CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Anticoagulation for Individuals with Stroke and Atrial Fibrillation*

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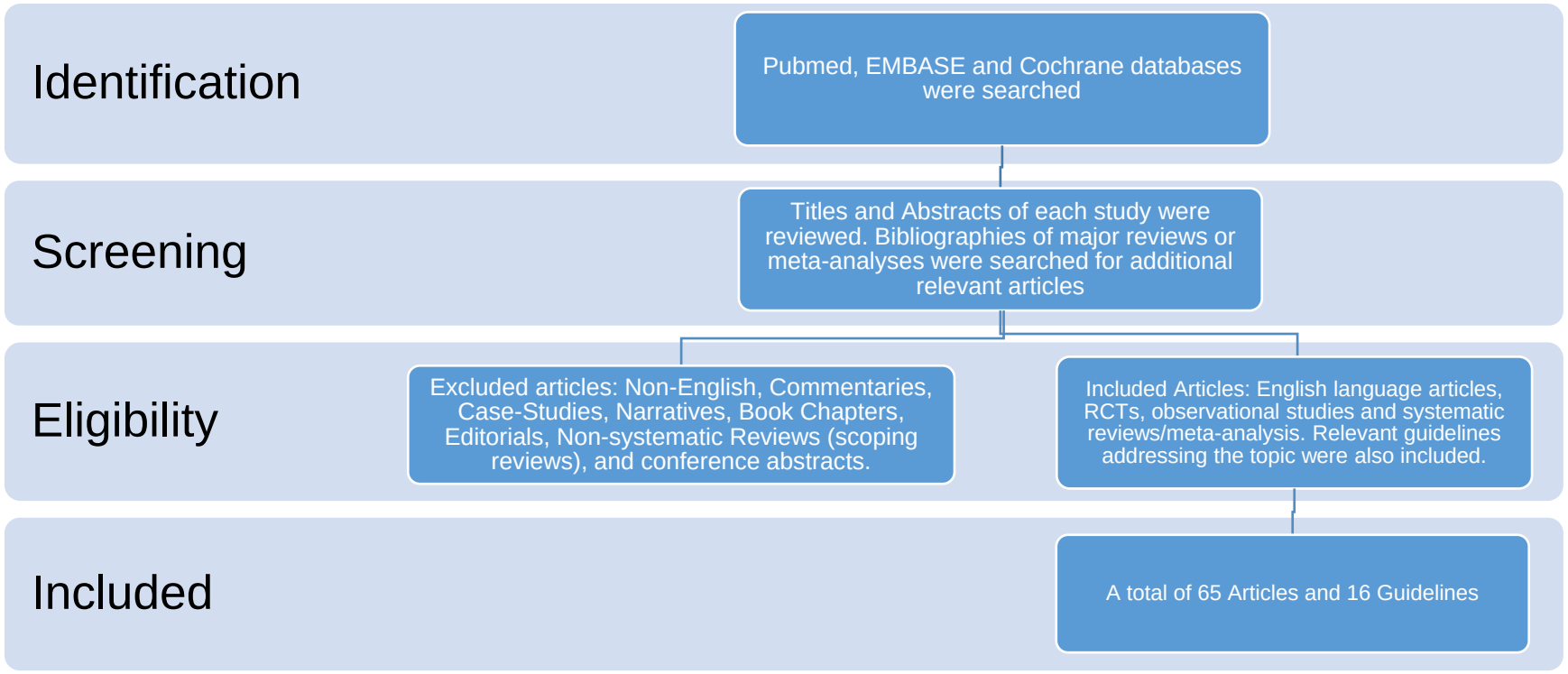
on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

Table of Contents

Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“stroke” AND [“warfarin” OR “anticoagulant” OR “direct factor Xa inhibitors” OR “direct oral anticoagulant” OR “novel oral anticoagulants” OR “antithrombins”]). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review.

Published Guidelines

Guideline	Recommendations
Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, Cox JL et al. members of the Secondary Panel. **The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation** ***Canadian Journal of Cardiology* 2020;36 (12):1847-1948.** **(selected)**	16. We recommend that all patients with AF should undergo assessment of their risk of stroke/systemic embolism at least annually, irrespective of their clinical pattern of AF (Strong Recommendation; High-Quality Evidence). 17. We recommend that the "CCS Algorithm" (CHADS-65) be used to facilitate the choice of appropriate antithrombotic therapy for the purposes of stroke/systemic embolism prevention in patients with nonvalvular AF (Strong Recommendation; High-Quality Evidence). 18. We recommend that OAC be prescribed for most patients with AF and age ≥65 years or CHADS2 ≥1 (Strong Recommendation; Moderate-Quality Evidence). 19. We suggest that no antithrombotic therapy be prescribed for stroke prevention for most patients with nonvalvular AF aged <65 years with no CHADS2 risk factors (Weak Recommendation; Moderate-Quality Evidence). 20. We recommend that the longitudinal follow-up of patients receiving OAC include assessment of bleeding risk, potential drug-drug interactions, as well as adherence and persistence to pharmacotherapy (Strong Recommendation; Moderate-Quality Evidence). 21. We recommend most patients should receive a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) in preference to warfarin when OAC therapy is indicated for patients with nonvalvular AF (Strong Recommendation; High-Quality Evidence). 67. We recommend that the timing of initiation of anticoagulant therapy following an ischaemic stroke should be individualised and take into account the competing risks of recurrent stroke against the risk of haemorrhagic transformation of infarction (Strong Recommendation; Moderate-Quality Evidence). 68. We suggest that percutaneous LAAO be considered for stroke prevention in patients with NVAF who are at moderate-to-high risk of stroke and have absolute contraindications to OAC (Weak Recommendation; Low-Quality Evidence).
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.**	**Atrial fibrillation** 1. For patients with ischaemic stroke or TIA with atrial fibrillation, the time of anticoagulation should be chosen according to the severity of ischaemia and the risk of bleeding transformation. It is suggested that anticoagulation therapy should be given within 14 days after the onset of neurological symptoms to prevent stroke recurrence. For patients with high risk of bleeding, the timing of starting anticoagulation should be appropriately prolonged (class IIa, level of evidence B). 2. If patients with ischaemic stroke or TIA with atrial fibrillation are unable to receive oral anticoagulant therapy, aspirin alone may be considered for treatment (class IIa, level of evidence B). Aspirin combined with clopidogrel should be carefully selected as the choice of antiplatelet therapy (class IIb, level of evidence B).

Guideline	Recommendations
(selected)	
Schnabel RB, Haeusler KG, Healey JS, et al. **Searching for Atrial Fibrillation Poststroke: A White Paper of the AF-SCREEN International Collaboration.** ***Circulation.* 2019;140:1834-50.**	**Key Points** 1. AF is a risk factor for thromboembolism and a strong marker for atrial myopathy. In cases of ischemic stroke of uncertain cause, signs of atrial myopathy can be used to inform decisions on the intensity or duration of monitoring for AF. 2. Signs of atrial myopathy without detected AF are not currently sufficient to initiate OAC. 3. The diagnosis of AF on poststroke monitoring requires documentation by an ECG of sufficient quality to allow confirmation by a health professional with expertise in ECG rhythm interpretation. 4. The concept of ESUS has not been proven to identify patients with stroke benefitting from OAC. However, there may be ESUS subgroups (eg, advanced age, significant atrial enlargement) that could benefit more from NOAC therapy than from aspirin. 5. Fulfilling ESUS criteria is neither an indication for NOAC treatment nor for withholding prolonged ECG monitoring. 6. Clinically diagnosed AF after a stroke and TIA is associated with a significantly increased risk of stroke or systemic embolism, in particular, in the presence of additional stroke risk factors. Patients with a recent cerebrovascular event and an episode of poststroke AF have not been specifically included in randomized trials, but the AF-SCREEN expert consensus is that OAC therapy (either well-controlled vitamin K antagonist or NOAC) is generally preferred for new AF detected by ECG monitoring after a stroke or TIA. 7. Patients with ischemic stroke or TIA should have continuous ECG monitoring after a stroke for at least 72 hours. 8. Cardiac imaging markers, excessive atrial ectopy, and blood biomarkers, including natriuretic peptides that are suggestive of atrial myopathy, increase the yield of AF detection, and could be used to guide the selection of patients for more intensive or prolonged poststroke ECG monitoring. 9. The AF detection rate after cryptogenic stroke is a function of length of monitoring, the definition of duration of AF that constitutes an episode, the interval from the index stroke to the start of monitoring, the type of stroke, and patient characteristics.
Ahmed N, Audebert H, Turc G, et al. **Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13 November 2018.**	**How to choose secondary prevention in ESUS?** Recommendation: 1. The best current secondary prevention in ESUS patients is antiplatelet treatment (Grade A) (pending publication of the RE-SPECT ESUS trial). 2. ESUS patients are relatively young and have 5% yearly stroke recurrence despite guideline recommended therapy and thus represent a substantial unmet need in secondary stroke prevention (Grade C).

Guideline	Recommendations
***European Stroke Journal* 2019; 4: 307-317.**	3. Subgroups of ESUS patients who may benefit from anticoagulation have not yet been validated by clinical trials (Grade C).
Klijn C, Paciaroni M, Berge E. Korompoki E, Kõrv J, Lal, A, Werring D. **Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline.** ***Eur Stroke J.* 2019, Vol. 4(3) 198–223** **(selected)**	In patients with non-valvular AF and previous ischemic stroke or TIA, we do not recommend antiplatelet agents, either as single or dual therapy, for secondary prevention of all events. Quality of evidence: Moderate; Strength of recommendations: Weak In patients with non-valvular AF and previous ischemic stroke or TIA, we recommend vitamin K Antagonists over no antithrombotic medication for secondary prevention of all events. Quality of evidence: Moderate; Strength of recommendations: Strong In patients with non-valvular AF and previous ischemic stroke or TIA we recommend vitamin K antagonists (INR 2–3) over antiplatelet therapy (single or dual) for secondary prevention of all events. Quality of evidence: Moderate; Strength of recommendations: Strong In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest adjusted-dose vitamin K antagonists (INR 2.0–3.0) over fixed-dose vitamin K antagonists (INR 1.2–1.5) plus aspirin for secondary prevention of all events. Quality of evidence: Moderate; Strength of recommendations: Weak In patients with non-valvular AF and previous ischemic stroke or TIA, we recommend non-vitamin K antagonist oral anticoagulants over vitamin K antagonists for secondary prevention of all events. Quality of evidence: High; Strength of recommendation: Strong In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest nonvitamin K antagonist oral anticoagulants over aspirin in patients who have failed or are unsuitable for vitamin K antagonist therapy for secondary prevention of all events. Quality of evidence: Moderate; Strength of recommendations: Weak We cannot make recommendations about the optimal time for initiating anticoagulation treatment in patients with acute ischemic stroke based on randomised trials. We encourage inclusion of patients in ongoing randomised controlled trials testing the efficacy and safety of early anticoagulation to answer this question. Quality of evidence: Low; Strength of recommendation: Weak In patients with non-valvular AF and previous ischemic stroke or TIA, we suggest avoiding routine bridging therapy prior to anticoagulation with vitamin K antagonists or non-vitamin K antagonist oral anticoagulants for secondary prevention of all events. Quality of evidence: Low; Strength of recommendation: Weak For patients with non-valvular AF and previous ischemic stroke or TIA, we cannot make any recommendation on whether left atrial appendage occlusion should be preferred over long-term vitamin K antagonists for secondary prevention of all events.

Guideline	Recommendations
	Quality of evidence: Low; Strength of recommendation: Weak Left atrial appendage occlusion: We cannot make recommendation on whether LAAO is an acceptable alternative to long-term anticoagulation with either VKAs or NOACs. Quality of evidence: Low; Strength of recommendation: Weak
January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. **AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society.** ***Circulation*. 2019 Jul 9;140(2):e125-e151** **(selected)**	*Recommendations for Selecting an Anticoagulant Regimen* 1. For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: • Warfarin (LOE: A) • Dabigatran (LOE: B) • Rivaroxaban (LOE: B) • Apixaban (LOE: B) or • Edoxaban (LOE: B-R). 2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve). COE 1; LOE A 5. For patients with AF who have mechanical heart valves, warfarin is recommended. COE 1; LOE B 6. Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent COE 1; LOE B *Recommendations for Interruption and Bridging Anticoagulation* 1. Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. COE 1; LOE C 2. For patients with AF without mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated COE 1; LOE B-R 3. Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure COE 1 LOE B-NR 4. Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding COE IIa; LOE B-NR *Recommendations for Device Detection of AF and Atrial Flutter* 2. In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF COE 11a; LOE B-R
Lip GYH, Banerjee A, Boriani G, Chiang Ce, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S, Moores L.	1. For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor-based approach, rather than an categorisation into low, moderate/high risk strata. We recommend use of the CHA2DS2VASc as a simple clinical based stroke risk score to initially identify 'low stroke risk' patients that should not be offered antithrombotic therapy to prevent stroke and reduce mortality (Strong recommendation, moderate quality evidence).

Guideline	Recommendations
Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report ***CHEST* 2018;154(5):1121-1201** **(selected)**	2. Subsequent to this initial step, for patients with AF, including those with paroxysmal AF, we recommend stroke prevention should be offered to those AF patients with one or more non-sex CHA2DS2VASc stroke risk factors (score of ≥1 in a male or ≥2 in a female) (Strong recommendation, moderate quality evidence). 3. For patients with AF, we recommend bleeding risk assessment should be performed for all patients with AF at every patient contact and should initially focus on potentially modifiable bleeding risk factors (Strong recommendation, low quality evidence). 6. For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk (Strong recommendation, moderate quality evidence) 7. In patients with AF who are eligible for OAC, we recommend NOACs over VKA (strong recommendation, moderate quality evidence).
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K et al; on behalf of the American Heart Association Stroke Council. **Guidelines for the early management of patients with acute ischemic stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** ***Stroke.* 2019;50:e344–e418.** **(selected)**	**6.6. Antithrombotic Treatment** **6.6.1.** For patients with noncardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. Class I; LOE A. 2. For early secondary prevention in patients with noncardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. Class I; LOE C-EO 3. For patients who have a noncardioembolic AIS while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for additional benefit in secondary stroke prevention is not well established. Class IIb; LOE B-R **6.3 Cardiac Evaluation** 1. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours. Class I; Level B-NR 2. The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after AIS is uncertain. Class IIb; Level C-LD
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Strong Recommendation** • For ischaemic stroke or TIA patients with atrial fibrillation (both paroxysmal and permanent), oral anticoagulation is recommended for long-term secondary prevention. • Direct oral anticoagulants (DOACs) should be initiated in preference to warfarin for patients with non-valvular atrial fibrillation and adequate renal function. • For patients with valvular atrial fibrillation or inadequate renal function, warfarin (target INR 2.5, range 2.0-3.0) should be used. Patients with mechanical heart valves or other indications for anticoagulation should be prescribed warfarin.

Guideline	Recommendations
Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G. **2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.** ***European Heart Journal* 2016; 37: 2893–2962.** **(selected)**	**Stroke Prevention** Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more. Class 1, LOE A. Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of 3 or more. Class 1, LOE A. Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves. Class 1, LOE B. When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist. Class 1, LOE A. When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored. Class I, LOE A AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve). Class IIb LOE Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition. Class III (harm), LOE B In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention. Class III (harm), LOE B Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk. Class III (harm), LOE A NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves. Class III, (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C). **Left Atrial Appendage** After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention. Class I, LOE B LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause). Class IIb, LOE B Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. Class IIb, LOE B

Guideline	Recommendations
	Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery. Class IIb LOE B. **Secondary Stroke Prevention** Anticoagulation with heparin or LMWH immediately after an ischaemic stroke is not recommended in AF patients. Class III (harm) LOE A In patients who suffer a TIA or stroke while on anticoagulation, adherence to therapy should be assessed and optimized. Class IIa LOE C In patients who suffer a moderate to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3–12 days based on a multidisciplinary assessment of acute stroke and bleeding risk. Class IIa, LOE C In AF patients who suffer a stroke, aspirin should be considered for prevention of secondary stroke until the initiation or resumption of oral anticoagulation. Class IIa LOE B Systemic thrombolysis with rtPA is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if aPTT is outside normal range). Class III (harm) LOE C NOACs are recommended in preference to VKAs or aspirin in AF patients with a previous stroke. Class I, LOE B After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended. Class III (harm), LOE B After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled. Class IIb, LOE B
Macle L, Cairns J, Leblanc K, et al. 2016 **2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation** ***Can J Cardiol 2016*; 32(10): 1170-1185** **(selected)**	General recommendations regarding antithrombotic therapy in the context of concomitant AF and CAD (asymptomatic, stable CAD [defined by the absence of ACS for the preceding 12 months], elective PCI, NSTEACS, or STEMI) are as follows. 1. We recommend that patients who have concomitant AF and CAD receive a regimen of antithrombotic therapy that is on the basis of a balanced assessment of their risks of stroke, of a coronary event, and of hemorrhage associated with use of antithrombotic agents (Strong Recommendation, High-Quality Evidence). 2. When OAC is indicated in the presence of CAD, we suggest a NOAC in preference to warfarin for NVAF (Conditional Recommendation, Low-Quality Evidence). Values and preferences. The suggestion for use of a NOAC rather than warfarin places relatively greater weight on the ease of use of NOACs vs warfarin and on the data from RCTs of NOACs vs warfarin for NVAF, showing equal or greater reduction of stroke, equal or less major bleeding, less intracranial bleeding, and no net increase in CAD outcomes. It places relatively less weight on the absence of long-term data on the effect of NOACs on coronary outcomes as opposed to the data for efficacy of warfarin.

