CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Other Cardiac Issues in Individuals with Stroke*

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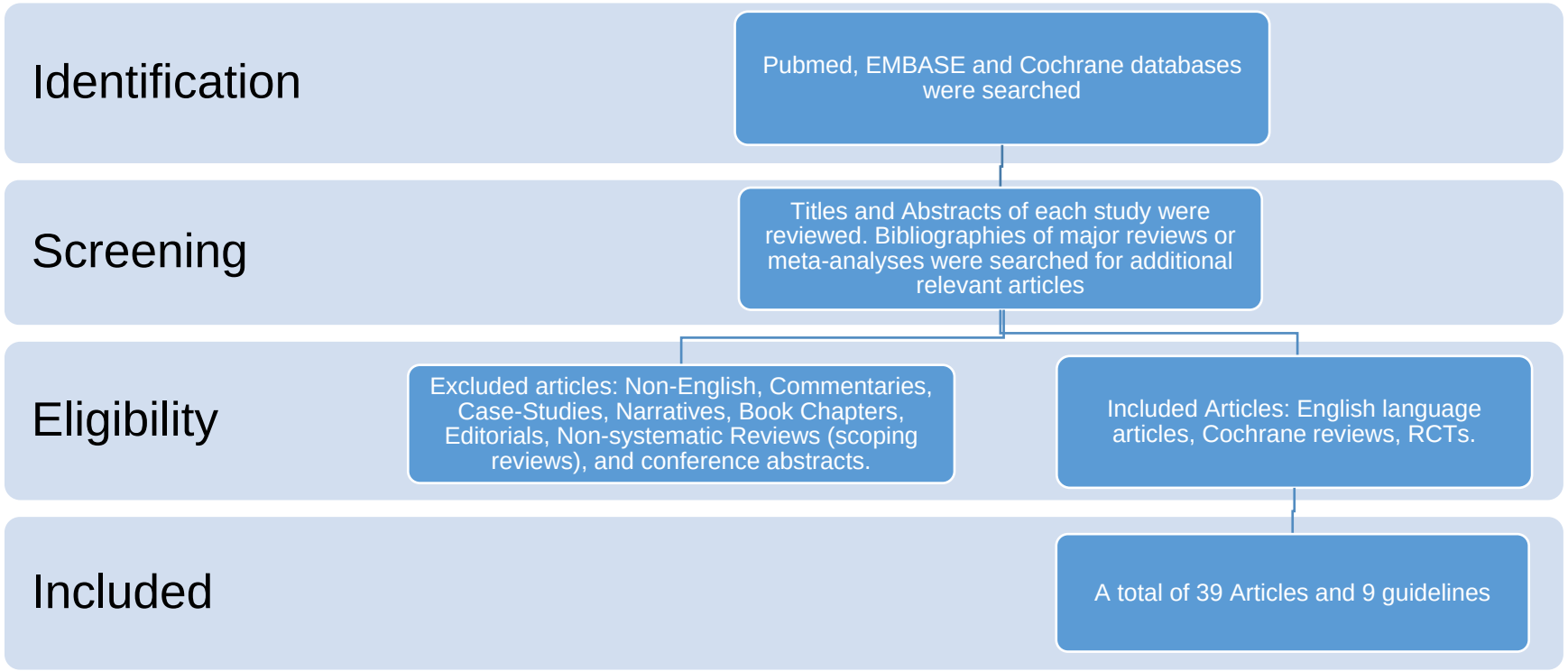
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

Table of Contents

Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were searched for potentially relevant articles. The title and abstract of each article was reviewed for relevance. Bibliographies were reviewed to find additional 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. A total of 39 articles and 9 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.** **(selected)**	Patients with rheumatic mitral valve disease who have been treated with warfarin, routinely combining with antiplatelet therapy after ischaemic stroke or TIA is not recommended (class III, level of evidence C). However, aspirin antiplatelet therapy can be added when ischaemic stroke or TIA still occurs during the treatment of sufficient amount of warfarin (class IIa, level of evidence B). Patients with ischaemic stroke or TIA with nonrheumatic mitral valve disease or other valve diseases (local aortic arch, mitral annulus calcification, mitral valve prolapse, etc) without atrial fibrillation may consider antiplatelet therapy (class IIa, level of evidence B). For patients with ischaemic stroke or TIA and mechanical artificial heart valve, long-term warfarin oral anticoagulation therapy is recommended (INR 2/5–3.5) (class IIa, level of evidence B). It is suggested that any decision on PFO closure should be made jointly by neurologists and cardiologists (class I, level of evidence A). Before PFO closure, other known causes of ischaemic stroke (including monitoring arrhythmias) should be carefully excluded. The possibility of PFO correlation with the stroke, risk factors and lifestyle changes should be assessed. And communication between patients and multidisciplinary clinical teams should be involved in making the decision. For ischaemic stroke caused by PFO, PFO closure can be performed to reduce the risk of stroke recurrence (class I, level of evidence A).
Messe S, Gronseth G, Kent, D. et al. **Practice advisory update summary: Patent foramen ovale and secondary stroke prevention Report of the Guideline Subcommittee of the American Academy of Neurology** ***Neurology* 2020;94(20):876-885.**	Analysis of evidence *In patients with a PFO who have had a cryptogenic ischemic stroke, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone?* When using a modified GRADE process, the overall confidence in the evidence for PFO closure efficacy was judged moderate, given the consistent Class II evidence. *In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does anticoagulation reduce the risk of stroke recurrence compared with antiplatelet medication?* With use of the AAN's modified GRADE process, the evidence was anchored at moderate confidence for this question but was then downgraded to low confidence because of imprecision. 12 guidance statements are included related to assessment and patient selection prior to PFO procedure; 5 statement are included related to risk/benefits and the role of shared decision making, and 2 statements related to indications for long-term antithrombotic use.
Ahmed N, Audebert H, Turc G, et al. **Consensus statements and recommendations from the ESO-Karolinska Stroke Update**	**Q1. Does percutaneous closure of PFO versus antiplatelet therapy reduce the risk of stroke recurrence?** Recommendation: In patients aged 18–60 years old with cryptogenic stroke/TIA and with high risk PFO features (moderate or severe shunt, atrial septal aneurysm (ASA), atrial septal hypermobility) we recommend percutaneous closure plus medical therapy instead of antiplatelet therapy alone (Grade A). In patients between 60 and 65 years, percutaneous closure plus medical therapy instead of antiplatelet therapy alone can be offered (Grade B).

Guideline	Recommendations
Conference, Stockholm 11–13 November 2018. ***European Stroke Journal* 2019; 4: 307-317. DOI: 10.1177/2396987319863606.** **(selected)**	Percutaneous closure plus medical therapy can be considered in place of antiplatelet therapy alone also for patients aged 65 years old on an individual basis (Grade C). **Q2: Does percutaneous closure of PFO versus oral anticoagulants reduce the risk of stroke recurrence?** Recommendation: Based on the few available data, percutaneous closure and Oral anticoagulation (OAC) therapy seem to perform equally (Grade C). Therefore, while waiting for further evidence and based on the superiority of percutaneous closure over medical therapy as a whole, patient engagement in the choice becomes pivotal. Adequately dimensioned randomised clinical trials addressing the comparison between percutaneous closure plus medical therapy versus OAC (vitamin-K antagonists or direct OAC) in carefully characterised patients with cryptogenic cerebrovascular accident and different risk characteristics, should be performed. **Q3: Does oral anticoagulant therapy versus antiplatelet therapy reduce the risk of stroke recurrence?** Recommendation: In patients in whom a medical therapy only is chosen, we recommend to choose the specific drugs weighing the individual risk of bleeding against the risk of PFO-related stroke recurrence, in close connection with the patient. Long-term OAC with vitamin K antagonists (VKAs) may be preferred if: (a) the patient has a low haemorrhagic risk, (b) a probable good therapeutic compliance is foreseen and (c) a proper anticoagulant monitoring can be guaranteed (Grade B). We recommend to perform adequately dimensioned head-to-head randomised clinical trials addressing the comparison between single antiplatelet drugs versus OAC (vitamin-K antagonists or Direct oral anticoagulants (DOAC)) in patients in which percutaneous closure has been excluded. **Q4**: In patients with non-valvular AF and previous ischaemic stroke or TIA, does left atrial appendage closure reduce risk of recurrent stroke or thromboembolism compared to oral anticoagulant treatment? **Q5**: In patients with non-valvular AF and previous ischaemic stroke or TIA, does left atrial appendage closure lead to lower risk of serious adverse events compared to oral anticoagulant treatment? **Q6:** In patients with non-valvular AF and previous ischaemic stroke or TIA submitted to left atrial appendage closure, does antiplatelet treatment reduce risk of thrombus formation on the device compared to oral anticoagulant treatment? Recommendation: Patients with non-valvular AF and previous ischaemic stroke or TIA with high risk of bleeding or other contraindications to OAC should be included in randomised controlled trials if possible (Grade C). Waiting for RCTs, LAA closure might be considered in selected patients with absolute contraindications to OAC/DOAC (Grade C). LAA closure is safer than OAC in terms of risk of bleeding in the long term, but is less safe in term of short-term complications. In case of LAA closure in patients at very high risk of intra- and/or extra-cranial bleeding, post-procedural aspirin as single antithrombotic therapy for at least six months or lifelong may be used (Grade C). **Oral anticoagulation and reversal agents after stroke** **Q1: In patients with ICH and oral anticoagulation, how is optimal reversal under VKAs or novel oral anticoagulants (NOAC) achieved to improve outcomes (mortality and functional outcome); specifically, in ICH to reduce haematoma growth?** Recommendation: In acute ICH, reversal of anticoagulation should be started as soon as possible after diagnosis of ICH (Grade B: VKA; Grade C: NOAC). In VKA–ICH, optimal reversal is achieved by immediate application of four-factor Prothrombine complex concentrate (PCC) (30 IU/kg): • If INR ≥ 2.0 (Grade B).

