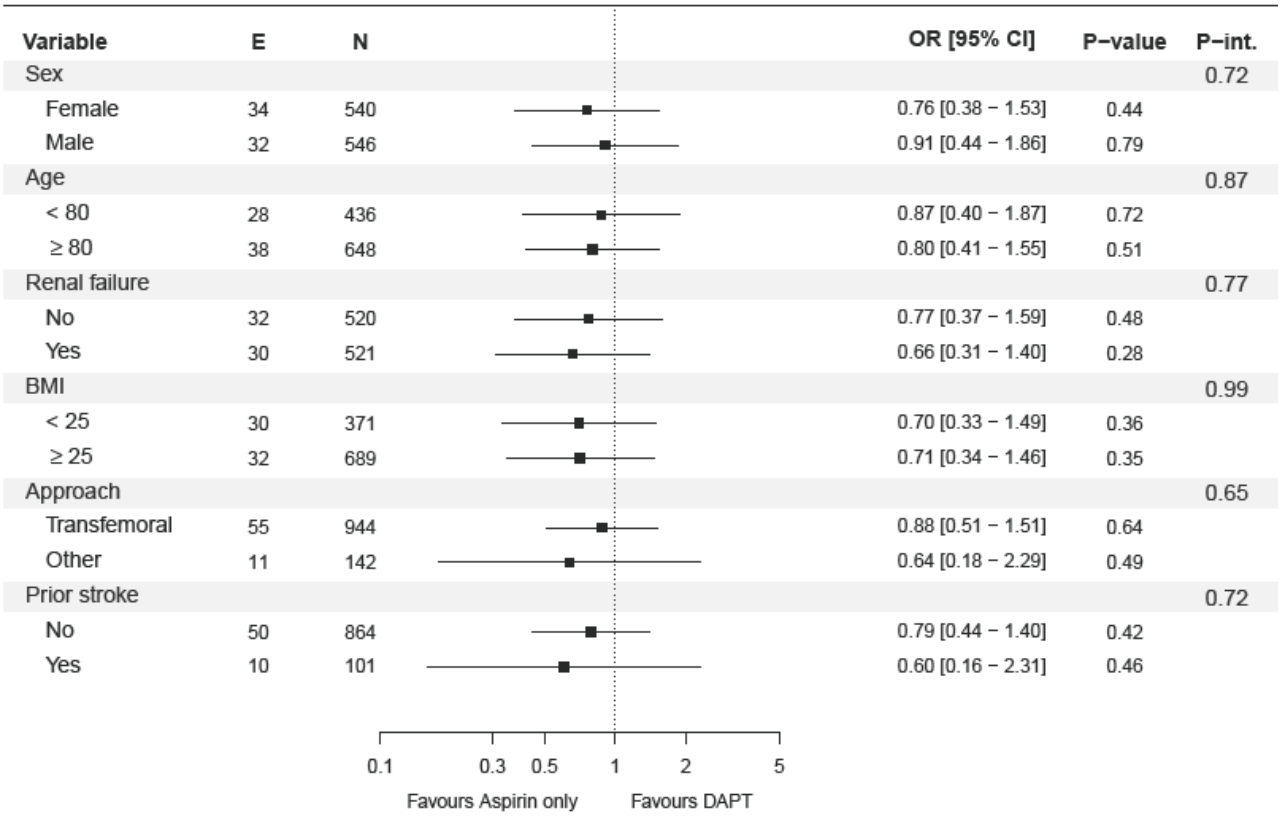
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S8. Prespecified Subgroup Analyses of the First Primary Composite Outcome of All-Cause Mortality, Major or Life-Threatening Bleeding, Stroke, or Myocardial Infarction at 30 Days