Guideline	Recommendations
	3. If the patient has no evidence of CAD/vascular disease and is aged < 65 years with no CHADS2 risk factors, we suggest no antithrombotic therapy for stroke prevention (Conditional Recommendation, Moderate Quality Evidence). 4. If the patient has stable CAD/vascular disease and is aged < 65 years with no CHADS2 risk factors, we suggest ASA 81 mg/d (Conditional Recommendation, Moderate-Quality Evidence). 5. If the patient has stable CAD/vascular disease and is aged 65 years or the CHADS2 score 1, we recommend OAC therapy alone (Strong Recommendation, High-Quality Evidence).
Intercollegiate Stroke Working Party. National clinical guideline for stroke, 5th Edition. London: Royal College of Physicians, 2016	A- For people with ischaemic stroke or TIA and paroxysmal, persistent or permanent atrial fibrillation (AF: valvular or non-valvular) or atrial flutter, anticoagulation should be the standard treatment. A anticoagulation: − should not be given until brain imaging has excluded haemorrhage; − should not be commenced in people with uncontrolled hypertension; − for people with disabling ischaemic stroke should be deferred until at least 14 days from onset - aspirin 300 mg daily should be used in the meantime; − for people with non-disabling ischaemic stroke should be deferred for an interval at the discretion of the prescriber, but no later than 14 days from the onset; − should be commenced immediately after a TIA once brain imaging has excluded haemorrhage, using an agent with a rapid onset (e.g. low molecular weight heparin or a direct thrombin or factor Xa inhibitor - the latter confined to people with non-valvular AF). B- People with stroke or TIA in sinus rhythm should not receive anticoagulation unless there is an indication such as a cardiac source of embolism, cerebral venous thrombosis or arterial dissection. C- Anticoagulation for people with TIA or stroke should be with: − adjusted-dose warfarin (target INR 2.5, range 2.0 to 3.0) with a target time in the therapeutic range of greater than 72%; or − a direct thrombin or factor Xa inhibitor (for people with non-valvular AF). D- For people with cardioembolic stroke for whom treatment with anticoagulation is considered inappropriate: − antiplatelet treatment should not be used as an alternative for people with absolute contraindications to anticoagulation (e.g. undiagnosed bleeding); − measures should be taken to reduce bleeding risk, using a tool such as HAS-BLED to identify modifiable risk factors. If after intervention for relevant risk factors the bleeding risk is considered too high for anticoagulation, antiplatelet treatment should not be used as an alternative; − consider a left atrial appendage occlusion device as an alternative. E- People with recurrent TIA or stroke should receive the same antithrombotic treatment as those who have had a single

Guideline	Recommendations
	event. More intensive antiplatelet therapy or anticoagulation treatment should only be given as part of a clinical trial or in exceptional clinical circumstances.
Monitoring for Atrial Fibrillation in Discharged Stroke and Transient Ischemic Attack Patients: A Clinical and Cost-Effectiveness Analysis and Review of Patient Preferences. Ottawa: CADTH; 2016 Mar. (CADTH optimal use report; vol.5, no.2b).	Clinical Evidence The overall findings suggest that for discharged ischemic stroke or TIA patients who have received no prior in-hospital continuous cardiac monitoring, seven days of continuous outpatient cardiac monitoring with ambulatory Holter or external loop recorders may be feasible, as these strategies are likely to identify a substantial number of patients with AF at an acceptable incremental cost. Cardiac monitoring for the detection of AF is warranted in patients with embolic stroke of undetermined source, as this subpopulation also demonstrated high diagnostic yields. Economic Evidence The economic findings were based on 3 individual RCTs, in which it was found that seven-day cardiac monitoring in patients with a very recent history of stroke or TIA who did not receive in-hospital continuous monitoring (patients who received ECG only) is likely to identify a substantial number of patients with AF at an acceptable incremental cost compared with standard practice. Patient Preference and Experience Evidence A review of 9 studies that included data regarding patient perspectives and experiences suggests that most patients perceive outpatient cardiac monitoring devices to be comfortable and easy to use, and satisfaction with outpatient cardiac monitoring is high.
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C). (New recommendation) VKA therapy (Class I; Level of Evidence A), apixaban (Class I; Level of Evidence A), and dabigatran (Class I; Level of Evidence B) are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy. (Revised recommendation) Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF (Class IIa; Level of Evidence B). (New recommendation) For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent, or permanent AF in whom VKA therapy is begun, a target INR of 2.5 is recommended (range, 2.0–3.0) (Class I; Level of Evidence A). The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement (Class IIb; Level of Evidence C). (New recommendation)

Guideline	Recommendations
	For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (Class I; Level of Evidence A). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (Class IIb; Level of Evidence B). (Revised recommendation) For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Class IIa; Level of Evidence B). (New recommendation) In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Class IIa; Level of Evidence B). (New recommendation) For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent anticoagulant agent if intolerant to heparin) is reasonable, depending on perceived risk for thromboembolism and bleeding (Class IIa; Level of Evidence C). The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain (Class IIb; Level of Evidence B). (New recommendation)
Jennings I, Kitchen D, Keeling D, Fitzmaurice D, Heneghan C **Patient self-testing and self-management of oral anticoagulation with vitamin K antagonists: guidance from the British Committee for Standards in Haematology** ***Br J Haematol* 2014;167(5):600-607.** **(selected)**	Patients on long-term warfarin who are motivated can be considered for Patient Self Testing/Patient Self-Management. They need to demonstrate competency and should be trained to a standard acceptable to both the patient and the person with clinical responsibility (1C). The point-of-care test (POCT) device selected should have had an acceptable evaluation by an expert body, such as the NH Supply Chain (1C), and be acceptable to the responsible healthcare professional. An agreement should be signed by the patient and healthcare professional clinically responsible and this should include: review of the patient at least every 6 months (2C), and documentation of results and dosing (1C). Patients self-managing should have demonstrated competence in dose adjustment (1C). A simple warfarin dosing algorithm should be used (2C). An INR >8.0 (if confirmed on a repeat sample) requires that a venous sample is analysed in a hospital laboratory, and that patients seek medical advice (2C).
Lopes RD, Crowley MJ, Shah BR, Melloni C, Wood KA, Chatterjee R, Povsic TJ, Dupre ME, Kong DF, Barros e Silva PGM, Santos MHH, Armaganijan LV, Katz M, Kosinski A, McBroom AJ, Chobot MM, Gray R, Sanders GD.	**KQ 3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events: – a. In patients with nonvalvular atrial fibrillation? – b. In specific subpopulations of patients with nonvalvular atrial fibrillation?** In patients not eligible for warfarin, the combination of aspirin + clopidogrel is more effective than aspirin alone for preventing any stroke. This conclusion is based on one large good-quality trial involving 7,554 patients that showed lower rates of stroke for combination therapy, but the strength of evidence was rated as only moderate because a much smaller study (593 patients) did not find any difference. In the large RCT, the combination of aspirin + clopidogrel was associated with higher

Guideline	Recommendations
Stroke Prevention in Atrial Fibrillation. Comparative Effectiveness Review No. 123. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290- 2007-10066-I.) AHRQ Publication No. 13-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. **www.effectivehealthcare.ahrq.gov/reports/final.cfm (selected)**	rates of major bleeding than aspirin alone (high strength of evidence). Based on one large good-quality RCT of 6,706 patients, warfarin is superior to aspirin + clopidogrel for the prevention of stroke or systemic embolism and reduction in minor bleeding, although this did not result in a difference in all-cause mortality (high strength of evidence for all three outcomes). There was moderate strength of evidence that warfarin increases hemorrhagic stroke risk and that there is no difference between therapies for MI or death from vascular causes. A retrospective good-quality study of 53,778 patients confirmed the stroke outcome findings. • Adding clopidogrel to warfarin shows a trend toward a benefit on stroke prevention (low strength of evidence) and is associated with increased risk of nonfatal and fatal bleeding compared with warfarin alone (moderate strength of evidence). These findings are based on one good-quality retrospective study involving 52,349 patients. Triple therapy with warfarin + aspirin + clopidogrel substantially increases the risk of nonfatal and fatal bleeding (moderate strength of evidence) and also shows a trend toward increased ischemic stroke (low strength of evidence) compared with warfarin alone. These findings are based on one good-quality retrospective study involving 52,180 patients. A factor IIa inhibitor (dabigatran) at a 150-mg dose is superior to warfarin in reducing the incidence of the composite outcome of stroke (including hemorrhagic) or systemic embolism, with no significant difference in the occurrence of major bleeding (high strength of evidence for both outcomes) or all-cause mortality (moderate strength of evidence). However, dabigatran increases MI risk (moderate strength of evidence). These findings are based on one large good-quality RCT involving 12,098 patients from the larger RE-LY trial of 18,113 patients. A factor IIa inhibitor (dabigatran) at a 110-mg dose is noninferior to warfarin for the composite outcome of stroke or systemic embolism and is associated with a reduction in major bleeding when compared with warfarin (high strength of evidence for both outcomes), but there is no difference in all-cause mortality (moderate strength of evidence). Dabigatran increases MI risk, although this finding did not reach statistical significance (low strength of evidence). The rates of ICH are significantly lower with both dabigatran doses (150 mg and 110 mg) compared with warfarin (high strength of evidence). These findings are based on one large good-quality RCT involving 12,037 patients from the larger RE-LY trial of 18,113 patients. The Xa inhibitor apixaban is superior to aspirin in reducing the incidence of stroke or systemic embolism, with similar major bleeding risk, in patients who are not suitable for oral anticoagulation (high strength of evidence for both outcomes). These findings are based on one good-quality RCT involving 5,599 patients. The Xa inhibitor apixaban is superior in reducing the incidence (separately) of (1) stroke or systemic embolism (high strength of evidence), (2) major bleeding (high strength of evidence), and (3) all-cause mortality (moderate strength of evidence) compared with warfarin. These findings are based on similar findings from one good-quality RCT involving 18,201 patients and one small fair-quality RCT involving 222 Japanese patients The Xa inhibitor rivaroxaban is noninferior to warfarin in preventing stroke or systemic embolism (moderate strength of evidence), with similar rates of major bleeding (moderate strength of evidence) and all-cause mortality (high strength of evidence). These findings are based on one large good-quality RCT involving 14,264 patients and a second good-quality

Guideline	Recommendations
	RCT involving 1,280 Japanese patients.
You JJ, Singer DE, Howard PA, et al. **Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.** ***Chest 2012*; 141(2)(Suppl):e531S–e575S**	**2.1.8 Recommendations for Patients with AF at Low Risk of Stroke (eg, CHADS2 Score of 0)** 2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS 2 score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). **2.1.9 Recommendations for Patients with AF at Intermediate Risk of Stroke (eg, CHADS2 Score of 1)** 2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, CHADS 2 score 5 1), we recommend oral anticoagulation rather than no therapy (Grade 1B). We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily) (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B). **2.1.10 Recommendations for Patients With AF at High Risk of Stroke (eg, CHADS2 Score of 2, Which Includes Prior Ischemic Stroke or TIA):** 2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, CHADS 2 score 2), we recommend oral anticoagulation rather than no therapy (Grade 1A) , aspirin (75 mg to 325 mg once daily) (Grade 1B) , or combination therapy with aspirin and clopidogrel (Grade 1B) . For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 1B) .For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3) we suggested dabigatran 150mg twice daily rather than adjusted-dose VKA therapy (target INr range, 2.0-3.0)(Grade 2B). **2.1.11 Recommendation Regarding Dabigatran vs Adjusted-Dose VKA Therapy:** 2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B) **2.2 Patients With AF and Mitral Stenosis** 2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 1B) . For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone (Grade 1B). **3.0 Antithrombotic Therapy for Patients with AF in Special Situations** **Specific therapy recommendations are made for: 3.1 Patients with AF and Stable Coronary Artery Disease, 3.2 Patients*

Guideline	Recommendations
	With AF and Placement of an Intracoronary Stent (With or Without Recent ACS), 3.3 Patients With AF and ACS Who Do Not Undergo Intracoronary Stent Placement, 3.4 Patients With AF Managed by a Rhythm Control Strategy, 3.5 Patients With Atrial Flutter

Evidence Tables

Monitoring for Atrial Fibrillation (AF)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
High-risk					
Steinhubl et al. 2018 **USA** **RCT** ***mHealth Screening to Prevent Strokes (mSToPS) Trial***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	2,659 individuals ≥ 75 years, (or a male ≥ 55 years or female ≥ 65 years with 1 or more comorbidities), at increased risk for AF (e.g., previous CVA, heart failure, mitral valve disease). Eligible participants were recruited through a solicitation from a large health insurer. Persons with a history of AF were excluded. Mean age was 72.4 years, 38.6% were women.14% had a previous stroke. Median CHA_2DS_2-VASc score was 3.	Participants were randomized 1:1 to wear a self-applied, single-use, continuous ECG monitoring patch at home either immediately, or after a 4-month delay during which time participants received usual care. These groups formed the actively monitored cohort. An additional 5,318 participants were selected from the pool of potentially eligible applicants and included as a control group. These persons were age, sex and CHA_2DS_2-VASc score matched.	**Primary outcome:** Detection of newly diagnosed AF/flutter (≥30 sec) within 4 months of wearing the device **Secondary outcomes:** Detection of newly diagnosed AF/flutter within 12 months	34.5% (n = 917) participants never wore the patch. At 12 months, 906 and 832 participants in the immediate and delayed groups, respectively, remained in the study. In the observational cohort, 3,476 remained. At 4 months, the incidence of new AF cases was 3.9% (53/1366) in the immediate monitoring group vs. 0.9% (12/1293) in the delayed monitoring group (absolute difference=3.0%, 95% CI, 1.8%-4.1%). In the observational study, over 12 months of follow-up, 190 new cases of AF were detected, 109 of 1738 (6.7 per 100 person-years) in the actively monitored cohort and 81 of 3476 (2.6 per 100 person-years) among observational controls (absolute difference=4.1, 95% CI 3.9-4.2). Active monitoring was associated with increased initiation of anticoagulants (5.7 vs. 3.7 per 100 person-years; difference= 2.0, 95% CI, 1.9-2.2), outpatient cardiology visits (33.5 vs. 26.0 per 100 person-years; difference= 7.5, 95% CI 7.2-7.9), and primary care visits (83.5 vs. 82.6 per 100 person-years; difference=0.9, 95% CI 0.4-1.5).
Following TIA and Non-Disabling Stroke					
Huang et al. 2020	CA: ☑ Blinding:	826 patients admitted to one of 6 hospitals with acute ischemic stroke, ≥ 65 years,	Patients were randomized 1:1 to receive serial 12-lead	**Primary outcome:** Newly detected AF	8.4% of patients who received serial ECGs experienced a new episode of AF compared with 6.9% episodes detected using Holter monitoring

