Appendix D: Clinical evidence tables

Study	POPular TAVI trial cohort A trial: Brouwer 2020[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=690 (665 analysed))
Countries and setting	Conducted in Belgium, Czech Republic, Luxembourg, Netherlands; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: All had data for 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed to have undergone TAVI
Stratum	Transcatheter replacement: Those scheduled to undergo TAVI and no indication for long-term oral anticoagulation
Subgroup analysis within study	Not applicable
Inclusion criteria	Provide written informed consent; scheduled to undergo TAVI; no indication for long-term oral anticoagulation
Exclusion criteria	Long-term indication for oral anticoagulation; drug-eluting stent implantation within 3 months of the TAVI procedure; bare-metal stent implantation within 1 month prior to TAVI; allergy, intolerance or contraindication to aspirin or clopidogrel.
Recruitment/selection of patients	All of those matching inclusion criteria, unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Aspirin alone, 80.4 (6.2) years; aspirin + clopidogrel, 79.5 (6.4) years. Gender (M:F): Aspirin alone, 167/164; aspirin + clopidogrel, 174/160. Ethnicity: Not reported

Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age >75 years in both groups). 2. Atrial fibrillation: No atrial fibrillation (Group with no existing indication for long-term oral anticoagulation). 3. Hepatic function : Not stated / Unclear (No details provided). 4. Renal function: Abnormal (Estimated glomerular filtration rate <60 ml/min/1.73 m2 in both groups - moderate dysfunction?)). 5. Sex: Mixed (Roughly equal proportions in each group). 6. Valve position: Aortic (TAVI performed in all cases).
Extra comments	NYHA class III or IV, 64.0% vs. 65.9%; body mass index, mean (SD): 27.0 (4.7) vs. 27.1 (4.6) kg/m²; STS risk score, median (IR): 2.6 (1.6-3.7) vs. 2.4 (1.7-3.7); indication for TAVI: normal-flow high-gradient AS (76.4% vs. 75.1%), low-flow low-gradient AS (19.3% vs. 17.4%), pure AR (2.4% vs. 2.1%) and combination (1.8% vs. 5.4%); hypertension, 73.4% vs. 76.3%; diabetes mellitus, 23.6% vs. 25.4%; coronary artery disease, 40.5% vs. 41.3%; previous myocardial infarction, 8.5% vs. 9.3%; peripheral artery disease, 14.2% vs. 20.4%; previous stroke, 5.4% vs. 3.6%; estimated golmerular filtration rate, mean (SD): 57.5 (18.1) vs. 57.9 (19.7) ml/min/1.73 m²; COPD, 15.7% vs. 22.2%; previous CABG, 18.4% vs. 19.5%; previous aortic valve surgery, 6.9% vs. 6.0%; LVEF >50% (73.7% vs. 73.4%), 31-50% (22.4% vs. 19.5%) and ≤30% (3.9% vs. 7.2%); type of valve: Sapien XT (1.5% vs. 1.8%), Sapien 3 (45.0% vs. 44.0%), Sapien Ultra (0.0% vs. 0.3%), CoreValve (3.3% vs. 3.0%), COreValve Evolut R (27.2% vs. 25.%), CoreValve Evolut Pro (11.2% vs. 10.5%), Engager (0.0% vs. 0.3%), Accurate Neo (4.5% vs. 3.9%), Lotus (3.9% vs. 4.8%), JenaValve (0.9% vs. 2.4%), Portico (1.5% vs. 3.3%) and Direct Flow (0.9% vs. 0.3%); maximal aortic valve gradient at discharge, mean (SD): 16.8 (9.5) vs. 17.3 (8.4) mmHg; mean aortic valve gradient at discharge, mean (SD): 9.1 (5.5) vs. 9.2 (4.9) mmHg; aortic valve area at discharge, mean (SD): 2.1 (0.7) vs. 2.2 (0.7) cm²; administration of oral anticoagulation during trial, 13.3% vs. 9.6%;
Indirectness of population	No indirectness
Interventions	(n=343) Intervention 1: Single antiplatelet therapy - Aspirin. Aspirin alone. Aspirin at a dose of 80-100 mg daily for duration of trial and advised to take it on a lifelong basis. For those that had not previously taken aspirin, a loading dose of 300 mg aspirin was administered within 1 day prior to the TAVI procedure. For those receiving clopidogrel prior to enrollment for medical reasons, the physician was contacted about the possibility of switching to aspirin and if permission was denied clopidogrel was continued at a dose of 75 mg daily (4.8% - these received clopidogrel alone for the entire study duration). For those assigned to aspirin, if a stroke occurred during the trial, at the attending physician's discretion they could be switched to clopidogrel. Duration 12 months. Concurrent medication/care: All other actively prescribed antiplatelet agents were discontinued at least 5 days prior to TAVI. TAVI procedures performed according to local protocol at each site. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds. In those that developed AF following TAVI, oral anticoagulation was initiated with a vitamin K antagonist or DOAC

	according to local practice. The protocol recommended that the oral anticoagulant should replace aspirin and, if applicable, be prescribed with clopidogrel. Indirectness: No indirectness (n=347) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin + clopidogrel (3 months with clopidogrel). Aspirin at a dose of 80-100 mg daily with 75 mg clopidogrel daily for 3 months, followed by aspirin alone at a dose of 80-100 mg daily for rest of trial duration. Patients were advised to take aspirin on a lifelong basis. For those that had not previously taken aspirin, a loading dose of 300 mg aspirin was administered within 1 day prior to the TAVI procedure. An initial single loading dose of 300 mg clopidogrel was given the day before or on the day of the TAVI procedure, followed by 75 mg daily for 3 months, with discretionary allowance for discontinuation of clopidogrel 1 month earlier (3.4%) or later than 3 months (34.5%). For those receiving clopidogrel prior to enrollment for medical reasons, the physician was contacted about the possibility of switching to aspirin and if permission was denied clopidogrel was continued at a dose of 75 mg daily (3.0% - these received clopidogrel for trial duration and aspirin for 3 months). For those assigned to aspirin, if a stroke occurred during the trial, at the attending physician's discretion they could be switched to clopidogrel. Duration 12 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds. In those that developed AF following TAVI, oral anticoagulation was initiated with a vitamin K antagonist or DOAC according to local practice. The protocol recommended that the oral anticoagulant should replace aspirin and, if applicable, be prescribed with clopidogrel. Indirectness: No indirectness
Funding	Other (Other (Sponsored by Netherlands Organization for Health Research and Development. No industry involvement in the trial.))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL (CLOPIDOGREL FOR 3 MONTHS)