Guideline	Recommendations
	• If INR ≥ 1.3 but <2.0, a dose reduction to 10–25 IU/kg (dose depending on the INR) can be considered. (Grade C). In VKA–ICH, the target INR after reversal is <1.3 (Grade B). In VKA–ICH, INR should be monitored serially to trigger possible rescue therapy (repeated PCC application) (Grade C). In VKA–ICH, all reversal treatments should be accompanied by Vitamin K administration (10 mg, i.v.; repeated doses depending on results of sequential INR measurements) (Grade C). In NOAC–ICH, reversal treatment should not be delayed by waiting for results of coagulation test (Grade C).
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**PFO** Strong Recommendation Patients with ischaemic stroke or TIA and PFO should receive optimal medical therapy including antiplatelet therapy or anticoagulation if indicated Weak Recommendation AGAINST Routine endovascular closure of patent foramen ovale is not recommended. Endovascular closure may be reasonable in highly selected young ischaemic stroke patients after thorough exclusion of other stroke aetiologies. Change (7/11/2019) Percutaneous PFO closure recommended in ischaemic stroke patients aged <60 when the PFO is considered the likely cause of stroke after other aetiologies have been thoroughly excluded. **Cervical Artery Dissection** Strong Recommendation Patients with acute ischaemic stroke due to cervical arterial dissection should be treated with antithrombotic therapy. There is no clear benefit of anticoagulation over antiplatelet therapy.
National Clinical Guideline for Stroke. 5th Edition. 2016 Intercollegiate Stroke Working Party, London UK	**PFO** A-People with ischaemic stroke or TIA and a patent foramen ovale should receive optimal secondary prevention, including antiplatelet therapy, blood pressure treatment, lipid lowering therapy and lifestyle modification. Anticoagulation is not recommended unless there is another recognised indication. B- People with stroke or TIA and patent foramen ovale should not be routinely offered device closure except in the context of a clinical trial or prospective register. **Cardioembolism** People with stroke or TIA should be investigated with transthoracic echocardiography if the detection of a structural cardiac abnormality would prompt a change of management and if they have: − clinical or ECG findings suggestive of structural cardiac disease that would require assessment in its own right, or − unexplained stroke or TIA, especially if other brain imaging features suggestive of cardioembolism are present. **Vertebral artery disease**

Guideline	Recommendations
	People with ischaemic stroke or TIA and symptomatic vertebral artery stenosis should receive optimal secondary prevention including antiplatelet therapy, blood pressure treatment, lipid lowering therapy and lifestyle modification. Angioplasty and stenting of the vertebral artery should only be offered in the context of a clinical trial. **Intracranial artery stenosis** People with ischaemic stroke or TIA due to severe symptomatic intracranial stenosis should be offered dual antiplatelet therapy with aspirin and clopidogrel for the first three months in addition to optimal secondary prevention including blood pressure treatment, lipid-lowering therapy and lifestyle modification. Endovascular or surgical intervention should only be offered in the context of a clinical trial.
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.**	**PFO** 1. There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO *(Class IIb; Level of Evidence B*). 2. For patients with an ischemic stroke or TIA and PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*. (Revised recommendation) 3. For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (Class I; Level of Evidence A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa; Level of Evidence C). (New recommendation) 4. For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A). (Revised recommendation) 5. In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C). (New recommendation) **Cardiomyopathy** 1. In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus demonstrated by echocardiography or another imaging modality, anticoagulant therapy with a VKA is recommended for ≥3 months (Class I; Level of Evidence C). (New recommendation) 2. In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) is reasonable in the absence of major contraindications (eg, active gastrointestinal bleeding) (Class IIa; Level of Evidence C). (New recommendation) 3. In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized (Class IIb; Level of Evidence B). (Revised recommendation) 4. In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke (Class IIb; Level of Evidence C). (New recommendation) **Prosthetic Heart Valve Recommendations** 1. For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0–3.0) (Class I; Level of Evidence B). (Revised recommendation) 2. For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5–3.5) (Class I; Level of Evidence C). (New recommendation)

Guideline	Recommendations
	3. For patients with a mechanical mitral or aortic valve who have a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/d to VKA therapy is recommended (Class I; Level of Evidence B). (New recommendation) 4. For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/d or increasing the target INR, depending on bleeding risk (Class IIa; Level of Evidence C). (Revised recommendation) 5. For patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before its insertion, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin 75 to 100 mg/d is recommended in preference to long-term anticoagulation (Class I; Level of Evidence C). (New recommendation) 6. For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite adequate antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered (Class IIb; Level of Evidence C). (Revised recommendation)
Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. **2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** ***J Am Coll Cardiol* 2014; 63:2438–88.**	**Prosthetic Heart Valves** CLASS I 1. Anticoagulation with a VKA and international normalized ratio (INR) monitoring is recommended in patients with a mechanical prosthetic valve. (Level of Evidence: A). 2. Anticoagulation with a VKA to achieve an INR of 2.5 is recommended in patients with a mechanical AVR (bileaflet or current-generation single tilting disc) and no risk factors for thromboembolism. (Level of Evidence: B) 3. Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical AVR and additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage). (Level of Evidence: B) 4. Anticoagulation with a VKA is indicated to achieve an INR of 3.0 in patients with a mechanical MVR. (Level of Evidence: B) 5. Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with a VKA in patients with a mechanical valve prosthesis. (Level of Evidence: A) CLASS IIa 1. Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve. (Level of Evidence: B) 2. Anticoagulation with a VKA is reasonable for the first 3 months after bioprosthetic MVR or repair to achieve an INR of 2.5. (Level of Evidence: C) CLASS IIb 1. Anticoagulation, with a VKA, to achieve an INR of 2.5 may be reasonable for the first 3 months after bioprosthetic AVR. (Level of Evidence: B) 2. Clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily. (Level of Evidence: C) CLASS III Harm 1. Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses. (Level of Evidence: B)
Whitlock RP, Sun JC, Fremes SE, Rubens FD and Teoh KH.	**PFO** 6.2.1. In patients with asymptomatic PFO or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C). 6.2.2. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A).

Guideline	Recommendations
Antithrombotic and Thrombolytic Therapy for Valvular Disease **Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines** ***CHEST 2012*; 141(2)(Suppl):e576S–e600S**	6.2.3. In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C). **Prosthetic Heart Valves** 8.2.3. In patients with a bioprosthetic valve in the mitral position, we suggest VKA therapy (target INR, 2.5; range, 2.0-3.0) over no VKA therapy for the first 3 months after valve insertion (Grade 2C). 8.3. In patients with bioprosthetic valves in normal sinus rhythm, we suggest aspirin therapy over no aspirin therapy after 3 months postoperative (Grade 2C). **Mechanical Heart Valves** 9.2. In patients with mechanical heart valves, we recommend VKA therapy over no VKA therapy for long-term management (Grade 1B). 9.5. In patients with mechanical heart valves in both the aortic and mitral position, we suggest target INR 3.0 (range 2.5-3.5) over target INR 2.5 (range 2.0-3.0) (Grade 2C). 9.6. In patients with a mechanical mitral or aortic valve at low risk of bleeding, we suggest adding over not adding an antiplatelet agent such as low-dose aspirin (50-100 mg/d) to the VKA therapy (Grade 1B) 9.7. For patients with mechanical aortic or mitral valves we recommend VKA over antiplatelet agents (Grade 1B).
Lansberg, M. G., O'Donnell, M. J., Khatri, P., Lang, E. S., Nguyen-Huynh, M. N., Schwartz, N. E. & Alonso-Coello, P. **Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines.** ***Chest.* 2012 Feb;141(2 Suppl):e601S-e636S**	**Timing of Resumption of Anticoagulation Following Ischemic Stroke** "*Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset. Earlier anticoagulation can be considered for patients at low risk of bleeding complications (eg, those with a small infarct burden and no evidence of hemorrhage on brain imaging). Delaying anticoagulation should be considered for patients at high risk of hemorrhagic complications (eg, those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).*"
Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM,	**Aortic Arch Atheroma** Class IIa 1. Treatment with a statin is a reasonable option for patients with aortic arch atheroma to reduce the risk of stroke. (Level of Evidence: C)