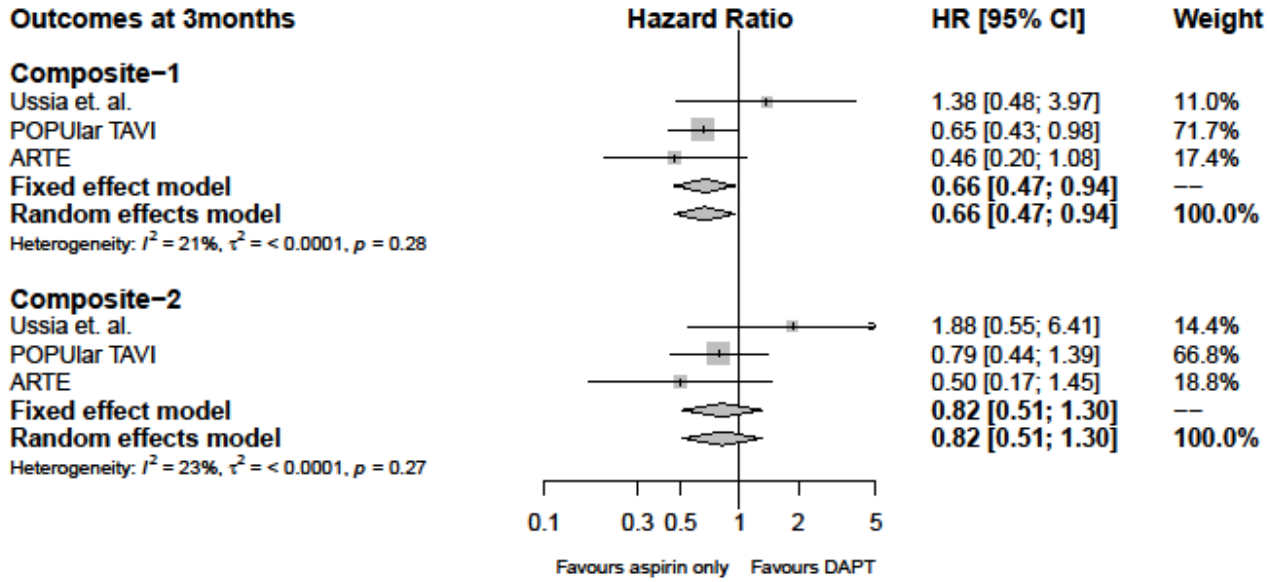
BMI = body mass index, CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), and OR = odds ratio. Sex = 0 denotes female and sex = 1 male.

Figure S9. Prespecified Subgroup Analyses of the Second Primary Composite Outcome of All-Cause Mortality, Stroke, or Myocardial Infarction at 30 Days



BMI = body mass index, CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), and OR = odds ratio. Sex = 0 denotes female and sex = 1 male.

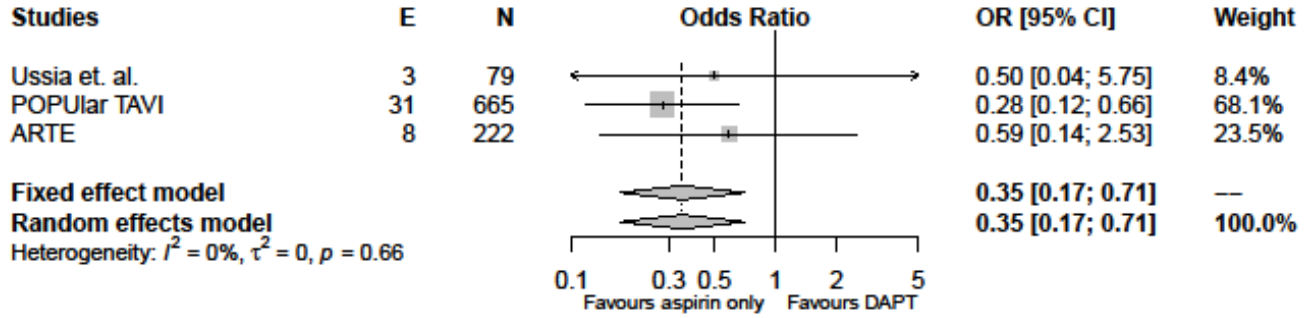
Figure S10. Meta-Analysis of the Primary Composite Outcomes at 3 Months



The first primary outcome was the composite of all-cause mortality, major or life-threatening bleeding, stroke, or myocardial infarction. The second primary outcome was the composite of all-cause mortality, stroke, or myocardial infarction.

