

SUPPLEMENTARY DATA

Table S1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	

Results of syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Table S2. Main trial characteristics

Study	Trial design	Primary endpoint	Secondary endpoint	Inclusion criteria	Exclusion criteria
CHAMPION-AF¹	Prospective, randomized, multicenter, open-label trial. Randomization: 1:1 Percutaneous LAAO with the WATCHMAN FLX device (Boston Scientific) or NOACs.	Efficacy endpoint: stroke (including ischemic and/or hemorrhagic), cardiovascular death (including hemorrhagic or unexplained death) and systemic embolism at 36-mo. Safety endpoint: nonprocedural bleeding (ISTH major bleeding and clinically relevant nonmajor bleeding) at 36 mo. Nonprocedural events are those occurring after 3 d.	Cardiovascular death, disabling stroke, systemic embolism, and nonprocedural bleeding (ISTH major bleeding and clinically relevant nonmajor bleeding) at 36 mo.	Documented nonvalvular AF (ie, AF in the absence of moderate or greater mitral stenosis or a mechanical heart valve), CHA ₂ DS ₂ -VASc score of ≥ 2 for men and ≥ 3 for women, the individual is deemed to be suitable for the protocol defined pharmacologic regimens in both the test and control arms, the individual or legal representative is able to understand and willing to provide written informed consent to participate in the trial, the individual is able and willing to return for required follow-up visits and examinations.	The individual requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (ie, even if the device is implanted, the individual would not be eligible to discontinue OAC due to other medical conditions requiring chronic OAC therapy, contraindicated or allergic to oral anticoagulation medication and/or aspirin, indication for chronic P2Y ₁₂ platelet inhibitor therapy, planning to have any cardiac or noncardiac intervention or surgical procedure within 30 d prior to or 60 d after implant (including, but not limited to: cardioversion, percutaneous coronary intervention (PCI), cardiac ablation, cataract surgery, etc), a prior stroke (of any cause, whether ischemic or hemorrhagic) or TIA within the 30 d prior to enrollment,

					a prior major bleeding event per ISTH definition within the 30 d prior to randomization. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event, active bleeding, reversible cause of AF or transient AF. Absence of a LAA or the LAA is surgically ligated, myocardial infarction (MI) documented in the clinical record as either a non-ST-elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 30 d prior to enrollment, history of atrial septal repair or has an ASD/PFO device, implanted mechanical valve prosthesis in any position, known contraindication to percutaneous catheterization procedure, known contraindication to TEE, cardiac tumor, LVEF < 30%, existing pericardial effusion
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					with a circumferential echo-free space > 5 mm, high-risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15 mm or length > 15 mm, significant mitral valve stenosis (ie, MV area < 1.5 cm ²).
CLOSURE-AF²	Prospective, multicenter, event-driven, randomized controlled trial. Randomization: 1:1 Percutaneous LAAO with the Amulet occluder (Abbott) or the Watchman device (Boston Scientific) or physician-directed best medical care.	Stroke (including ischemic or hemorrhagic stroke), systemic embolism, major bleeding (BARC type 3-5), cardiovascular or unexplained death.	Primary endpoint events per y, combined endpoint: MACCE (stroke/systemic embolism/cardiovascular death/myocardial infarction), mortality (including all-cause death, cardiovascular death, noncardiovascular death, periprocedural death), major bleeding (BARC type 3-5), systemic embolism, ischemic/hemorrhagic stroke including TIA, defined as neurological deficit of vascular origin lasting ≤ 24 h without corresponding brain	Age ≥ 18 y, documented AF (paroxysmal, persistent, long-standing persistent or permanent), CHA ₂ DS ₂ VASc-score ≥ 2, high risk of bleeding under oral anticoagulation or contraindication for (N)OAC therapy, in particular patients with at least 1 of the following conditions: -HAS-BLED-Score ≥ 3. - Prior intracranial/intraspinal	Absolute contraindication to aspirin, comorbidities other than AF requiring chronic (N)OAC therapy, eg, mechanical heart valve prosthesis, symptomatic carotid disease (if not treated), complex aortic atheroma with mobile plaque (Kronzon classification grade V), heart transplant, active infection or symptoms suggestive of COVID-19 infection or active endocarditis or other infections producing bacteremia, cardiac tumor,

			lesion), myocardial infarction, hospitalization for bleeding or cardiovascular event, changes in cognitive function assessed by MoCA (= Montreal Cognitive Assessment), changes in health-related quality of life (EQ-5D-5L). Safety endpoint(s): device thrombus/fracture/erosion, vascular access-related complications requiring intervention, procedure-related death, technical and procedural success of device implantation, postprocedure infection rate, periprocedural outcomes at 7 and 30 calendar d after implantation.	bleed, intraocular bleed compromising vision (BARC: type 3c). Hemorrhagic/bleeding complication fulfilling BARC type 3a or 3b: gastrointestinal tract, genitourinary tract or respiratory tract bleeding, where the patient is considered to be at a persistently increased risk of bleeding, eg, the cause of bleeding cannot be successfully eliminated. Chronic kidney disease with eGFR 15-29 mL/min/1.73 m². Any recurrent bleeding making chronic anticoagulation not feasible. Patient eligible for an LAA occluder device. Signed written Informed consent.	severe liver failure (Child-Pugh class C or liver failure with coagulopathy), severe renal failure (GFR < 15 mL/min/1.73 m² or current requirement for dialysis (defined as current, regular renal replacement therapy performed at least weekly (including hemodialysis and peritoneal dialysis) within the last 30 d), pregnancy or breastfeeding. For female patients of reproductive potential: unwilling to agree to use a highly effective method of contraception (Pearl index < 1) throughout the study period. Patient with participation in another interventional clinical trial during this trial or within 30 d before entry into this trial, known terminal disease with life expectancy < 1 y (including those with end-stage heart failure), patients who are committed to an institution due to binding official or court order, patients who are dependent on the site, the site Investigator, any subinvestigator, his/her
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					representative and/or the sponsor, persons who are not proficient in the German language, unstable/not fully recompensated acute heart failure corresponding to NYHA class III and/or IV, patients with known antiphospholipid syndrome.
PRAGUE-17³	Prospective, multicenter, randomized, controlled, open label trial. Randomization: 1:1 Comparison of DOACs with LAAC in high-risk patients with AF.	<i>a)</i> stroke (ischemic or hemorrhagic) or TIA <i>b)</i> systemic embolism <i>c)</i> clinically significant bleeding <i>d)</i> cardiovascular death <i>e)</i> a significant periprocedural or device-related complications.	Secondary endpoints included the individual components of the primary endpoint.	Moderate- or high-risk patients with nonvalvular AF were eligible if indicated for anticoagulation and had: <i>a)</i> history of bleeding requiring intervention or hospitalization; <i>b)</i> history of a cardioembolic event while taking anticoagulation agents <i>c)</i> moderate to high risk profile, defined as CHA ₂ DS ₂ -VASc (congestive heart failure, hypertension,	Mobile aortic plaque, symptomatic carotid arterial atherosclerosis, clinically significant bleeding within 30 d, cardioembolic event within 30 d, creatinine clearance of < 30 mL/min.