Guideline	Recommendations
Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. **2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine.** ***Circulation 2010*;121:1544 – 1579. (selected)**	Class IIb 1. Oral anticoagulation therapy with warfarin (INR, 2.0 to 3.0) or antiplatelet therapy may be considered in stroke patients with aortic arch atheroma 4.0 mm or greater to prevent recurrent stroke. (Level of Evidence: C)

Evidence Tables

Prevalence of Patent Foramen Ovale & Association with Increased Risk of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mazzucco et al. 2018 **UK** **Prospective study**	NA	572 consecutive participants of the OXVASC study, recruited between 2014 and 2017, with minor stroke or TIA. Mean age was 70 years. 77% of patients were >60 years.	The prevalence of any right-to-left shunt (RLS), and of large RLS (>20 microbubbles), was assessed using contrast-enhanced transcranial Doppler (bubble-TCD) during an outpatient visit to an urgent TIA clinic visit or 1 month after hospitalization. The frequency of RLS (probable PFO) was compared between cryptogenic events and those of known cause. A systematic review was also conducted.	Prevalence of PFO	Bubble-TCD was feasible in 523 (91%) patients, of whom 397 (76%) were >60 years and 264 (50%) had cryptogenic events. RLS was found in 157 (30%) patients, and large RLS in 68 (13%) patients. The odds of any RLS in persons with cryptogenic events was significantly higher compared with those of known cause (OR=1·93, 95% CI 1·32-2·82, p= 0·001) and higher in those >60 years (OR=2·06, 95% CI 1·32–3·23, p=0·001). Using the results from 3 studies that used bubble TCD, identified in the systematic review, the odds of any RLS were increased significantly in persons of any age and older persons with cryptogenic events compared with those with events of known cause (OR=3·11, 95% CI 1·53–6·34, p=0.002 and OR=2·35, 95% CI 1·42–3·90, p=0.0009, respectively). Using the results from the same 3 studies, the overall prevalence of PFO, regardless of screening method or etiology was 0.27, 95% CI 0.20-0.33), which was higher than in the 5 studies based on transoesophageal echocardiography (0.17, 95% CI 0.13-0.23).
Katsanos et al. 2014 **Greece**	NA	14 prospective studies including 4,251 patients with and without PFO who had experienced a cryptogenic recurrent ischemic stroke or TIA,	The risk of recurrent stroke in medically treated with PFO was compared with patients who had suffered a cryptogenic stroke without PFO. PFO was	Recurrent ischemic stroke, TIA	The mean duration of follow-up ranged from 3-66 months. The risk of recurrent stroke was not significantly increased among patients with PFO (RR=0.85, 95% CI 0.59-1.22). Results from 8 studies included

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & Meta-analysis		referred to an urgent TIA clinic.	diagnosed using echocardiography or transcranial Doppler		The risk of recurrent stroke or TIA was not significantly increased among patients with PFO (RR=1.18, 95% CI 0.78-1.79). Results from 5 studies included. The risk of recurrent stroke was not significantly increased among patients with moderate-large shunt compared with small shunt (RR=1.43, 95% CI 0.60-3.40, p=0.42).
Di Tullio et al. 2007 **USA** **Prospective study**	NA	1,100 community-dwelling, stroke-free participants ≥ 39 years, included in the Northern Manhattan Study (NOMAS), recruited from 1993-1999. Mean age was 68.7 years, 58% were female.	Transthoracic echocardiography with contrast injection as part of NOMAS at baseline. Participants were contacted annually by telephone. Any mention of a vascular event triggered an in-person interview, and seen by a neurologist if stroke was suspected.	Prevalence of PFO, stroke incidence	PFO prevalence was 14.9% Mean duration of follow-up was 80 months. Ischemic stroke occurred in 68 participants (6.2%). Stroke incidence was 12.2 per 1,000 person-years in those with a PFO and 8.9 per 1,000 person-years in those without it (p=0.5). After adjustments for other stroke risk factors, the risk of stroke given the presence of PFO was not significantly increased (HR= 1.79, 95% CI 0.93-3.45).
Meissner et al. 1999 **US** **Prospective study**	NA	588 participants ≥45 years recruited from the general population who were participants of the Stroke Prevention: Assessment of Risk in a Community (SPARC) study. Individuals with dementia, severe disability, and/or terminal illness were excluded. Mean age was 67 years, 50% were male.	Transesophageal echocardiography (including 2-dimensional, color flow, and Doppler imaging with biplane or multiplane transduces) was used to detect the presence of PFOs.	Prevalence of PFO	Of the 581 patients who underwent transesophageal echocardiography, 148 (25.6%) were found to have a PFO. Of those with a PFO, 46% had a defect ≥1mm in size, 57% had shunts at rest, and 92% had shunts with maneuvers.
Steiner et al. 1998	NA	95 patients >39 years with first acute ischemic stroke.	Patients were examined by the study neurologist within one week of the	Prevalence of PFOs	Of the 95 patients who underwent transesophageal echocardiography, 31 (33%) were found to have a PFO.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
US **Prospective study**			index stroke event. Data was collected through in-person interview and hospital record review. Diagnosis of PFOs were based on findings from contrast studies.		PFOs were significantly more frequent in patients with cryptogenic stroke compared to those with a known cause of stroke (45% vs 23%, p=0.02).

Antiplatelet vs. Anticoagulation Therapy for Prevention of Recurrent Stroke in Persons with PFO

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sagris et al. 2019 **Greece** **Systematic review & meta-analysis**	Risk of bias was assessed as low in 2 trials	5 RCTs (n= (1,720) including patients with stroke or TIA of undetermined cause and medically treated PFO	Trials compared anticoagulant vs. antiplatelet treatment. Anticoagulants included warfarin, dabigatran and rivaroxaban. The majority of trials used aspirin only as the antiplatelet (100 mg or 32.5 mg), while a small percentage of patients in the CLOSE trial used dual antiplatelet therapy (2.6%) or clopidogrel (10.8%).	**Primary outcomes:** Stroke recurrence, major bleeding, and the composite of stroke recurrence or major bleeding	Mean duration of follow-up was 2.3 years. There were 33 stroke recurrences among anticoagulant-assigned patients (1.73 per 100 patient-years) and 49 among antiplatelet-assigned patients (2.39 per 100 patient-years. The risk of stroke recurrence was not significantly different between groups (HR=0.68; 95% CI, 0.32–1.48). The rate of major bleeding was not significantly different between groups (1.16 per 100 patient-years in anticoagulant-assigned patients vs. 0.68 in antiplatelet-assigned patients (HR=1.61; 95% CI, 0.72–3.59). The composite outcome occurred in 52 anticoagulant-assigned and 54 antiplatelet-assigned patients (OR=1.05; 95% CI, 0.65–1.70).
Kasner et al. 2018 **Canada/ International** **RCT** ***New Approach Rivaroxaban Inhibition of***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	7,213 patients ≥50 years, recruited from 459 centers in 31 countries who had an ischemic, non-lacunar stroke of undetermined source, 7 days to 6 months previously, that was not associated with extracranial vessel	Patients were randomized 1:1 to receive 15 mg rivaroxaban + aspirin placebo or 100 mg of enteric coated aspirin + rivaroxaban placebo for the duration of the trial.	**Primary efficacy outcome:** First recurrent stroke (ischemic, hemorrhagic, or undefined stroke) or systemic embolism **Primary safety outcome:**	The trial was terminated early due to an excess risk of bleeding among patients in the rivaroxaban group and an absence of benefit. The trial was planned to recruit until at least 450 events of the primary efficacy outcome had occurred. Median duration of follow-up was 11 months. The median time from the qualifying stroke to randomization was 37 days.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) subgroup analysis **(Full results are presented in the antiplatelet section)**		atherosclerosis causing ≥50% stenosis in arteries supplying the area of ischemia or with an identified cardioembolic source. Mean age was 67 years, 62% were men. Median NIHSS score was 1.	For this analysis, the outcomes of persons with and without PFO detected, were compared.	Major bleeding at any site in the body	The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR=1.07; 95% CI, 0.87 to 1.33; p=0.52). The risk of the primary safety outcome was significantly increased among patients in the rivaroxaban group (annual rate 1.8 vs. 0.7, HR=2.72, 95% CI 1.68–4.39, p <0.001). The risks of life-threatening and clinically relevant bleeding and intracerebral hemorrhage were significantly increased among patients in the rivaroxaban group. A total of 1% of the patients were lost to follow-up after a mean of 15 months, and an additional 1% of patients withdrew consent for follow-up after a mean of 5 months. **PFO vs. No PFO** PFO was detected in 534 participants following transthoracic echocardiography (TTE) or transoesophageal echocardiography (TOE). Patients with PFO were younger, had a lower burden of traditional vascular risk factors, and had less severe strokes than did those without PFO. Among persons with known PFO, the rate of recurrent stroke was non-significantly lower among persons randomized to rivaroxaban (2.6 vs. 4.8 events/100 person- years, HR= 0·54, 95% CI 0·22-1·36). Among persons without known PFO, the rate of recurrent stroke was similar between those receiving rivaroxaban vs. aspirin (4.9 vs. 4.6