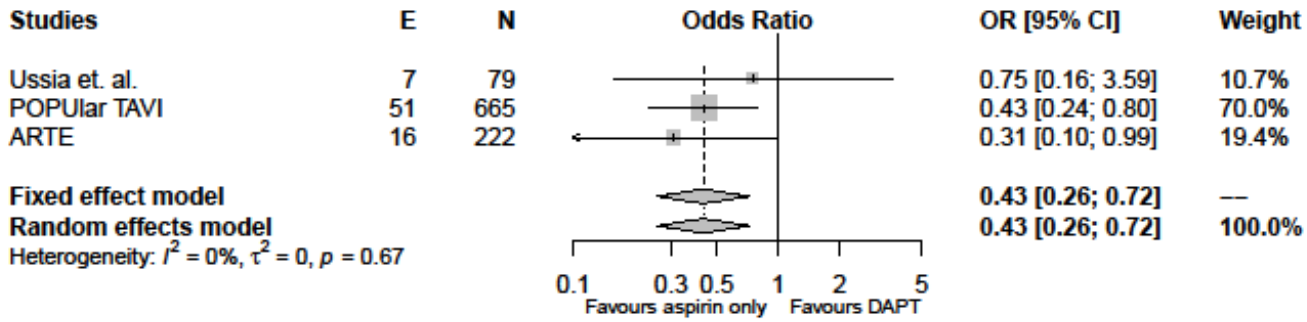
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and HR = hazard ratio.

Figure S11. Meta-Analysis of the Secondary Outcome Major Bleeding at 3 Months



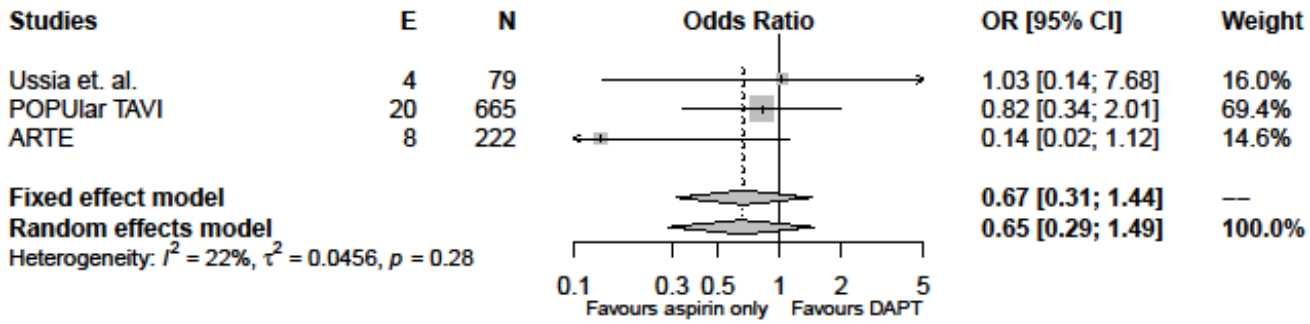
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S12. Meta-Analysis of the Secondary Outcome Major or Life-Threatening Bleeding at 3 Months



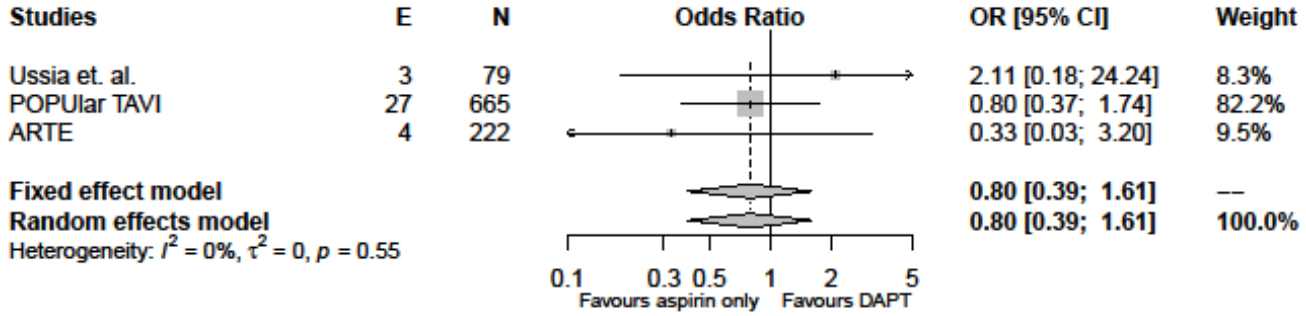
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S13. Meta-Analysis of the Secondary Outcome Life-Threatening Bleeding at 3 Months