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Taiwan **RCT**	Patient ☒ Assessor ☒ ITT: ☑	with neither AF history nor any presence of AF on baseline electrocardiogram at admission. Median age was 76 years, 60% were men. Median baseline NIHSS was 4.	ECGs once daily, within 2 days of stroke onset, for five days vs. 24-h Holter monitoring (during their hospitalization).		(OR=1.17, 95% CI 0.69–2.01). The results were similar in the per protocol analysis. Independent predictors of increased odds of new-onset AF were age >80 years and a history of heart failure, while lacunar infarcts were associated with lower odds.
Tsivgoulis et al. 2019 **Greece** **Systematic review & meta-analysis**	All studies had at least one methodological component with unclear and/or high risk of bias.	4 studies (2 RCTs, [Crystal AF and FIND-AF] and 2 non RCTs) that included a total of 1,102 persons with history of cryptogenic ischemic stroke or TIA. Mean age was 68 years, 41% were women.	The outcomes of persons who received prolonged cardiac monitoring (PCM) were compared with patients who received conventional (non-PCM) cardiac monitoring. 3 trials used implantable cardiac monitoring and one used ambulatory ECG monitoring to provide PCM.	**Primary outcome:** Recurrent stroke and recurrent stroke/TIA during follow-up **Secondary outcomes:** AF detection and anticoagulation initiation	Duration of follow-up ranged from 6 to 30 months. PCM was associated with significantly lower risks of recurrent stroke and recurrent stroke or TIA during follow-up (RR=0.45; 95% CI, 0.21–0.97 and RR=0.49; 95% CI, 0.30–0.81, respectively) AF was detected significantly more frequently in persons who received PCM (RR=2.46; 95% CI, 1.61–3.76). Anticoagulation was initiated more frequently in persons who received PCM (RR=2.07; 95% CI, 1.36–3.17). Results were similar between RCTs and non-RCTs.
Wachter et al. 2016 **Germany** **RCT** ***Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	398 patients, >60 years admitted with acute ischemic stroke within 7 days of symptom onset, in sinus rhythm at admission and without history of AF, and a premorbid mRS score ≤2. Mean age was 73 years, 40.2% were female.	Patients were randomized to receive prolonged Holter ECG monitoring (10-days), repeated at 3 and 6 months (n=200) vs. standard care (minimum of 24 hours of cardiac monitoring, n=198)	**Primary outcome:** Detection of newly diagnosed AF/flutter (≥30 sec) within 6 months and before stroke recurrence **Secondary outcomes:** Detection of newly diagnosed AF/flutter within 12 months, recurrent stroke or systemic embolism, and death	At 6 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 4.5%; absolute difference 9%, 95% CI 3.5-14.6, p=0.002; NNS=11). At 12 months, detection of AF was significantly higher in the prolonged monitoring group (13.5% vs. 6.1%; absolute difference 7.4%, 95% CI 1.6-13.2; p=0.02; NNS=13). There were no differences between groups in stroke recurrence (2.5 vs. 4.5%, p=0.28) or death (3.0 vs. 4.5%, p=0.45).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(FIND-AF)					There were no interactions based on subgroup analyses based on age, sex, baseline NIHSS, CHADS-2 score, symptoms at admission and imaging (lacunar vs. non-lacunar). At 12 months, there were 5 patients with recurrent stroke in the intervention group vs. 9 in the control group, p=0·28. There were 6 deaths in the intervention group vs. 9 in the control group, p=0·45.
Gladstone et al. 2014 **Canada** **RCT** ***Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	572 patients ≥55 years without known atrial fibrillation (AF), who had sustained a cryptogenic ischemic stroke or TIA of undetermined cause following standardized testing (including 24-hr ECG), within the previous 6 months. Mean age: 73 yrs. 56% male, 63% of patients sustained an ischemic stroke, 37%, a TIA.	Patients were randomized (1:1) to undergo ambulatory ECG monitoring with a 30-day event-triggered loop recorder or one additional round of 24-hour Holter monitoring (control group).	**Primary outcome:** Occurrences of AF or atrial flutter ≥30 seconds in duration, detected during 90-day follow-up. **Secondary outcomes:** Anticoagulant use at 90 days, AF ≥30 seconds and ≥2.5 minutes in duration, and any AF	Patients were randomized an average of 75 days following qualifying event. The primary outcome was detected more frequently in patients in the enhanced monitoring group (16.1% vs. 3.2%, absolute difference =12.9%, 95% CI 8.0-17.6%, p<0.001, number need to screen [NNS] 8). AF ≥30 seconds was detected more frequently in patients in the enhanced monitoring group (15.5% vs. 2.5%, absolute difference =13.0%, 95% CI 8.4-17.6%, p<0.001, NNS=8). AF ≥2.5 minutes was detected more frequently in patients in the enhanced monitoring group (9.9% vs. 2.5%, absolute difference =7.4%, 95% CI 3.4-11.3%, p<0.001, NNS=14). A higher number of patients in the enhanced monitoring group were treated with anticoagulants (18.6% vs. 11.1%) and switched from antiplatelet to anticoagulant therapy (13.6% vs. 4.7%).
Sanna et al. 2014 **International**	CA: ☑ Blinding: Patient ☒	441 patients >40 years with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring	Patients were randomized (1:1) to received ECG monitoring on a	**Primary outcome:** Time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months	The mean time between the index event and randomization was 38 days. Most patients completed 18 months of follow-up.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Cryptogenic Stroke and Underlying AF (CRYSTAL-AF)***	Assessor ☒ ITT: ☑	associated with a cryptogenic symptomatic TIA or cryptogenic ischemic stroke, sustained within 90 days of the event. Mean age: 61 yrs. 63% male	schedule at the discretion of their treating physician or long-term monitoring with an insertable cardiac monitor (ICM) using the Reveal® XT device, inserted within 10 days of the event.	**Secondary outcome:** Time to first detection of atrial fibrillation at 12 months of follow-up, recurrent stroke or TIA, and the change in use of oral anticoagulant drugs For patients for patients in both groups were scheduled at 1, 6, and 12 months.	Maximum duration of follow-up was 36 months (n=48). At 6 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (8.9% vs. 1.4%, HR=6.4, 95% CI 1.9- 21.7, p<0.001). At 12 months, the rate of detection of AF was significantly higher among patients assigned to the ICM group (12.4% vs. 2.0%, HR=7.3, 95% CI 2.6- 20.8, p<0.001). Most patients completed 18 months of follow-up. Maximum duration of follow-up was 36 months (n=48). There were no significant interactions observed in subgroup analysis (age, sex, race or ethnic group, type of index event, presence or absence of patent foramen ovale, and $CHADS_2$. 2.4% of devices were removed due to infection at the insertion site or pocket erosion
Higgins et al. 2013 **UK** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	100 patients admitted within 7 days of ischemic stroke, from 2 centres with no history of AF, presenting in sinus rhythm. Mean age was 65.8 years, 56% were male	Patients were randomized to receive standard practice (SP) investigations or SP + additional investigations, which included 7 days of additional non-invasive cardiac event monitoring. Patients in the SP group underwent cardiac investigations for the detection of AF, at the discretion of the local physician.	**Primary outcome:** Detection of paroxysmal atrial fibrillation (PAF) at 14 and 90 days	The detection of sustained PAF at 14 days was significantly higher in the group that received additional investigations (44% vs. 4%, p<0.001). The detection of any PAF at 14 days was significantly higher in the group that received additional investigations (18% vs. 2%, p<0.05) The detection of sustained PAF at 90 days was not significantly higher in the group that received additional investigations (22% vs. 8%, p<0.09). The detection of any PAF at 90 days was higher in the group that received additional investigations (48% vs. 10%, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Significantly more patients that received additional monitoring were started on anticoagulants for AF associated thromboembolic prophylaxis at day 14 (16% vs. 0%, p<0.01) and at day 90 (22% vs. 6%, p<0.05).

Cost-effectiveness of Prolonged Monitoring for Atrial Fibrillation Following TIA and Non-Disabling Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Yong et al. 2016 **Canada** **Economic evaluation**	NA	NA	A Markov model, using AF rates and anticoagulation treatment observed from the EMBRACE trial was used to estimate the lifetime costs and effectiveness of 30-day ECG monitoring after recent ischemic stroke. A risk of 4.5%/yr was used as an estimate of stroke recurrence. Anticoagulation was assumed to reduce the risk of future stroke by 50%	**Primary outcome**: Cost-effectiveness of endovascular therapy: cost gained/ QALY A value of <$20,000/QALY gained was considered to be highly cost-effective; a value of >$100,000 was considered low value	30-day ECG monitoring detected 129 more cases of AF. Total cost of stroke, including cost of $447 for 30-day monitoring was $59,712 vs. total cost for stroke including repeat Holter monitoring ($131) was $59,798. Incremental cost-effectiveness was $2,166/QALY gained. Number needed to screen to prevent 1 ischemic stroke =63

Effectiveness of Warfarin in the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Xian et al. 2015	NA	12,552 patients discharged	Patients were divided into two groups according to discharge	**Primary outcomes:** Major adverse	Patients treated with warfarin were younger (80 vs. 83 years), were less likely to have a history of previous

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
USA **Observational study** ***Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER)***		following admission for acute ischemic stroke with documented persistent or paroxysmal AF/flutter from 2009-2011 from 1,487 hospitals participating in the Get with the Guidelines Stroke registry. Patients who previously received any anticoagulation therapy were excluded	drug treatment: patients treated with warfarin (n=11,039) and those not treated with any oral anticoagulant (n=1,513) at discharge. Their outcomes were compared. As novel anticoagulants were not recorded in GWTG-Stroke until October 2011, patients discharged on novel oral anticoagulants or other agents such as low molecular weight heparin or fondaparinux were excluded.	cardiovascular event (MACE), time spent at home without complications **Secondary outcomes:** All-cause mortality, cardiovascular readmission, stroke readmission	stroke (14.8% vs. 20.6%) or coronary artery disease (30.8% vs. 37.1%). Patients in both groups had similar stroke severity (median NIHSS of 6 and 5). Over 2 years following discharge from hospital, fewer patients discharged on warfarin experienced a MACE (54.7% vs. 66.8%; adj HR=0.87, 99% CI 0.78-0.98, p=0.003) and spent more days at home (47.6 days, 99% CI 26.9-68.2, p<0.001). All-cause mortality was significantly lower among patients discharged on warfarin (32.4% vs. 50.0%, adj HR=0.72, 99% CI 0.63-0.84, p<0.001) as was readmission for ischemic stroke (7.9% vs. 11.8%, adj HR=0.63, 99% CI 0.48-0.83, p<0.001). The number of all-cause readmissions and readmission for ICH or other cardiovascular causes did not differ between groups
Mant et al. 2007 **UK** **RCT** ***Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	973 patients ≥75 years, with AF or atrial flutter, recruited between April 2001 and November 2004 from 260 participating centres. Mean age was 81.5 (±4.2) years, 54% females.13% had a previous stroke or TIA.	Patients were randomized to receive either warfarin (target INR of 2.5, n=488)) or aspirin (75 mg daily, n=485). If a patient already being treated with warfarin was randomly assigned to aspirin, then warfarin therapy was stopped, vice versa.	**Primary outcome:** First occurrence of fatal and non-fatal disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, and other clinically significant arterial embolism **Secondary outcome:** Major extracranial hemorrhage, other vascular events, all-cause mortality	The risk of the primary outcome was significantly higher in the aspirin group (yearly risk of 3.8% vs. 1.8%, RR=0.48, 95% CI 0.28-0.80, p=0.0027, absolute yearly risk reduction 2%, 95% CI 0.7–3.2, NNT to prevent one primary event was 50). In the warfarin group, of the 24 primary events, there were 21 strokes, 2 other intracranial hemorrhages, 1 systemic embolus. In the aspirin group, of the 48 primary events, there were 44 strokes, 1 other intracranial hemorrhage, 3 systemic emboli. The yearly risk of extracranial hemorrhage was 1.4% (warfarin) vs. 1.6% (aspirin), RR=0.87,95% CI 0.43-1.73, p=0.67. Warfarin use was associated with a significantly reduced risk of all strokes (2.5% vs. 4.9%/yr, RR=0.52, 95% CI 0.33-0.80, p=0.002) and all strokes + TIA

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					(3.1% vs. 5.7%/yr, RR=0.55, 95% CI 0.36-0.82, p=0.002).
Hart et al. 2007 **USA** **Systematic Review and Meta-Analysis** ***(Update to the seminal 1999 review by Hart et al.)***	N/A	29 RCTs with a total of 28,044 participants diagnosed with non-valvular atrial fibrillation (AF). Trials were conducted between 1966 and March 2007.	All trials evaluated long-term (≥12 weeks) use of anti-thrombotic therapy. Interventions included warfarin, aspirin, low molecular weight heparin, indobufen, dipyridamole, fluindione, ximelagatran, triflusal,	**Primary outcomes:** Occurrences of ischemic and haemorrhagic stroke, major extra-cranial bleeding and death.	Most studies examined the use of Vitamin-K inhibitors or ASA administered in varying regimens. Other identified treatments included LMWT heparin, ximelagatran [*development halted*], dabigatran). **Warfarin vs. Placebo**: No new trials were added which demonstrated that (based on 6 RCTs, n=2900, 20% with history of stroke), treatment with adjusted dose warfarin was associated with a 64% reduction in all strokes (95% CI 49%, 74%) [ARR= 2.7%/year, NNT=37 for primary prevention. ARR=8.4%/year, NNT=12 for secondary prevention of stroke] when compared to placebo or no treatment conditions. Ischemic stroke alone, RR=67% (95% CI 54%, 77%) for treatment with dose-adjusted warfarin. Mean INRs ranged from 2.0 – 2.6 in primary prevention studies and was 2.9 in the only secondary prevention study included. **Adjusted-dose warfarin vs. antiplatelet therapy**: Adjusted dose warfarin has been evaluated most often against ASA; however, the authors also included 3 other trials in which the effectiveness of warfarin was assessed against other antiplatelets including clopidogrel and dipyridamole. Based on the comparison between adjusted-dose warfarin and "antiplatelet therapy", the use of warfarin was associated with a 37% reduction in all strokes (95% CI 23%, 48%). **Bleeding risks**: There was an increased risk reported for intracranial hemorrhage associated with the use of adjusted dose warfarin (ARI=0.2%/year), although the relative risk = 128% (95% CI 399%, 4%). When compared to placebo or to ASA, there was an increase in risk for major extra-cranial hemorrhage associated with warfarin use (66 and 70%, respectively; ARR=0.3% and 0.2%). However, there was also a

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					reduction in all-cause mortality demonstrated in the groups assigned to treatment with adjusted dose warfarin vs. control (RR=26%, 95% CI 3%, 43%. ARR not reported).
Saxena & Koudstaal 2004 **Netherlands** **Cochrane Review**	NA	2 RCTs comparing the effectiveness of oral anti-coagulants with antiplatelet therapy in individuals with non-rheumatic (non-valvular) AF and history of previous stroke or TIA (n=1371)	The European Atrial Fibrillation Trial (EAFT) included 455 patients, who received either anticoagulants or aspirin, with mean follow-up of 2.3 years The Studio Italiano Fibrillazione Atriale (SIFA) trial, included 916 patients with NRAF and a TIA or minor stroke within the previous 15 days who received open label anticoagulants or indobufen, with mean follow-up of one year.	**Primary outcomes:** Major vascular events including all fatal or non-fatal strokes, intracranial bleeding events, extracranial bleeding events.	**Overall**: There was a significant protective effect in favour of anti-coagulant therapy over antiplatelet therapy for all vascular events (OR=0.67, 95%CI 0.50, 0.91) and for recurrent stroke (OR=0.49, 95% CI 0.33, 0.72). Anticoagulant therapy was associated with an absolute risk reduction of approximately 4% per year in both studies, whereas the risk was 10%/year and 5%/year for individuals assigned to treatment with antiplatelet therapy in the EAFT and SIFA study, respectively. **Bleeding Events**: Assignment to warfarin therapy was not associated with a significant increase in odds for intracranial bleeding vs. antiplatelet therapy (OR=1.99, 95% 0.44, 9.88). However, warfarin therapy was associated with increased odds for the outcome of major extracranial bleeding events when compared to antiplatelet therapy (OR=5.16, 95% I 2.08, 12.83). Note: INR control varied substantially. In the SIFA trial, patients were controlled within the pre-specified range on 83.5% of the testing occasions. In EAFT, 32% were below 2.5 and 9% were above 4.0.
Hart et al. 2004 **USA** **Pooled analysis**	NA	834 participants from the European Atrial Fibrillation Trial (EAFT) and Stroke Prevention in Atrial Fibrillation (SPAF) III trial, who had previous history of stroke, TIA or both. In the EAFT, all patients had experienced a minor stroke or TIA,	In EAF, patients were randomly assigned to receive adjusted-dose oral vitamin K antagonist, aspirin 300 mg/d, or placebo as previously described.7 The target international normalized ratio (INR) range was 3 to 4.5. Mean follow-up was 2.3 years. In SPAF III, patients were randomly assigned to receive either adjusted-dose warfarin (target INR, 2 to 3) vs. aspirin 325 mg/d plus low, fixed-dose	**Primary outcomes:** Annualized rate of stroke recurrence, relative risk reduction (RRR) of recurrent stroke	There was no significant difference in the risk of recurrence of ischemic stroke or TIA for the treatment contrast of adjusted-dose warfarin vs. aspirin. The annualized rate of ischemic stroke during aspirin therapy was 7% per year (95% CI, 4%-12%) for patients with prior TIA and 11% per year (95% CI, 9%- to 15%) for those with prior stroke. The annualized rate of ischemic stroke during anticoagulation therapy was 3% per year (95% CI, 1-7%) for patients with prior TIA and 4% per year (95% CI, 3%-6%) for those with prior stroke.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		while 36% of patients in the SPAF III trial had. Mean age was 71 years, 64% were male.	warfarin (mean achieved INR, 1.3). The trial was terminated after a mean follow-up of 1.1 years.		The RRR of ischemic stroke by warfarin compared with aspirin was 56% (p=0.09) for those with prior TIA and 63% (p<0.001) for those with prior stroke.
Reynolds et al 2004 **USA** **Systematic Review and Meta-analysis**	N/A	Studies in which individuals with non-valvular AF received anti-coagulation therapy with warfarin alone (no combination therapy). **Overall**: 21 studies were included: 11 RCTs (n=4,405), 9 observational studies (n=1,808) and 1 uncontrolled case series (n=35). Four studies were of individuals with previous stroke/TIA.	To examine the relationship between the INR and selected outcomes, the authors attempted to quantify risk associated with both over (INR > 3) and under (INR <2) anti-coagulation with warfarin therapy in individuals with non-valvular AF.	**Primary outcomes:** Stroke, bleeding events	**Overall**: In 9 studies, the participants received adjusted dose warfarin with a target INR of 2.0 – 3.0. In these trials, participants were reported to spend approximately 60% of the time in the target INR range. In 11 additional studies, the INR targets were variable and ranged from 1.4 – 4.5. Studies with wider and more variable INR ranges were associated with higher reported incidence of stroke and bleeding events. Groups receiving fixed low or mini-dose therapy or combination therapy were not analyzed. **Ischemic Events**: Compared to INR of 2-3, INRs of <1.5 and 1.5-2.0 were associated with significantly increased odds of stroke (OR=3.25, 95% CI 0.45-23.5, n=761 and OR=2.11, 95% CI 1.06-4.2, n=703, respectively) **Bleeding Events**: Relative to INR 2-3, over-coagulation was associated with a significant increase in risk for major bleeding events (INR 3-4, OR = 2.34, 95% CI 0.54-10.10: 2 studies, n=507) and INR>4.0, OR = 33.23, 95% CI 9.12-121.07; 2 studies, n=409).