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					events/100 person-years, HR=1·06, 95% CI 0·84-1·33). The risks of major bleeding with rivaroxaban vs. aspirin were similar in patients with and without PFO detected. **Systematic review & meta-analysis** The results from the present trials plus 2 additional trials (CLOSE and PICSS) were pooled. The risk of recurrent stroke was significantly lower in persons treated with rivaroxaban (OR=0·48, 95% CI 0·24–0·96, p=0.04).
Homma et al. 2002 **USA** **RCT** ***PFO in Cryptogenic Stroke Study (PICSS)***	CA: ☒ Blinding: Patient: ☑ Assessor ☑ ITT: ☒	630 patients 30-85 years who had experienced ischemic stroke within the previous 30 days and had Glasgow Outcome Scale scores ≥3 and who underwent transesophageal echocardiography (TE) to identify PFO. Mean age was 59 years. 41.6% of strokes were cryptogenic.	Patients were randomized 1:1 to receive warfarin (adjusted to maintain an INR of 1.4-2.8) or 325 mg aspirin daily for the duration of the trial.	**Primary outcome:** Recurrent ischemic stroke or death from any cause **Safety outcomes:** Major or minor bleeding	PFO was present in 203 (33.8%) of the patients, of which 58.6% (119/203) were classified as small and 41.4% (84/203) as large. After 2 years of follow-up, there was no significant difference in the time to primary end points between those with and those without PFO in the overall population (HR= 0.96; 95% CI 0.62 to 1.48; 2-year event rates 14.8% vs 15.4%) or in the cryptogenic subset (HR=1.17; 95% CI 0.60 to 2.37; 2-year event rates 14.3% vs. 12.7%). Among persons in the entire PICSS cohort with PFO (n=203), the risk of the primary outcome did not differ between treatment groups (16.5% warfarin vs. 13.2% aspirin; HR=1.29, 95% CI 0.63–2.64, p= 0.49). Among persons in the cryptogenic cohort with PFO (n=98), the risk of the primary outcome did not differ between treatment groups (9.5% warfarin vs. 17.9% aspirin; HR= 0.52, 95% CI 0.16–1.67, p=0.16).

Patent Foramen Ovale Closure vs. Medical Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews & Meta-Analyses					
Turc et al. 2018 **France** **Systematic review& Meta-Analysis**	NA	6 RCTs (,3560) comparing PFO closure with antithrombotic therapy to prevent stroke recurrence in patients with PFO-associated cryptogenic stroke. (3 additional trials compared oral anticoagulation with antiplatelet therapy).	Pooling of results from Closure, PC, RESPECT, GORE-Reduce, CLOSE and DEFENSE PFO (all described below)	**Primary outcome:** Fatal or nonfatal recurrent stroke **Secondary outcomes:** TIA, all-cause mortality, major bleeding, major procedural complications and new-onset atrial fibrillation	The absolute risk of stroke recurrence was 0.29 and 1.27 per 100 person-years in the PFO closure group and the antithrombotic group, respectively. The risk of recurrent stroke was significantly lower in the PFO group (37/1,889 vs. 79/1,671; RR= 0.36, 95% CI 0.17–0.79, p=0.01). In patients with higher-risk anatomical features (atrial septal aneurysm or large shunt), the benefit of recurrent stroke was more pronounced for patients in the PFO closure group compared with those with lower-risk features (pooled RR=0.27, 95% CI, 0.11–0.70, p=0.01 vs. RR=0.80, 95% CI 0.43–1.47, p=0.41). The risk of TIA was not significantly lower for patients in the PFO closure group (64/1,889 vs. 64/1,671; RR=0.85, 95% CI 0.60–1.21, p=0.38). The risk of all-cause mortality was not reduced significantly for patients in the PFO closure group (13 vs. 15, RR=0.79, 95% CI 0.39–1.60, p=0.51). Major bleeding occurred in 34/1,820 patients in the PFO closure group vs. 28/1,583 patients in the medical therapy group. Major procedural complications occurred in 52/ 1,844 patients randomized to PFO closure (incidence per 100 patients treated: 2.40, 95% CI, 1.03–4.25). The risk of new-onset AF was significantly higher in the PFO closure group (RR=4.56, 95% CI 3.58–5.63 per 100 patients treated)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Kent et al. 2016 **USA** **Meta-Analysis**	NA	3 RCTs (n=2,303) comparing percutaneous catheter-based PFO closure to medical therapy in patients with cryptogenic stroke or TIA.	Patient-level pooling of results from RESPECT, PC Trial and Closure 1 trials. (all described below). Analyses were adjusted for covariates including age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke vs. TIA), hypermobile septum, and PFO shunt size (large vs. small).	**Primary outcome:** Composite of ischemic stroke, TIA or death from any cause **Secondary outcome:** Ischemic stroke	Patients were followed for 5,849 person-years. Overall, 442 patients (263 in the medical therapy arm; 171 in the device arm) withdrew or were otherwise lost to follow-up. There were 108 composite endpoint events (ischemic stroke/TIA/death) of which 58 were ischemic strokes, 54 were TIAs and 7 were death. The rate of stroke was 0.98 per 100 person-years across both arms; the composite event rate was 1.8 per 100 person-years. Using intention-to-treat, unadjusted analysis, closure did not reduce the risk of the primary outcome (HR=0.69, 95% CI 0.47–1.01, p=0.0531), while in adjusted analysis, the risk was reduced significantly (HR=0.68, 95% CI 0.46–1.00, p=0.0491). Using ITT analysis, the risk of recurrent stroke was reduced significantly in both unadjusted and adjusted analysis (HR=0.58, 95% CI 0.34–0.99, p= 0.0443). Using “as treated” analysis the risks of the primary outcome and recurrent stroke were both significantly reduced (HR=0.63, 95% CI 0.43–0.94, p=0.025 and HR=0.53, 95% CI 0.30–0.92, p=0.025, respectively). The authors estimated that to avoid one primary composite outcome, the NNT over 2.5 years was 50, and to avoid one ischemic stroke, the NNT was 67.
Li et al. 2015 **China** **Cochrane Review**	NA	3 RCTs (n=2,303) comparing percutaneous catheter-based PFO closure to medical therapy in	Pooling of results from RESPECT, PC Trial and Closure 1 trials. (all described below)	**Primary outcome:** Composite of recurrent stroke (non-fatal or fatal) or transient ischemic attack (TIA)	Risk of recurrent stroke or TIA was not reduced significantly with PFO closure (RR=0.73, 95% CI 0.45-1.17, based on the results from 2 RCTs with 1,323 patients.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		patients with cryptogenic stroke or TIA.		**Secondary outcomes:** Composite of all-cause mortality or serious adverse events (atrial fibrillation, myocardial infarction and bleeding	The risk of fatal or non-fatal stroke was not reduced significantly with PFO closure (RR= 0.55, 95% CI 0.26-1.18, based on the results from 3 RCTs with 2,303 patients. The risk of all-cause mortality or serious adverse events was not reduced significantly with PFO closure (RR=0.65, 95% CI 0.23-1.84), based on the results from 3 RCTs with 2,303 patients.
Spencer et al. 2014 **Canada** **Systematic Review & Meta-Analysis**	NA	3 RCTs (n=2,303) comparing percutaneous catheter-based PFO closure to medical therapy in patients with cryptogenic stroke or TIA.	Pooling of results from RESPECT, PC Trial and Closure 1 trials. (all described below)	**Primary outcomes:** Recurrence of non-fatal ischemic stroke, TIA, and mortality.	All primary analyses are based on 1,967 participants from 3 trials. The risks of non-fatal ischemic stroke, TIA or mortality was not reduced significantly in patients in the PFO closure group. **Non-fatal ischemic stroke**: RR=0.61, 95% CI 0.34 to 1.07. The estimated risk of ischemic stroke associated with PFO closure was 20 (95% CI 4 to 34) ischemic strokes per 1000 persons treated over 5 years. **TIA**: The corresponding estimated reduction for TIA was 6 (95% CI 9 to 15) TIAs per 1000 persons treated over 5 years. (RR= 0.76, 95% CI 0.44 to 1.32). **Mortality**: Risk Difference -0.00, 95% CI -0.01 to 0.01. No deaths in any of the trials were determined to be secondary to treatment. **Adverse events**: For patients randomized to PFO closure vs medical therapy, atrial fibrillation was reported in 32 vs. 8 patients (RD 0.02, 95% CI -0.02 to 0.06) whereas bleeding events were reported in 13 vs. 7 patients (RD 0.00, 95% CI -0.01 to 0.02), respectively.
Riaz et al. 2013	NA	3 RCTs (n=2,303) comparing transcatheter PFO closure to medical	Pooling of results from RESPECT, PC Trial and	**Primary outcome:** Composite outcome of recurrent stroke, TIA, or death.	Across the 3 included trials, mean follow-up time was 2.5 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Review & Meta-Analysis		therapy for the prevention of stroke.	Closure 1 trials. (all described below)		Based on ITT analysis: There was a non-significant trend in favour of PFO closure (HR= 0.66, 95% CI 0.43 to 1.01, p=0.056). Based on per protocol analysis: There was a significant treatment effect in favour of PFO closure (HR= 0.64, 95% CI 0.41 to 0.98, p=0.04). In subgroup analysis, there were no significant differences between groups based on the presence of atrial septal aneurysm, age or shunt size, but males appeared to benefit preferentially form PFO closure (HR= 0.48, 95% CI 0.24-0.96, p= 0.04).
Major Trials					
Lee et al. 2018 **South Korea** **RCT** ***Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale (DEFENSE-PFO)***	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☑	120 patients aged 18-80 years, with a cryptogenic ischemic stroke occurring within the previous 6 months with no identifiable cause other than a high risk PFO with right-to-left shunting. Patients with ≥50% stenosis of a major vessel or with occlusion of a major vessel were excluded, as were patients with stroke resulting from small-vessel occlusive disease. Mean age was 51.8 years, 56% were men. A high-risk PFO included: one with an atrial septal aneurysm, hypermobility or PFO size ≥2 mm.	Participants were randomized 1:1 to receive medical therapy with antiplatelet or anticoagulation alone, or PFO closure using the Amplatzer PFO Occluder device + medical therapy. Antiplatelet therapy included aspirin (100 mg/day), aspirin in combination with clopidogrel (75 mg/day), or aspirin in combination with cilostazol (200 mg/day). Warfarin was used to maintain the target INR of 2.0 to 3.0.	**Primary outcome:** Composite of recurrence of nonfatal stroke/ vascular death/ TIMI-defined major bleeding within 2 years of follow-up **Secondary outcomes:** Individual components of the primary outcome and asymptomatic ischemic stroke (assessed by MRI)	45 eligible patients did not participate in the trial. Median duration of follow-up was 2.8 years. Dual antiplatelet therapy was used by the majority of patients in both groups at 30 days and 6 months. At 12 months, more patients in the PFO group were taking a single antiplatelet, compared with the medical therapy group. Anticoagulants were used by ≤25% of patients at any assessment point. There were significantly more primary outcome events in the medication-only group (6 vs. 0, p=0.013), of which 5 were ischemic strokes. There were 3 new ischemic lesions in the PFO closure group vs. 7 in the medication-only group (p=0.24). There were no cases of major bleeding in the PFO closure group vs. 2 in the medication-only group (p=0.15). The authors estimated that the NNT to avoid one stroke at 2 years, was 10.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Søndergaard et al. 2017 **Denmark** **RCT** ***Gore REDUCE Clinical Study***	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☑	664 patients, recruited from 63 sites, aged 18-59 years, with a cryptogenic ischemic stroke occurring within the previous 180 days, with a PFO with a right-to-left shunt. Patients were excluded if they had uncontrolled diabetes mellitus, uncontrolled hypertension, autoimmune disease, or a recent history of alcohol or drug abuse, or if they had a specific indication for anticoagulation. Mean age was 45.2 years, 60% were men.	Patients were randomized 2:1 to undergo PFO closure plus antiplatelet therapy (n=441) or to receive antiplatelet therapy alone (n=223). Antiplatelet therapy could consist of aspirin alone (75 to 325 mg once daily), a combination of aspirin (50 to 100 mg daily) and dipyridamole (225 to 400 mg daily), or clopidogrel (75 mg once daily).	**Primary outcomes:** Clinical ischemic stroke, new brain infarction (clinical ischemic stroke or silent brain infarction)	Median duration of follow-up was 3.2 years. 81% of patients had a moderate or large interatrial shunt. 8.8% of the patients in the PFO closure group and 14.8% in the antiplatelet-only group discontinued the trial prematurely. Complete PFO closure with a study device was accomplished in 73.2% of the patients immediately after the procedure and in 75.6% of the patients at 12 months. The risk of clinical ischemic stroke during a minimum of 2 years of follow-up was significantly lower in the PFO closure group (1.4% vs. 5.4%, HR=0.23, 95% CI 0.09–0.62, p=0.002). The risk of any new brain infarction during a minimum of 2 years of follow-up was significantly lower in the PFO closure group (5.7% vs. 11.3%, RR=0.51, 95% CI 0.29–0.91, p=0.04). The frequency of any serious adverse event was similar between groups (23.1% PFO closure group vs. 27.8%, p=0.22). The frequency of new-onset atrial fibrillation or flutter was significantly higher in the PFO closure group (6.6% vs 0.4%, p<0.01)
Mas et al. 2017 **France** **RCT** ***Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke***	CA: ☑ Blinding: Patient ☒ Assessor☑ ITT: ☑	633 patients (900 planned), recruited from 32 sites, aged 16-60 years, who had sustained an ischemic stroke within the previous 6 months with no identifiable cause other than a PFO with an associated atrial septal aneurysm or large interatrial shunt. Mean age was 43 years, 58% were men.	**Group 1 (n=524)** Patients were randomized 1:1:1 to undergo PFO closure followed by long-term antiplatelet therapy or to receive antiplatelet therapy alone, or to receive oral anticoagulation alone **Group 2 (n=129)**	**Primary outcome:** Fatal or nonfatal stroke **Secondary outcomes:** Composite of ischemic stroke, TIA, or systemic embolism; disabling stroke, ischemic stroke, cerebral hemorrhage, TIA, systemic embolism, all-cause mortality, death from vascular-related	The mean duration of follow-up was 5.3 years. **PFO closure plus antiplatelet therapy vs. antiplatelet therapy alone (Groups 1 and 2 combined)** In the intention-to-treat analysis, there were no strokes in the PFO closure group (n=238) vs.14 in the antiplatelet only group (n=235) (HR=0.03, 95% CI 0.00–0.26, p <0.001). The outcome was similar in the per protocol analysis using data from 217