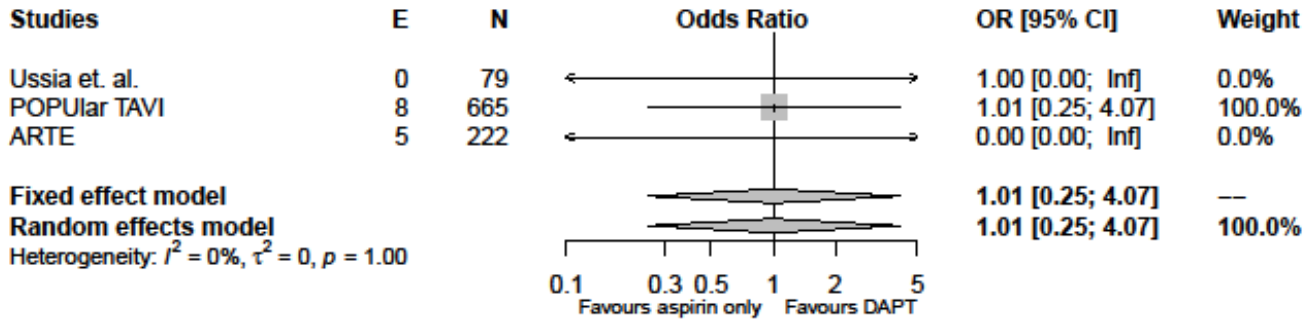
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S14. Meta-Analysis of the Secondary Outcome Stroke at 3 Months



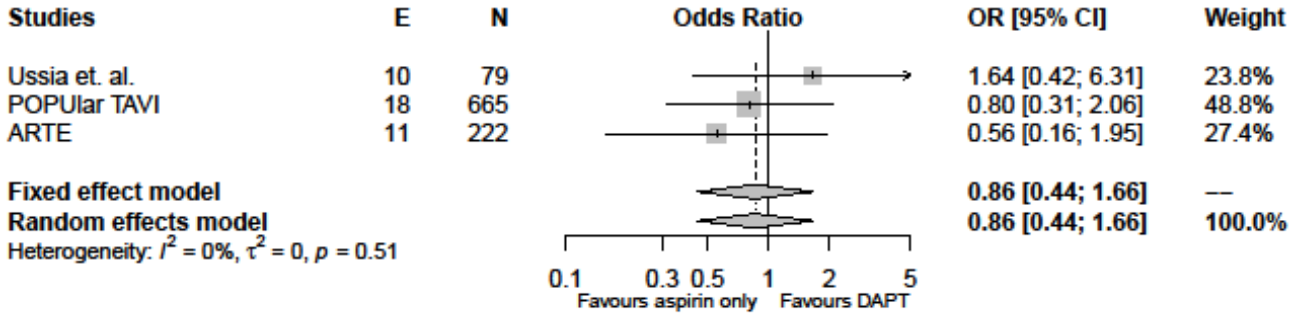
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S15. Meta-Analysis of the Secondary Outcome Myocardial Infarction at 3 Months



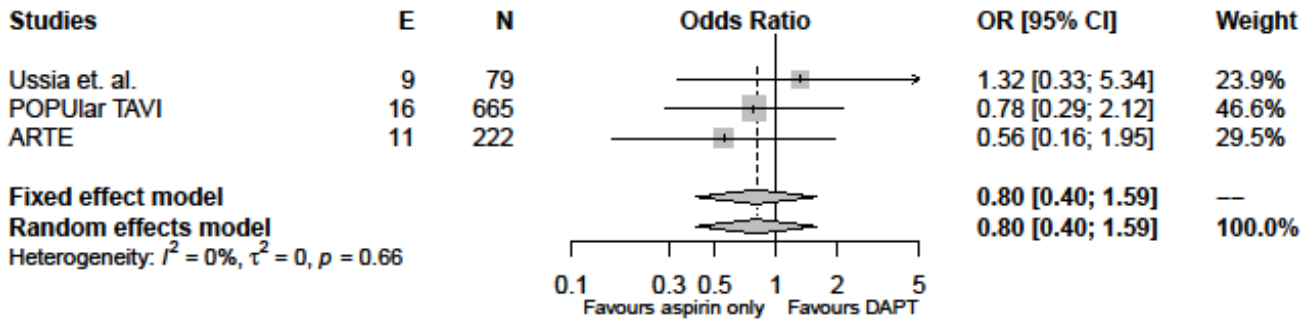
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S16. Meta-Analysis of the Secondary Outcome All-Cause Mortality at 3 Months