				age > 75 y, diabetes mellitus, prior stroke, TIA, or thromboembolism, vascular disease, age 65-74 y, sex category [female]) of > 3 plus HAS-BLED (uncontrolled hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs, or alcohol) of > 2.	
PREVAIL⁴	Prospective, multicenter, randomized controlled, open label trial. Randomization: 2:1. LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138).	3 coprimary endpoints: efficacy: composite of hemorrhagic or ischemic stroke, SE, and cardiovascular/unexplained death. Late ischemic efficacy: late-ischemic efficacy, a composite of ischemic stroke or SE, excluding the first 7 d after randomization. Early safety: a composite of all-cause death, ischemic stroke, SE, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention.	The second endpoint was based on a 1-tailed test, in which the null hypothesis would be rejected if either the ratio or the difference between rates in the randomized groups satisfied the noninferiority criteria.	Nonvalvular AF (NVAf), including paroxysmal, persistent, or permanent forms. CHADS ₂ score ≥ 2. CHADS ₂ = 1 plus at least 1 of the following additional high-risk features: female sex, age ≥ 75 y. LVEF ≥ 30% but < 35%. Age 65-74 y with diabetes mellitus or coronary artery disease	Requirement for chronic anticoagulation for reasons other than AF. Contraindication to warfarin or aspirin therapy. History of stroke or TIA within 90 d prior to enrolment. Symptomatic carotid artery disease. PFO or ASD requiring closure or other treatment. Indication for chronic clopidogrel (thienopyridine) therapy, to avoid confounding effects of stroke, thromboembolism, or bleeding risk.

PROTECT-AF⁵	Prospective, multicenter, randomized, open label trial. Randomization: 2:1. LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or administration of chronic warfarin therapy (control group, n = 138).	All stroke (including ischemic and hemorrhagic), cardiovascular death (limited to any cardiovascular and unexplained), and systemic embolism.	TIA (defined as an acute focal neurological event lasting at least 5 min and up to 24 h that is MR imaging negative). All TIAs will be adjudicated by the CEC. Other individual complication rates including, but not limited to MI and death. For the Watchman group: technical success defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary. Procedural success defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay. 30-Day major complication rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 d or through hospital discharge (whichever is	Age $18 \geq y$ or older; paroxysmal, persistent, or permanent nonvalvular AF; 1 or more CHADS risk factors (age ≥ 75 y, hypertension, diabetes, heart failure or LV systolic dysfunction, prior TIA or stroke); and eligibility for long-term anticoagulation with warfarin. Race and ethnicity data were self-reported.	Major exclusion criteria were PFO with atrial septal aneurysm, an atrial septal defect, mechanical valve prosthesis, LV ejection fraction < 30%, mobile aortic atheromata, and symptomatic carotid disease.
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			longer). Individual complication rates including, but not limited to hematomas, and pseudoaneurysms. For the coumadin control group: Nontherapeutic INR > 3.0, INR < 2.0 and stopped therapy 1. Excessive anticoagulation INR > 4.0 Bleeding complications: hematuria, rectal bleeding, epistaxis, bleeding from varicose veins, oral bleeding, prolonged bleeding from a laceration, or bruising-hematoma, hemathorax, red eye, thrombosis.		
OPTION⁶	Prospective, multicenter, randomized, open label trial. Randomization: 1:1.to undergo left atrial appendage closure (device group) or receive oral	The primary safety end point was nonprocedure-related bleeding—a combination of major bleeding (as defined by the ISTH) and clinically relevant nonmajor bleeding (bleeding that required medical intervention, led to hospitalization or increased level of care, or prompted a	The secondary end point was ISTH major bleeding, including procedure-related bleeding, through 36 mo.	The individual is of legal age to participate in the study as per the laws of their respective region. Underwent a prior catheter ablation procedure for nonvalvular AF between 90 and 180 d prior to randomization (sequential) or is	The individual is currently enrolled in another investigational study that would directly interfere with the current study, except when the individual is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance

	anticoagulation (anticoagulation group), with randomization stratified according to site and timing of the catheter ablation procedure.	face-to-face evaluation)—through 36 mo.		planning to have clinically indicated catheter ablation within 10 d of randomization (concomitant). The individual has a calculated CHA₂DS₂-VASc score of 2 or greater for males or 3 or greater for females. The individual is deemed by the treating physician to be suitable for the protocol-defined pharmacologic regimens. The individual is able to undergo TEE examinations. The individual or legal representative is able to understand and is willing to provide written informed consent to participate in the trial. The individual is able and willing to return for required follow-up visits and examinations.	must be brought to the attention of the sponsor to determine eligibility, regardless of the type of coenrollment being proposed. The individual requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction, for example due to an underlying hypercoagulable state (ie, even if the device is implanted, the individuals would not be eligible to discontinue OAC due to other medical conditions requiring chronic OAC therapy). The individual is deemed by the treating physician to be unsuitable for chronic anticoagulation and/or aspirin therapy due to bleeding risk, allergy, or other reasons. The individual had or is planning to have any cardiac or major noncardiac interventional or surgical procedure (excluding nonvalvular AF ablation and cardioversion) within 30 d prior to or 60 d after randomization [including, but not limited to: percutaneous
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					coronary intervention, other cardiac ablation (VT ablation, etc), etc]. The individual had a stroke or TIA within the 60 d prior to randomization. The individual had a prior major bleeding event per ISTH definition within the 14 d prior to randomization. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event. The individual has had a myocardial infarction documented in the clinical record as either a non-ST elevation MI or as an ST-elevation MI, with or without intervention, within 90 d prior to randomization. The individual has a history of atrial septal repair or has an ASD/PFO device. The individual has an implanted mechanical valve prosthesis in any position. The individual is of childbearing potential and is,
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					or plans to become pregnant during the time of the study (method of assessment at study physician's discretion). The individual has a documented life expectancy of < 2 y. The individual has a cardiac tumor. The individual has signs/symptoms of acute or chronic pericarditis. There is evidence of tamponade physiology. The individual has contraindications (anatomical or medical) to percutaneous catheterization procedures. The individual has documented NYHA Class IV heart failure. The individual has documented surgical closure of the left atrial appendage. The individual has an active infection.
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WATCH-TAVR 7	Prospective, multicenter, randomized, open label trial. Randomization: 1:1. TAVR with concomitant Watchman implantation (TAVR + LAAO) or TAVR with anticoagulation according to treating physician preference (TAVR + medical therapy).	The primary endpoint was a composite of the first occurrence of all-cause mortality, stroke (ischemic or hemorrhagic), or bleeding (life-threatening and major) events within 2 y after randomization.	The secondary endpoints were: time from randomization to each component of the primary endpoint: all cause-mortality, any stroke and any occurrence of major or life-threatening bleeding (as per VARC2 definition of bleeding), time to death from cardiovascular causes, time to ischemic stroke, time to hemorrhagic stroke, arterial or venous thrombosis or embolism, rehospitalization related to the Watchman procedure or Watchman device.	Men and Women ≥ 18 y of age. The patient meets criteria for and is eligible to undergo TAVR procedure. The patient has documented paroxysmal, persistent, or permanent AF. The patient meets the Watchman labelling guidelines and is eligible to undergo the Watchman implantation procedure. The patient is eligible for short-term warfarin therapy. The patient or legal representative is able to understand and is willing to provide written informed consent to participate in the trial. The patient is able and willing to return for required follow-up visits and examinations.	The patient had a stroke or TIA within the last 6 mo prior to enrolment. Contraindication for short-term anticoagulation. Moderate or severe MS with mean gradient across MV > 10 mmHg or MVA < 1.2 cm ² . The patient has symptomatic carotid disease (ie, carotid stenosis $> 50\%$ associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs, or ipsilateral stroke within 6 mo). The patient requires long-term warfarin therapy. The patient is actively enrolled in another trial of a cardiovascular device or an investigational drug (postmarketing study participation and registries are acceptable). The patient is pregnant or pregnancy is planned during the course of the investigation if the patient is of child-bearing potential. Any clinically significant medical condition or
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					presence of any laboratory abnormality prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study or not meeting procedure guidelines for TAVR or Watchman. The patient has a life expectancy of < 2 y.
AF, atrial fibrillation; CHADS score, congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA; CHA₂DS₂-VASc score, congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, vascular disease, age, sex category; CLOSURE-AF, catheter-based left atrial appendage closure in patients with atrial fibrillation; DOAC, direct oral anticoagulant; HAS-BLED score, hypertension, abnormal renal function, abnormal liver function, stroke, bleeding, labile INRs, elderly, drugs; ISTH, International Society on Thrombosis and Haemostasis; LAOO, left atrial appendage occlusion; OPTION, comparison of anticoagulation with left atrial appendage closure after atrial fibrillation ablation; PRAGUE-17, left atrial appendage closure vs novel anticoagulation agents in atrial fibrillation; PREVAIL, prospective evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy; PROTECT-A, Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation trial; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; VKA, vitamin K antagonist; WATCH-TAVR, Watchman for patients with AF undergoing TAVR.					

Table S3. Endpoint definition across all trials

Study	All cause death	Cardiovascular death	Stroke	Systemic embolism	Major bleeding	Life-threatening bleeding	Minor bleeding
CHAMPION-AF¹	Death that does not meet the definition for cardiovascular or unexplained death. Sudden or unwitnessed death defined as a nontraumatic, unexpected fatal event occurring within 1 h of symptom onset in an apparently healthy individual. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event; death from unknown cause.	Death due to proximate cardiac cause, eg, myocardial infarction, cardiac tamponade, worsening heart failure, endocarditis, cardiac arrest; death due to hemorrhage or bleeding; death caused by noncoronary, non-CNS vascular conditions such as pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease; death from vascular CNS causes;	Duration of focal or global neurological deficit > 24 h; duration of focal or global neurological deficit < 24 h in the event of imaging documented new hemorrhage or infarct; a neurological deficit resulting in death.	Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanisms (eg, trauma, atherosclerosis, or instrumentation). In the presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.	ISTH major bleeding is defined as having a symptomatic presentation and: <i>a</i>) fatal bleeding, and/or <i>b</i>) bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or <i>c</i>) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol per liter) or more, or leading to	ISTH clinical relevant nonmajor bleeding is defined as any sign or symptom of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least 1 of the following criteria: <i>a</i>) requiring medical intervention by a health care professional (ie, any action taken by a health care professional such as medication	Any bleeding reported by the patient, which did not meet the criteria for major or clinically significant nonmajor bleeding.