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Recurrence (CLOSE)			Patients with a contraindication to oral anticoagulation were randomly assigned 1:1 to PFO closure plus antiplatelet therapy or to antiplatelet therapy alone **Group 3 (n=10)** Patients with a contraindication to PFO closure were randomly assigned to anticoagulant therapy (n=7) or to antiplatelet therapy (n=3) Antiplatelet therapy included aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole (except for the 3 months after PFO closure during which time dual-antiplatelet therapy was used). All treatments were initiated within 3 weeks of randomization	causes, success of device implantation and success of PFO closure.	patients in PFO closure group and 234 in antiplatelet group. The risk of ischemic stroke, TIA or systemic embolism was significantly reduced in the PFO closure group (8 vs. 21, HR=0.39, 95% CI 0.16–0.82, p=0.01). PFO closure was not associated with significant reductions in the risks of disabling stroke or TIA. There were no cases of cerebral hemorrhage, systemic embolism or death from any cause in either group. Success of PFO closure was 88.6%. There were 14 major procedural-related complications. The frequency of new-onset atrial fibrillation or flutter was significantly higher in the PFO closure group (11 vs. 2, p=0.02). **Oral anticoagulation vs. antiplatelet therapy alone (Groups 1 and 3 combined).** There were no differences between groups for the primary or any secondary outcomes. For the primary outcome (ITT analysis), there were 3/187 recurrent strokes in the anticoagulant group vs. 7/124 in the antiplatelet group.
Carroll et al. 2013, Saver et al. 2017 (long-term follow-up) **US & Canada** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☑	980 patients, recruited from 69 sites, aged 18-59 years with cryptogenic ischemic stroke occurring during the previous 270 days, and with a confirmed diagnosis of PFO. Patients with mechanism of stroke other than paradoxical	Participants were randomized to receive medical therapy alone (n=481) or PFO closure + antiplatelet therapy with the Amplatzer PFO Occluder device (n=499). Medical therapy consisted of	**Primary outcome:** Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death following randomization (primary endpoint: 45 days post-randomization or 30 days following PFO closure).	Mean duration of follow-up was 2.6 years. During the study period, 25 primary end-points (all nonfatal ischemic strokes) occurred, 9 in the closure group (0.66 events per 100-person years) and 16 in the medical therapy group (1.38 events per 100-person years): HR= 0.49, 95% CI 0.22 to 1.11, p=0.08.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT)		embolization, lacunar infarct likely due to intrinsic small-vessel disease, or an arterial hypercoagulable state, were excluded. Mean age was 45.9 years, 54.7% were men.	aspirin, warfarin, clopidogrel, or aspirin plus extended release dipyridamole.		In the per protocol analysis, a total of 20 end point events was included, 6 in the closure group (0.46 events per 100-person years) and 14 in the medical therapy group (1.30 events per 100-person years): HR with closure = 0.37, 95% CI 0.14 to 0.96, p=0.03. The occurrence of serious adverse events was not significantly higher for those in the closure group (23.0% vs. 21.6%, p=0.65). There were significantly more dropouts in the medical management group (17.2% vs. 9.2%, p=0.009). **Long-term follow-up (2017)** Median duration of follow-up was 5.9 years. A significantly higher proportion of patients in the medical management group were lost to follow-up (33.3% vs. 20.8%, p<0.001) The risk of recurrent ischemic stroke was significantly lower in the PFO closure group (3.6% vs. 5.8%; HR=0.55, 95% CI 0.31-0.999, p=0.046). The risk of recurrent ischemic stroke of undetermined cause was significantly lower in the PFO closure group (2.0% vs. 4.8%; HR=0.38, 95% CI 0.17-0.79, p=0.007). The risk of recurrent cryptogenic ischemic stroke was significantly lower in the PFO closure group (0.2% vs. 2.3%; HR=0.08, 95% CI 0.01-0.58, p=0.01). PFO closure was not associated with a significantly reduced risk of TIA (3.4% vs. 4.8%, HR=0.64, 95% CI 0.34-1.20, p=0.16).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The frequency of serious adverse events was similar between groups (40.3% in the PFO closure group vs. 36.0% in the medical-therapy group, p=0.17). The risk of pulmonary embolism was significantly higher in the PFO closure group (HR=3.48; 95% CI, 0.98-12.34, p=0.04). There were 25 serious adverse events among patients in the PFO closure group, of which 12 were procedure related and 13 were device related.
Meier et al. 2013 **Europe, Canada, Brazil, & Australia** **RCT** ***Percutaneous closure of patent foramen ovale in cryptogenic embolism (PC Trial)***	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☑	414 patients ≤60 years with a PFO and cryptogenic ischemic stroke, TIA, or peripheral thromboembolism. Mean age was 44.5 years, 45.2% were men.	Participants were randomized to receive medical therapy alone (n=210) or PFO closure (n=204). Participants in the PFO closure group received antithrombotic treatment (ASA + ticlopidine or clopidogrel). Participants in the medical therapy group received at least one antithrombotic agent, chosen at the discretion of the treating physician.	**Primary outcome**: Composite of death, nonfatal stroke, TIA, or peripheral embolism. **Secondary outcome**: each component of the primary outcome, new arrhythmias, MI, PFO-related hospitalization, device problems, and bleeding.	Mean duration of follow-up was 4.1 years. During the study period, 18 primary outcome events occurred, with 7 (3.4%) in the PFO closure group and 11 (5.2%) in the medical therapy group: ITT analysis HR=0.63, 95% CI 0.24 to 1.62, p=0.34. Per protocol analysis resulted in similar findings (HR=0.70, 95% CI 0.27 to 1.85, p=0.48). Serious adverse events occurred in 43 (21.1%) patients in the PFO closure group and 37 (17.6%) patients in the medical therapy group. Dropouts: PFO closure group=15.2%; Medical therapy group=20.0%.
Furlan et al. 2012 **US and Canada** **RCT** ***Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical***	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☑	909 patients aged 18-59 years with a PFO and an ischemic stroke or TIA within 6 months of study enrollment. Mean age was 66 years, 51.8% were men.	Participants were randomized to receive medical therapy alone (n=462) or PFO closure + antiplatelet therapy consisting of clopidogrel for 6 months + aspirin for 2 years) (n=447). Medical therapy consisted of treatment with warfarin, aspirin, or both, at the discretion of the treating physician.	**Primary outcome**: Composite of stroke or TIA within 2 years, death from any cause within 30 days, and death from neurologic cause within 2 years. **Secondary outcome**: Major bleeding, death from any cause, and stroke and TIA. **Timing of Assessment**: Follow-up at 1 month, 6	During the study, 52 primary outcome events occurred, with 23 (5.5%) in the PFO closure group and 29 (6.8%) in the medical therapy group: adjusted HR=0.78, 95% CI 0.45 to 1.35, p=0.37. Per protocol analysis resulted in similar findings (adjusted HR=0.74, 95% CI 0.42 to 1.29, p=0.29). The occurrence of serious adverse events was not significantly different for those in the closure group (16.9%), as compared to those in the medical therapy group (16.6%), p=090; however, participants in the PFO closure group were significantly more likely to experience a major vascular procedural complication (13 vs. 0, p<0.001) or atrial fibrillation (23 vs 3, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Embolism through a Patent Foramen Ovale (CLOSURE I)				months, 1 year, and 2 years.	Dropouts: PFO closure group=15.4%; Medical therapy group=18.8%.
Long-term Follow up PFO Closure					
Patti et al. 2015 **Italy** **Systematic Review & Meta-Analysis**	NA	21 studies (4 RCTs, 17 observational studies), including 3,311 patients who had suffered a cryogenic stroke or TIA.	Treatment strategies for management of PFO with follow-up of ≥12 months. Treatment contrasts included i) medical management with antiplatelet vs. anticoagulation (n=18 studies, 2,798 patients); ii) PFO closure vs. antiplatelets (n=11 studies) and PFO closure vs. anticoagulation (n=13 studies)	Stroke/TIA, major bleeding events, clinical adversity (cumulative incidence of stroke and/or TIA or major bleeding event)	*i) Antiplatelet vs. Anticoagulant* Antiplatelet therapy was associated with a significantly increased risk of recurrent stroke or TIA (OR=1.53, 95% CI 1.04-2.23, p=0.03). Mean duration of follow-up was 36 months. Anticoagulant therapy was associated with a significantly increased risk of major bleeding events. (OR=6.49, 95% CI 3.25-12.99, p<0.0001). Mean duration of follow-up was 42 months. *ii) PFO closure vs. antiplatelet therapy* PFO closure was associated with a significantly decreased risk of recurrent stroke or TIA (OR=0.50, 95% CI 0.35-0.71, p<0.0001). Mean duration of follow-up was 36 months. PFO closure was not associated with a significantly decreased risk of major bleeding events. (OR=0.62, 95% CI 0.28-1.40, p=0.25). PFO closure was associated with significantly lower risk of clinical adversity (OR=0.30, 95% CI 0.18-0.51, p<0.0001) *iii) PFO closure vs. anticoagulant therapy* PFO closure was not associated with a significantly decreased risk of recurrent stroke or TIA (OR=0.66, 95% CI 0.42-1.04, p=0.07). PFO closure was associated with a significantly decreased risk of major bleeding events. (OR=0.18, 95% CI 0.09-0.36, p<0.0001). PFO closure was associated with significantly lower risk of clinical adversity (OR=0.32, 95% CI 0.18-0.59, p=0.0003).
Mirzada et al. 2015	NA	314 patients referred for PFO closure to a single centre from 2006-2009.	The outcomes of patients who were accepted for PFO	**Primary outcome:** Composite of all-cause mortality, stroke and TIA	Mean duration of follow-up was 5 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sweden **Prospective study**		Patients were considered for PFO closure: combination of first-ever cryptogenic stroke or TIA and PFO with high-risk features. Patients with recurrent CS or TIA and PFO without other high-risk features were also considered. Mean age was 54 years, 62% were male. The index event was stroke in 68% of cases.	closure (and underwent the procedure, n=152) were compared with those who were not accepted (n=162)	**Secondary outcomes:** Stroke/TIA or all-cause mortality	At baseline, all patients in the closure group received some form of antiplatelet/anticoagulation vs. 97.6% in the non-closure group. At follow-up, the corresponding percentages were 66 and 82.6 The cumulative risk of the primary outcome was non-significantly lower in the closure group (10.6% vs. 12.9%, p=0.53). The cumulative incidence of the individual components of the primary outcome did not differ significantly between groups. There were 12 serious adverse events (5 procedure related).