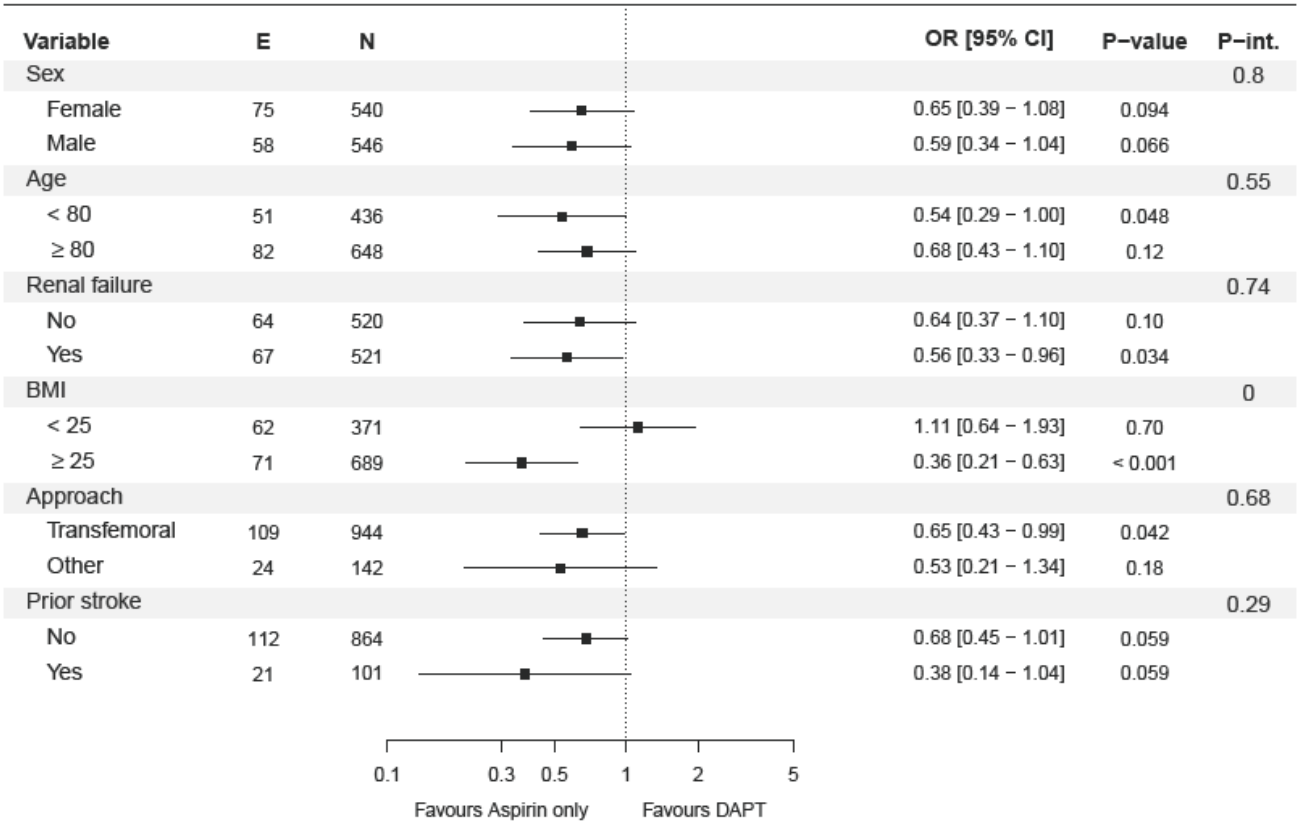
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

Figure S17. Meta-Analysis of the Secondary Outcome Cardiovascular Mortality at 3 Months