Risk of Intracerebral Hemorrhage Associated with Anticoagulation Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Wilson et al. 2018 **UK**	N/A	1,490 patients aged ≥18 years, recruited from 79 hospitals with atrial fibrillation	All patients underwent baseline brain MRI. Baseline demographics and risk factor profiles between those with	**Primary outcome:** Symptomatic intracranial hemorrhage (sICH) rate occurring at any time	Mean duration of follow-up was 850 days. The median time from stroke symptoms until starting anticoagulation was 11 days. 894 (60%) patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Prospective study ***CROMIS-2***		and recent acute ischaemic stroke or TIA, treated with a vitamin K antagonist (VKA) or direct oral anticoagulant. Median age was 76 years, 58% were men. Median HAS-BLED score was 3. Median CHA_2DS_2VASc score was 5.	and without cerebral microbleeds, and between those with and without the primary outcome event (symptomatic intracranial haemorrhage), were compared	before the final follow-up at 24 months **Secondary outcomes:** Recurrent ischemic stroke and death from any cause.	started a VKA and 542 (36%) patients started a DOAC. 311 patients had MRI evidence of a cerebral microbleed (strictly lobar in 116 patients, strictly non-lobar (deep) in 120 patients, and mixed in 75 patients). There were 14 symptomatic intracranial hemorrhages: (11 intracerebral hemorrhages, two subdural hemorrhages, and one subarachnoid hemorrhage). The sICH rate in patients with cerebral microbleeds was significantly higher compared with those without microbleeds (9·8 vs. 2.6 per 1,000 patient-years; adj HR=3·67, 95% CI 1·27–10·60). Models that included cerebral microbleeds + HAS-BLED scores and cerebral microbleeds, diabetes, anticoagulant type, and HAS-BLED scores predicted symptomatic intracranial hemorrhage better than HAS-BLED alone (C index 0·66, 95 % CI 0·53–0·80 and 0·74,95% CI, respectively vs. C-index 0·41, 95% CI 0·29–0·53).

Trials of Direct Oral Anticoagulants (DOACs) vs. Warfarin and/or Aspirin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Dabigatran Extilate (direct thrombin inhibitor)					
Diener et al. 2019 **Germany/ International** **RCT** ***Randomized, Double-Blind, Evaluation in***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,390 patients ≥60 years, recruited from 564 sites with stroke of undetermined source, sustained within the previous 3 months, or, if there was at least one vascular risk	Patients were randomized 1:1 to receive 150 or 110 mg (in patients ≥75 years, or those who had an estimated creatinine clearance of 30 to 50 ml per minute) dabigatran twice daily or 100 mg plain aspirin once daily for the duration of the trial (planned for a minimum of 6 months, maximum of 3.5 years)	**Primary efficacy outcome:** First recurrent stroke (ischemic, hemorrhagic, or undefined stroke) **Secondary efficacy outcomes:** Ischemic stroke and a composite of death from	Median duration of follow up was 19 months. The risk of recurrent stroke was not reduced significantly in the dabigatran group (4.1% vs. 6.6%, HR=0.85; 95% CI 0.69 to 1.03; p=0.10), nor was the risk of ischemic stroke (4.0% vs. 4.7% per year, HR=0.84, 95% CI 0.68–1.03), or the composite outcome (4.8% vs. 5.4% per year, HR=0.88, 95% CI 0.73–1.06).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS)		factor identified within the previous 6 months. Mean age was 64.2 years, 36.9% were women. Median time from qualifying event to randomization was 44 days.		cardiovascular causes, nonfatal stroke and nonfatal MI, death from any cause, disabling stroke (mRS 4-5) at 3 months **Primary safety outcome:** Major bleeding at any site in the body **Secondary safety outcomes:** Clinically relevant nonmajor bleeding resulting in hospitalization, and a composite of major bleeding or clinically relevant nonmajor bleeding	The risk of disabling stroke was significantly reduced in the dabigatran group (0.6% vs. 0.9% per year, HR=0.59, 95% CI 0.36–0.96). The risk of bleeding was not significantly higher in the dabigatran group (1.7% vs. 1.4% per year, HR= 1.19; 95% CI, 0.85 to 1.66). The risk of clinically relevant nonmajor bleeding was significantly higher in the dabigatran group (1.6% vs. 0.9% per year, HR= 1.73, 95% CI 1.17–2.54), as was the composite safety outcome (3.3% vs. 2.3% per year, HR=1.44, 95% CI 1.12–1.85).
Ferro et al. 2019 **Portugal/ International** **RCT (Pilot)** ***RE-SPECT-CVT***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	120 patients recruited from 51 sites in 9 countries following acute CVT who were stable following 5-15 days of treatment with LMWH/UFH. Mean age was 45.2 years, 55.0% were women.	At 5-15 days post event, patients were randomized to receive 150 mg dabigatran or dose-adjusted warfarin (INR 2.0-3.0) for 24 weeks	**Primary outcome:** A composite of major bleeding or new VTE (recurrent CVT, DVT of any limb, pulmonary embolism, and splanchnic vein thrombosis), assessed 7 days after the end of treatment **Secondary outcome:** Recanalization	There were no new VTEs in either group. There was one major bleeding event in the dabigatran group and 2 in the warfarin group. Recanalization occurred in 60.0% of patients in the dabigatran group and in 67.3% of patients in the warfarin group.
Connolly et al. 2009 **International** **RCT** ***Randomized Evaluation***	CA: ☑ Blinding: Patient* ☒ Therapist* ☒ Assessor ☑	18,113 patients with atrial fibrillation and risk for stroke (i.e. one of previous stroke/TIA, left ventricular ejection fraction <40%, heart failure within past 6	Participants were randomly assigned to receive either a fixed dose of dabigatran (110 mg or 150 mg. b.i.d.) or dose-adjusted warfarin. Concurrent ASA (or other antiplatelet) use was permitted. Enrolment was balanced for previous therapy	**Primary outcomes:** Stroke or systemic embolism (efficacy), major hemorrhage (safety). **Secondary outcomes**: Any stroke, myocardial infarction, and death. Net	**Primary study outcome**: Both doses of dabigatran were found to be noninferior to warfarin therapy in terms of risk for stroke or systemic embolism. In addition, the fixed dose of 150 mg. b.i.d. was found to be superior to warfarin therapy for the primary study outcome (RR=0.66, 95% CI 0.53, 0.82, p<0.001). However, when the subgroup of patients with

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
of Long-Term Anticoagulation Therapy (RE-LY trial)	ITT:☑ **though not blinded to therapy, pts. and therapists were blinded to dose of dabigatran*	months, age ≥75 years or 65-75 with diabetes, HTN or coronary artery disease). Mean age of participants was approximately 71.5 years in each treatment condition. Approx. 63% of participants were male. Approximately 67% of participants in each treatment condition had $CHADS_2$ scores of 0, 1 or 2. The remaining 33% scored 4-6. Approximately 40% of participants were taking ASA at the same time as the assigned anti-coagulation therapy.	with a vitamin K antagonist (e.g. warfarin naive vs. previously treated for more than 60 days). Follow-up with participants occurred 14 days post-randomization, at 1 month and 3 months and then every 3 months thereafter for the first year of the trial. Following that, visits were conducted every 4 months until the end of the trial. Median duration of follow-up was 2 years.	clinical benefit outcome was estimated using the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding.	previous TIA/stroke were analysed separately, neither the 110 mg dose of dabigatran nor the 150 mg dose was associated with significant reductions in risk for recurrent events when compared with warfarin (p=0.65 and 0.34, respectively). **Safety outcomes**: The risk for major bleeding events were reduced (vs. warfarin) in the 110 mg group only (RR=0.80, 95% CI 0.69, 0.93, p = 0.003). When life threatening bleeding events and intracranial bleeding were considered separately, both doses of dabigatran were associated with reduced risks for these outcomes when compared to warfarin therapy. For life threatening bleeding RR= 0.68 (95% CI 0.55-0.83, p<0.001) and 0.81 (95% CI 0.66-0.99, p=0.04) for 110 and 150 mg doses respectively, while for intracranial bleeding RR=0.31 (95% CI 0.20, 0.47, p<0.001) and 0.40 (95% CI 0.27, 0.60, p<0.001). Use of dabigatran 150 mg b.i.d. was associated with increased risk for gastrointestinal bleeding (RR=1.50, 95% CI 1.19, 1.89, p<0.001). When examining the net clinical benefit outcome there was a small reduction in risk associated with dabigatran 150 mg/b.i.d. vs. warfarin (RR=0.91, 95% CI 0.82, 1.0, p=0.04).
Connolly et al. 2013 **RE-LY trial, Long term follow-up (RELY-ABLE)**	Per original study	N=5,891. 2,937 participants were enrolled in the 150 mg dose condition and 2,914 in the 110 mg condition. At 28 months, there were 1102 and 1086 patients in each of the above conditions. Approximately 14%	Participants assigned to either of the dabigatran dosing schedules in the original RE-LY trial were eligible to continue in the RELY-ABLE study if they did not discontinue study medication at the termination of the RELY trial. Participants continued to receive the same dose of dabigatran (still blinded to the dose condition) as they had throughout the original trial.	Same as for the parent study.	During the study period, annual rates of stroke or systemic embolism were 1.46% and 1.6% in the 150mg and 110 mg dose groups, respectively. Risk of this combined outcome was not significantly different between groups (HR=0.91, 95% CI 0.69, 1.20). Similarly, annual rates of ischemic stroke were 1.15% in the 150 mg group and 1.24% in the 110 mg group (HR=0.92, 95% CI 0.67, 1.27). Rates of hemorrhagic stroke and of myocardial infarction were very low in both groups.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		of patients in each condition discontinued medications prior to the end of the trial. Patients choosing to enroll in RELY-ABLE were more likely to be male and have paroxysmal AF than patients who did not choose to continue in the study. Mean age of patients enrolled was 71 years. Approximately 20% of patients in RELY-ABLE had experienced a previous stroke or TIA.	Patients enrolled in the warfarin condition did not continue in the trial. After a short interruption (8 weeks), patients continued with a schedule of follow-up visits as follows: 4, 8, 13, 18, 23 and 28 months after study enrollment. Laboratory sampling occurred at baseline, 8, 18 and 28 months. Median duration of follow-up for the patients enrolled in RELY-ABLE was 5.5 years.		**Bleeding events**: In the group receiving dabigatran 150 mg, the annual rate of major bleeding events was 3.74%. In the lower dose group, the rate was also slightly lower 2.99%. In this case, the higher dose did carry a significant increase in risk (HR=1.26, 95% CI 1.04, 1.53). However, annual rates for gastrointestinal bleeding were similar in both groups (1.54% and 1.56%/year). **Mortality**: Mortality rates were similar in both dose conditions (3.1% and 3.02% per year). **Serious Adverse Events**: Dyspeptic symptoms were reported in 141 patients in the 110 mg group and 156 patients in the 150 mg group over the period of the RELY-ABLE follow-up (approximately 5%). In addition, there were instances (n=4 in the 110 mg group and 1 in the 150 mg group) on which aspartame aminotransferase or alanine aminotransferase was elevated >3 times the upper limit of normal + elevated total bilirubin >2 times the upper limit of normal.
Diener et al. 2010 **RE-LY subgroup analysis (previous stroke or TIA)**	Per original study	Patients who had sustained a previous stroke or TIA were younger, more likely to be on statin therapy at baseline and were vitamin K naïve, compared to patients with no previous history of stroke (regardless of group assignment)	3623 patients (20.0%) had sustained a previous stroke or TIA. Of these, 1195 were randomized to the 100 mg dabigatran group, 1233 were randomized to the 150 mg dabigatran group and 1195 were randomized to the warfarin group.	Per original study protocol	There was no difference in the risk of stroke or systemic embolism between patients with a previous history of stroke or TIA and those without prior stroke. 100 mg dabigatran: Previous stroke: RR=0.84, 95% CI 0.58-1.20 No prior stroke: RR=0.93, 95% CI 0.73-1.18, p for interaction=0.62 There was no difference in the risk of stroke or systemic embolism between patients with a previous history of stroke or TIA and those without prior stroke 150 mg dabigatran: Previous stroke: RR=0.75, 95% CI 0.52-1.08

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					No prior stroke: RR=0.60, 95% CI 0.45-0.78, p for interaction=0.34 There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the outcomes of interest (stroke, ICH, ischemic or unknown stroke, disabling or fatal stroke, MI, vascular death, or death from any cause). There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the safety outcomes (major bleeding, life-threatening bleeding, non-life-threatening bleeding, major GI bleed).
Factor Xa Inhibitors (Rivaroxaban, Apixaban, Edoxaban)					
Hart et al. 2018, Healey et al. 2019, Ntaios et al. 2019, Veltkamp et al. 2020 **Canada/ International** **RCT** ***New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	7,213 patients ≥50 years, recruited from 459 centers in 31 countries who had an ischemic, non-lacunar stroke of undetermined source, 7 days to 6 months previously, that was not associated with extracranial vessel atherosclerosis causing ≥50% stenosis in arteries supplying the area of ischemia or with an identified cardioembolic source. Mean age was 67 years, 62% were men. Median NIHSS score was 1.	Patients were randomized 1:1 to receive 15 mg rivaroxaban + aspirin placebo or 100 mg of enteric coated aspirin + rivaroxaban placebo for the duration of the trial.	**Primary efficacy outcome:** First recurrent stroke (ischemic, hemorrhagic, or undefined stroke) or systemic embolism **Secondary efficacy outcomes:** A composite of death from cardiovascular causes, recurrent stroke, systemic embolism, and MI; death from any cause; disabling stroke (mRS 4-5) at hospital discharge) or fatal stroke, and individual components of the primary and secondary efficacy outcomes. **Primary safety outcome:** Major bleeding at any site	The trial was terminated early due to an excess risk of bleeding among patients in the rivaroxaban group and an absence of benefit. The trial was planned to recruit until at least 450 events of the primary efficacy outcome had occurred. Median duration of follow-up was 11 months. The median time from the qualifying stroke to randomization was 37 days. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR=1.07; 95% CI, 0.87 to 1.33; p=0.52). There were no significant differences between groups in the risks of any of the secondary efficacy outcomes, except for a significantly increased risk of hemorrhagic stroke among patients in the rivaroxaban group (annual rate 0.4 vs. 0.1, HR=6.50, 95% CI 1.47–28.8).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
ESUS)				in the body **Secondary safety outcomes:** Life-threatening or fatal bleeding, clinically relevant nonmajor bleeding, symptomatic intracranial hemorrhage	The risk of the primary safety outcome was significantly increased among patients in the rivaroxaban group (annual rate 1.8 vs. 0.7, HR=2.72, 95% CI 1.68–4.39, p <0.001). The risks of life-threatening and clinically relevant bleeding and intracerebral hemorrhage were significantly increased among patients in the rivaroxaban group. A total of 1% of the patients were lost to follow-up after a mean of 15 months, and an additional 1% of patients withdrew consent for follow-up after a mean of 5 months. Healey et al. 2019 (secondary analysis) 239 patients (3%) developed atrial fibrillation during follow-up. Among a small subgroup of patients (n=361) with left atrial diameter of >4.6 cm, of whom 23 had atrial fibrillation, the risk of recurrent ischemic stroke was significantly reduced in the rivaroxaban group (3 [1.7%] vs. 11 [6.5%], HR=0.26, 95% CI 0.07-0.94, p for interaction=0.02). Ntaios et al. 2019 (subgroup analysis based on presence of atherosclerosis) Mild carotid atherosclerosis stenosis (20-49%) was identified in 10.5% of participants and carotid plaque (based on local definitions) was identified in 40.3% of participants. Mild carotid stenosis The rate of ischemic stroke recurrence during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (5.0 vs. 5.9 per 100 patient-years, HR=0.85; 95% CI,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					0.39–1.87). For patients without carotid stenosis the rate of ischemic stroke during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (4.8 vs. 5.9 per 100 patient-years, HR=0.96; 95% CI, 0.72-1.87). There was no treatment interaction between rivaroxaban/aspirin and carotid stenosis status (P for interaction 0.78). The risk of major bleeding was not significantly increased in persons in the rivaroxaban treated group (HR=5.67, 95% CI 0.68–47.08, p= 0.11). Carotid plaque The rate of ischemic stroke recurrence during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (5.9 vs. 4.9 per 100 patient-years, respectively, HR=1.20; 95% CI, 0.86–1.68). The corresponding rates for patients without carotid plaque were 4.0 vs.4.5 per 100 patient-years, respectively, HR= 0.90; 95% CI, 0.67–1.2. There was no treatment interaction between patients with and without carotid plaque (P for interaction =0.2). The risk of major bleeding was significantly increased in persons in the rivaroxaban treated group (HR=3.75, 95% CI 1.63–8.65, p<0.01). Veltkamp et al. 2020 (Characteristics of patients with recurrent stroke) 309 patients had an ischemic stroke during follow-up. Of 270 classifiable ischemic strokes, 58% were ESUS and 42% were non-ESUS. Of the non-ESUS, 32% were cardioembolic, 23% were atherosclerotic, 31% were lacunar, and 14% were

