CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Anticoagulation for Individuals with Stroke and Atrial Fibrillation

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PREVENTION of STROKE Writing Group

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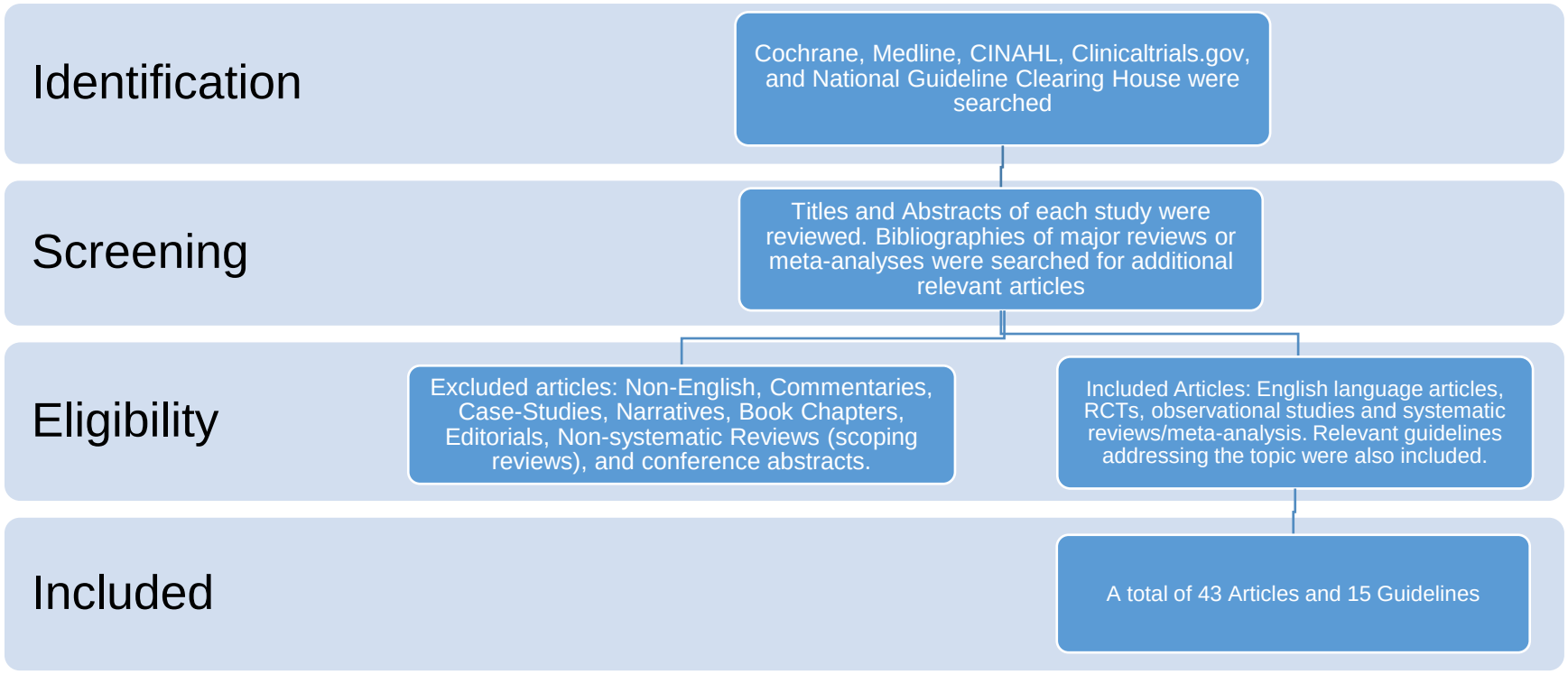
Search Strategy



Cochrane, Medline, CINAHL, Cochrane, Medline, CINAHL, National Guideline Clearing House and clinicaltrials.gov were search using the terms (“stroke” AND “dipyridamole” OR “antiplatelet” OR “clopidogrel” OR “blood platelets”). 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
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

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	Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. Class IIb, LOE B 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

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	efficacy of warfarin. 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

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	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) For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended

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	(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)
January CT, Wann LS, Alpert JS et al. **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 Practice Guidelines and the Heart Rhythm Society** ***Circulation* 2014;130(23):e199-e267.** **(selected)**	For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA_2 DS_2 -VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran (Level of Evidence: B), rivaroxaban (Level of Evidence: B), or apixaban. (Level of Evidence: B) Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable. (Level of Evidence: A) For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended. (Level of Evidence: C)
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.**	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

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(selected)	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. **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)**	**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 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

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	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 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**

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	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 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*
Camm AJ, Lip GY, De Caterina R, et al. **2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association.** ***Eur Heart J 2012*;33(21):2719-2747.**	**Recommendations for prevention of thromboembolism in non-valvular AF—general** Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications. (Class I; Level A) The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient. (Class I; Level A) The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF. (Class I; Level A) In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: adjusted-dose VKA (INR 2–3); or a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended, unless contraindicated. (Class I; Level A) In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with adjusted-dose VKA (INR 2–3); or a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) should be considered, based upon an assessment of the risk of bleeding complications and patient preferences. (Class IIa; Level A) Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered. (Class IIa; Level B) When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily. (Class IIa; Level B) **Recommendations for prevention of thromboembolism in non-valvular AF—NOACs**

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	When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) is recommended. (Class I; Level B) Where OAC is recommended, one of the NOACs, either: a direct thrombin inhibitor (dabigatran); or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit. (Class IIA; Level A) Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: elderly patients, age ≥ 80 concomitant use of interacting drugs (e.g. verapamil) high bleeding risk (HAS-BLED score ≥3) moderate renal impairment (CrCl 30–49 mL/min). (Class IIa; Level B) Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: high bleeding risk (HAS-BLED score ≥3) moderate renal impairment (CrCl 30–49 mL/min). (Class IIa; Level C) Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year. (Class IIa; Level B) NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min). (Class III; Level A) **Recommendations for prevention of thromboembolism in non-valvular AF—bleeding** Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin). (Class I; Level a) The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates ‘high risk’ and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B). (Class IIa; Level A/B) The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the

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	elderly – also with aspirin monotherapy) should be considered as being similar to OAC. (Class IIa; Level B) **Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion** For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological). (Class I; Level B) In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion. (Class I; level B).
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010. Melbourne, Australia	**Anticoagulation therapy** Anticoagulation therapy for secondary prevention for people with ischeamic stroke or TIA from presumed arterial origin should NOT be routinely used. (Grade A). Anticoagulation therapy for long-term secondary prevention should be used in people with ischeamic stroke or TIA who have atrial fibrillation or cardioembolic stroke (Grade A) In stroke patients, the decision to begin anticoagulation therapy can be delayed for up to two weeks but should be made prior to discharge (Grade C) In patients with TIA, anticoagulation therapy should begin once CT or MRI has excluded intracranial haemorrage as the cause of the current event (GPP)
Stroke Foundation of New Zealand and New Zealand Guidelines Group. Clinical Guidelines for Stroke Management 2010. Wellington: Stroke Foundation of New Zealand; 2010.	**Anticoagulant therapy** Anticoagulation therapy for secondary prevention for those people with ischaemic stroke or TIA from presumed arterial origin should NOT be routinely used as there is no evidence of additional benefits over antiplatelet therapy (Sandercock et al, 2009). (Grade A) Anticoagulation therapy for long-term secondary prevention should be used in all people with ischaemic stroke or TIA who have atrial fibrillation or cardioembolic stroke and no contraindication (Saxena & Koudstaal, 2004a; Saxena & Koudstaal, 2004b). (Grade A) In acute ischaemic stroke, the decision to commence anticoagulation therapy can be delayed for up to two weeks but should be made prior to discharge (Ovbiagele et al, 2004). (Grade C) In patients with TIA, commencement of anticoagulation therapy should occur once CT or MRI has excluded intracranial haemorrhage as the cause of the current event. **Anticoagulation therapy after intracerebral haemorrhage** There is insufficient evidence to allow firm recommendations regarding the use of anticoagulant or antiplatelet therapy in patients with ICH who are considered to be at high risk of future thromboembolic events. (Grade D)