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: All-cause mortality at 12 months; Group 1: 21/331, Group 2: 19/334; Comments: RR of 1.12 (95% CI, 0.61 to 1.04) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12,

Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Major, life-threatening or disabling bleeding according to VARC-2 at 12 months; Group 1: 17/331, Group 2: 19/334; Comments: RR of 0.48 (95% CI, 0.27-0.83) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 3: Minor bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Minor bleeding according to VARC-2 at 12 months; Group 1: 33/331, Group 2: 53/334; Comments: RR of 0.63 (95% CI, 0.42-0.94) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 4: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: Stroke at 12 months; Group 1: 17/331, Group 2: 19/334; Comments: RR of 0.90 (95% CI, 0.48-1.71) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)
- Actual outcome for Transcatheter replacement: Myocardial infarction at 12 months; Group 1: 4/331, Group 2: 6/334; Comments: RR of 0.67 (95% CI, 0.19-2.36) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

	Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4) - Actual outcome for Transcatheter replacement: Lung embolism at 12 months; Group 1: 1/331, Group 2: 0/334 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4) Protocol outcome 5: Thrombus on imaging at ≤12 months - Actual outcome for Transcatheter replacement: Valve thrombosis at 12 months; Group 1: 3/331, Group 2: 1/334 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4) Protocol outcome 6: Valve degeneration (transvalvular gradient) at ≤12 months - Actual outcome for Transcatheter replacement: Mean aortic valve gradient at Mean (SD): 6 (3) months; Group 1: mean 10.6 mmHg (SD 6.2); n=331, Group 2: mean 10.8 mmHg (SD 5.5); n=334; Comments: Values at discharge from TAVI: 9.1 (5.5) vs. 9.2 (4.9) mmHg Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 55, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); screening failure (n=5); and missing data for this outcome at follow-up (n=43); Group 2 Number missing: 59, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); screening failure (n=4); and missing data for this outcome at follow-up (n=46)
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-

	admission at 12 months; Withdrawal due to adverse events at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Colli 2007[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative after aortic valve replacement
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged at least 18 years who required, for the first time, isolated aortic valve replacement and were in sinus rhythm before implantation (patients receiving the EPIC porcine bioprosthesis)
Exclusion criteria	The presence of a previously implanted prosthetic valve; double valve implantation; concomitant coronary artery bypass grafting; intra-aortic balloon pump at any time before, during or after intervention; the use of ASA or VKA therapy or any other antithrombotic drug; a recent positive pregnancy test, breast-feeding or the possibility of future pregnancy; active infective endocarditis; aortic dissection; a history of cerebral ischaemia; coagulopathy; a history of gastrointestinal bleeding or increased bleeding risk; vascular disease requiring medical or surgical treatment; previous chronic anticoagulation therapy; and allergy or contraindication to ASA and/or VKA.
Recruitment/selection of patients	No further details given in the paper
Age, gender and ethnicity	Age - Mean (SD): ASA arm: 70.7±3.7, Warfarin arm: 69.5±3.3. Gender (M:F): 59:10. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): <75 years (ASA arm: 70.7±3.7, Warfarin arm: 69.5±3.3). 2. Atrial fibrillation: No atrial fibrillation (No AF pre-randomisation). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (Predominantly male (59:10) but is mixed). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Vitamin K antagonist - Warfarin. On day 1 after surgery all received a single, body weight-adjusted dose of prophylactic LMWH. Warfarin began from day 2 with target INR 2.0-3.0. Duration 3 months, then aspirin (100mg/day) for 3 months. Concurrent medication/care: Not reported. LMWH was given until the INR was within the target range. A number of patients in each group had comorbid hypertension, diabetes and dyslipidaemia so could have been receiving relevant medication for this. Comments: At 3 months switches from warfarin to aspirin 100mg/day for 3 months

	(n=35) Intervention 2: Single antiplatelet therapy - Aspirin. On day 1 after surgery all received a single, body weight-adjusted dose of prophylactic LMWH. From day 2 aspirin was given 100mg/day. Duration 6 months. Concurrent medication/care: Not reported. LMWH was given until active mobilisation was achieved. A number of patients in each group had comorbid hypertension, diabetes and dyslipidaemia so could have been receiving relevant medication for this. Indirectness: No indirectness
Funding	Principal author funded by industry (Andrea Colli is a clinical investigator for St. Jude Medical, Minneapolis, MN, USA (this paper is investigating the St. Jude Medical heart valve))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus ASPIRIN Protocol outcome 1: All-cause mortality at ≤12 months - Actual outcome for Surgical replacement: Death at follow up at 6 months; Group 1: 2/34, Group 2: 2/35 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0 Protocol outcome 2: Major bleeding at ≤12 months - Actual outcome for Surgical replacement: Major bleeding (as per guidelines in reference 3 of the article - Edmunds et al. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1988;46:257-259) at 6 months; Group 1: 3/34, Group 2: 1/35 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0 Protocol outcome 3: Arterial thromboembolic events at ≤12 months - Actual outcome for Surgical replacement: Postoperative cerebral ischaemia at 6 months; Group 1: 1/34, Group 2: 2/35; Comments: Reports at 24h to 3 months and at >3 months. Numbers were added together to determine the total at 6 months. Does not report any other arterial thromboembolic events. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial

	thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	GALILEO trial: Dangas 2020[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1644)
Countries and setting	Conducted in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom, USA; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: Median trial duration was 17 months (IQR, 13-21)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TAVI performed and success determined by echocardiography
Stratum	Transcatheter replacement: Those that received successful TAVI for treatment of aortic stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years; successful TAVI (correct positioning of single prosthetic heart valve into proper anatomical location, intended performance of the valve as defined by mean aortic valve gradient <20 mmHg, peak transvalvular velocity <3.0 m/s and no severe or moderate aortic valve regurgitation, and absence of periprocedural complications including stroke, life-threatening bleeding, acute coronary obstruction requiring intervention, major vascular complication needing intervention, unresolved acute valve thrombosis and any requirement of a repeat procedure) for aortic stenosis (either native or valve-in-valve procedure); iliofemoral or subclavian access used; TAVI performed with any approved/marketed device; and written informed consent obtained
Exclusion criteria	Current or previous atrial fibrillation with an ongoing indication for oral anticoagulant treatment; any other indication for continued treatment with any oral anticaogulant; known bleeding diathesis (including but not limited to active internal bleeding, clinically significant bleeding, bleeding at a non-compressible site or bleeding diathesis, platelet count ≤50,000 mm^3 at screening, haemoglobin level <8.5 g/dl, history of

	intracranial haemorrhage or subdural haematoma, major surgery, biopsy of a parenchymal organ or serious trauma within 30 days prior to randomisation, and active peptic ulcer or known upper GI bleeding within last 3 months); ongoing indication for dual-antiplatelet therapy at time of screening that is unrelated to TAVI procedure; known hypersensitivity or contraindication to acetylsalicylic acid, clopidogrel or rivaroxaban or hypersensitivity to contrast media that could not be solved by switching to alternative contrast media or by pre-treating with appropriate medication; routine use of NSAIDs; concomitant treatment with systemic drugs that are strong inhibitors of cytochrome P450 3A4 and P-gp; concomitant treatment with drugs that are strong CYP3A4 inducers; concomitant therapy with omeprazole or esomeprazole that cannot be switched to an alternative medication; planned coronary or vascular intervention or major surgery; clinically overt stroke within last 3 months; severe renal impairment (eGFR <30 ml/min/1.73 m²) or on dialysis, or post-TAVI unresolved acute kidney injury with renal dysfunction stage 2 or above; moderate and severe hepatic impairment or any hepatic disease associated with coagulopathy; active infective endocarditis; active malignancy (diagnosed within 5 years) apart from adequately treated non-melanoma skin cancer or other non-invasive or in situ neoplasm; dementia or forgetfulness affecting compliance with medication intake or other study procedures; cannot provide informed consent; previous (30 days prior to enrollment) or concomitant participation in another clinical study with medicinal products being investigated; previous assignment to treatment during this study; close affiliation with the investigational site; female of childbearing potential
Recruitment/selection of patients	Unclear if consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Rivaroxaban, 80.4 (7.1); antiplatelet, 80.8 (6.0). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age in both groups >75 years). 2. Atrial fibrillation: No atrial fibrillation (Atrial fibrillation listed as an exclusion criterion). 3. Hepatic function : Normal (Moderate or severe hepatic dysfunction listed as an exclusion criterion). 4. Renal function: Not stated / Unclear (Severe renal dysfunction listed as an exclusion criterion, unclear how many with milder forms of renal dysfunction may be included. Mean values for eGFR consistent with mild dysfunction). 5. Sex: Mixed (Males and females included). 6. Valve position: Aortic (TAVI performed in all patients).
Extra comments	Body mass index, mean (SD): 28.1 (5.5) vs. 28.2 (5.7); hypertension, 87.2% vs. 85.2%; diabetes mellitus, 28.6% vs. 28.7%; EuroSCORE II, mean (SD): 4.1 (3.9) vs. 4.1 (3.7); STS risk score, mean (SD): 4.0 (3.2) vs. 4.3 (3.5); congestive heart failure, 47.7%vs. 46.5%; NYHA class III or IV, 30.3% vs. 27.1%; coronary artery disease, 39.3% vs. 37.3%; previous stroke, 6.2% vs. 4.3%; peripheral artery disease, 10.0% vs. 10.0%; previous venous thromboembolism, 2.2% vs. 1.8%; permanent pacemaker, 9.7% vs. 9.8%; COPD, 13.3% vs.

	10.8%; glomerular filtration rate, mean (SD): 73.4 (23.8) vs 73.2 (23.2) ml/min/1.73 m²; TAVI valve type: Sapien XT (1.6% vs. 1.6%), Spaien 3 (46.6% vs. 42.3%), CoreValve (4.0% vs. 4.3%), CoreValve Evolut R (24.9% vs. 27.5%), Lotus (5.3% vs. 4.9%), Portico (5.3% vs. 4.9%), Acurate Neo (9.9% vs. 10.9%) and other (2.3% vs. 3.7%); valve-in-valve procedure, 5.1% vs. 6.0%); aortic valve area post-TAVI, mean (SD): 1.8 (0.6) vs. 1.9 (0.5) cm²; mean aortic valve gradient post TAVI, mean (SD): 10.0 (4.7) vs. 10.1 (4.6) mmHg; LVEF post-TAVI, mean (SD): 57.4 (10.9)% vs. 58.2 (11.2)%; mild paravalvular aortic regurgitation post-TAVI, 19.0% vs. 20.5%; moderate or severe paravalvular aortic regurgitation post-TAVI, 1.2% vs. 1.2%
Indirectness of population	No indirectness
Interventions	(n=826) Intervention 1: Direct oral anticoagulants (DOACs) - Rivaroxaban. Rivaroxaban at 10 mg daily + aspirin at 75-100 mg daily for 3 months, followed by rivaroxaban monotherapy 10 mg daily. In those that developed atrial fibrillation, rivaroxaban at 20 mg was received once daily (or 15 mg for those with estimated glomerular filtration rate 30-50 ml/min/1.73 m²). Median exposure to rivaroxaban was 428 days (IQR, 171-581) and median exposure to aspirin was 90 days (IQR, 84-94). Duration Median treatment with rivaroxaban 428 days. Concurrent medication/care: Reports that various medications were allowed concomitantly but no information on the number that were taking concomitant medications/treatments. Indirectness: No indirectness (n=818) Intervention 2: Single antiplatelet therapy - Aspirin. Antiplatelet group received aspirin 75-100 mg daily + clopidogrel 75 mg daily for 3 months (patients that had not previously received clopidogrel were recommended to have a single loading dose of ≥300 mg), followed by aspirin monotherapy (75-100 mg daily). Median exposure to aspirin was 474 days (IQR, 298-603) and median exposure to clopidogrel was 90 days (IQR, 85-93). Duration Median treatment with aspirin 474 days. Concurrent medication/care: Reports that various medications were allowed concomitantly but no information on the number that were taking concomitant medications/treatments. Patients that developed atrial fibrillation received vitamin K antagonists (targeting INR ratio of 2-3) to replace clopidogrel within 3 months or to replace aspirin thereafter. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Bayer and Janssen Pharmaceuticals. Sponsors involved in design and supervision of trial.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN (+ASPIRIN FOR FIRST 3 MONTHS) versus ASPIRIN (+ CLOPIDOGREL FOR FIRST 3 MONTHS)	