Heart Failure and Increased Risk of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Risk of Recurrent Stroke					
Katsanos et al. 2016 **Greece** **Systematic review & Meta-analysis**	NA	7 studies including 9,173 patients that reported the recurrence of ischemic stroke in patients with heart failure. The percentage of patients with heart failure ranged from 4.8% to 33.9%. Mean age of patients in included studies ranged from 70-74 years (n=3) and was not reported in 4 studies. A portion of patients in 3 studies had concomitant AF (3.6%, 53.6% and 53.7%)	The risk of recurrent ischemic stroke in patients with heart failure was estimated. The definitions used for heart failure were based on medical history (n=3), ejection fraction (n=1), Framingham criteria (n=1) or were not reported (n=3).	**Primary outcome:** Recurrent ischemic stroke	The mean duration of follow-up ranged from 7 days to 5 years. The risk of recurrent stroke was significantly increased among patients with heart failure (RR=1.96, 95% CI 1.49 -2.60, p<0.0001). Results from 3 studies included.
Pongmoragot et al. 2016 **Canada**	NA	12,396 patients ≥18 years, included in the Registry of the Canadian Stroke Network (2003-2008) with acute ischemic stroke.	The outcomes of patients with heart failure were compared with patients without heart failure. Heart failure was defined as pre-	**Primary outcome:** Death or disability at discharge **Secondary outcomes:** Recurrent stroke	Of the total sample, 1,124 (9.1%) had heart failure. 44 (3.9%) of patients with heart failure suffered a recurrent stroke within 30 days