		from hemorrhagic stroke; from ischemic stroke; all-cause mortality during the index procedure, any procedure-related death within 30 d after the index procedure or during postoperative hospitalization for the index procedure (if > 30 d); including those related to a complication of the procedure or treatment for a complication of the procedure; unexplained death.			transfusion of 2 or more units of whole blood or red cells.	change, any treatment to stop bleeding or address blood loss) or <i>b</i>) leading to hospitalization or increased level of care (eg, ER visit, diagnostic procedure). Examples include fall or accident-related injury, hemorrhage, and hematoma.	
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CLOSURE-AF²	Noncardiovascular mortality: -Death from a primary cause that is clearly related to another condition (eg, trauma, cancer, suicide). Procedural mortality: -All-cause mortality during the index procedure, any procedure-related death within 30 d after the index procedure or during postoperative hospitalization for the index procedure (if >30 d). Immediate procedural mortality: -All-cause mortality <72 h after commencing the index procedure.	Death due to proximate cardiac cause, eg, myocardial infarction, cardiac tamponade, worsening heart failure, or endocarditis. -Death caused by noncoronary, non-CNS vascular conditions such as: pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other vascular disease. -Death from vascular CNS causes from hemorrhagic and ischemic stroke. -All procedure-related deaths including those related to a	A stroke is an acute episode (lasting > 24 h) of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.	A noncentral nervous system systemic embolism is defined as abrupt vascular insufficiency of an extremity or organ associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, (eg, trauma, atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires angiographic demonstration of abrupt arterial occlusion.	Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery OR -Pericardial bleeding with tamponade occurring during the index procedure or during hospitalization for the index procedure. -Bleeding causing discontinuation of antithrombotic	Fatal bleeding (BARC type 5) OR -Symptomatic bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR -Symptomatic pericardial bleeding (with or without tamponade) occurring after hospital discharge for the index procedure OR -Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR -Overt source of bleeding with drop in hemoglobin ≥ 5	Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life threatening, disabling, or major.
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		complication of the procedure or treatment for a complication of the procedure. -Sudden or unwitnessed death defined as nontraumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy individual. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event. - Death from unknown cause.			therapy for stroke prevention, including antiplatelet, VKA and NOAC AND - does not meet criteria of life-threatening or disabling bleeding.	g/dL or whole blood or packed RBCs transfusion $\geq$ 4 units (BARC type 3b).	
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OPTION⁶	Not available	Not available	Sudden onset of a localized/generalized neurological impairment with neurological signs or symptoms compatible with stroke and classified as ischemic or hemorrhagic. The diagnosis had to be verified (by a neurology or neurosurgery expert, neuroimaging technique, or spinal tap).	Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (eg, trauma, atherosclerosis, or instrumentation). In the presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.	ISTH major bleeding is defined as having a symptomatic presentation and - fatal bleeding, and/or - bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome, and/or - bleeding causing a fall in hemoglobin level of 20 g L ⁻¹ (1.24 mmol L ⁻¹) or more or leading to transfusion of 2 or more units of	ISTH clinically-relevant nonmajor bleeding is defined as any sign or symptom of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least 1 of the following criteria. - requiring medical intervention by a health care professional - leading to hospitalization or increased level of care (eg, ER visit, diagnostic procedures, medication change)	Not available
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					whole blood or red cells.	-prompting a face to face * (ie, not just a telephone or electronic communication) evaluation *such as office or telehealth visit to evaluate the event	
PRAGUE-17³	Not available	Not available	A stroke is defined as the sudden onset of a focal neurologic deficit, from a nontraumatic cause, in a location consistent with the territory of a major cerebral artery and categorized as either ischemic, hemorrhagic, or unspecified. An imaging examination (CR, MRI) will be required.	Systemic cardioembolic events will be defined as an acute vascular occlusion of an extremity or organ, documented with imaging (CT angiography, percutaneous interventional angiography), surgery, or autopsy.	Clinically relevant major bleeding will be defined according to the criteria of the ISTH, as clinically overt bleeding accompanied by 1 or more of the following: a decrease in hemoglobin level ≥ 20 g/L over a 24-h period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial,	Clinically relevant nonmajor bleeding (nonmajor clinically relevant bleeding) will be defined as any bleeding requiring hospitalization or invasive procedure, which does not meet the ISTH major criteria.	Not available

					intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.		
PREVAIL⁴	Not available	Not available	Not available	Not available	Not available	Not available	Not available
PROTECT AF⁵	Not available	Not available	Not available	Not available	Not available	Not available	Not available
WATCH-TAVR⁷	Any death in which the primary cause is clearly related to another condition (eg, trauma, cancer, suicide). A cardiovascular cause of death is excluded. Noncardiovascular causes of death include the following: Infections- noncardiovascular death attributable to an infectious disease, including	Cardiovascular death includes death with any of the following criteria: -Any death due to proximate cardiac disease cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure). -Unwitnessed death or sudden cardiac death. -All	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Duration of a focal or global neurological deficit > 24 h; OR < 24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit	Definition available for arterial thrombotic event, venous and pulmonary artery thromboembolic event.	Overt bleeding either: associated with a decrease in hemoglobin level of at least 3.0 g/dL OR requiring transfusion of 2 or 3 units of whole blood/RBC OR causing hospitalization or permanent injury or requiring surgery and	Fatal bleeding OR bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring	Any bleeding worthy of clinical mention (eg. access site hematoma) that does not qualify as life-threatening, disabling, or major.

	sepsis and pneumonia. Systemic inflammatory response system syndrome. Pulmonary-noncardiovascular death attributable to disease of the lungs (excludes malignancy and pneumonia). Renal-noncardiovascular death attributable to renal failure. Gastrointestinal-noncardiovascular death attributable to disease of the esophagus, stomach, or intestines (excludes malignancy). Malignancy-noncardiovascular death attributable to leukemia, lymphoma, or other malignancy. Prescription drug	cardiovascular procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure. -Death caused by noncoronary vascular conditions such as neurological event, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease. -All valve-related deaths including structural or NVSD or other valve related adverse events.	results in death. No other readily identifiable non stroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with a designated neurologist.		does not meet criteria of life-threatening or disabling bleeding.	vasopressors or surgery OR overt source of bleeding with drop in Hgb of ≥ 5 g/dL OR overt source of bleeding with whole blood or packed RBCs transfusion ≥ 4 units*.	
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	error- noncardiovascular death attributable to a prescription drug error, reaction or overdoes. Note: includes anaphylaxis. Nonprescription drug overdose. Noncardiovascular death attributable to a nonprescription drug reaction or overdose. Note: includes overdose of a prescription drug for which the individual did not have a legal prescription Accident or trauma- noncardiovascular death attributable to accident or trauma, including homicide. Hemorrhage- noncardiovascular death attributable	-Death of unknown cause.					
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	to bleeding that is not considered cardiovascular hemorrhage or stroke. Suicide-noncardiovascular death attributable to suicide. Hepatobiliary-noncardiovascular death attributable to disease of the liver, gallbladder, or biliary ducts (excludes malignancy). Pancreatic-noncardiovascular death attributable to disease of the pancreas (excludes malignancy). Noncardiovascular procedure or surgery-death caused by the immediate complication(s) of a noncardiovascular procedure or						
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	surgery. Neurological-noncardiovascular death attributable to disease of the nervous system. Note: excludes malignancy and cardiovascular death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or cardiovascular hemorrhage of the central nervous system. Other noncardiovascular; specify-noncardiovascular death attributable to a cause other than those listed in this classification (specify organ system).						
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BARC, Bleeding Academic Research Consortium, CNS, central nervous system, CR, computed radiography; CT angiography, computed tomography angiography; ER, emergency room; Hbg, hemoglobin; ISTH, International Society on Thrombosis and Haemostasis; MRI, magnetic resonance imaging; NOAC, nonvitamin K antagonist

oral anticoagulants/novel oral anticoagulants; non-CNS, noncentral nervous system; NVSD, nonstructural valve deterioration; RBC, red blood cell; VKA, vitamin K antagonists.