Protocol outcome 1: All-cause mortality at >12 months
- Actual outcome for Transcatheter replacement: All-cause deaths during follow-up. Includes all deaths within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 64/826, Group 2: 38/818; Comments: HR of 1.69 (95% CI, 1.13-2.53) reported. Causes of death - sudden death (1.7% vs. 1.0%), congestive heart failure of cardiogenic shock (0.6% vs. 1.0%), intracranial haemorrhage (0.1% vs. 0.1%), ischaemic stroke (0% vs. 0.4%), myocardial infarction (0.2% vs. 0%), non-intracranial haemorrhage (0.1% vs. 0%), dysrhythmia (0.2% vs. 0%), directly related to cardiac procedure or surgery (0.4% vs. 0.2%), unknown death (0.8% vs. 0.6%), cancer (1.2% vs. 0.5%), respiratory failure (1.0% vs. 0.4%), liver failure (0.1% vs. 0.1%), infection or sepsis (0.7% vs. 0.2%), renal failure (0.4% vs. 0.1%) accident or trauma (0.1% vs. 0%).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Major bleeding at >12 months
- Actual outcome for Transcatheter replacement: Life-threatening, disabling or major bleeding, according to VARC-2, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 46/826, Group 2: 31/818; Comments: Rivaroxaban: 18 life-threatening or disabling bleeding, 2 fatal bleeding and 30 major bleeding; aspirin: 17 life-threatening or disabling bleeding, 1 fatal bleeding and 15 major bleeding.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Major bleeding according to ISTH, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 49/826, Group 2: 30/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: BARC type 2, 3 or 5 bleeding, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 148/826, Group 2: 85/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Minor bleeding at >12 months
- Actual outcome for Transcatheter replacement: Major or minor bleeding according to TIMI, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 42/826, Group 2: 24/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Does not report number of minor events

separately - combined with major events.; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Arterial thromboembolic events at >12 months
- Actual outcome for Transcatheter replacement: Stroke during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. Includes ischaemic and haemorrhagic. at Median treatment duration 428 days; Group 1: 30/826, Group 2: 25/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Myocardial infarction during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 23/826, Group 2: 17/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Pulmonary embolism during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 3/826, Group 2: 2/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Systemic embolism during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 1/826, Group 2: 1/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Withdrawal due to adverse events at 12 months
- Actual outcome for Transcatheter replacement: Premature study drug discontinuation due to adverse events - includes any discontinuation with any of the following occurring within 30 days before the discontinuation: thromboembolic events (stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism not involving the CNS, deep vein thrombosis or pulmonary embolism), life-threatening, disabling or major bleeding and other adverse events. Does not include deaths. at Median treatment duration 428 days; Group 1: 185/826, Group 2: 91/818; Comments: Rivaroxaban: 23 due to thromboembolic events, 68 due to bleeding events and 94 due to other adverse events. Aspirin: 21 due to thromboembolic events, 9 due to bleeding events and 61 due to other adverse events.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Measurement - types of events included under 'other adverse events' not reported; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Thrombus on imaging at ≤12 months - Actual outcome for Transcatheter replacement: Symptomatic valve thrombosis (confirmed on echocardiography). Defined as any thrombus attached to or near an implanted valve that occludes part of blood flow path, interferes with valve function or is sufficiently large to warrant treatment. at Median treatment duration 428 days; Group 1: 3/826, Group 2: 7/818 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: May include some events occurring >12 months but unclear; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Minor bleeding at ≤12 months; Arterial thromboembolic events at ≤12 months; Hospital re-admission at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Duraes 2016[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in Brazil; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-surgical patients (up to 3 months post-operatively)
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	18-64 years old, who underwent mitral and/or aortic bioprosthetic valve replacement at least 3 months prior to entering the study and had documented AF postoperatively.
Exclusion criteria	Exclusion of atrial thrombus or valve prosthesis thrombosis by TEE. CT without haemorrhagic or findings of acute cerebral infarction on the last 2 days of screening.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): Dabigatran arm: 48.8±10.4; Warfarin arm: 45.7±6. Gender (M:F): 10:17. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): <75 years (Mean age 48.8±10.4 (dabigatran) and 45.7±6 (warfarin)). 2. Atrial fibrillation: Atrial fibrillation (Patients were included if they had post-operative atrial fibrillation). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (10:17 (male to female)). 6. Valve position: Mixed (Aortic and mitral).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Direct oral anticoagulants (DOACs) - Dabigatran. 110mg twice daily. Duration 90 days. Concurrent medication/care: None noted. However, some patients had diabetes and hypertension and so could have been on other medications. Indirectness: No indirectness Comments: People with previous use of warfarin underwent washout with immediate introduction of dabigatran once the international normalised ratio (INR) was <2.5. (n=12) Intervention 2: Vitamin K antagonist - Warfarin. Target INR 2.0-3.0 (doses between 5 and 10mg in the first days for most individuals). Duration 90 days. Concurrent medication/care: None noted. However, some patients had diabetes and hypertension and so could have been on other medications. Indirectness:

	No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN versus WARFARIN

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Surgical replacement: Death at 90 days; Group 1: 0/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Surgical replacement: Bleeding at 90 days; Group 1: 1/15, Group 2: 2/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Surgical replacement: Stroke or systemic embolism at 90 days; Group 1: 1/15, Group 2: 1/12; Comments: Reports stroke and systolic embolism (1 event in the warfarin arm, 0 events in the dabigatran arm) and reversible ischaemic neurological deficit (0 events in the warfarin arm, 1 event in the dabigatran arm).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Hospital re-admission at 12 months
- Actual outcome for Surgical replacement: Hospitalisation at 90 days; Group 1: 1/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Thrombus on imaging at ≤12 months
- Actual outcome for Surgical replacement: Intracardiac thrombus at 90 days; Group 1: 0/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Withdrawal due to adverse events at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Hassell 2015[31]
Study type	Systematic Review
Number of studies (number of participants)	2 (n=199)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Studies containing patients with aortic stenosis after being treated with TAVI
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Studies containing patients with aortic stenosis after being treated with TAVI, clear description of postprocedural antithrombotic treatment including one group treated with single antiplatelet therapy and another treated with dual antiplatelet therapy, and a minimum follow-up of 1 month.
Exclusion criteria	If only one intervention was considered or when the treatment groups mere included dual versus single antiplatelet therapy in combination with vitamin K antagonist treatment.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Stabile: 80±5.2. Ussia: 81±5.1. Gender (M:F): 76:123. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): 75 years or over (Stabile: 80±5.2. Ussia: 81±5.1.). 2. Atrial fibrillation: Mixed (0 patients in Stabile study. 10 patients in Ussia study (12.7% or 10:69). (AF: not AF)). 3. Hepatic function: Not stated / Unclear 4. Renal function: Mixed (Stabile: 54 (45% or 54:66), Ussia: 11 (13.9% or 11:68) (renal impairment: normal renal function)). 5. Sex: Mixed (Stabile: 80 (66.7% or 40:80), Ussia: 43 (54.4% or 36:43) (M:F)). 6. Valve position: Aortic
Extra comments	Paper also includes observational studies but the RCTs are reported separately.
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Single antiplatelet therapy - Aspirin. Stabile: 81mg OD orally; Ussia: 100mg OD orally. Duration Lifelong. Concurrent medication/care: None stated. Indirectness: No indirectness (n=100) Intervention 2: Dual antiplatelet therapy - Aspirin + clopidogrel. Stabile: 75mg clopidogrel OD orally, 81mg aspirin OD orally. Ussia: 75mg clopidogrel OD orally, 100mg aspirin OD orally. Both studies included a preloading dose of 300mg clopidogrel 1 day preprocedural. Duration Aspirin lifelong. Stabile: Clopidogrel for 6 months. Ussia: Clopidogrel for 3 months. Concurrent medication/care: None stated. Indirectness: No

	indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPIRIN + CLOPIDOGREL

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: All-cause mortality at 3-6 months; Group 1: 4/99, Group 2: 5/100; Comments: OR for Stabile: 1.00 (0.06-16.37)
OR for Ussia: 0.75 (0.16-3.59)
Risk of bias: All domain – High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports: unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Life-threatening and major bleeding at 3-6 months; Group 1: 8/99, Group 2: 10/100; Comments: OR for Stabile: 0.83 (0.24-2.90)
OR for Ussia: 0.75 (0.16-3.59). Stabile: Bleeding events lead to withdrawal of the clopidogrel in 1 person (due to muscular haematoma). There was withdrawal of ticlopidine in 1 person due to thrombocytopenia but no explicit report of bleeding as a consequence.
Risk of bias: All domain - High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: ACS and Stroke at 3-6 months; Group 1: 4/99, Group 2: 2/100; Comments: OR for Stabile: 2.03 (0.18-23.06)
OR for Ussia: 2.11 (0.18-24.24)
No ACS events in either arms. 4 strokes in the aspirin arm, 2 strokes in the aspirin and clopidogrel arm.
Risk of bias: All domain – High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial

	thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	POPular TAVI cohort B trial: Nijenhuis 2020[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=326 (313 analysed))
Countries and setting	Conducted in Belgium, Czech Republic, Luxembourg, Netherlands; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: All followed for at least 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed to have undergone TAVI
Stratum	Transcatheter replacement: Those suitable for TAVI, based on dedicated heart team at each institution, eligible for enrollment (this study covers those with an existing indication for long-term oral anticoagulation)
Subgroup analysis within study	Not applicable
Inclusion criteria	Long-term indication for oral anticoagulation; underwent TAVi procedure; written informed consent provided
Exclusion criteria	Drug-eluting stent implantation within 3 months prior to TAVI; bare-metal stent implantation within 1 month prior to TAVI; allergy, intolerance or contraindication to oral anticoagulation or clopidogrel.
Recruitment/selection of patients	All of those matching inclusion criteria, unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Oral anticoagulation + clopidogrel, 81 (5.5) years; oral anticoagulation only, 80.9 (6.2) years. Gender (M:F): Oral anticoagulation + clopidogrel, 83/73; oral anticoagulation only, 88/69. Ethnicity: Not reported

Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age in both groups >75 years). 2. Atrial fibrillation: Atrial fibrillation (>90% in each group have atrial fibrillation at baseline). 3. Hepatic function : Not stated / Unclear (No details provided). 4. Renal function: Abnormal (Estimated glomerular filtration rate <60 ml/min/1.73 m2 in both groups - moderate dysfunction?). 5. Sex: Mixed (Males and females included). 6. Valve position: Aortic (TAVI performed in all cases).
Extra comments	Oral anticoagulant therapy: vitamin K antagonist, 70.5% vs. 75.2% (acenocoumarol, 58.3% vs. 61.8%, phenprocomon, 10.3% vs. 11.5% and warfarin, 1.9% vs. 1.9%); DOAC, 29.5% vs. 23.6% (apixaban, 16.0% vs. 8.9%; dabigatran, 2.6% vs. 4.5%; edoxaban, 2.6% vs. 2.5%; and rivaroxaban, 7.6% vs. 7.6%); and low molecular weight heparin, 0% vs. 1.3%. NYHA class III or IV, 70.5% vs. 75.8%; body mass index, mean (SD): 27.5 (5.1) vs. 27.4 (5.3); logistic EuroSCORE, median (IQR): 14.1 (10.6-22.8) vs. 15.6 (9.2-23.8); STS risk score, median (IQR): 3.1 (2.3-4.5) vs. 3.2 (2.2-4.8); indication for TAVI: normal-flow high-gradient AS (62.8% vs. 62.4%), low-flow low-gradient AS (32.1% vs. 32.5%), pure AR (2.6% vs. 3.8%) or combination (2.6% vs. 1.3%); atrial fibrillation, 94.2% vs. 95.5%; hypertension, 67.3% vs. 73.2%; diabetes mellitus, 29.5% vs. 27.4%; coronary artery disease, 44.2% vs. 41.4%; previous myocardial infarction, 12.8% vs. 8.9%; peripheral artery disease, 17.9% vs. 19.1%; previous stroke, 9.6% vs. 9.6%; estimated GFR, mean (SD): 55.6 (17.1) vs. 53.4 (17.7) ml/min/1.73 m²; COPD, 19.2% vs. 21.0%; previous CABG, 19.2% vs. 19.1%; previous aortic valve surgery, 5.8% vs. 4.5%; LVEF >50%, 62.2% vs. 58.0%; LVEF 31-50%, 29.5% vs. 34.4%; LVEF ≤30%, 8.3% vs. 7.6%; transfemoral TAVI approach, 84.6% vs. 86.6%; transapical TAVI approach, 11.5% vs. 9.6%; direct aortic TAVI approach, 3.2% vs. 3.8%; trans-subclavia TAVI approach, 0.6% vs. 0%; unfractionated heparin during TAVI, 100% vs. 100%; valve type: Sapien XT (2.6% vs. 4.5%), Sapien 3 (52.6% vs. 41.4%), CoreValve (7.7% vs. 2.5%), CoreValve Evolut R (23.1% vs. 28.7%), CoreValve Evolut Pro (3.2% vs. 5.7%), Engager (1.9% vs. 1.3%), Lotus (4.5% vs. 6.4%), JenaValve (1.9% vs. 3.2%), Portico (0.6% vs. 1.3%) and Direct Flow (1.9% vs. 3.2%); VARC-2 vascular complication, 22.4% vs. 12.7%; red blood cell transfusion following TAVI, 8.3% vs. 7.0%; mild PV leak at discharge, 26.9% vs. 28.7%; moderate PV leak at discharge, 2.6% vs. 1.9%; severe PV leak at discharge, 0% vs. 0%; maximal aortic valve gradient at discharge, mean (SD): 17.0 (10.2) vs. 15.8 (8.0) mmHg; mean aortic valve gradient at discharge, mean (SD): 8.8 (5.6) vs. 8.6 (4.6) mmHg; aortic valve area at discharge, mean (SD): 2.2 (0.8) vs. 2.1 (0.7) cm²
Indirectness of population	No indirectness
Interventions	(n=162) Intervention 1: Anti-coagulation + antiplatelet therapy – VKA/DOAC + clopidogrel. Oral anticoagulation (vitamin K antagonist or DOAC) + clopidogrel. Patients continued using the oral anticoagulation they were receiving prior to randomisation, which could be a vitamin K antagonist or a DOAC. Randomised prior to TAVI to receive clopidogrel for 3 months in addition to their oral anticoagulation. Loading

	dose of 300 mg clopidogrel administered 1 day prior to or on the day of TAVI ocedure, followed by 75 mg once daily for 3 months. There was a discretionary allowance of cessation of clopidogrel 1 month earlier or later than 3 months. Adherence to clopidogrel was 95.5% for the period of 3 months. 70.5% were on a vitamin K antagonist and 29.5% were on a DOAC. No patients in this group discontinued oral anticoagulation. Duration 3 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. Protocol advised physicians to continue oral anticoagulation during admission for the TAVi procedure with a target of INR 2.0 for vitamin K antagonists, but the choice to continue or interrupt oral anticoagulation periprocedurally was left to discretion of attending physician. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds or >200 seconds in patients with continued oral anticoagulation therapy. Indirectness: Serious indirectness; Indirectness comment: Includes a mixture of those receiving vitamin K antagonists and DOACs under the term 'oral anticoagulation', whereas in protocol ideally wanted to separate vitamin K antagonists and DOACs (n=164) Intervention 2: Anti-coagulation – VKA/DOAC. Oral anticoagulation (vitamin K antagonist or DOAC) alone. Patients continued using the oral anticoagulation they were receiving prior to randomisation, which could be a vitamin K antagonist or a DOAC. Randomised prior to TAVI not to receive clopidogrel for 3 months in addition to their oral anticoagulation. 75.2% were on a vitamin K antagonist and 23.6% were on a DOAC. 2 patients discontinued oral anticoagulation during the trial. Duration 3 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. Protocol advised physicians to continue oral anticoagulation during admission for the TAVi procedure with a target of INR 2.0 for vitamin K antagonists, but the choice to continue or interrupt oral anticoagulation periprocedurally was left to discretion of attending physician. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds or >200 seconds in patients with continued oral anticoagulation therapy. Two patients in this group were discharged with low molecular weight heparin, which was used until an adequate INR with vitamin K antagonist was obtained. Indirectness: Serious indirectness; Indirectness comment: Includes a mixture of those receiving vitamin K antagonists and DOACs under the term 'oral anticoagulation', whereas in protocol ideally wanted to separate vitamin K antagonists and DOACs
Funding	Other (Sponsored by Netherlands Organization for Health Research and Development. No industry involvement in the trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL ANTICOAGULATION (VITAMIN K OR DOAC) + CLOPIDOGREL versus ORAL ANTICOAGULATION (VITAMIN K ANTAGONIST OR DOAC) ALONE