Guideline	Recommendations
	All patients with ICH should have their individual risk of future thromboembolic events and their risk of recurrent ICH assessed, taking into account patient specific factors. The risk of recurrent ICH is thought to be greatest in those with lobar and previous ICH and less with deep "hypertensive ICH" when blood-pressure control can be optimised. In general, thromboembolism risk is highest in patients with mechanical heart valves (particularly mitral valves), and is high in those with atrial fibrillation and patients with previous ischemic events. Expert advice should be sought and the potential benefits and risks of anticoagulant and antiplatelet therapy after ICH discussed with patients and their families, and documented
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** ***Cerebrovasc Dis 2008*;25:457–507**	**Antithrombotic Therapy** It is recommended that patients receive antithrombotic therapy (Class I, Level A) It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A) The combination of aspirin and clopidogrel is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A) It is recommended that patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP) Oral anticoagulation (INR 2.0–3.0) is recommended after ischaemic stroke associated with AF (Class I, Level A). Oral anticoagulation is not recommended in patients with comorbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding (Class III, Level C). Increasing age alone is not a contraindication to oral anticoagulation (Class I, Level A) It is recommended that patients with cardioembolic stroke unrelated to AF should receive anticoagulants (INR 2.0–3.0) if the risk of recurrence is high (Class III, Level C) It is recommended that anticoagulation should not be used after non-cardio-embolic ischaemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery, cervical artery dissection, or PFO in the presence of proven deep vein thrombosis (DVT) or atrial septal aneurysm (Class IV, GCP) It is recommended that combined low-dose aspirin and dipyridamole should be given if oral anticoagulation is contraindicated (Class IV, GCP)

Evidence Tables

Monitoring for Atrial Fibrillation Following TIA and Non-Disabling Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Wachter et al. 2016 **Germany** **RCT** ***Finding Atrial Fibrillation in Stroke - Evaluation of Enhanced and Prolonged Holter Monitoring (FIND-AF)***	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). There were no interactions based on sub group analyses based on age, sex, baseline NIHSS, CHADS-2 score, symptoms at admission and imaging (lacunar vs. non-lacunar). Detection of AF at 12 months was significantly higher in the prolonged monitoring group (13.5% vs. 6.1%, p=0·02). 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***	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.	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,	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
a Cerebral Ischemic Event (EMBRACE)		Mean age: 73 yrs. 56% male, 63% of patients sustained an ischemic stroke, 37%, a TIA.		and any AF	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** **RCT** ***Cryptogenic Stroke and Underlying AF (CRYSTAL-AF)***	CA: ☑ Blinding: Patient ☒ Assessor ☒ ITT: ☑	441 patients >40 years with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring associated with a cryptogenic symptomatic TIA or cryptogenic ischemic stroke, sustained within 90 days of the event. Mean age: 61 yrs. 63% male	Patients were randomized (1:1) to received ECG monitoring on a 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.	**Primary outcome:** Time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months **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.	The mean time between the index event and randomization was 38 days. Most patients completed 18 months of follow-up. 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 $CHADS_2$.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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.	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). 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).

CA: concealed allocation; ITT: intention-to-treat

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	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			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%		$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 **USA** **Observational study** ***Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER)***	NA	12,552 patients discharged with 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	Patients were divided into two groups according to discharge 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.	**Primary outcomes:** Major adverse cardiovascular event (MACE), time spent at home without complications **Secondary outcomes:** All-cause mortality, cardiovascular readmission, stroke readmission	Patients treated with warfarin were younger (80 vs. 83 years), were less likely to have a history of previous 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**	CA: ☑ Blinding: Patient ☒ Assessor ☑	973 patients ≥75 years, with AF or atrial flutter, recruited between April 2001 and	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	**Primary outcome:** First occurrence of fatal and non-fatal disabling stroke (ischemic or hemorrhagic), intracranial	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)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
RCT ***Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA)***	ITT: ☑	November 2004 from 260 participating centres. Mean age was 81.5 (±4.2) years, 54% females.13% had a previous stroke or TIA.	with warfarin was randomly assigned to aspirin, then warfarin therapy was stopped, vice versa.	hemorrhage, and other clinically significant arterial embolism **Secondary outcome:** Major extracranial hemorrhage, other vascular events, all-cause mortality	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 embolus 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 (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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					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 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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					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, while 36% of patients in the SPAF III trial had. Mean age was 71 years, 64% were male.	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 warfarin (mean achieved INR, 1.3). The trial was terminated after a mean follow-up of 1.1 years.	**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. 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.	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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					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).