Table S4. Full electronic database search process for EMBASE

EMBASE		
Search line	Search Terms	No. citations
1	'atrial fibrillation':ab,ti AND [embase]/lim	185510
2	'left atrial appendage closure':ab,ti AND [randomized controlled trial]/lim AND [embase]/lim	106
3	'left atrial appendage closure device':ab,ti AND [embase]/lim	178
4	'watchman':ab,ti AND [embase]/lim	2242
5	'amulet':ab,ti AND [embase]/lim	691
6	'oral anticoagulation':ab,ti AND [embase]/lim	13176
7	af:ab,ti AND [embase]/lim	114382
8	#1 OR #2 OR #6	191942
9	#1 AND #3	119
10	#1 AND #2	90

Table S5. Full electronic database search process for MEDLINE

MEDLINE		
Search line	Search Terms	No. citations
1	'atrial fibrillation':ab,ti AND [medline]/lim	88173
2	'left atrial appendage closure':ab,ti AND [randomized controlled trial]/lim AND [medline]/lim	41
3	'left atrial appendage closure device':ab,ti AND [medline]/lim	86
4	'watchman':ab,ti AND [medline]/lim	722
5	'amulet':ab,ti AND [medline]/lim	294
6	'oral anticoagulation':ab,ti AND [medline]/lim	6341
7	af:ab,ti AND [medline]/lim	5374
8	#1 OR #2 OR #6	91521
9	#1 AND #3	45
10	#1 AND #2	35

Table S6. IRRs for all-cause death, stroke, and any bleeding at the longest available follow up

	IRR	95%CI	Weight (%)
<i>All-cause death</i>			
CHAMPION-AF	1.06	(0.76-1.48)	17.3
CLOSURE-AF	1.09	(0.87-1.37)	30.1
OPTION	0.85	(0.52-1.39)	8.9
PRAGUE-17	0.79	(0.53-1.19)	12.6
PREVAIL/PROTECT AF	0.76	(0.56-1.02)	20.6
WATCH-TAVR	0.92	(0.59-1.44)	10.5
Random effects model	0.93	(0.78-1.11)	
$I^2 = 0.0\%$; $P = .32$			
<i>Stroke</i>			
CHAMPION-AF	1.52	(0.98-2.35)	28.0
CLOSURE-AF	0.95	(0.56-1.64)	19.3
OPTION	0.79	(0.37-1.70)	10.1
PRAGUE-17	1.27	(0.58-2.80)	9.3
PREVAIL/PROTECT AF	0.95	(0.59-1.51)	24.9
WATCH-TAVR	0.81	(0.40-1.87)	8.3
Random effects model	1.08	[0.82-1.42]	
$I^2 = 0.0\%$; $P = .51$			
<i>Any bleeding</i>			
CHAMPION-AF	0.95	(0.70-1.29)	27.7
CLOSURE-AF	1.14	(0.80-1.60)	21.3
OPTION	0.78	(0.48-1.26)	10.9
PRAGUE-17	0.75	(0.44-1.27)	9.0

PREVAIL/PROTECT AF	0.89	(0.62-1.26)	20.6
WATCH-TAVR	1.13	(0.70-1.85)	10.5
Random effects model	0.95	(0.80-1.21)	
$I^2 = 0.0\%$; $P = .47$			
<i>Ischemic stroke</i>			
CHAMPION-AF	1.67	(1.04-2.69)	36.9
CLOSURE-AF	1.19	(0.60-2.36)	17.9
OPTION	0.89	(0.36-2.20)	10.4
PREVAIL/PROTECT AF	1.68	(0.92-3.06)	23.4
WATCH-TAVR	0.88	(0.38-2.08)	11.5
Random effects model	1.37	(0.95-1.97)	
$I^2 = 0.0\%$; $P = .07$			
<i>Nonprocedural bleeding</i>			
CHAMPION-AF	0.59	(0.49-0.72)	53.2
OPTION	0.47	(0.35-0.63)	25.4
PRAGUE-17	0.56	(0.32-1.00)	6.9
PREVAIL/PROTECT AF	0.49	(0.33-0.73)	14.5
Random effects model	0.54	(0.45-0.66)	
$I^2 = 0.0$; $P = .002$			