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					from other determined cause. Atrial fibrillation was found in 27 patients (9%) with recurrent ischemic stroke and was associated with higher morbidity and mortality (15% vs 1%) than other causes.
Giugliano et al. 2013 **International** **RCT** ***The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	21,105 patients diagnosed with AF, $CHADS_2 \geq 2$ and anticoagulation planned until the end of the trial. Median age: 72 years (IQR 64-78) Sex: 37.5% female (warfarin group), 37.9% (high-dose edoxaban group), 38.8% (low-dose edoxaban group) Approximately 28% reported prior stroke or TIA	Patients were randomly allocated to one of three treatment regimens: dose adjusted warfarin (INR target 2.0 – 3.0), high-dose edoxaban (60mg), or low-dose edoxaban (30mg). All patients received a placebo tablet in addition to the active medication. Sham INR values were generated for patients allocated to the edoxaban groups. The dose of edoxaban was reduced by half if the patient was experiencing a creatinine clearance of 30 to 50ml/min, was ≤60kg, or was using verapamil or quinidine at baseline. Median duration of treatment was approximately 2.5 years with visits scheduled at day 8, 15, 29, 60, 90, and then every three-months.	**Primary outcomes:** Time to first stroke or systemic embolic event (efficacy end point), major bleeding during treatment (safety). Secondary composite end points: 1. Primary endpoints or death from cardiovascular causes, and 2. Primary end points, myocardial infraction or death from any cause.	**Primary efficacy end point:** Both high-dose edoxaban and low-dose edoxaban were found to be noninferior to warfarin for the occurrence of stroke or systemic embolic event (HR 0.79, 97.5% CI 0.63 to 0.99, p<0.001 and HR 1.07, 97.5% CI 0.87 to 1.31, p=0.005). **Primary safety end point**: The annualized rate of bleeding events was significantly lower for both the high-dose edoxaban and low dose edoxaban (HR 0.8, 95% CI 0.71 to 0.91, p<0.001 and HR 0.47, 95% CI, 0.41 to 0.55, p<0.001). **Secondary composite end point** (events from cardiovascular causes and events from all-causes): Patients receiving high-dose edoxaban had significantly lower secondary composite outcomes compared to patients receiving warfarin. There were no significant differences between low-dose edoxaban and warfarin for secondary composite outcomes. **Rost et al. 2016** Subgroup analysis of patients with previous stroke or TIA (n=5,973) vs. those with no previous history (n=15,132) Median duration of follow-up was 2.8 years Patients with previous stroke or TIA were at higher risk of: stroke/systemic embolic events (2.83% vs.1.42% per year, <0.001; HR=1.97, 95% CI 1.75, 2.24, p<0.001), major bleeding (3.03% vs. 2.64% per year, p<0.001I and ICH

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					(0.70% vs. 0.40% per year, p<0.001 Among patients with previous IS/TIA, annualized ICH rates were lower with high-dose edoxaban compared with warfarin (0.62% vs. 1.09%, absolute risk difference, 47, 95% CI 8-85/10, 000 patient-years; HR=0.57, 995% CI 0.36–0.92, p=0.02). No treatment subgroup interactions were found for primary efficacy (P=0.86) or for intracranial hemorrhage (P=0.28). **Edoxaban only:** Fatal bleed among those with previous stroke or TIA: 25 (2–47) per 10,000 patients Fetal bleeds among those without previous stroke or TIA: 14 (0–27) per 10 000 patient-years Compared to those without a history of stroke or TIA, those with previous stroke or TIA randomized to edoxaban had a: higher absolute reduction in death or disabling stroke: 100 (13 to 187) vs. 12 (-36 to 60)/10,000 person years and al higher absolute reduction in composite of death, disabling stroke or life-threatening bleeding: 137 (44 to 230) vs. 30 (-21 to 80)/10,000 patient years **Low dose Edoxaban versus Warfarin** Compared to patients randomized to warfarin, those randomized to low dose Edoxaban had a larger reduction in: Primary hemorrhagic stroke among those with prior (p=0.004) and no prior (p<0.001) stroke or TIA Primary ischemic stroke among those with prior (p=0.02) and no prior stroke or TIA (p<0.001) All-cause death among those with prior stroke or TIA (p=0.002) only

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					Cardiovascular death among those with prior (p=0.002) only
Hori et al. 2012 **Japan** **RCT** ***Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation (J-ROCKET-AF)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	1,278 Japanese patients aged ≥20 years with non-valvular AF with a history of previous stroke, TIA or systemic embolism or had 2 or more risk factors for thromboembolism. Mean age was 71 years, 81% were male. Mean $CHADS_2$ score was 3.25. 90% of patients had used warfarin previously.	Patients were randomly allocated to treatment with either rivaroxaban (15 mg, n=637) or dose-adjusted warfarin (INR target 2.0 – 3.0, or 1.6-2.6 if aged ≥70 years, n=637). Both groups received a placebo tablet in addition to active medication in order to preserve blinding and patients in the rivaroxaban group received sham INR reports. Maximum treatment duration was 30 months INR values for patients assigned to treatment with dose-adjusted warfarin were within the therapeutic range a mean of 65% of the time over the course of the study.	**Primary outcomes:** All-cause strokes+ non-CNS systemic embolism **Secondary outcome:** Composite of stroke systemic embolism and vascular death	In the per-protocol analysis, the primary outcome occurred in 1.26%/year in patients in the rivaroxaban group compared with 2.61%/year in the warfarin group (HR=0.49, 95% CI 0.24-1.00, p=0.05). In the ITT analysis, the primary outcome occurred in 2.38%/year in patients in the rivaroxaban group compared with 2.91%/year in the warfarin group (HR=0.82, 95% CI 0.46-1.45, p=0.05). The risk of any stroke was significantly reduced in the rivaroxaban group (HR=0.46, 95% CI 0.22-0.98). The risk of ischemic stroke was also reduced significantly (HR=0.40, 95% CI 0.17-0.96); while the risk of ICH was not (HR=0.73, 95% CI 0.16-3.25). The risk of the secondary outcome was not significantly reduced in the rivaroxaban group (HR=0.65, 95% CI 0.34-1.22). The event rates/year for major or non-major clinically relevant bleeding were 18.04 and 16.42, respectively for the rivaroxaban and warfarin groups (HR=1.11, 95% CI 0.87-1.42)
Patel et al. 2011 **International** **RCT** ***Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	14,264 patients with AF and elevated risk for stroke ($CHADS_2$≥2)	Patients were randomly allocated to treatment with either rivaroxaban (20 mg) or dose-adjusted warfarin (INR target 2.0 – 3.0). Both groups received a placebo tablet in addition to active medication to preserve blinding and patients in the rivaroxaban group received sham INR reports. Median length of treatment = 590	**Primary outcome:** Composite of stroke and systemic embolism	There were 269 primary events for individuals assigned to treatment with rivaroxaban vs. 306 patients treated with dose-adjusted warfarin (HR = 0.88, 95% CI 0.74, 1.03; p<0.001 for non-inferiority, p=0.12 for superiority). There were no significant between group differences reported for major or clinically relevant bleeding events (HR=1.03, 95% CI 0.96, 1.11; p=0.44). Rates of major bleeding events were similar

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)			days. INR values for patients assigned to treatment with dose-adjusted warfarin were within the therapeutic range a mean of 55% of the time over the course of the study.		between groups (p=0.58), though there were fewer instances of intracranial hemorrhage in the rivaroxaban group than the warfarin group (HR=0.67, 95% CI 0.47, 0.93; p=0.02). **Hankey et al. 2012** Subgroup analysis of 7,468 patients with previous stroke or TIA. The number of events/1000 person years for the primary outcome was similar between groups. Previous stroke: 2.79% rivaroxaban vs 2.6% warfarin; HR=0.94, 95% CI 0.77-1.16) No previous stroke: (1.44% vs 1.88%; HR=0.77, 95% CI 0.58-1.01). P for interaction=0.23 There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the outcomes of interest (stroke, ICH, ischemic or unknown stroke, disabling stroke, non-disabling stroke, fatal stroke, MI, vascular death, or death from any cause). There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the safety outcomes (major bleeding, fatal bleeding, ICH, intracranial hemorrhage, extracranial hemorrhage and non-major clinically relevant bleeding).
Connolly et al. 2011 **International** **RCT** ***Apixaban Versus Acetylsalicylic***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	5,599 participants with AF and at least one other risk factor for stroke and were not appropriate (or willing) candidates for therapy with a vitamin-K antagonist. 40% of	Participants were randomly assigned to receive either ASA (81 mg – 324 mg daily) or apixaban (5 mg b.i.d). Median length of study follow-up was 1.1 years.	**Primary outcomes:** Composite of stroke (both hemorrhagic and ischemic) and systemic embolism (efficacy), occurrence of major bleeding events (safety).	The trial was terminated early given the clear benefit demonstrated in favour of apixaban. **Efficacy outcomes**: There were significantly fewer primary outcome events recorded in the apixaban group (113 vs. 51, HR=0.45, 95% CI 0.32, 0.62; p<0.001). There were significantly fewer ischemic events in individuals treated with apixaban (HR=0.37, 95% CI 0.25, 0.55; p<0.001),

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES)		individuals had used a vitamin-K antagonist prior to study enrollment. Mean age was 70 years, 58% were male and approximately 14% of participants reported previous stroke/TIA. More than 70% of participants had a $CHADS_2$ score of 0, 1, 2.			although there were no significant between group differences in hemorrhagic stroke (p=0.45). **Bleeding events**: There were 44 major bleeding events reported (annual rate = 1.4%) in the group assigned to treatment with apixaban and 39 events among participants assigned to the ASA condition (annual rate = 1.2%) (HR=1.13, 95% 0.74, 1.75, p=0.57). **Mortality**: There were fewer deaths from any cause reported in the group receiving treatment with apixaban vs. ASA (111 vs 140), although this difference did not reach statistical significance (p=0.07).
Granger et al. 2011, Easton et al. 2012, Hohnloser et al. 2019 **International** **RCT** ***Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation (ARISTOTLE)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT ☑	18,201 participants with AF and at least one other risk factor for stroke (age of ≥75 years, previous stroke/TIA or systemic embolism, symptomatic heart failure with the past 3 months, left ventricular ejection fraction <40%, diabetes mellitus, HTN requiring treatment). Enrollment of >40% of vitamin K antagonist naïve patients was encouraged. Mean age was 70 years in both groups. 35% of	Participants were randomly assigned to treatment with apixaban (5 mg b.i.d) or dose-adjusted warfarin (INR 2.0-3.0). Warfarin (or matching placebo) was given as 2.0 mg tablets). Randomization was stratified by site and by whether the participant had been treated with warfarin previously. The trial was designed to demonstrate non-inferiority; however, superiority was also evaluated on intention to treat analysis. Clinic visits were conducted every 3 months to assess study outcomes and monitor adverse events. Median duration of study follow-up = 1.8 years. Patients assigned to treatment with dose-adjusted warfarin were within the therapeutic range for INR a	**Primary outcomes:** Composite of stroke (hemorrhagic and ischemic) and systemic embolism (efficacy), major bleeding events (safety) **Secondary outcome:** All-cause mortality	**Efficacy outcome**: There were 212 patients with events in the apixaban condition vs. 265 in the warfarin condition (HR=0.79, 95% CI = 0.66, 0.95; p=0.01). There was no between group difference for ischemic stroke alone (p=0.42); however, treatment with apixaban was associated with a significant reduction in risk for hemorrhagic stroke (HR=0.51, 95% CI 0.35, 0.75; p<0.001). There were fewer reported myocardial infarctions in the apixaban group, but the between group difference did not reach significance. Prespecified subgroup analysis revealed no significant interaction between treatment efficacy and whether the participant had a history of previous stroke or TIA (p=0.71). **Mortality:** There was a significant reduction in risk for death from any cause associated with apixaban (HR=0.89, 95% CI 0.80, 0.99; p=0.047). **Bleeding events**: There was a significant reduction in risk for death from any cause associated with apixaban (HR=0.89, 95% CI 0.80,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		participants was female. Approximately 19% of individuals assigned to each condition had a history of previous stroke or TIA.	median of 66% of the time over the course of the study.		0.99; p=0.047). Intracranial bleeding occurred more often in individuals assigned to treatment with warfarin (HR=0.42, 95% CI 0.3 to 0.58; p<0.001); there were no between group differences in bleeding from gastrointestinal sites (p=0.37). **Subgroup analysis of patients with previous stroke or TIA** Of the trial sample, 3436 (19%) had a previous stroke or TIA. Patients with previous stroke were significantly older, and were more likely to have had previous MI. The rate of stroke or systemic embolism was 2.46 per 100 patient-years of follow-up in the apixaban vs. 3.24 in the warfarin group (HR= 0.76, 95% CI 0.56-1.03). In the subgroup of patients without previous stroke or TIA, the rate of stroke or systemic embolism was 1.01 per 100 patient-years of follow-up with apixaban vs. 1.23 with warfarin (HR= 0.38, 95% CI 0.65-1·03). P for interaction=0·71). There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the other outcomes of interest (ischemic or unknown type of stroke, hemorrhagic stroke, disabling or fatal stroke, death from any cause or cardiovascular death). There were no significant interactions reported between groups (previous stroke vs. no previous stroke) for any of the safety outcomes (total bleeding, major bleeding, intracranial bleeding or major GI bleeding). **Subgroup analysis of patients based on weight (low ≤60 kg, mid range >60-120 kg and high >120 kg)**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					1,985 patients (10.9%) were in the low weight group, 15,172 (83.6%) in the mid-range group and 982 (5.4%) in the high group. There was no effect modification for any of the efficacy outcomes (i.e. apixaban was superior to aspirin across all weight categories). There was an interaction effect for the safety outcomes whereby the risks of major bleeding or major/clinically relevant or non-major bleeding were lower in the low weight group compared with the other 2 groups.