CA: concealed allocation; ITT: intention-to-treat

Self-testing and Self-Management for Anti-Coagulation (warfarin) Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Cumberworth et al. 2013 **UK** **Review of systematic reviews**	N/A	4 systematic reviews + meta-analyses, and one meta-analysis were identified as representing the highest level of available evidence with which to address the topic question.	*Topic review structured to answer the question: "In patients taking warfarin, is home self-monitoring of INR safer than clinic-based testing in reducing bleeding, thrombotic events and death?" (p. 198)* A search of the Medline database was conducted (1950 – 2012) to identify articles examining the use of self-management vs. standard management of oral anti-coagulation using warfarin. Articles were selected according to "best evidence".	Bleeding, thrombotic events and death	**Bleeding events**: All five reviews reported data on major hemorrhage (resulting in death, critical bleeding requiring surgical intervention or transfusion). One meta-analysis (Heneghan et al. 2006) reported that self-monitoring was associated with a 35% reduction in risk for these events, while the other 4 studies reported no significant risk reduction. **Thrombo-embolic events**: Major thromboembolic events were defined as those resulting in death, stroke, arterial thrombosis or arterial thromboembolism. All studies that were included in the review reported reduced risk of thrombo-embolic events associated with self-management interventions. The most recent meta-analysis (Heneghan et al. 2012) reported a reduction in risk of 49%). **Mortality**: Data pertaining to the outcome of mortality was also available in all reviews included in the present study. Four reported all-cause mortality specifically – reductions in risk ranged from 26% - 42%. **Time in Therapeutic Range (INR):** Only one meta-analysis reported definitive improvement in time spent within the therapeutic INR range. In the remainder, pooling of data was not possible for reasons of heterogeneity – or no significant difference was noted.
Heneghan et al. 2012 **UK**	NA	11 RCTs (including 6,417 participants) Mean ages of participants ranged	Included trials compared the effects of self-monitoring (self-testing) or self-management (self-testing and self-dosage) of anti-coagulation with	**Primary outcomes:** Time to death, first major hemorrhage (fatal bleeding event, symptomatic bleeding in a critical area	**Thrombo-Embolic Events:** Self-monitoring was associated with a significant reduction in risk for thrombo-embolic events (HR=0.51, 95% CI 0.31, 0.85, p=0.01). At one year, NNT=78 and at 5 years, NNT=27. Subgroup analysis demonstrated that

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Systematic review &meta-analysis		from 42-74, 99 participants were aged ≥ 85 years. 10 trials included a portion of participants with AF (17%-77%). 1 trial was specific to individuals with AF.	control and dosage by personal physician, anticoagulation management clinics, or managed services Study durations ranged from 3-36 months	or organ, bleeding requiring a transfusion) and first thrombo-embolic event (stroke, arterial embolism, DVT, pulmonary embolism). **Secondary outcome:** Time in therapeutic range (INR)	reduction of risk may be confined primarily to younger individuals – participants under the age of 55 experienced significant reduction in risk (HR=0.33, 95% CI 0.17, 0.66; p=0.002) while age groups over the age of 55 years experienced no significant reduction in risk (p for interaction = 0.052). In subgroup analysis the reduction of risk associated with self-monitoring was greater for individuals with mechanical heart valves (HR=0·52, 95% CI 0·35–0·77, while in participants with AF, the reduction in risk did not reach statistical significance (HR=0.67, 95% CI 0.28- 1.57; p for the interaction =0.032). There were no significant effects for age or sex in the group of individuals with AF. Analysis also confirmed a greater reduction in risk associated with self-management (p<0.001) than for self-testing alone (p = ns; p for interaction = 0.002). **Death**: There was no significant reduction in deaths associated with self-management (HR=0.82, 95% CI 0.62, 1.09). Pre-specified subgroup analyses demonstrated no significant interactions by age, sex, indications for treatment or type of management intervention. **Major Hemorrhagic Events**: There was no significant reduction in major bleeding events associated with self-management over conventional care (HR=0.88, 95% CI 0.74- 1.06). Pre-specified subgroup analyses demonstrated no significant interactions by age, sex, indications for treatment or type of management intervention. **Outcomes in the very elderly (n=75):** No significant adverse effects associated with self-monitoring. A reduction in mortality was reported (HR=0.44, 95% CI, 0.20-0.98, p=0.04). **Time in therapeutic range**: There is no pooled analysis provided for this secondary outcome. At 90