Figure S1. PRISMA 2020 flowchart for study selection

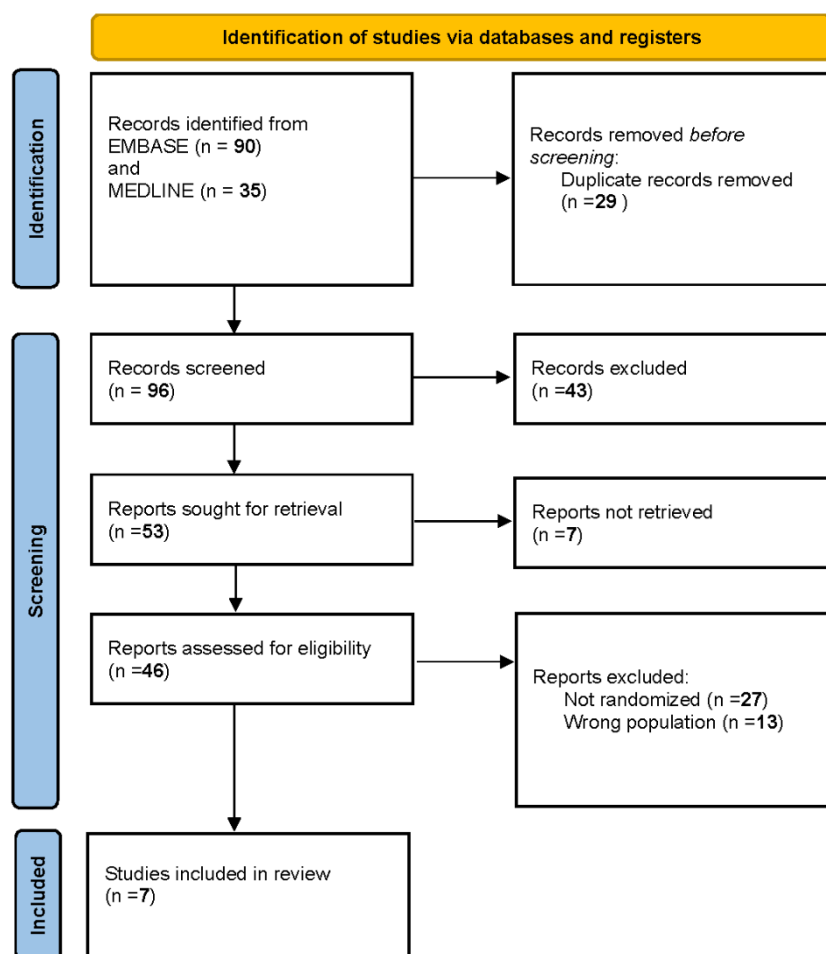


Figure S2. Risk-of-bias assessment with Cochrane RoB tool v2 for randomized trials

	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>	
CHAMPION-AF	+	+	+	!	+	!	Low risk
CLOSURE-AF	+	+	+	+	+	+	Some concerns
OPTION	+	+	+	+	+	+	High risk
PRAGUE-17	+	+	+	+	+	+	
PREVAIL	+	+	+	+	+	+	D1 Randomisation process