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: All-cause mortality at 12 months; Group 1: 24/156, Group 2: 21/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Major, life-threatening or disabling bleeding according to VARC-2 at 12 months; Group 1: 26/156, Group 2: 14/157; Comments: Anticoagulation +clopidogrel: 13 life-threatening or disabling and 13 major bleeding; anticoagulation alone, 6 life-threatening or disabling and 8 major bleeding.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 3: Minor bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Minor bleeding according to VARC-2 at 12 months; Group 1: 28/156, Group 2: 20/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 4: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: Stroke. Includes ischaemic and haemorrhagic. at 12 months; Group 1: 9/156, Group 2: 9/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.
- Actual outcome for Transcatheter replacement: Myocardial infarction at 12 months; Group 1: 1/156, Group 2: 1/157
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1. Protocol outcome 5: Valve degeneration (transvalvular gradient) at ≤12 months - Actual outcome for Transcatheter replacement: Mean aortic valve gradient at mean (SD) follow-up 6(3) months; Group 1: mean 10.5 mmHg (SD 5.3); n=129, Group 2: mean 9 mmHg (SD 4.7); n=135; Comments: Values at discharge from TAVI: anticoagulation + clopidogrel, 8.8 (5.6) mmHg; anticoagulation alone, 8.6 (4.6) mmHg. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 33, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; screening failure, n=2; further n=27 with missing data at follow-up; Group 2 Number missing: 29, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1; further n=22 with missing data at follow-up	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Rafiq 2017[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=328)
Countries and setting	Conducted in Denmark; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative patients
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients referred for first time aortic valve replacement with or without concomitant coronary artery bypass grafting surgery aged 60 years or older and in sinus rhythm.
Exclusion criteria	Other concomitant procedures, active endocarditis, history of atrial fibrillation or flutter, previous TIA or stroke, neurological deficits, coagulopathy, haematological disorders/cancers, permanent pacemaker, HIV/AIDS, liver cirrhosis, renal dialysis, narcotics or alcohol abuse, not able to give informed consent, patients from Greenland and Faroe Islands (not available for follow-up).
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Warfarin arm: 73.1±6.4, Aspirin arm: 72.7±7.2. Gender (M:F): 229:99. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Mixed (Warfarin arm: 73.1±6.4, Aspirin arm: 72.7±7.2. Crosses the line due to the confidence interval.). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function : Normal (No liver cirrhosis (sufficient?)). 4. Renal function: Normal (Not on renal dialysis (sufficient?)). 5. Sex: Mixed (Predominantly male but by a 2:1 ratio.). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=167) Intervention 1: Vitamin K antagonist - Warfarin. Initial dose 5mg orally. Target INR of 2.0 to 3.0. Duration 3 months. Concurrent medication/care: Enoxaparin 40mg SC once daily until INR stabilised for 2 days. Indirectness: Very serious indirectness; Indirectness comment: 63 patients had a CABG while having the valve replacement surgery and so were put on warfarin and aspirin 75mg once a day post-operatively. (n=161) Intervention 2: Single antiplatelet therapy - Aspirin. 150mg orally. Duration 3 months. Concurrent medication/care: Enoxaparin 40mg SC once daily was given for the first 3 days. Indirectness: No indirectness

	Comments: 56 patients had a CABG at the same time. They received the same treatment otherwise.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus ASPIRIN

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Surgical replacement: Total mortality at 3 months; Group 1: 8/167, Group 2: 6/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed by ITT.

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Surgical replacement: Major bleeding at 3 months; Group 1: 9/167, Group 2: 3/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Surgical replacement: Thromboembolic complications at 3 months; Group 1: 10/167, Group 2: 11/161; Comments: They included MI, DVT, TCI/Stroke and other thromboembolic complications. This included 2 MIs in the warfarin arm, 5 MIs in the aspirin arm, 8 TCIs/Strokes in the warfarin arm and 4 TCIs/Strokes in the aspirin arm. We did not include the other thromboembolic complications reported, which included a pulmonary embolus (as this would not be a relevant arterial thromboembolic event in this scenario) and intramural cardiac thrombus (as this is counted in another outcome).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 4: Hospital re-admission at 12 months
- Actual outcome for Surgical replacement: Re-admission to hospital at 3 months; Group 1: 25/167, Group 2: 21/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 5: Thrombus on imaging at ≤12 months
- Actual outcome for Surgical replacement: Left ventricle mural thrombus at 3 months; Group 1: 0/167, Group 2: 1/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients

developed AF and were switched to use warfarin. These patients were analysed with ITT.	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Withdrawal due to adverse events at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Rodes-Cabau 2017[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=222)
Countries and setting	Conducted in Canada, Chile, Spain, Switzerland; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months (90 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative patients
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with clinical indications for TAVR with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve
Exclusion criteria	Need for chronic anticoagulation treatment, major bleeding within the 3 months before the TAVR procedure, allergy to clopidogrel and/or aspirin.
Recruitment/selection of patients	Selected from 9 centers across Canada, Europe and South America
Age, gender and ethnicity	Age - Mean (SD): 79±9. Gender (M:F): 129:93. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Mixed (79±9 - Crosses the middle point). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function: Not stated / Unclear 4. Renal function: Mixed (140 patients (70 in each arm) had chronic renal failure (GFR <60mL/min)). 5. Sex: Mixed (129:93 (male:female)). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Single antiplatelet therapy - Aspirin. Aspirin 80-100mg per day. Duration 3 months. Concurrent medication/care: Not stated. No specific recommendations regarding proton pump inhibitors. Indirectness: No indirectness (n=111) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin 80-100mg per day, Clopidogrel 75mg per day. Duration 3 months. Concurrent medication/care: Not stated. No specific recommendations regarding proton pump inhibitors. Indirectness: No indirectness
Funding	Principal author funded by industry (The study was also funded by industry (a grant from Edwards Lifesciences) and from academic sources (the Foundation of the Research Center of the Quebec Heart and Lung Institute). Several authors had funding from industry.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: Death at 3 months; Group 1: 4/111, Group 2: 7/111
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Life threatening/major bleeding at 3 months; Group 1: 3/111, Group 2: 5/111; Comments: Bleeding events lead to withdrawal of clopidogrel in 8 people.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: Stroke and MI at 3 months; Group 1: 2/111, Group 2: 7/111; Comments: MIs in aspirin arm: 1, MIs in aspirin and clopidogrel arm: 4
Strokes in aspirin arm: 1, Strokes in aspirin and clopidogrel arm: 3
No TIAs in both arms.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months; Withdrawal due to adverse events at 12 months