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		Mean age was 72 years. 65% of patients were admitted with mild strokes.	existing, pulmonary edema present at the time of arrival to hospital.		of admission, compared with 360 (3.2%) of patients without heart failure (p=0.194). Stroke fatality at discharge, 30 days and 1 year was significantly higher for patients with heart failure. Heart failure was an independent predictor of death or disability at discharge (OR=1.18, 95% CI 1.01-1.37), 30-day survival (HR=1.22, 95% CI 1.05-1.41) and 30-day readmission (OR=1.32, 95% CI 1.05-1.65), after adjusting for age, sex, stroke severity and medical comorbidities.
Risk of Incident Stroke Associated with Myocardial Infarction					
Sundbøll et al. 2016 **Denmark** **Retrospective study**	NA	258,806 patients admitted to all hospitals from 1980-2009 with first occurrence of MI. Median age was 70.4 years, 63% were male. An age and sex-matched cohort of 1,244, 773 persons was drawn from the general population without a history of stroke or MI was used as a comparison group.	All hospitalizations associated with stroke were obtained prospectively from the index date of MI until Dec 2012, or 30 years. (The index date for persons in the comparison group was assigned, based on the admission date for the corresponding MI patient). The cumulative risk of stroke was assessed and compared between the two groups.	Risk of stroke at 30-days, 365 days and 30 years Analyses were adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes mellitus, chronic kidney disease, and chronic pulmonary disease.	**Ischemic stroke** The cumulative stroke rate for the MI group from 1-30 years was 12.6% (95% CI 12.4-12.8%) vs. 11.9% (95% CI 11.8-12.0%) for the non-MI group. The 1-30 day and 31-365 day risks of stroke were significantly higher in the MI group (RR=31.9, 95% CI 28.4-35.8 and RR=3.1, 95% CI 3.0-3.33, respectively). The 1-30-year risk ratio was 1.6, 95% CI 1.6-1.6. **ICH** The cumulative stroke rate for the MI group from 1-30 years was 1.6% (95% CI 1.6-1.7%) vs. 1.2% (95% CI 1.2-1.3.0%) for the non-MI group. The 1-30 day and 31-365 day risks of stroke were significantly higher in the MI group (RR=21.8, 95% CI 16.6-28.5 and RR=2.1, 95% CI 1.9-2.5, respectively).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The 1-30-year risk ratio was 1.1, 95% CI 1.0-1.2. **SAH** The cumulative stroke rate for both groups was less than 1% from 1-30 days, 31-365 days and 1-30 years. The 1-30 day and 31-365 day risks of stroke were significantly higher in the MI group (RR=16.6, 95% CI 8.7-32.0 and RR=1.5, 95% CI 1.1-2.1, respectively). The 1-30-year risk ratio was 1.1, 95% CI 0.94-1.2.
Witt et al. 2006 **USA** **Systematic review & meta-analysis**	Mean quality score was 13.8 on a 23-point scale (7 items)	22 observational studies (registries, hospital and community-based) in which data on stroke and MI were reported separately. Mean ages ranged from 59-76 years.	Ischemic stroke rates for each study were reported as the number of events per 1,000 MI during hospitalization, at 30 days and 1 year following MI.	Stroke	There were that 11.1 (95% CI 10.7 to 11.5) ischemic strokes/1,000 MIs that occurred during hospitalization (based on results from 1 studies), 12.2 (95% CI 10.4 to14.0) at 30 days (based on results from 3 studies) and 21.4 (95% CI (14.1 to 28.7) at 1 year (based on results from 2 studies). Age, diabetes, HTN, prior stroke, anterior location of index MI, prior MI, atrial fibrillation, heart failure, and nonwhite race were all associated with increased risk of stroke,
Loh et al. 1997 **Prospective study** ***Survival and Ventricular Enlargement (SAVE) Study***	NA	2,231 patients included in the SAVE RCT, which compared ACE inhibitor (captopril) vs. placebo following acute MI with left ventricular dysfunction (LVEF ≤40%). Mean age was 59 years, 82% were male.	The characteristics and outcomes of patients who sustained a stroke were compared with those who did not. Independent predictors of stroke were identified.	Stroke	Mean duration of follow-up was 42 months. There were 103 strokes (4.6%) during follow-up. Five-year cumulative rate of stroke was 8.1%. Independent risk factors for stroke were LVEF (per each decrease of 5 points). RR=1.18, 95% CI 1.02-1.36, p=0.03 and age (per each 5-year increase) RR=1.18, 95% CI 1.05-1.33, p<0.001.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Anticoagulant therapy and aspirin therapy during follow-up were protective factors RR=0.19, 95% CI 0.13-0.27, p<0.001 and RR=0.44, 95% CI 0.29-0.65, p<0.001, respectively.

Antithrombotic Treatment for Heart Failure

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Zannad et al. 2018 **France/International** **RCT** ***A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER HF)***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	5,081 participants ≥18 years, with at least a 3-month history of chronic heart failure, a left ventricular ejection fraction of ≤40%, with coronary artery disease and who had been treated for an episode of worsening heart failure (i.e., the index event) within the previous 21 days, and without atrial fibrillation. Participants also had a plasma concentration of brain natriuretic peptide (BNP) ≥ 200 pg/mL or N-terminal pro–brain natriuretic peptide (NT-proBNP) ≥ 800 pg/mL measured at any time during the screening period. Mean age was 66 years, 77% were men. 9% had a prior stroke.	Patients were randomized 1:1 to receive 2.5 mg rivaroxaban twice daily or matching placebo for the duration of the trial, in addition to standard care .	**Primary outcomes:** Composite of death from any cause, MI, or stroke **Secondary outcomes:** Death from cardiovascular causes, rehospitalization for worsening heart failure, rehospitalization for cardiovascular events, and the composite of death from cardiovascular causes or rehospitalization for worsening heart failure. **Primary safety outcome:** Composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.	Median duration of follow-up was 21.1 months. The rate of the primary outcome did not differ significantly between groups (rivaroxaban 13.44 events/100 persons yrs vs. placebo 14.27 events/100-person years; HR=0.94, 95% CI 0.84–1.05, p=0.27). The risks of the individual components of the primary outcome did not differ significantly between groups; with the exception of the risk of stroke, which was reduced significantly with rivaroxaban (1.08 vs. 1.63 events/100-person years; HR=0.66, 95% CI 0.47–0.95). There were no differences between groups in the rate of the secondary outcomes between groups. The risk of the primary safety outcome did not differ between groups (rivaroxaban 0.44 events/100 persons yrs vs. placebo 0.55 events/100-person