PROTECT AF	+	!	+	+	+	!	D2 Deviations from the intended interventions
WATCH-TAVR	+	+	+	+	+	+	D3 Missing outcome data
							D4 Measurement of the outcome
							D5 Selection of the reported result

Figure S3. L'Abbé plots for primary outcomes

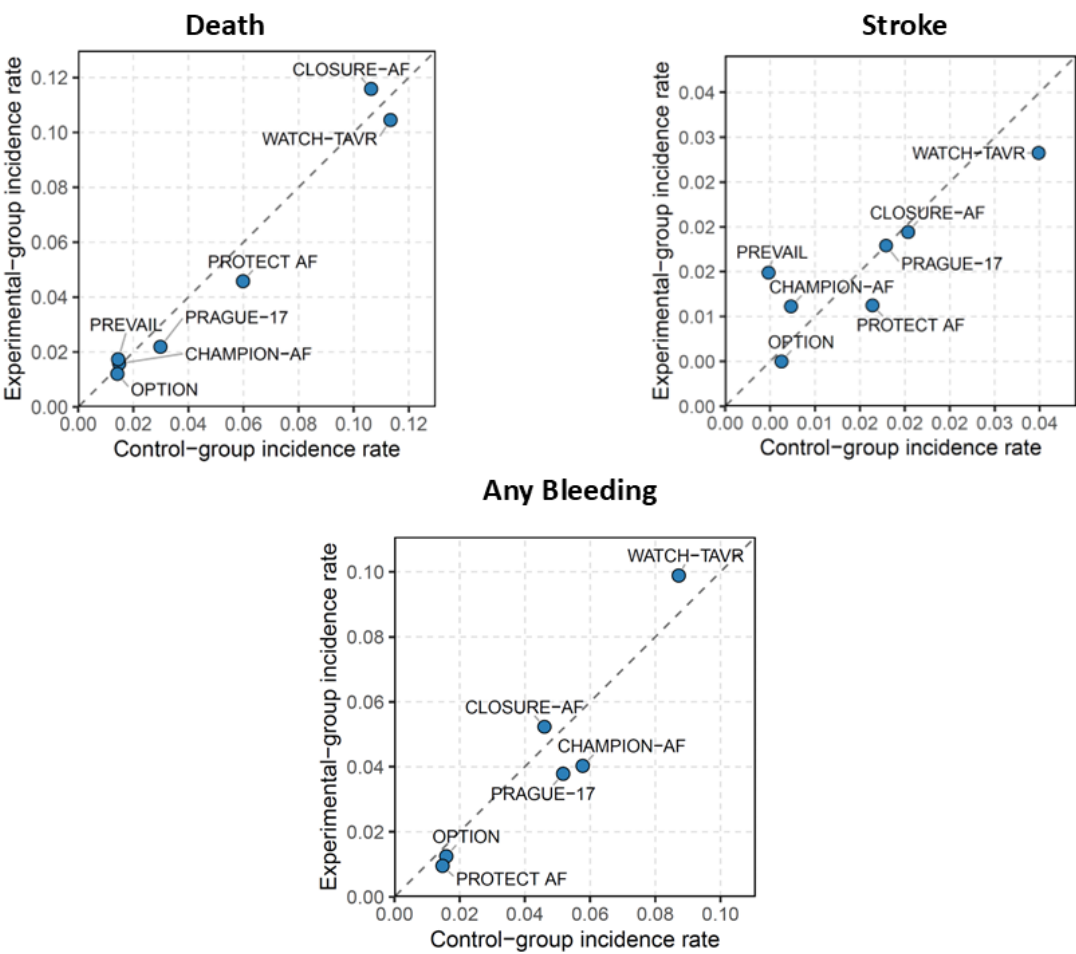
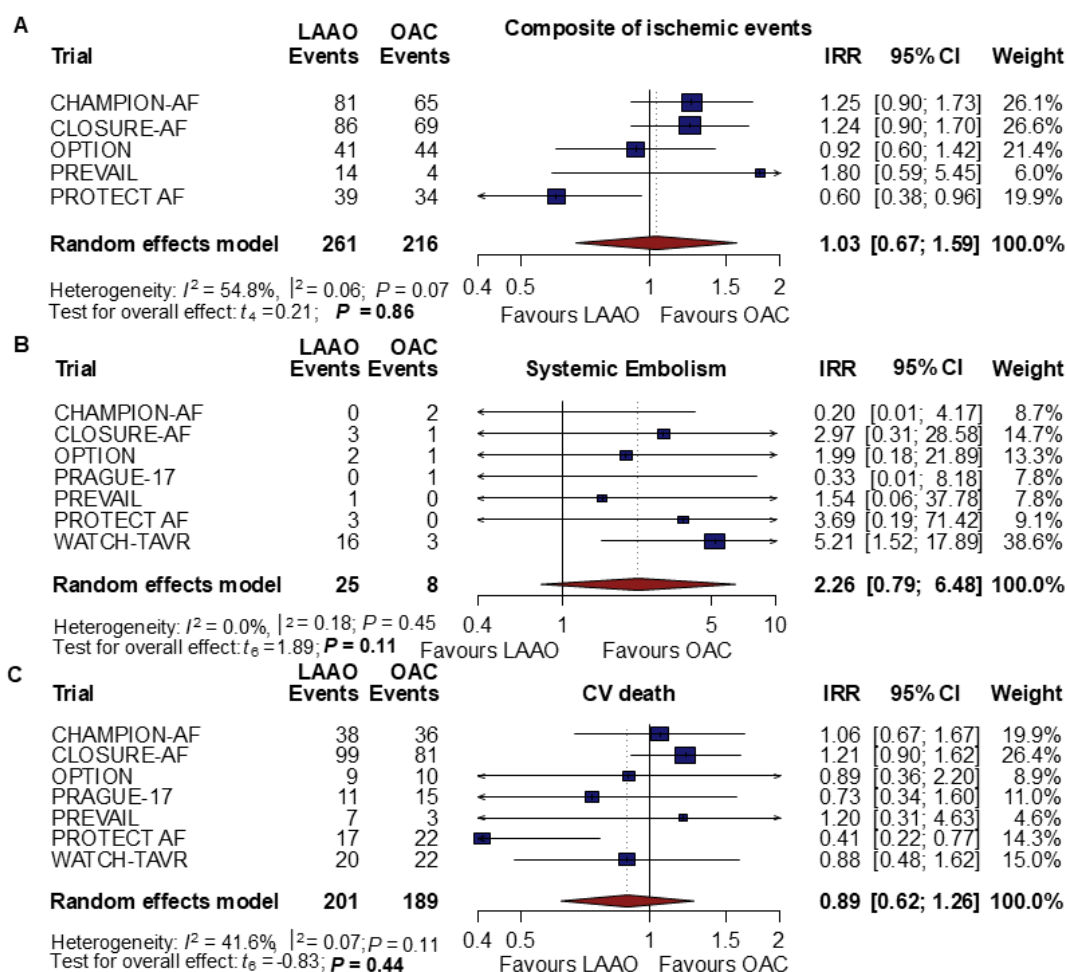
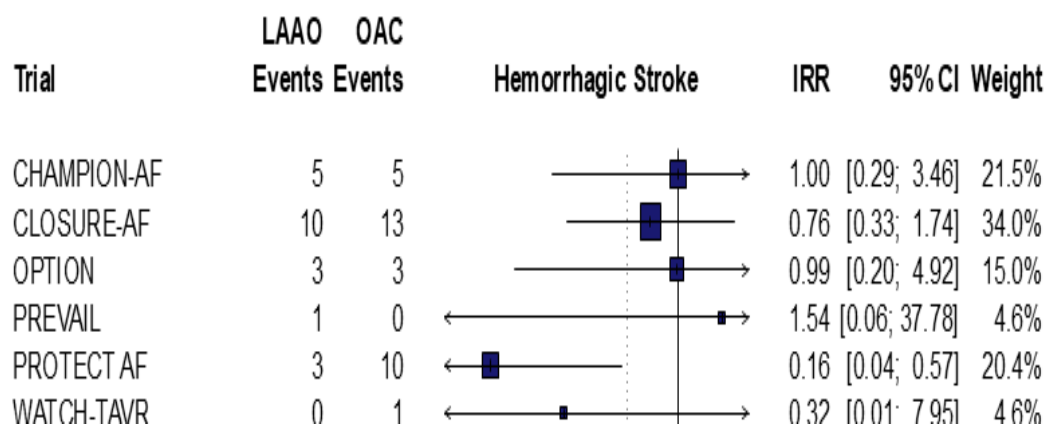