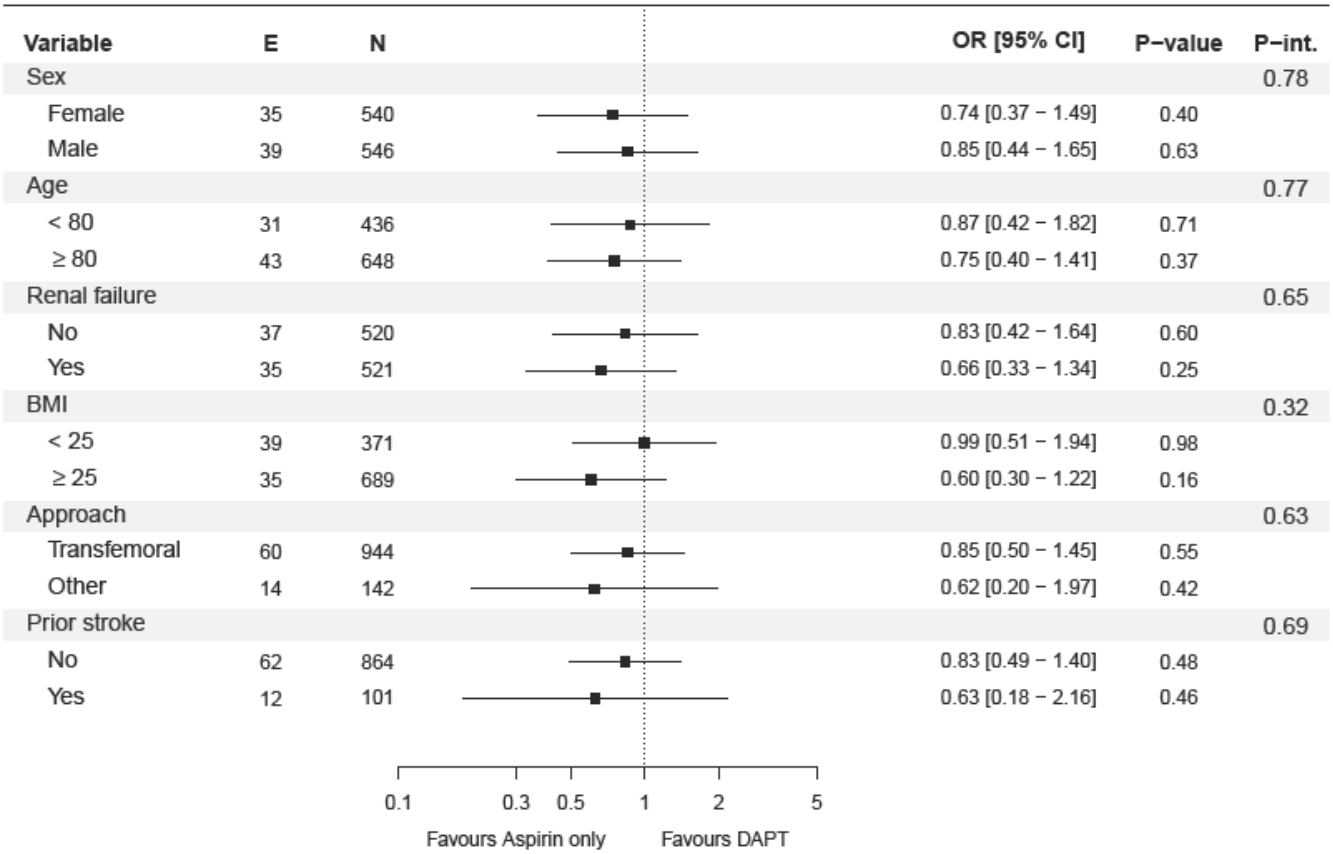
CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), FE model = fixed-effect model and OR = odds ratio.

S18. Prespecified Subgroup Analyses of the First Primary Composite Outcome of All-Cause Mortality, Major or Life-Threatening Bleeding, Stroke, or Myocardial Infarction at 3 Months



BMI = body mass index, CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), and OR = odds ratio. Sex = 0 denotes female and sex = 1 male.

Figure S19. Prespecified Subgroup Analyses of the Second Primary Composite Outcome of All-Cause Mortality, Stroke, or Myocardial Infarction at 3 Months



BMI = body mass index, CI = confidence interval, DAPT = dual antiplatelet therapy (aspirin with clopidogrel), and OR = odds ratio. Sex = 0 denotes female and sex = 1 male.