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					days (1 trial), time in therapeutic range improved. At 1 year 4 trials demonstrated improvements associated with self-monitoring/self-testing, but 3 did not. Self-monitoring did tend to lead to an increase in number of tests taken.
Bloomfield et al. 2011 **USA** **Systematic review & meta-analysis**	NA	22 RCTs examining long-term (>3 months), oral anti-coagulation therapy with a vitamin K antagonist in adult outpatients. Only 2 studies were specific to individuals with AF. Mean age of study participants overall was 65 years (range = 42-75).	Trials compared therapy using patient self-testing (with or without self-management) vs. therapy managed by healthcare professionals (within traditional in clinical settings). 5 studies examined self-testing only (with dose adjustment made by a clinic) while 14 examined self-management interventions (testing and dose adjustment done by the participant). Usually, interventions included 2-4 group training sessions of 1-3 hours over a period of several weeks followed by home practice and a test to ensure competency prior to commencement of the intervention. Throughout the intervention, patients often had access to a 24-hour help telephone help line. Control groups (usual care) usually consisted of anticoagulation therapy/management in clinic, physician offices or primary care settings	Major thromboembolic complications (stroke, new or recurrent DVT, pulmonary embolism or arterial embolism), all-cause mortality and major bleeding events.	Warfarin was the most commonly used anti-coagulant therapy. Self-testing/management was associated with significantly reduced odds for major thromboembolic events (OR=0.58, 95% CI 0.45-0.75, p<0.001) and total mortality (OR=0.74, 95% CI 0.63-0.87, p<0.001) with no increased odds for major bleeding events (OR=0.89, 95% CI 0.75-1.05) There was no difference in the percentage of INRs in the therapeutic range between self-testing/self-management vs. usual care.
Garcia-Alamino et al. 2010	NA	18 RCTs (n=4,723) including both adult and pediatric	Trials compared self-monitoring or self-management of oral	**Primary outcomes:** Occurrence of thromboembolic events,	Data from 13 trials demonstrated that self-testing and management was associated with reduced risk for a thromboembolic event (RR = 0.50, 95% CI 0.36-0.69)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
UK **Cochrane Review**		patients on long-term anticoagulation therapy for a variety of indications (e.g. valve replacement, venous thromboembolism, atrial fibrillation). Two trials included only individuals treated for atrial fibrillation – 13 additional studies included individuals treated for any indication. Duration of studies varied from 2 months to over 24 months (mean = 12 months	anticoagulation vs. anticoagulation managed services, clinics or physicians	morality (all cause), major hemorrhages (defined as those requiring hospitalization or transfusion), time in and proportion of measurements in therapeutic range (INR) appropriate to each condition for which anti-coagulation therapy was being administered.	and for all-cause mortality (RR = 0.64, 95% CI 0.46-0.90). While trials that examined only self-management showed similarly significant reductions in risk of thromboembolic events and mortality, those that examined self-testing or monitoring did not (RR=0.57, 95% CI 0.32-1.0 for thromboembolism and RR=0.84, 95% CI 0.50-1.41 for mortality). 12/18 trials reported improvement in terms of the percentage of mean INR measurements falling within the therapeutic range.