Systematic Reviews of DOACs vs. Warfarin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Systematic review & meta-analyses					
Seiffge et al. 2019 **Switzerland** **Patient-level meta-analysis**	Risk of bias was low to medium. One trial had high risk of bias.	Data from 7 prospective, observational studies, including 4,912 patients with atrial fibrillation who had sustained an ischemic stroke or TIA who received oral anticoagulation with DOAC or VKA, either continued, started, or resumed within 3 months after the index event, with minimum follow-up of 3 months. Median age was 78 years, 47.5% were women.	Trials evaluated VKAs, DOACs or compared VKAs with DOACs.	**Primary outcome:** Composite endpoint of recurrent acute ischemic stroke, ICH, and mortality. **Secondary outcome:** Individual components of the primary outcome	After the index event, 45.9% patients received VKA and 54.1% received any DOAC. Median time to initiation of treatment was 5 days for both groups. 81.3% of patients were started on VKA or DOAC within the first 14 days. The risk of the primary outcome was significantly lower in the DOAC group (11.0% vs. 15.0% per year; HR=0.82; 95% CI, 0.67–1.00; p = 0.05) compared with VKA. The risk of ICH was significantly higher in the VKA group (1.6% vs. 0.9% per year; HR=0.4, 95% CI 0.24–0.71, p<0.01). The risk of recurrent ischemic stroke was similar between groups (4.2% vs. 4.4% per year).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					The risk of mortality was not significantly different between groups (VKA 10.8%/year vs. DOAC 6.3% per year, p=0=09).
López-López et al. 2018 **UK** **Network meta-analysis**	Most trials were judged to be at a low or unclear risk of bias for sequence generation, allocation concealment and blinding of outcome assessment. Since most trials were open label, most were at high risk of bias for blinding of participants and staff.	23 RCTs (n=94,656) including persons with atrial fibrillation eligible for treatment with an oral anticoagulant. Median age of participants was 70 years, 63.3% were men.	Trials compared DOACs, or antiplatelets vs. warfarin (INR 2-3). Treatment durations ranged from 3 to 30 months.	**Primary outcomes:** Stroke or systemic embolism, ischemic stroke, MI, all-cause mortality **Safety outcomes:** Major bleeding, intracranial bleeding, gastrointestinal bleeding and clinically relevant bleeding	**Efficacy outcomes** Compared with warfarin, treatment with antiplatelets at both <150 mg and ≥150 mg per day significantly increased the risk of stroke or systemic embolism and ischemic stroke. Compared with warfarin, 5 mg per day of apixaban was associated with significant reductions in the risks of stroke or systemic embolism (OR=0.79, 95% CI 0.66-0.94) and all-cause mortality (OR=0.88, 95% CI 0.79-0.98). Compared with warfarin, 150 mg dabigatran twice daily was associated with significant reductions in the risks of stroke or systemic embolism (OR=0.65, 95% CI 0.52-0.81) and ischemic stroke (OR=0.76, 95% CI 0.58-0.98), while doses of 110 mg twice a day did not reduce the risks of any of the primary outcomes. Compared with warfarin, 30 mg of edoxaban per day increased the risk of ischemic stroke (OR= 1.44, 95% CI 1.21-1.71), while significantly decreasing the risk of all-cause mortality (OR=0.86, 95% CI 0.78-0.96). Doses of 60 mg per day did not significantly reduce the risks of any of the primary outcomes. **Safety outcomes (compared with warfarin)** Antiplatelets did not significantly increase or decrease the risk of bleeding. 5 mg apixaban significantly reduced the risk of major, intracranial and clinically relevant bleeding 110 mg dabigatran significantly reduced the risk

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					of major and intracranial bleeding. 150 mg of dabigatran significantly decreased the risk of intracranial bleeding but increased the risk of g.i. bleeding (OR=1.52, 95% CI 1.20-1.91). 30 mg once daily edoxaban significantly reduced the risk of all the safety (bleeding outcomes). 60 mg once daily edoxaban significantly decreased the risks of major, intracranial and clinically relevant bleeding, but increased the risk of g.i. bleeding (OR= 1.22, 95% CI 1.01-1.49). 30 and 60 mg doses, twice daily significantly increased the risk of clinically relevant bleeding.
Chen et al. 2015 **China** **Systematic review**	NA	4 RCTs (n=23,001) that examined long-term treatment (≥12 weeks duration) with edoxaban or warfarin) including patients with non-valvar AF, aged 65-72 years, with $CHADS_2$ scores of 1.8-3.1. 55%-86% had used warfarin previously. 23%-30% had experienced a previous stroke or TIA.	Trials compared edoxaban (30 and 60 mg) with warfarin. The duration of follow-up ranged from 12 weeks to 2.8 years. The majority of data (92%) came from ENGAGE AF-TIMI 48.	**Primary outcomes:** Thromboembolic events (stroke/TIA, systemic embolism), mortality **Secondary outcome:** Safety (bleeding events)	The risk of any thromboembolic event was not significantly decreased in the edoxaban group (RR=1.00, 95% CI 0.88-1.13, p=0.99). The results from 3 trials included. The results were similar when restricted to low and high doses of edoxaban vs. warfarin. The use of edoxaban was associated with a significantly reduced risk of mortality (RR=0.90, 95% CI 0.83-0.97, p=0.0008). In subgroup analysis, the risk of mortality associated with 30 mg of edoxaban was significantly reduced compared with warfarin (RR=.88, 95% CI 0.80-0.96, p=0.0006), while 60 mg was not (RR=0.92, 95% CI 0.84-1.01, p=0.06). The risks of major and minor bleeding events were significantly reduced in the edoxaban group. Compared with 60 mg dose, 30 mg of edoxaban was associated with significantly reduced risk of all bleeding, major bleeding, minor bleeding and clinical relevant non-major bleeding
Bruins Slot & Berge 2013 **Norway**	N/A	10 RCTs that examined long-term treatment (≥4 weeks duration) with factor Xa inhibitors with	Interventions included Xa factor inhibitors: apixaban, betrixaban, darexaban, edoxaban, idraparinux or rivaroxaban vs.	**Primary outcome:** Composite endpoint of all strokes and other embolic events.	**Primary outcome:** Compared to dose-adjusted warfarin, there was a significant decrease in the odds for stroke associated with treatment with a Xa factor inhibitor (OR=0.81, 95% CI, 0.72- 0.91).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Cochrane Review		traditional oral (dose-adjusted) vitamin K antagonists (e.g. warfarin) in individuals with atrial fibrillation (AF). n=42,084 adult participants (mean age = 65, 36% female). Median duration of follow-up was 12 weeks – 1.9 years.	vs. oral vitamin K antagonists The majority of data was obtained from studies examining the efficacy of apixaban and rivaroxaban.	**Secondary outcomes:** Fatal or disabling stroke, intracranial hemorrhages, major bleeding events, non-major clinically relevant bleeding events, systemic embolic events, myocardial infarction, vascular death, all-cause mortality and other adverse events.	Results from 9 trials included (n=40,777). Analysis of strokes and systemic embolic events separately demonstrated a significant reduction in the odds for each, although the reduction in systemic embolic events was far more dramatic (OR=0.78 and 0.53, respectively). **Bleeding events**: Treatment with Xa factor inhibitors was associated with reduced odds for major bleeding events when compared to treatment with warfarin (OR=0.89, 0.81, 0.98; all studies); and with a reduction in odds for ICH (OR=0.56, 95% CI 0.45, 0.70. Results from 8 studies included. **Mortality:** Treatment with Xa factor inhibitors was associated with reduced odds for mortality when compared to treatment with dose-adjusted warfarin (OR= 0.88, 95% CI 0.81, 0.97). Results from 6 trials included (n=38,924).
Kwong et al. 2013 **China** **Systematic Review & Meta-analysis**	N/A	13 RCTs (n=61,406) evaluating the use of new oral anticoagulants for the prevention of stroke in individuals with atrial fibrillation. Mean age ranged from 64-74 years, 58% - 86% of the study participants were male. Mean $CHADS_2$ score ranged from 1.7 – 3.48. Follow-up ranged from 2 weeks to 2 years.	8 trials evaluated some form of direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban), 5 trials examined the efficacy of oral direct thrombin inhibitors (ADZ0837 and dabigatran). Most studies used dose-adjusted warfarin as the comparison treatment condition. Most studies were open-label with blinded doses – only five studies used double-blind, placebo-controlled design. Studies examining compounds that have are not yet available (darexaban) or have been withdrawn from development	**Primary outcomes**: Major and clinically relevant bleeding events, all strokes and systemic embolic events and all-cause mortality.	**Bleeding Events**: There were no significant between group differences noted between treatment with factor Xa inhibitor vs. control groups or vs. warfarin treatment groups. However, use of direct thrombin inhibitors was associated with significant reduction in risk for major and clinically relevant bleeding events compared to control groups (RR=0.88, 95% 0.78, 0.98) and to vitamin-k antagonists (RR=0.88, 95% CI 0.78, 0.98). **Combined stroke/systemic embolism**: Use of factor Xa inhibitors was associated with reduced risk for stroke/embolism compared to control conditions (RR=0.71, 95% CI 0.54, 0.92) and compared to vitamin-k antagonists (RR=0.84, 95% CI 0.94, 0.94). Direct thrombin inhibitors were also associated with reduced risk vs. controls (RR=0.79, 95%CI 0.66, 0.93) and vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
			(ximelagatran) were excluded.		vitamin k antagonists (RR=0.78, 95%CI 0.66, 0.93). **All-cause mortality**: Treatment with direct factor Xa inhibitors was associated with reduced risk of mortality when compared to control conditions (RR=0.90, 95% CI 0.84, 0.90) or to vitamin-K antagonists (RR=0.91, 95% CI, 0.84, 0.98). There were no significant between group differences in risk reported for comparisons between control/comparative treatment conditions and use of direct thrombin inhibitors.
Dogliotti et al. 2013 **USA** **Systematic Review & Meta-analysis**	N/A	5 RCTs with sample sizes >300 participants comparing treatment with a novel oral anticoagulant vs. warfarin (active/treatment control condition) for the prevention of stroke/embolism in individuals with AF. Reported mean age ranged from 70 – 73 years. The proportion of male participants ranged from 60.3 – 70.	The 5 included trials were: SPORTIF III, SPORTIF V (ximelagatran), RE-LY (dabigatran), ROCKET AF (rivaroxaban) and ARISTOTLE (apixaban). Mean/median follow-up ranged from 16-24 months	**Primary Outcome**: Composite of stroke and systemic embolism. **Secondary outcomes:** All-cause mortality, ischemic stroke, systemic embolism, hemorrhagic stroke and major bleeding events.	**Stroke/systemic embolism**: Risk for the combined primary outcome was reduced in individuals assigned to treatment with novel anticoagulant therapy (RR=0.82, 95% CI, 0.69, 0.98, NNT=200). Factor Xa inhibitors alone demonstrated a similar reduction in risk (RR= 0.84, 95% CI, 0.74, 0.94) **Mortality**: Use of novel anticoagulants was associated with a reduced risk for morality events (RR=0.91, 95% CI 0.85, 0.96, NNT=145) vs. warfarin. There was no interaction effect associated with drug class (p=1.0). **Bleeding Events**: Use of novel anticoagulants was associated with a significant reduction in risk for hemorrhagic stroke (RR=0.51, 95% CI 0.41, 0.64.). In addition, there was a non-significant trend toward reduced risk for less major and minor bleeding associated with the use of novel anticoagulants (vs. warfarin), but neither of these comparisons reached statistical significance. There was no between group difference in major, non-cerebral bleeding events reported between groups receiving novel oral anticoagulation and those receiving warfarin (RR=0.88, 95% CI, 0.72, 1.08).
Ntaios et al.	N/A	3 RCTs (n=14,527)	The included trials were: RE-LY,	**Primary outcome:**	**Stroke or systemic embolism**: There was a

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
2012 **Greece** **Systematic Review & Meta-analysis**		examining the use of non-vitamin K antagonist oral anticoagulants in individuals with atrial fibrillation who had a previous history of either stroke or TIA.	ROCKET AF, and ARISTOTLE. 7,876 received non-VKA therapies, and 6,651 received treatment with warfarin). Median follow-up was 1.8 – 2.0 years.	Stroke or systemic embolism. **Secondary outcomes:** Stroke (any type) ischemic or stroke of unknown etiology, disabling or fatal stroke hemorrhagic stroke, cardiovascular death, any cause mortality and MI. The primary safety outcome was major bleeding events.	significant reduction in risk for the primary outcome associated with non-VKAs (RRR=15%, ARR =0.7%, NN=134, OR = 0.85, 95% CI 0.74, 0.99). There was also a significant reduction in the odds for hemorrhagic stroke associated with non-VKA therapies (OR=0.44, 95% CI, 0.32-0.62), but no significant reduction in ischemic/unknown stroke (OR=1.03, 95% CI, 0.87, 1.21). There was a trend toward increased odds for myocardial infarction among individuals assigned to non-VKA vs. warfarin (OR=1.08, 95% CI 0.84, 1.40). **Mortality**: Non-VKAs were associated with a non-significant reduction in cardiovascular death (OR=0.92, 95% CI 0.80, 1.06). There was a similar trend toward a reduction in mortality from any cause (OR=0.90, 95% CI, 0.81, 1.01). **Safety Outcomes/Bleeding events**: The use of non-VKAs was associated with a reduction in risk for significant bleeding events (RRR=13%, ARR=0.8%, NNT to prevent one major bleeding event = 125). This result, the authors report, was due primarily to the reduction in intracranial bleeding events associated with non-VKA use vs. warfarin (RRR=53.9%, ARR=1.0%, NNN=98). The authors also noted a trend toward more gastrointestinal bleeding events among individuals assigned to treatment with non-VKAs that warfarin (mostly within groups assigned to high-dose dabigatran).

DOACs vs. Each other

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Rasmussen et al.	NA	Phase III clinical	Indirect comparison analysis of	**Primary outcomes:**	*Secondary Prevention*

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
2012 **Review and Indirect comparison analysis**		trials – focusing on the population of individuals with previous stroke or TIA. As a secondary aim, an indirect comparison analysis was performed in the primary prevention cohort. Mean age of secondary prevention subgroup identified = 71 years. The proportion of women in this group was 38%.	apixaban vs. dabigatran (2 doses – 110 mg twice daily and 150 mg twice daily) and of rivaroxaban vs. dabigatran (2 doses). Main efficacy and safety endpoint of RE-LY, ROCKET-AF AND ARISTOTLE trials were used.	Stroke/systemic embolism, ischaemic/uncertain stroke, hemorrhagic stroke, death (any cause), MI **Safety outcomes**: major bleeding, intracranial bleeding	**Apixaban vs. Dabigatran**. There were no significant differences noted between apixaban and dabigatran on any of the efficacy outcomes – at either dose of dabigatran. Examination of the indirect comparison of safety outcomes demonstrated a reduction in risk for myocardial infarction associated with apixaban when compared to dabigatran 150 mg twice daily (HR=0.39, 95% CI 0.16, 0.95). **Rivaroxaban vs. Dabigatran**: Again, there were no significant differences in terms of efficacy outcomes demonstrated in the comparison between rivaroxaban and dabigatran 150 mg (twice daily). However, there was an increased risk for "other location" bleeding events (not intracranial or gastrointestinal) associated with dabigatran 150 mg (HR=2.56, 95% CI 1.12, 5.88). Dabigatran 110 mg, however, was associated with reduced risk for hemorrhagic stroke (HR=0.15, 95% CI 0.03, 0.66), death from any cause (HR=0.72, 95% CI 0.52, 1.0), death from cardiovascular causes (HR=0.64, 95% CI, 0.42, 0.99), major bleeding events (HR=0.68, 95% CI 0.47, 0.99) and intracranial bleeding (HR=0.27, 95% CI 0.10, 0.73). **Apixaban vs. Rivaroxaban**: There were no significant differences reported in the indirect comparisons for either efficacy or safety outcomes. *Primary Prevention:* The profile of comparison results differed slightly within the population of individuals with no history of previous stroke/TIA **Apixaban vs. Dabigatran**: Compared to dabigatran 110 mg, apixaban was associated with a reduced risk in disabling or fatal stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					(HR=0.59, 95% CI 0.36, 0.97). In terms of safety outcomes, apixaban when compared to dabigatran (at either dose) was associated with significant reduction in risk for major bleeding events (HR = 0.80 and 0.75 for 110 mg and 150 mg, respectively) and other location bleeding (HR = 0.78 and 0.74). Apixaban was also associated with reduced risk for gastrointestinal bleeding when compared to dabigatran 150 mg (HR=0.61, 95% CI 0.42, 0.89). **Rivaroxaban vs. Dabigatran.** Dabigatran 110 mg twice daily was associated with increased risk for the outcomes of disabling or fatal stroke (HR=1.74, 95% CI 1.04, 2.93) and myocardial infarction (HR=1.73, 95% CI 1.09, 2.75). However, in terms of safety outcomes, dabigatran 110 mg appeared to be associated with a reduction in risk for major bleeding events (HR=0.77, 95% CI 0.60, 0.98). There were no significant differences noted between rivaroxaban and dabigatran 150 mg for either efficacy or safety endpoints. **Apixaban vs. Rivaroxaban:** There were no differences noted in terms of efficacy outcomes. However, apixaban was associated with less risk for major bleeding events than rivaroxaban (HR=0.61, 95% CI 0.48, 0.78).