Study	Stabile 2014[68]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with severe AS, cardiac symptoms (NYHA ≥2, syncope) and high surgical risk.
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe AS (echo-derived AVA <0.8cm² and mean AVG >40mmHg or peak jet velocity >4.0m/s), cardiac symptoms (NYHA functional class ≥2) or high surgical risk (predicted risk of operative mortality ≥15% as determined by surgeon and cardiology or STS scope ≥10
Exclusion criteria	Aortic annulus diameter <18mm or >25mm; aortic dissection or iliac-femoral dimensions or disease precluding safe sheath insertion; untreated coronary artery disease requiring revascularisation; severe aortic regurgitation or mitral regurgitation or prosthetic valve (any location); acute myocardial infarction within 1 month; upper gastrointestinal bleeding within 3 months; cerebrovascular accident or transient ischaemic attack within 6 months; any cardiac procedure, other than balloon aortic valvuloplasty within 1 month or within 6 months for drug eluting stent; indication for oral anticoagulation therapy (i.e. atrial fibrillation); aspirin intolerance/allergy; thienopiridine intolerance/allergy
Recruitment/selection of patients	144 consecutive patients, scheduled for TAVI, were screened.
Age, gender and ethnicity	Age - Mean (SD): ASA arm: 81.1±4.8, DAPT arm: 80.2±5.7. Gender (M:F): 40:80. Ethnicity: Not specified
Further population details	1. Age (<75 vs ≥75): 75 years or over (ASA arm: 81.1±4.8, DAPT arm: 80.2±5.7). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (40:80 - predominantly female, but not exclusively). 6. Valve position: Aortic
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Single antiplatelet therapy - Aspirin. 75-160mg/day. Duration 6 months. Concurrent medication/care: Patients received unfractionated heparin at the start of the procedure and were given additional heparin at the operator's discretion. Indirectness: No indirectness

	(n=60) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin 75-160mg/day. Clopidogrel 75mg four times a day OR ticlopidine 500mg twice a day. Duration 6 months. Concurrent medication/care: Patients received unfractionated heparin at the start of the procedure and were given additional heparin at the operator's discretion. Indirectness: Serious indirectness; Indirectness comment: Ticlopidine 500mg twice a day. Not able to distinguish patients who took ticlopidine instead of clopidogrel.
Funding	Other author(s) funded by industry (G. Sorropago and P. Rubino are proctors for Edwards Lifesciences.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL No additional outcomes reported	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at ≤12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months; Withdrawal due to adverse events at 12 months

Study	Turpie 1993[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=In trial: 370, with bioprosthetic valves: 89)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean 2.5 years, maximum 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Surgery was performed with specific valves.
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with mechanical or bioprosthetic valves plus pre-operative atrial fibrillation or a history of thromboembolism. Patients with replacements in the aortic, mitral or tricuspid positions (singly or in combination) were potentially eligible, as were patients who had concurrent coronary artery bypass graft surgery.
Exclusion criteria	Allergy to aspirin; contraindication to either anticoagulant or antiplatelet therapy; were geographically inaccessible for follow up; were not willing to give consent
Recruitment/selection of patients	Consecutive patients from 3 different Canadian hospitals
Age, gender and ethnicity	Age - Mean (range): Study in total: Aspirin arm 58.1 (26-82), Placebo arm: 58.1 (22-79). Gender (M:F): Total for study 187:183. Not able to distinguish for patients with biological valves only. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Not stated / Unclear (Unclear for our strata, generally <75). 2. Atrial fibrillation: Not stated / Unclear (Unclear for our strata. One of the inclusion criteria included the presence of AF as a possible option.). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Not stated / Unclear (Unclear for our strata, generally mixed). 6. Valve position: Mixed (Aortic and mitral).
Extra comments	. Am not able to distinguish ages and sex of the people in the biological valve arm.
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Vitamin K antagonist - Warfarin. Warfarin and aspirin (100mg OD). Target INR 3.0-4.5. Duration Mean 2.4 years. Concurrent medication/care: Low-dose heparin postoperatively until 3 days after oral anticoagulant started. Indirectness: No indirectness (n=44) Intervention 2: Vitamin K antagonist - Warfarin. dose/quantity, brand name, extra details. Duration Mean 2.4 years. Concurrent medication/care: Low-dose heparin postoperatively until 3 days after oral

	anticoagulant started. Indirectness: No indirectness
Funding	Academic or government funding (Grant from the Heart and Stroke Foundation or Ontario.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN AND ASPIRIN versus WARFARIN Protocol outcome 1: Arterial thromboembolic events at ≤12 months - Actual outcome for Surgical replacement: Major systemic embolism OR death from vascular causes at Mean follow up 2.4 months; Group 1: 2/45, Group 2: 4/44 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Includes vascular mortality. Appeared to fit better into this outcome than the all-cause mortality outcome.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Ussia 2011[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients after TAVI insertion
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Criteria for inclusion of a TAVI (previously reported). Patients with severe symptomatic aortic stenosis with a valve area <1cm². Eligibility for TAVI was established at each centre by the consensus of a local multidisciplinary team. All procedures were approved for compassionate use in patients with no reasonable surgical option.
Exclusion criteria	Additional exclusion factors were: previous percutaneous coronary intervention or ACS requiring DAPT, the need for oral anticoagulation therapy, and allergy or intolerance to any of the study drugs.
Recruitment/selection of patients	Consecutive patients who met the anatomic and clinical criteria.
Age, gender and ethnicity	Age - Mean (SD): 81±4. Gender (M:F): 36:43. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): 75 years or over (81±4). 2. Atrial fibrillation: Mixed (Permanent AF in 10 patients (13%)). 3. Hepatic function: Mixed (1 patient with liver cirrhosis, otherwise normal hepatic function). 4. Renal function: Mixed (11 patients (14%) with CKD). 5. Sex: Mixed (36:43 (M:F)). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Dual antiplatelet therapy - Asprin + clopidogrel. Oral aspirin 100mg OD and oral clopidogrel 75mg OD. Loading dose of 300mg clopidogrel on the day before TAVI. Duration Aspirin lifelong. Clopidogrel for 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=39) Intervention 2: Single antiplatelet therapy - Aspirin. Oral aspirin 100mg OD. Duration Lifelong. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Principal author funded by industry (Dr Ussia is a proctor physician for Medtronic Incorporation. All other authors have no conflicts of interest to declare.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPRIN + CLOPIDOGREL versus ASPIRIN Protocol outcome 1: Minor bleeding at ≤12 months - Actual outcome for Transcatheter replacement: Minor bleeding at 6 months; Group 1: 3/40, Group 2: 4/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: The dual antiplatelet group generally has more patients that would fall into a higher clinical risk bracket (ex. diabetes, heart failure, peripheral vascular disease, previous PCI, COPD, previous valvuloplasty); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at ≤12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months