Systematic Reviews of Novel Anticoagulants (vs. Warfarin)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
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%-	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 sub group 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		30% had experienced a previous stroke or TIA.			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** **Cochrane Review**	N/A	10 RCTs that examined long-term treatment (≥4 weeks duration) with factor Xa inhibitors with 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.	Interventions included Xa factor inhibitors: apixaban, betrixaban, darexaban, edoxaban, idraparinux or rivaroxaban vs. vs. oral vitamin K antagonists The majority of data was obtained from studies examining the efficacy of apixaban and rivaroxaban.	**Primary outcome:** Composite endpoint of all strokes and other embolic events. **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.	**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). 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.	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	**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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		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.	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 (ximelagatran) were excluded.		**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. 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Ntaios et al. 2012 **Greece** **Systematic Review & Meta-analysis**	N/A	3 RCTs (n=14,527) 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.	The included trials were: RE-LY, 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.	**Primary outcome:** 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.	**Stroke or systemic embolism**: There was a 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).

Landmark Trials Associated with Novel Anticoagulants

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Dabigatran Extilate (direct thrombin inhibitor)					
Connolly et al. 2009 **International** **RCT** ***Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY trial)***	CA: ☑ Blinding: Patient* ☒ Therapist* ☒ Assessor ☑ ITT:☑ **though not blinded to therapy, pts. and therapists were blinded to dose of dabigatran*	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 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.	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 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.	**Primary outcomes:** Stroke or systemic embolism (efficacy), major hemorrhage (safety). **Secondary outcomes**: Any stroke, myocardial infarction, and death. Net clinical benefit outcome was estimated using the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding.	**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 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	Per original study	N=5,891. 2,937 participants were enrolled in the 150	Participants assigned to either of the dabigatran dosing schedules in the original RE-LY trial were	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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
RE-LY trial, Long term follow-up (RELY-ABLE)		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% 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.	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. 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.		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. **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	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	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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		vitamin K naïve, compared to patients with no previous history of stroke (regardless of group assignment)	150 mg dabigatran group and 1195 were randomized to the warfarin group.		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 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)					
Giugliano et al. 2013 **International** **RCT** ***The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 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)	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	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
(ENGAGE AF-TIMI 48)		Approximately 28% reported prior stroke or TIA	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.		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 **International** **RCT ENGAGE AF-TIMI 48 (sub group analysis)**	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	As above	Comparison between patients with previous stroke or TIA (n=5,973) and those with no previous history (n=15,132)	As above	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 (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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					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 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					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 Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)***	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 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.	**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 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 **ROCKET-AF** **subgroup analysis (previous stroke or TIA)**	Per original study protocol	7468 (52%) patients had a previous stroke or TIA. Patients with previous stroke were younger, had a lower BMI, and were less likely to have HTN, CHF, or diabetes.	Among patients with previous stroke or TIA, 3754 were randomized to receive rivaroxiban and 3714 to receive warfarin	Per original study protocol	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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Connolly et al. 2011 **International** **RCT** ***Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES)***	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 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.	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), 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 **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%	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	**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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
		of vitamin K antagonist naïve patients was encouraged. Mean age was 70 years in both groups. 35% of participants was female. Approximately 19% of individuals assigned to each condition had a history of previous stroke or TIA.	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 median of 66% of the time over the course of the study.		**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, 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).
Easton et al. 2012 **ARISTOTLE subgroup analysis (previous stroke or TIA)**	Per original study protocol	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		Per original study protocol	In the subgroup of patients with previous stroke or TIA, 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).