Antithrombotic Treatment for Atherosclerotic Vascular Disease

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Eikelboom et al. 2017, Sharma 2019, Perera et al. 2019 Canada/	CA: ☑ Blinding: Patient ☑ Assessor ☑	27,395 patients with coronary artery disease, peripheral arterial disease, or both. Mean age was 68.2 years, 22% were women.	Patients were randomly assigned (1:1:1) to receive 2.5 mg rivaroxaban twice daily plus 100 mg aspirin once daily, 5 mg	**Primary outcomes:** Composite of cardiovascular death, stroke, or MI **Secondary outcomes:**	The dual therapy arm of the trial was stopped early due to superiority, after a mean of 23 months

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
International ***Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS)***	ITT:☑	3.8% of patients had a previous stroke. 90.6% and 27.3% of patients had a history of coronary artery disease, and peripheral arterial disease, respectively.	rivaroxaban twice daily with an aspirin-matched placebo once daily, or 100 mg aspirin once daily with a rivaroxaban matched placebo twice daily for the duration of the study	Ischemic stroke, MI, acute limb ischemia, or death from CHD	The primary outcomes occurred in 4.1% of patients taking rivaroxaban plus aspirin, 4.9% on patients taking rivaroxaban and 5.4% in patients taking aspirin. The risk of the primary outcome was significantly lower for patients on dual therapy compared to aspirin alone (HR=0.76, 95% CI 0.66–0.86, p<0.001). The risk of the primary outcome was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (HR=0.90, 95% CI 0.79–1.03, p=0.12). The risk of any stroke was significantly lower for patients on dual therapy compared to aspirin alone (0.9% vs.1.6%; HR=0.58, 95% CI 0.44-0.76, p<0.001). The risk of any stroke was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (1.3% vs. 1.6%, HR=0.82, 95% CI 0.65–1.05, p=0.12). Major bleeding occurred in 3.1% of patients taking rivaroxaban plus aspirin, 2.8% on patients taking rivaroxaban and 1.9% in patients taking aspirin. **2019 (stroke outcomes)** The risk of ischemic stroke was significantly lower for patients on dual therapy compared to aspirin alone (0.7% vs.1.4%; HR=0.51, 95% CI 0.38-0.69, p<0.001), and was also reduced in the rivaroxaban group, compared with aspirin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(0.9% vs. 1.4%, HR 0.66, 95% CI 0.50-0.88, p= 0.004). The risk of hemorrhagic stroke was significantly increased by rivaroxaban compared with aspirin (0.3% vs. 0.1%, HR= 2.70, 95% CI 1.31-5.58, *p*=0.005) but not with dual therapy vs. aspirin alone (0.2% vs. 0.1%, HR= 1.49, 95% CI 0.67-3.31, *p*=0.33). The risk of fatal or disabling stroke (mRS 3-6) at day 7 or hospital discharge was significantly reduced in the dual therapy group compared with aspirin (0.3% vs. 0.6%, HR= 0.58, 95% CI 0.37-0.89, p< 0.01), but not in the rivaroxaban group vs aspirin group. However, significantly fewer patients in the dual therapy group were likely to have a good outcome (mRS 0-2) at 7 days compared to aspirin (0.6% vs. 1.0%, HR= 0.56, 95% CI 0.40-0.79), p<0.001). Independent predictors of stroke were increased age, increased SBP, HTN, diabetes, previous stroke and Asian race. **Perera et al. 2019 (Ischemic stroke subtypes)** Of 291 ischemic strokes, 59 were cardioembolic, 54 were due to large artery atherosclerosis, 21 were lacunar strokes and 155 were due to stroke of undetermined cause, of which 42 were due to embolic stroke of undetermined source (ESUS) Compared with patients who received aspirin only, the risks of cardioembolic

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					stroke, ESUS were all significantly lower among those who received rivaroxaban + aspirin (HR=0.40, 95% CI 0.20-0.78, p=0.005, HR=0.30, 95% CI 0.12-0.74, p<.006, respectively). The risk of lacunar stroke was not reduced significantly with rivaroxaban + aspirin.

Antithrombotic Treatment Following Heart Valve Replacement

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mechanical Valve Replacement					
Massel & Little 2013 **USA** **Cochrane Review**	NA	13 RCTs (n=4,122 participants) including patients of any age with at least one prosthetic heart valve (mitral, aortic or multiple position) who were enrolled within two weeks following valve surgery. Sample sizes ranged from 78-1,496. Mean ages ranged from 34-63, but were not reported in many included trials.	Patients were randomized to receive either oral anticoagulant therapy (OAC) with warfarin + antiplatelet therapy (aspirin 75-500 mg daily n=7, or dipyridamole 225-400 mg daily, n=6) or OAC monotherapy for a minimum of 6 months. Two trials compared different intensities of OACs Target INRs ranged from 1.8-2.5 to 3.0-4.5.	Rates of thromboembolism, total mortality and major hemorrhagic complications	Duration of study follow-up ranged from 1-2.5 years. The addition of an antiplatelet agent significantly reduced the risk of thromboembolic events (OR= 0.43, 95% CI 0.32- 0.59, p < 0.00001) and total mortality (OR= 0.57, 95% CI 0.42- 0.78, p = 0.0004). Results from 13 RCTs were included. The additions of either aspirin or dipyridamole equally reduced the risk of thromboembolisms (OR=0.45, 95% CI 0.31- 0.67 and OR=0.40, 95% CI 0.24- 0.66, respectively). The risk of major bleeding was increased significantly when antiplatelets were added to oral anticoagulants (OR=1.58, 95% CI 1.14- 2.18, p= 0.006). Results from 11 RCTs were included.
Puskas et al. 2014	CA: ☒	425 patients ≥18 years, from 33 centres with a clinical indication for aortic	Patients were randomized to receive lower-dose warfarin (test group: target	**Primary outcomes:** Major bleeding events, minor bleeding events, total bleeding	Mean duration of follow-up was 3.82 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **RCT** ***Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT)***	Blinding: Patient ☒ Assessor☑ ITT: ☑	valve replacement, at high risk of thromboembolism due to chronic AF, LVEF<30%. 27% of patients underwent concomitant CABG surgery. Mean age was 55 years, 80% were male.	INR 1.5-2.0, n=185) or standard therapy (target INR=2.0-3.0, n=190), 3 months following surgery. All patients received 81 mg aspirin daily.	events, TIA, stroke, any neurological event	>80% of patients were minimally compliant with the home monitoring procedures; >20% were ideally compliant. Mean INR for the test group was significantly lower (1.89 vs. 2.5, p<0.0001). There were significantly fewer major, minor and total bleeding events in the test group (10 vs. 25, RR=0.45, 95% CI 0.21-0.94, p=0.032; 8 vs. 25, RR=0.36, 95% CI 0.16-0.79, p=0.011 and 18 vs. 50, RR=0.40, 95% CI 0.24-0.69, p<0.001, respectively). The risks of hemorrhagic, ischemic stroke and TIA were similar between groups (1 vs. 2, RR=0.56, 95% CI 0.001-10.7, p=0.63; 5 vs. 5, RR=1.12, 95% CI 0.32-3.87, p=0.859 and 9 vs. 6, RR=1.68, 95% CI 0.60-4.72. p=0.326, respectively). The risks of any neurological events and all-cause mortality were similar between groups (14 vs. 11, RR=1.42, 95% CI 0.65-3.14, p=0.380 and 10 vs. 11, RR=1.02, 95% CI 0.43-2.40, p=0.968, respectively).
Eikelboom et al. 2013 **International** **RCT** ***Randomized, Phase II Study to Evaluate the Safety and***	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☑	252 patients aged 18-75 years, recruited from 39 centres in 10 countries, who had undergone bileaflet mechanical heart valve replacement (aortic and/or mitral valve). Mean age was 56 years, 65% were male,	Patients were divided into 2 groups- those who had undergone valve replacement surgery within the past 7 days (Group A, n=127) and those who had undergone such replacement at least 3 months earlier (Group B, n =35) and were randomized	**Primary outcome:** Stroke, systemic embolism, TIA, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death.	The trial was stopped early due to an excess of thromboembolic and bleeding events in the dabigatran group. **Population A:** There was 1 death in each group. There were 9 strokes and 2 TIAs in the dabigatran group and 0 strokes and 2 TIAs in the warfarin group, respectively.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pharmokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN)			to receive dabigatran at 3 dose levels (150, 220 or 300 mg bid), to maintain a plasma level of 50 ng/mL vs. adjusted –dose warfarin to achieve and maintain an INR or 2-3 or 2.5-3.5, based on thromboembolism risk. Both treatments were provided for 12 weeks.		There were 35 bleeding events in the dabigatran group and 8 in the warfarin group. **Population B:** There were no deaths or strokes in either group. There was 1 TIA in the dabigatran group and 0 in the warfarin group. There were 10 bleeding events in the dabigatran group and 2 in the warfarin group. There was a significantly increased risk for any bleeding event associated with dabigatran (both groups combined) HR=2.45, 95% CI 1.23-4.86, p=0.01.
Torella et al. 2010 Trial **Italy** **RCT** ***LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: (LOWERING-IT)***	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☑	396 patients aged 20-60 years recruited from a single centre, scheduled to undergo single valve bileaflet replacement (aortic position), with normal ejection fraction, in sinus rhythm. Patients were considered to be a low risk for thromboembolism. Mean age was 50 years, 69% were male.	Patients were randomized to receive lower-dose warfarin following surgical drain removal, post procedure (target INR 1.5-2.0, n=197) or standard therapy (target INR 2.0-3.0, n=199) for the study duration	**Primary outcome:** Thromboembolic events, bleeding events	Median follow-up was 5.6 years. Mean INR for lower-dose group was significantly 1.94 vs. 2.61 in the standard therapy group (p<0.01). There were 3 thromboembolic events in the standard therapy group (1 TIA and 2 strokes) and 1 (stroke) in the lower INR group. The odds of thromboembolic events associated with lower-dose warfarin were not reduced significantly (OR=0.33, 95% CI 0.0006-4.20, p=0.62). There were significantly fewer bleeding events in the lower-INR group (6 vs. 16, (OR=0.36, 95% CI 0.11-0.99, p=0.04).
Koertke et al. 2007	CA: ☑	2,673 patients ≥18 years from 6 centres who had undergone heart valve	Patients were randomized to a low-dose group oral anticoagulation (INR targets	Thromboembolic events that required hospitalization, bleeding events	532 patients terminated the study early.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **RCT** ***Early Self-controlled Anticoagulation Trial (ESCAT II)***	Blinding: Patient ☒ Assessor☒ ITT: ☒	replacement surgery (mitral, aortic, and/or tricuspid). Mean age was 60 years, 71% were male.	of 1.8-2.8 for aortic valves and 2.5-3.5 for mitral valve or double valve patients, n=1,327) or conventional dose oral anticoagulation (INR target range 2.4-4.5, n=1,327) for 24 months. All patients participated in an INR self-management program. Training began 6 to 11 days after surgery. Every patient who passed the INR self-management examination received a coagulation monitor.		77% of INR values for patients in the low-dose group, and 75% of patients in the conventional group were within the group-specific target ranges. In total, there were 12 thromboembolic events and 63 bleeding events. The incidences of thromboembolic events and bleeding events did not differ significantly between groups (0.19 vs. 0.37%/patient year, p=0.79 and 1.42 vs. 1.52%/patient year, respectively). There were 65 deaths in the low-dose group (1 from stroke) and 60 deaths in the conventional group (2 from stroke).
Bioprosthetic Valve Replacement					
Guimarães et al. 2020 **Brazil** **RCT** ***RIVER Trial***	CA: ☑ Blinding: Patient ☒ Assessor☑ ITT: ☑	1,005 patients with atrial fibrillation and a bioprosthetic mitral valve, who had undergone the procedure ≥48 hours, recruited from 49 sites. Mean age was 59.3 years, 60.4% were women. 15% had a previous stroke or TIA.	Patients were randomized to receive 20 mg/day rivaroxaban or dose-adjusted warfarin (target INR 2.0 to 3.0) for the duration of the trial.	**Primary outcomes:** Composite of death, major cardiovascular events (stroke, TIA, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months. **Secondary efficacy outcome:** A composite of death from cardiovascular causes or thromboembolic events (stroke, TIA, DVT, pulmonary embolism, valve thrombosis, or systemic embolism not related to the CNS), plus individual components of the composite primary and secondary efficacy outcomes. **Safety outcomes:**	A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference= 7.4 days; 95% CI −1.4 to 16.3; p<0.01 for non-inferiority and p=0.10 for superiority). At 12 months, the composite secondary outcome occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (HR=0.65; 95% CI, 0.35 to 1.20). The risk of any stroke was significantly lower in the rivaroxaban group (0.6% vs. 2.4, HR=0.25; 95% CI, 0.07 to 0.88). The risks of other secondary outcome were similar between groups. The risk of any bleeding was similar between groups (13.0% rivaroxaban vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Bleeding events (major, clinically relevant nonmajor, minor, and total)	15.4% warfarin, HR=0.83, 95% CI 0.59–1.15)
Brennan et al. 2012 **USA** **Retrospective study**	NA	25,656 patients ≥ 65 years who received aortic valve bioprostheses at 797 hospitals from 2004-2006. Median age was 77 years, 60% were men.	The outcomes of patients who were discharged on the most common anticoagulation strategies were compared: aspirin-only (49%), warfarin-only (12%), and warfarin plus aspirin (23%)	**Primary outcomes:** Death or readmission for embolic (cerebrovascular accident, transient ischemic attack, and noncerebral arterial thromboembolism) or bleeding events	Mean duration of follow-up was 3 months. No anticoagulants were prescribed for 6.5% of discharged patients. The incidence of death was low (aspirin-only, 3.0%; aspirin plus warfarin, 3.1%; warfarin-only, 4.0%) The risk of death or any embolism was significantly lower in the aspirin plus warfarin group vs. aspirin only (adj RR= 0.80, 95% CI 0.66 to 0.96 and adj RR=0.52, 95% C 0.35 to 0.76, respectively) but there was a significantly higher risk of bleeding (RR= 2.8, 95% CI 2.18 to 3.6). When aspirin alone was compared with warfarin alone, there were no differences in the risk of death or embolic events.
Merie et al. 2012 **Denmark** **Retrospective study**	NA	4,075 patients ≥18 years included in a National Registry who had undergone bioprosthetic aortic valve replacement (with and without CABG surgery) from 2007-2009. Mean age was 75 years, 59% were male.	Hospital records were used to obtain information related to demographics, procedures and outcomes. Medication use was obtained from a National prescription database.	Stroke, thromboembolic events, cardiovascular deaths, and bleeding incidence. The outcomes of patients taking warfarin vs. those who had discontinued its use were compared at 5 time intervals following surgery (30-89 days, 90-179 days, 180-364 days and 365-729 days and ≥730 days) Models were adjusted for age, sex, concomitant CABG	Median duration of follow-up was 6.6 person-years. Following surgery, 2,278 patients received warfarin only and 916 received both warfarin and aspirin. (The 181 patients who received aspirin only and 700 who did not receive any antithrombotic agents were not included in the results). Numbers of patients who discontinued warfarin following surgery. 30-89 days: 982

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				surgery, comorbidity and calendar year	90-179 days: 1359 180-364 days: 281 365-729 days:122 ≥730 442 days: 442 The risk of stroke associated with patients who discontinued warfarin was significantly higher 30-89 days following surgery (13 vs. 11 events, Incident Rate Ratio (IRR)=2.46, 95% CI 1.09-5.55, p=0.03), but not at any of the other time points. The risk of thromboembolic events associated with patients who discontinued warfarin was significantly higher 30-89 and 90-179 days following surgery (24 vs. 16 events, IRR=2.93, 95% CI 1.54-5.55, p<0.01 and 26 vs. 6, IRR=2.65, 95% CI 1.08-6.51, p=0.03, respectively). The risk of cardiovascular deaths associated with patients who discontinued warfarin was significantly higher at all time points with the exception of 365-729 days following surgery.