Figure S4. Forest plots displaying IRRs for composite ischemic events, systemic embolism, and cardiovascular death



CV, cardiovascular; IRR, incidence rate ratio; OAC, oral anticoagulation; LAO, left atrial appendage occlusion.

Figure S5. Forest plots displaying IRRs for hemorrhagic stroke



IRR, incidence rate ratio; OAC, oral anticoagulation; LAO, left atrial appendage occlusion.

Figure S6. L'Abbé plots for the ischemic stroke and nonprocedural bleeding

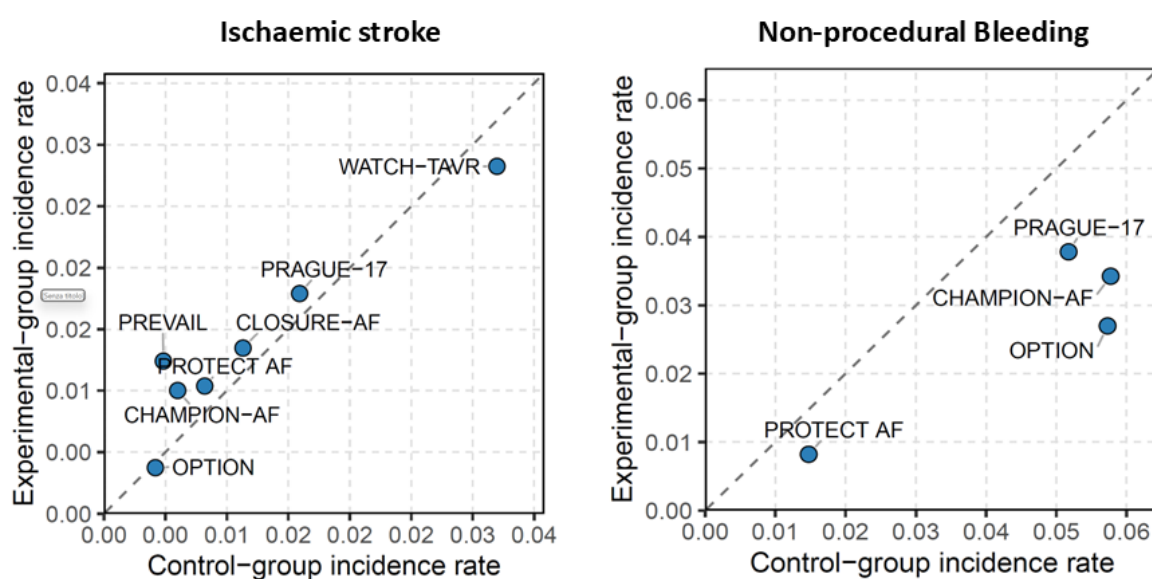
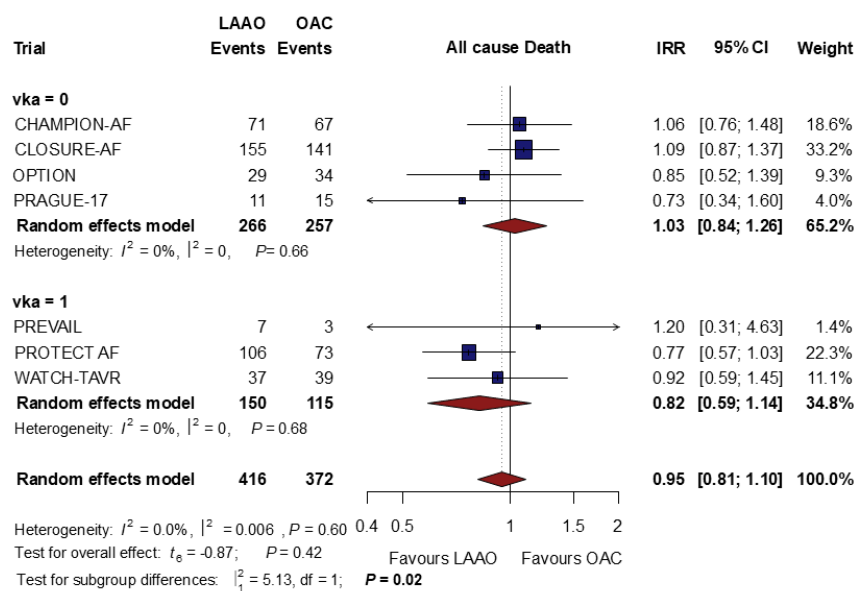
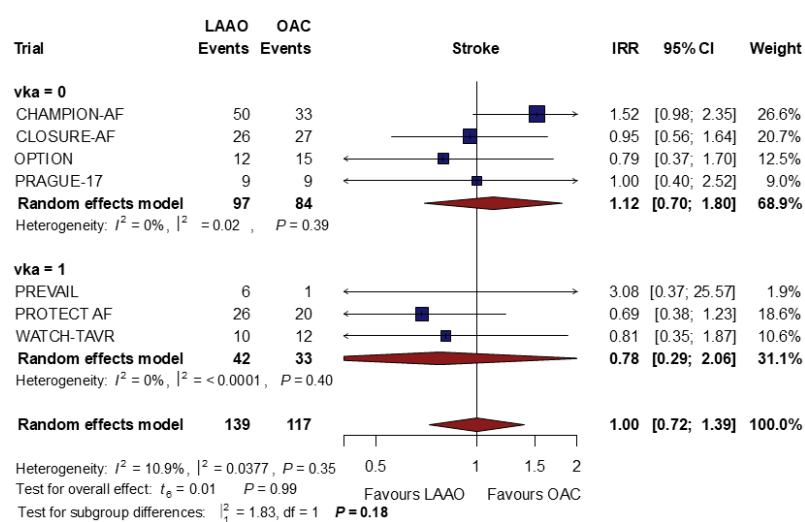


Figure S7. Forest plot displaying IRRs for all-cause death according to VKA and DOAC as comparator type



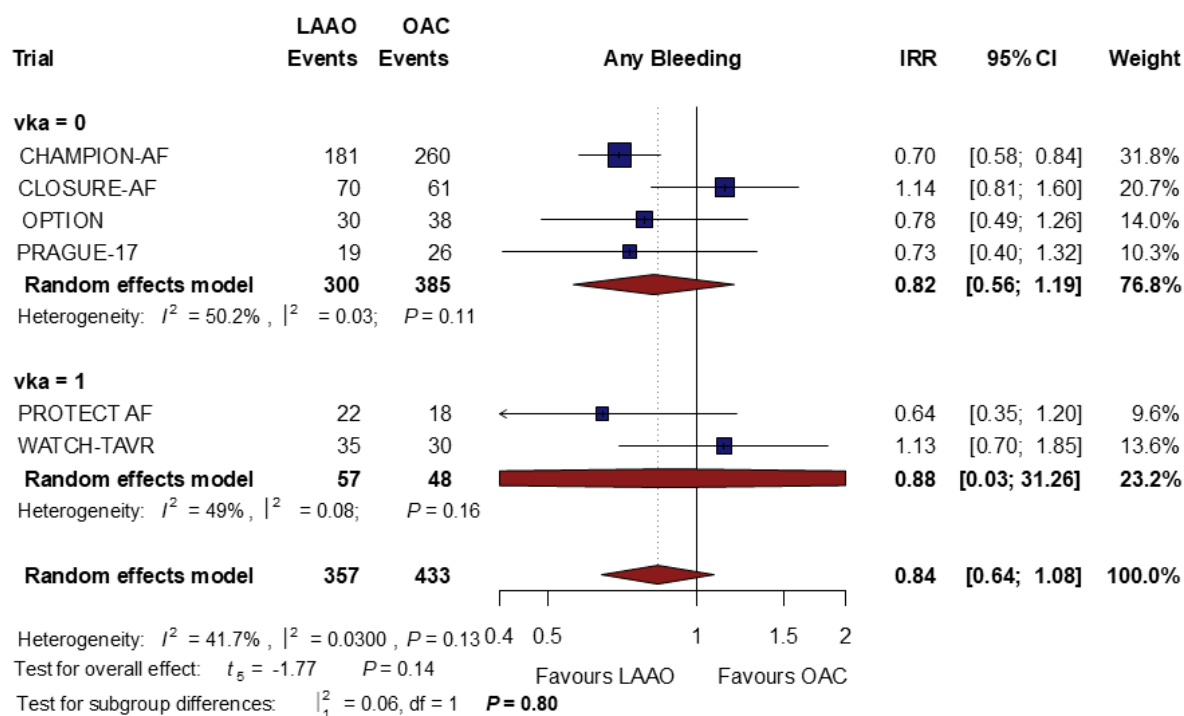
IRR, incidence rate ratio; OAC, oral anticoagulation; LAOA, left atrial appendage occlusion.

Figure S8. Forest plot displaying IRRs for stroke according to comparator type



IRR, incidence rate ratio; OAC, oral anticoagulation; LAAO, left atrial appendage occlusion.

Figure S9. Forest plot displaying IRRs for any bleeding according to comparator type



IRR, incidence rate ratio; OAC, oral anticoagulation; LAO, left atrial appendage occlusion.

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