CA: concealed allocation; ITT: intention-to-treat

Novel Anticoagulants (vs. each other)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Rasmussen et al. 2012 **Review and Indirect comparison analysis**	NA	Phase III clinical 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%.	Indirect comparison analysis of 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.	**Primary outcomes:** Stroke/systemic embolism, ischaemic/uncertain stroke, hemorrhagic stroke, death (any cause), MI **Safety outcomes**: major bleeding, intracranial bleeding	*Secondary Prevention* **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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
					Apixaban vs. Dabigatran: Compared to dabigatran 110 mg, apixaban was associated with a reduced risk in disabling or fatal stroke (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 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 **USA** **RCT** ***Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT)***	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☑	425 patients ≥18 years, from 33 centres with a clinical indication for aortic 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.	Patients were randomized to receive lower-dose warfarin (test group: target 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.	**Primary outcomes:** Major bleeding events, minor bleeding events, total bleeding events, TIA, stroke, any neurological event	Mean duration of follow-up was 3.82 years. >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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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 Pharmokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN)***	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 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.	**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. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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 **Germany** **RCT** ***Early Self-controlled Anticoagulation Trial (ESCAT II)***	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☒	2,673 patients ≥18 years from 6 centres who had undergone heart valve replacement surgery (mitral, aortic, and/or tricuspid). Mean age was 60 years, 71% were male.	Patients were randomized to a low-dose group oral anticoagulation (INR targets 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.	Thromboembolic events that required hospitalization, bleeding events	532 patients terminated the study early. 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bioprosthetic Valve Replacement					
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 surgery, comorbidity and calendar year	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 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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
Paciaroni et al. 2015 **UK** **Italy** **Prospective study** ***Early Recurrence and cerebral bleeding in patients with acute ischemic stroke and Atrial Fibrillation (RAF)***	NA	1,029 patients 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 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.	**Primary outcome:** Composite of stroke, TIA, symptomatic systemic embolism, symptomatic cerebral bleeding, and major extracerebral bleeding at 90 days.	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 times from index stroke to recurrent ischemic stroke was 34 days. Significantly fewer patients treated with oral anticoagulants had an outcome 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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					95% CI 0.30–0.93, *p*=0.025 and HR=0.43, 95% CI 0.19–0.97, p=0.043, respectively).
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, factor Xa inhibitors and specific thrombin inhibitors Two studies examined treatment with oral vitamin K antagonist	**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 period or during long-term follow-up	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)

Left Atrial Appendage Devices vs Warfarin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Holmes et al. 2014 **USA** **RCT** ***Prospective Randomized Evaluation of the Watchman LAA***	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	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	**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	Mean duration of follow-up was 11.8 months. Primary efficacy end-point: 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-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial		characteristics: women ≥75 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.	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. Patients in the control group received warfarin with a target INR of 2.0-3.0.	systemic embolism, 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	month event rates were 0.0253 for the device 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)

Reference List

Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, Reddy P, Wilt TJ: Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011; 154:472-482.

Bruins Slot KMH, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD008980. DOI: 10.1002/14651858.CD008980.pub2.

Chen J, Zhuang X, Long M, Su C, Wang L. Efficacy and Safety of Edoxaban in Nonvalvular Atrial Fibrillation: A Meta-analysis of Randomized Controlled Trials. *J Stroke Cerebrovasc Dis* 2015; 24(12);.2710-2719.

Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, et al: Apixaban in Patients with Atrial Fibrillation. *New Engl J Med* 2011; 364:806-817.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al: Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *New Engl J Med* 2009; 361:1139-1151.

Connolly SJ, Wallentin L, Ezekowitz MD, Eikelboom J, Oldgren J, Reilly PA, Brueckmann M, Pogue J, Alings M, Amerena JV, et al: The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. *Circulation* 2013;128:237-243.

Cumberworth A, Mabvuure NT, Hallam MJ, Hindocha S: Is home monitoring of international normalised ratio safer than clinic-based monitoring? *Interact Cardiovasc Thorac Surg* 2013;6:198-201.

Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S: Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation* 2013; 127:634-640.

* De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *Eur Heart J 2014*;35(47):3328-3335.

* Di Biase L. Use of Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Lesions. *J Am Heart Assoc.* 2016;8;5(2). pii: e002776.

Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di PG, Yusuf S: Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010;9:1157-1163.

Dogliotti A, Paolasso E, Giugliano RP: Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. *Clin Cardiol 2013*; 36:61-67.

Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, Alings M, Goto S, Lewis BS, Rosenqvist M, Hanna M, Mohan P, Alexander JH, Diener HC: Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;11:503-511.

Eikelboom JW, Connolly SJ, Brueckmann M et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med 2013*;369(13):1206-1214.

Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, Heneghan CJ. Self-monitoring and self-management of oral anticoagulation. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD003839. DOI: 10.1002/14651858.CD003839.pub2.

Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al: Apixaban versus Warfarin in Patients with Atrial Fibrillation. *New Engl J Med* 2011; 365:981-992.

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM: Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med 2013*;369:2093-2104.

Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M: Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370:2467-2477.

Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, Diener HC, Donnan GA, Halperin JL, Mahaffey KW, Mas JL, Massaro A, Norrving B, Nessel CC, Paolini JF,

Roine RO, Singer DE, Wong L, Califf RM, Fox KA, Hacke W: Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;11:315-322.

Hart RG, Pearce LA, Aguilar MI: Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Ann Intern Med 2007*; 146:857-867.

Hart RG, Pearce LA, Koudstaal PJ. Transient ischemic attacks in patients with atrial fibrillation: implications for secondary prevention: the European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III trial. *Stroke* 2004;35(4):948-951.

Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, Bradford K, Tyndel S, Alonso-Coello P, Ansell J, et al: Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *The Lancet* 2012, 379:322-334.

Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. *Stroke 2013*;44(9):2525-2531.

Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P, Protect AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374(9689):534-42.

Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;64(1):1-12.

Hori M, Matsumoto M, Tanahashi N et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. *Circ J* 2012;76(9):2104-2111.

Koertke H, Zittermann A, Tenderich G et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007;28(20):2479-2484.

Kwong JS, Lam YY, Yan BP, Yu CM: Bleeding of new oral anticoagulants for stroke prevention in atrial fibrillation: a meta-analysis of randomized controlled trials. *Cardiovasc Drugs Ther* 2013; 27:23-35.

* Macle L, Cairns JA, Andrade JG, Mitchell LB, Nattel S, Verma A. The 2014 Atrial Fibrillation Guidelines Companion: A Practical Approach to the Use of the Canadian Cardiovascular Society Guidelines. *Can J Cardiol 2015*;31(10):1207-1218.

Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370(9586):493-503.

Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD003464. DOI: 10.1002/14651858.CD003464.pub2.

Merie C, Kober L, Skov OP et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA* 2012;308(20):2118-2125.

Morocutti C, Amabile G, Fattapposta F, Nicolosi A, Matteoli S, Trappolini M, Cataldo G, Milanesi G, Lavezzari M, Pamparana F, Coccheri S: Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA (Studio Italiano Fibrillazione Atriale) Investigators. *Stroke* 1997;28:1015-1021.

Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P: Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012; 43:3298-3304.

Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, Csiba L. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation. *Stroke 2*015 ;46(8):2175-82.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.

New Eng J Med 2011; 365:883-891.

Puskas J, Gerdisch M, Nichols D et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg* 2014;147(4):1202-1210.

Rasmussen LH, Larsen TB, Graungaard T, Skjoth F, Lip GY: Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. *BMJ (Clinical research ed)* 2012;345:e7097.

Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L: Warfarin anticoagulation and outcomes in patients with atrial fibrillation*: A systematic review and metaanalysis. *CHEST Journal* 2004, 126:1938-1945.

Rost NS, Giugliano RP, Ruff CT, et al. Outcomes With Edoxaban Versus Warfarin in Patients With Previous Cerebrovascular Events: Findings From ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). *Stroke* 2016;47(8):2075-2082.

Sandercock PAG, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database of Systematic Reviews 2015*, Issue 3. Art. No.: CD000024. DOI: 10.1002/14651858.CD000024.pub4.

Sanna T, Diener HC, Passman RS, Di L, V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J: Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med 2014*;370:2478-2486.

Saxena R, Koudstaal PJ. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD000187. DOI: 10.1002/14651858.CD000187.pub2.

Torella M, Torella D, Chiodini P et al. LOWERing the INtensity of oral anticoaGulant Therapy in patients with bileaflet mechanical aortic valve replacement: results from the "LOWERING-IT" Trial*. Am Heart J 2010*;160(1):171-178.

Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F, Messerschmid A. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF RANDOMISED): an open-label randomised controlled trial. *Lancet Neurol* 2017;16(4):282-90.

Yong JH, Thavorn K, Hoch JS, et al. Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke. *Stroke 2016*;47(9):2380-2385.

Xian Y, Wu J, O'Brien EC et al. Real world effectiveness of warfarin among ischemic stroke patients with atrial fibrillation: observational analysis from Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. *BMJ* 2015;351:h3786.

(*publications included in evidence summary but not included in evidence tables)