Timing of Resumption of Anticoagulation following Ischemic Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Yaghi et al. 2020 **USA** **Retrospective study**	NA	1,289 patients admitted to 8 comprehensive stroke centres from 2015-2018, with acute ischemic stroke.	The outcomes of patients who initiated anticoagulation from 0-3 days (n=617), 4-14 days (n=535), or >14 days (n=137) following stroke, were examined. Analysis	**Primary outcome:** Composite of recurrent ischemic stroke, TIA, and systemic arterial embolism, and sICH, or major extracranial	872 patients received DOACs, 399 received warfarin, and 203 received bridging therapy with heparin or LMWH. 216 patients were not started on anticoagulation therapy.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Initiation of Anticoagulation after Cardioembolic stroke (IAC) study		Median age was 77 years, 50.3% were women.	was adjusted for age and sex, hypertension, diabetes, hyperlipidemia, prior stroke, congestive heart failure, coronary artery disease, CHA_2DS_2-Vasc, and admission NIHSS.	hemorrhage (ECH) within 90 days.	The combined endpoint occurred in 10.1% (n = 130) subjects (87 ischemic events, 20 sICH, and 29 ECH). Overall, there was no significant difference in the composite endpoint between the three groups: 0-3 days (10.3%), 4-14 days (9.7%) and >14 days (10.2%), p=0.933, nor was there a difference in the occurrence of anticoagulation related sICH between the 3 groups: 0-3 days (1.1%), 4-14 days (1.7%), and >14 days ([2.9%), p=0.295. Patients started on anticoagulation between 4-14 days did not have a significantly lower risk of sICH compared to the 0-3 day interval (OR=1.49 95% CI 0.50 – 4.43), neither did they have a significantly lower risk of recurrent ischemic events compared to initiation after 14 days (OR= 0.76 95% CI 0.36 – 1.62, p = 0.482).
Wilson et al. 2019 **UK** **Prospective study *CROMIS-2* (Post hoc analysis)**	NA	1,355 patients aged ≥18 years, recruited from 79 hospitals with atrial fibrillation and recent acute ischaemic stroke or TIA, treated with a vitamin K antagonist (VKA) or direct oral anticoagulant. Median age was 76 years, 57% were men.	The outcomes of patients who initiated oral anticoagulation (OAC) within 4 days of stroke (n=358) were compared with those who initiated OAC therapy late (5-14) days following stroke (n=481) or very late (≥15 days) or not at all (n=516).	**Primary outcome:** Composite outcome of TIA, stroke (ischaemic stroke or intracranial haemorrhage) or death within 90 days	55 patients had ≥1 event within 90 days. The median time to ischemic stroke was 14 days, the median time to ICH was 72 days. There were 48/997 (5%) primary outcomes in the late-OAC group (2 ICHs, 16 ischaemic strokes, 2 TIAs and 31 deaths compared with 7/358 (2%) in the early-OAC group (three ischaemic strokes (all cardioembolic), 2 TIAs and 2 deaths). After adjusting for all potential confounders, there was no increased risk of the of the composite outcome in the late OAC group compare with the early

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					group (OR= 1.17, 95% CI 0.48 to 2.84), nor was there an increased risk of ischemic stroke or TIA (OR=1.25, 95% CI 0.36 to 4.41). Multivariable sensitivity analyses comparing later (5 to 14 days) (n=481) and very late OAC (≥15 days or not started at all) (n=516) to early OAC (0 to 4 days) (n=358) showed little difference in the odds of the primary composite outcome: starting late, OR 1.19 (95% CI 0.45 to 3.90) and starting very late, OR 1.14 (95% CI 0.42 to 3.09).
Paciaroni et al. 2017 **Italy** **Prospective study** ***Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non–Vitamin-K Oral Anticoagulants (RAF-NOACs)***	NA	1,127 patients, recruited from April 2014 to June 2016, from 35 stroke units in Europe the US and Asia, with acute ischemic stroke and known or newly diagnosed AF. Mean age was 75.6 years, 46.8% were men. 26% had a previous stroke. 74.3% had a CHA_2DS_2-VASc score >4 after index stroke.	Following admission, all patients received standard care, including thrombolytic agents. Patients were initiated on NOACS during hospitalization, of whom 395 (34.0%) were treated with dabigatran, 390 (33.6%) with rivaroxaban and 376 (32.4%) with apixaban. Their initiation with the primary outcome was examined.	**Primary outcome:** Composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding within 90 days of stroke	There was a total of 59 primary outcome events (5.2%). Of these, 11 patients had initiated treatment with dabigatran, 28 with apixaban and 20 with rivaroxaban. There were 32 cases (2.8%) of ischemic stroke, TIA, or systemic embolism, and 27 (2.4%) cases of symptomatic intracranial bleeding or major extracerebral bleeding. Mean latency from index stroke to recurrent ischemic event (stroke, TIA, systemic embolism) was 23.2±27.4 days (median: 17 days; IQR 2–39 days) and to severe bleeding was 18.1±30.7 days (median: 7 days; IQR: 2 to 42 days). Primary outcome events were experienced by 12.4% of patients who initiated NOACs within 2 days from the index stroke, 2.1% who initiated NOACs between 3 and 14 days, and 9.1% who initiated NOACs after 14 days ($p<0.0001$); however, in multivariable modeling, the risk of the primary outcome

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					was not associated with the timing of initiation of NOACs. <3 days; OR=1.00 (ref) Days 3-7: OR=1.30, 95% CI 0.54–3.71 Days 8-14: OR=1.44, 95% CI, 0.36–3.02 >14 days: OR=0.59, 95% CI 0.15–1.95 80% of patients received NOACs within the first 15 days following stroke. Early recurrence and major bleeding occurred in 1.8% and 0.5% in patients receiving dabigatran, 1.6% and 2.5% in those receiving rivaroxaban, and 4.0% and 2.9% in those receiving apixaban. LMWH preceding oral anticoagulants was a significant independent predictor of the primary outcome (OR= 4.13, 95% CI 1.73–8.96; p=0.0003) Ischemic and hemorrhagic outcome events were 60% lower than in the RAF study that included mainly patients treated with vitamin K antagonists (Paciaroni et al. 2015)
Paciaroni et al. 2015 **UK** **Italy** **Prospective study** ***Early Recurrence and cerebral bleeding in patients with acute***	NA	1,029 patients recruited from January 2012 to March 2014, from 29 European stroke units admitted with acute ischemic stroke and known or newly diagnosed AF without contraindications to anticoagulation. Mean age was 77 years, 45.5% were men, mean NIHSS score was 9.2	Following admission, as part of routine care, physicians prescribed anticoagulant treatment (LMWH or oral anticoagulants), at their discretion, as well as the day to initiate it. Models were developed to predict: (1) the risk of recurrent ischemic embolic event and severe bleeding (both intra and extracranial); (2) the risk factors associated	**Primary outcome:** Composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding within 90 days of stroke.	776 patients received anticoagulant therapy following stroke, while 263 did not. There were 128 primary outcome events: 77 (7.6%) ischemic stroke, TIA or systemic embolism, 37 (3.6%) had symptomatic cerebral bleeding, and 14 (1.4%) had major extracranial bleeding. The mean time from index stroke to recurrent ischemic stroke was 34 days. Significantly fewer patients treated with oral anticoagulants had an outcome

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
ischemic stroke and Atrial Fibrillation (RAF)			with ischemic stroke recurrence, systemic embolism, and symptomatic cerebral bleeding, and severe extracerebral hemorrhage; and (3) the risk of recurrence and bleeding associated with anticoagulant therapy and its timing.		event compared with patients treated with either LMWHs alone or LMWH followed by oral anticoagulants (7% vs. 16.8% and 12.3%, respectively, p=0.003) Adjusted for age, sex, CHA_2DS_2-VASc score, lesion size, reperfusion therapy, and NIHSS on admission, patients who had been initiated on treatment with anticoagulants between 4 and 14 days had a significantly reduced risk of the primary outcome and in ischemic events compared with patients who had their treatments initiated before 4 or after 14 days from stroke onset (HR=0.53, 95% CI 0.30–0.93, *p*=0.025 and HR=0.43, 95% CI 0.19–0.97, p=0.043, respectively). The authors concluded the optimal time for initiating anticoagulation treatment for secondary stroke prevention may be 4 to 14 days from stroke onset.
Sandercock et al. 2015 **UK** **Cochrane Review**	**NA**	24 RCTs (n=23,748 participants) including patients who had sustained an ischemic stroke and were treated with any form of anticoagulant within the first 2 weeks of the event.	Trials comparing patients who received treatment with early anticoagulants (AC) within the first two weeks of confirmed ischemic stroke vs. patients who did not receive AC therapy. The following anticoagulants were included: subcutaneous and intravenous standard unfractionated heparin, low-molecular weight heparins, subcutaneous and intravenous heparinoids, oral vitamin K antagonists,	**Primary outcome:** Death or dependency **Secondary outcomes:** (2 related to intracranial hemorrhage) i) Symptomatic intracranial (intra or extracerebral) hemorrhage, including symptomatic hemorrhagic transformation of the cerebral infarct, during the scheduled treatment period and during follow-up. ii) recurrent stroke or symptomatic intracranial hemorrhage during the	Treatment with oral anticoagulants was not associated with an increased risk of Symptomatic intracranial hemorrhage during treatment period. OR=2.78, 95% CI 0.37- 21.00. Results from a single trial included (n=51) Treatment with oral anticoagulants was not associated with an increased risk of any recurrent stroke or symptomatic intracranial hemorrhage during treatment period or follow up (> 1 month). OR=1.24, 95% CI 0.32- 4.88). Results from 2 trials included (n=81)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			factor Xa inhibitors and specific thrombin inhibitors Two studies examined treatment with oral vitamin K antagonist	treatment period or during long-term follow-up	

Bridging with Low-Molecular-Weight Heparin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Yaghi et al. 2020 **USA** **Retrospective study (Initiation of Anticoagulation after Cardioembolic study)**	NA	1,289 patients with acute ischemic stroke and atrial fibrillation included in a database of 8 comprehensive stroke centres from 2015-2018. Patients with mechanical heart valves were excluded. Median age was 76 years, 48% were women.	The outcomes of patients who received bridging therapy with heparin or LMWH therapy (n=203) were compared with those that did not receive bridging therapy (n=1,086).	**Primary outcomes:** Recurrent ischemic events (stroke/TIA/systemic embolism) and delayed sICH within 90 days	The risk of delayed sICH was significantly higher in the bridging group (4.4% vs. 1.0%, p=0.002, adj HR=2.74, 95% CI,1.01–7.42, p=0.047). The risk of recurrent ischemic events was not significantly lower with bridging therapy (5.9% vs. 6.9%, p=0.760, adj HR=1.23, 95% CI, 0.63–2.40, p=0.551).
Altavilla et al. 2019 **Italy** **Retrospective study**	NA	1,810 patients included in the RAF and RAF-NOACs studies. Of these, 371 (20%) underwent bridging therapy with full-dose low-molecular-weight heparin (LMWH). The mean age of persons who were bridged was significantly younger compared with non-bridged patients (73.0 vs.76.1 years, p<0.001). 53.1% of bridged patients were men vs. 46.1% of non-bridged patients (p=0.017).	The association between bridging therapy, defined as any temporary full dose of LMWH started together before or with VKAs, to cover the time needed to reach the therapeutic effect or as any full dose of LMWH before the use of an NOAC, and the risk of the primary outcome was examined.	**Primary outcome:** Composite of ischemic stroke, TIA, systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding within 90 days after stroke Models were adjusted for model NIHSS score, diabetes, arterial hypertension, dyslipidemia, paroxysmal AF, pacemaker, lesion size, leukoaraiosis, CHA_2DS_2 -VASc score after the event, and history of stroke or TIA, current smoking habit, congestive heart failure, and MI	Bridging therapy was associated with significantly increased odds of the primary outcome (11.3% vs. 5.1%, OR=2.3; 95% CI, 1.4–3.7; P<0.0001), ischemic events (7.8% vs. 3.1%; OR= 2.2; 95% CI, 1.3–3.9, p=0.005), and hemorrhagic event (5.1% vs. 3.1% OR= 2.4; 95% CI, 1.2–4.9, p=0.01).

Left Atrial Appendage Devices vs Warfarin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Holmes et al. 2015 **USA** **Meta-analysis**		2,406 patients with 5,931 patient-years of follow-up from the PROTECT AF and PREVAIL trials, both described below, and their respective registries	Patient-level meta-analysis	**Primary outcomes:** All-cause stroke (hemorrhagic and ischemic), systemic embolization and CV death	Mean duration of follow-up was 2.7 years. Including the results from the 2 trials, the risk of the primary outcome was not significantly different between groups (2.72 per 100-person years for device and 3.50 for warfarin; HR=0.79, 95% CI 0.53 to 1.2, p=0.22). The risk of hemorrhagic stroke was significantly lower in the device group (0.15 per 100-person years, vs. 0.96 for warfarin (HR=0.22; 95% C 0.08 to 0.61; p = 0.004), as was the risk of CV/unexplained death (HR= 0.48,95% CI: 0.28 to 0.81; p= 0.006). The risk of major, non-procedural bleeding occurring ≥7 days after implantation was significantly lower in the device group (HR= 0.51, 95% CI: 0.33 to 0.77; p =0.02). The pattern of all results was similar when including additional patients from the 2 registries.
Holmes et al. 2014 **USA** **RCT** ***Prospective Randomized Evaluation of the Watchman LAA Closure Device***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT ☑	475 patients recruited from 50 sites, aged ≥18 years, with non-valvular atrial fibrillation (paroxysmal, persistent, or permanent) and a $CHADS_2$ score ≥2. Patients could be enrolled with a $CHADS_2$ score of 1 if they also had any of the following higher-risk characteristics: women ≥75	Patients were randomly assigned to undergo LAA occlusion with the Watchman device and subsequent discontinuation of warfarin (intervention group, n=269) or to receive chronic warfarin therapy (n=138). After implantation, patients in the intervention group received 81 mg	**Co-primary outcomes:** i) Primary efficacy end-pint: a composite of ischemic or hemorrhagic stroke, systemic embolism and cardiovascular death. ii) Late ischemic efficacy endpoint: a composite of ischemic stroke or systemic embolism,	Mean duration of follow-up was 11.8 months. Primary efficacy endpoint: The 18-month event rates were similar between groups (0.064 vs. 0.063, RR=1.07, 95% Cr I: 0.57 to 1.89), which did not reach the pre-specified noninferiority margin of 1.75 for the upper Cr I limit. ii) Late ischemic efficacy endpoint: The 18-month event rates were 0.0253 for the device

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial		years, baseline ejection fraction ≥30-34%, 65- 74 years with either diabetes or coronary disease, and ≥65 years with congestive heart failure. Persons with a previous stroke or TIA were excluded. Mean age was 74.5 years, 70% were men.	aspirin per day for 45 days plus warfarin with target INR of 2.0-3.0. Thereafter, the regimen changed depending on whether there was complete closure of the LAA (dual antiplatelet only, if closure vs continuation of warfarin and low-dose aspirin), for 6 months. Patients in the control group received warfarin with a target INR of 2.0-3.0.	excluding the first 7 days after randomization iii) safety, a composite of all-cause death, ischemic stroke, systemic embolism, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention, occurring within 7 days of the procedure	group and 0.0200 for the control group (RR= 1.6, 95% Cr I 0.5 to 4.2). The associated risk difference was 0.0053, 95% Cr I: –0.0190 to 0.0273). Because the 95% upper Cr I of the risk difference was <0.0275, noninferiority of the device group was achieved. iii) Safety outcomes: There were 6 safety events among patients in the device group (2.2%).
Holmes et al. 2009 **USA** **RCT (non-inferiority)** ***The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT ☑	707 patients, recruited from 59 centres, aged ≥18 years with paroxysmal, persistent, or permanent non-valvular atrial fibrillation, with $CHADS_2$ risk score of ≥1 (i.e., previous stroke or TIA, CHF, diabetes, hypertension, or aged ≥ 75 years). Mean age was 72 years, 70% were men. 18% had previous stroke or TIA.	Patients were randomized to receive percutaneous closure of the LAA using the Watchman device (with discontinuation of warfarin, n=463) or to warfarin treatment with a target INR between 2.0-3.0 (n=244). After implantation, patients in the intervention group received 81 mg aspirin per day for 45 days plus warfarin with target INR of 2.0-3.0. Thereafter, the regimen changed depending on whether there was complete closure of the LAA (dual antiplatelet only, if closure vs continuation of warfarin and low-dose aspirin), for 6 months.	**Primary outcome:** Composite of the occurrence of stroke, cardiovascular or unexplained death, or systemic embolism **Primary safety outcome:** Events related to excessive bleeding (eg, intracranial or gastrointestinal bleeding) or procedure-related complications (eg, serious pericardial effusion, device embolisation, procedure-related stroke).	Mean duration of follow-up was 18 months. The event rate/100 patient- years for the primary outcome was 3.0 for the intervention group vs. 4.9 for the control group (RR=0.62, 95%, Cr I 0.35 to1.25), which met the threshold for non-inferiority. The probability of non-inferiority of the intervention was >99.9%. The event rate/100 patient- years for all stroke was 2.3 for the intervention group vs. 3.2 for the control group (RR=0.71, 95% Cr I 0.35-1.64). The risk of the primary safety outcome was significantly higher in the intervention group (7.4 vs. 4.4/100 patient-years, RR=1.69, 95% Cr I 1.01-3.19)

Abbreviations

ARR: absolute risk reduction	CA: concealed allocation	CI: confidence interval
HR: hazard ratio	ITT: intention-to-treat	NNTB: number needed to benefit
NNTH: number needed to harm	OR: odds ratio	RR: relative risk
RRR: relative risk reduction		

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