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					years; HR=0.80, 95% CI 0.43–1.89, p=0.48).
Homma et al. 2012 **USA** **RCT** ***Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF)***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	2,022 patients ≥18 years recruited from 168 centres in 11 countries, in normal sinus rhythm and a LVEF of ≤35%, mRS ≤4 and planned treatment with a β-blocker or ACE inhibitor. Patients were excluded if they were at high risk of cardiac embolism. Mean age was 61 years, 80% were male. 12.5% has sustained a previous stroke. Persons with atrial fibrillation were excluded.	Patients were randomized to receive 325 mg aspirin daily (n=1,163) or warfarin (n=1,142) with target INR of 2.75 for the study duration. Follow-up was conducted by telephone, or in-person at the time of blood collection	**Primary outcome:** Time to first event of composite outcome of ischemic stroke, ICH or death from any cause **Secondary outcomes:** Composite endpoint of hospitalization for heart failure, myocardial infarction, ischemic stroke, intracerebral hemorrhage, or death.	Mean duration of follow-up was 3.5 years. Mean LVEF was 24.7%. The rates for the primary outcome were 7.47 and 7.93 events/100 patient years for warfarin and aspirin, respectively. HR for warfarin=0.93, 95% CI 0.79-1.10, p=0.40. The risk of ischemic stroke was significantly decreased for patients in the warfarin group (HR=0.52, 95% CI 0.33-0.82, p=0.005), but not for ICH (HR=2.22, 95% CI 0.43-11.66, p=0.35). The risks of major and minor hemorrhages were significantly increased for patients taking warfarin (OR=2.05, 95% CI 1.36-3.12, p<0.001, and OR=1.56, 95% CI 1.34-1.81, p<0.001, respectively). 69 patients withdrew consent or were lost to follow-up.
Homma et al. 2013 WARCEF study (subgroup analysis) **USA** **RCT**	As above	As above	Secondary analysis of sub groups including sex, race ethnicity, LVEF, New York Heart Association class, etiology of heart failure, age, BMI, education, country, diabetes, hypertension, smoking, alcohol use, 6-minute walk distance, prior stroke or TIA, SBP/DBP, atrial fibrillation, MI, defibrillator or pacemaker use,	As per original trial + intracerebral hemorrhage (ICH)	Age and country of origin were the only subgroups for which an interaction was found in phase 1 (unadjusted) analysis. *Unadjusted analysis* Patients <60 years treated with warfarin had a significantly lower risk of the primary outcome (HR=0.65, 95% CI 0.49-0.86, p=0.002). Patients ≥60 yrs treated with warfarin had a similar risk of the primary outcome compared with those treated with aspirin (HR=1.16, 95% CI 0.94-1.43, p=0.16)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			coronary artery disease, peripheral vascular disease, statin use, prerandomization use of warfarin, aspirin or other antiplatelets, mini-mental status examination, blood urea nitrogen, estimated glomerular filtration rate, WBC, serum sodium, hematocrit, and hemoglobin.		p for interaction <0.001 *Adjusted analysis* Patients <60 years treated with warfarin had a significantly lower risk of the primary outcome (HR=0.63, 95% CI 0.48-0.84, p=0.003). Patients ≥60 yrs treated with warfarin had a similar risk of the primary outcome (HR=1.09, 95% CI 0.88-1.35, p=0.44) p for interaction =0.003 Patients <60 years treated with warfarin had a significantly lower risk of death (HR=0.65, 95% CI 0.48-0.89, p=0.007). Patients ≥60 yrs treated with warfarin had a similar risk of death (HR=1.18, 95% CI 0.94-1.49, p=0.16) p for interaction =0.003 For the outcome of ischemic stroke, there was no interaction by age group (<60 vs. ≥60 yrs, p=0.64). The risk was reduced significantly (HR=0.51, 95% CI 0.32-0.81, p=0.005) for patients in both age groups. 2 patients <60 years and 5 patients ≥65 years suffered an ICH. Patients <60 years treated with warfarin had a significantly lower risk of the primary outcome plus any major hemorrhage (HR=0.68, 95% CI 0.52-0.89, p=0.005). Patients ≥60 yrs treated with warfarin had a higher risk (HR=1.25, 95% CI 1.02-1.53, p=0.03) p for interaction <0.001
Massie et al. 2009 **USA**	CA: ☑ Blinding: Patient ☑	1,587 patients recruited from 142 centres in US, Canada and the UK, ≥18	Patients were randomized to receive 162 mg aspirin daily (n=523), 75 mg	**Primary outcome:**	The mean duration of follow-up was 1.9 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial***	(aspirin and clopidogrel groups) Assessor☑ ITT: ☑	years, with symptomatic heart failure (New York Heart Association class II to IV) for 3 months before entry, LVEF <35%, in sinus rhythm, and had been treated with a diuretic and an ACE inhibitor for at least 60 days. Mean age was 63 years, 85% were male. 5% had suffered a prior stroke	clopidogrel daily (n=524) or warfarin, with target INR of 2.5 to 3.0 (n=540), for the duration of the study. Follow-up was conducted by telephone and clinic visits at regular intervals.	Composite of all-cause mortality, nonfatal MI, and nonfatal stroke. **Secondary outcomes:** Components of the primary end point and hospitalizations for heart failure.	The primary outcome occurred in 108 patients (20.7%) in the aspirin group, 113 (21.6%) in the clopidogrel group and 106 (19.6%) in the warfarin group. The associated risks among the groups were: Warfarin vs. aspirin: HR=0.98, 95% CI 0.86-1.12, p=0.77 Clopidogrel vs. aspirin: HR=1.08, 95% CI 0.83-1.40, p=0.57 Warfarin vs. clopidogrel: HR=0.89, 95% CI 0.68-1.16, p=0.39. The number of nonfatal strokes among study groups was: aspirin 9 (1.7%), clopidogrel 11 (2.1%) and warfarin 1 (0.2%). Warfarin was associated with significantly fewer number of nonfatal strokes compared with aspirin (p=0.0095) and clopidogrel (p=0.0031). The total number of strokes among study groups was: aspirin 12 (2.3%), clopidogrel 12 (2.3%) and warfarin 3 (0.6%). Warfarin was associated with significantly fewer number of nonfatal strokes compared with aspirin (p=0.0163) and clopidogrel (p=0.0164). The number of major hemorrhage events among study groups was aspirin 19 (3.6%), clopidogrel 12 (2.1%) and warfarin 30 (5.2%). Warfarin was associated with significantly more major bleeding events compared with clopidogrel (p=0.0074). 76 patients were lost to follow-up
Cokkinos et al. 2006 **Greece**	CA: ☒	197 patients aged 20-75 years with symptomatic HF,	Patients were randomized to receive 2.5-10 mg warfarin daily with a target	**Primary outcome:** Any of the following: non-fatal stroke, peripheral or pulmonary	The mean duration of follow-up ranged from 18.5- 21.9 months across groups.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Heart Failure Long-term Antithrombotic (HELAS) Study***	Blinding: Patient ☑ Assessor☑ ITT: ☒	in NYHA class II– IV with ejection fraction < 35%. Mean ages ranged across the 4 study groups from 54 to 63 years. Males comprised 78%-93% across study groups. Mean EF ranged from 27%-29%.	INR of 2- 3, 325 mg ASA daily or placebo for up to 2 years. Treatment allocation was based on type of heart failure. Treatment allocation: Patients with IHD received aspirin (n=61) or warfarin (n=54). Patients with idiopathic dilated cardiomyopathy (DCM) received warfarin (n=38) or placebo (n=44).	embolism, myocardial (re)infarction, re-hospitalization, exacerbation of heart failure, or death from any cause	The occurrences of the primary endpoint/100 patient years were: IHD(ASA): 14.9 (14 events) IHD (warfarin): 15.7 (13 events) DCM (placebo): 14.8 (10 events) DCM (warfarin): 8.9 (6 events) The occurrences of the stroke/100 patient years were: IHD(ASA): 2.1 (2 events) IHD (warfarin): 2.4 (2 events) DCM (placebo): 1.5 (1 events) DCM (warfarin): 0 (0 events) Major hemorrhage occurred only in the warfarin group (4.6/100 patient years)
Cleland et al. 2004 **UK** **RCT** ***Warfarin/Aspirin Study in Heart Failure (WASH) Study***	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☑	297 patients with a clinical diagnosis of heart failure requiring treatment with diuretics, and evidence of left ventricular systolic dysfunction on echocardiography. 6% of patients had atrial fibrillation. Mean age was 64 years, 75% were male.	Patients were randomized to receive 300 mg of aspirin (n=91), warfarin, with a target INR of 2.5 (range 2–3, n=89), or to no antithrombotic therapy (n=99) for the study duration.	**Primary outcome:** Composite of death, nonfatal MI and nonfatal stroke **Secondary outcomes:** Death or cardiovascular hospitalization, death or all cause hospitalization, total number of hospitalizations, and the composite of death, cardiovascular hospitalization, and increase in diuretic therapy for worsening heart failure	Mean duration of follow-up was 27 months. The primary outcome occurred in 26% of patients in the no treatment group, 32% in patients in the aspirin group and 26% of patients in the warfarin group. The differences were not significant among groups. There were 2 cases of stroke in both the no treatment and aspirin groups and none in the warfarin group. Significantly more patients randomized to aspirin were hospitalized for any reason (64% vs. 48% and 47%, p=0.044). Significantly more patients randomized to warfarin suffered a major hemorrhage (4 vs. 1 vs. 0, p=0.028).

Aortic Arch Atheroma

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Amarenco et al. 2014 **France** **RCT** ***Aortic Arch Related Cerebral Hazard Trial (ARCH)***	CA: ☑ Blinding: Patient ☒ Assessor☒ ITT: ☑	351 patients >18 years with previous ischemic stroke, TIA, or peripheral embolism with plaque in the thoracic aorta >4 mm and no other identified embolic source. Patients with extracranial or intracranial atherosclerotic stenosis ≥70%, those scheduled for carotid revascularization, were excluded as were patients with an absolute indication or contraindication for oral anticoagulant use. Mean age was 69 years, 72% were male. Mean time from qualifying event to randomization was 2.16 months.	Patients were randomized (1:1) to receive 75 to 150 mg/d aspirin + 75 mg/d clopidogrel (A + C) or dose-adjusted warfarin with a target INR of 2.5 (2-3) for the duration of the trial. Recruitment lasted for 8 years, 3 months and was stopped prematurely (planned recruitment was 372 patients/treatment arm)	**Primary outcome:** Composite of cerebral infarction, MI, peripheral embolism, vascular death, or intracranial hemorrhage. **Secondary outcomes:** Individual components of the primary outcome, + primary end point or major hemorrhage, TIA or infarction, primary end point or revascularization procedures, primary end points or revascularization procedures or TIA and primary end point or total death Analysis was adjusted for age, sex, country, history of MI, SBP/DBP	Median duration of follow-up was 3.4 years. The primary endpoint occurred in 7.6% of patients in the A+C group vs. 11.3% in the warfarin group (HR=0.76, 95% CI 0.36-1.61, p=0.50) Rates of the primary outcome per 100-person years were 2.17 (A+C) and 3.49 (warfarin), respectively. There were no significant differences between groups on any of the secondary outcomes except for vascular death, which was significantly lower in the A+C group (0% vs. 3.4%, log-rank, p=0.013). Total death occurred in 4.7% and 8.4% in the A+C and warfarin groups, respectively (log-rank p=0.3). Major hemorrhages occurred in 2.3% and 3.4% in the A+C and warfarin groups, respectively (log-rank p=0.2).
Tunik et al. 2002 **USA** **Prospective study**	NA	519 patients with severe aortic arch plaque (≥4 mm), who were in-and outpatients referred for TEE due to embolic events. Mean age was 76 years, 76% were men.	Follow-up information was obtained though telephone interviews or medical records. Information was collected related to outcome (embolic events, death) and the use of medications including statins, warfarin, and antiplatelet drugs. A (within-group) matched pair analysis was performed whereby patients taking medications (listed above)	**Primary outcome:** Embolic events	Mean duration of follow-up was 34 months. Patients who took statins and warfarin were monitored for an average of 27 and 32 months, respectively, which was significantly shorter than those not taking the medications. There were 111 embolic events (21%) during follow-up, including 56 strokes and 39 TIAs (35%). There were 102 deaths. Medications use (% of patients): Statins (38%), warfarin (40%), antiplatelet medications (49%), statin +

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			were matched to another patient not taking medications.		warfarin (16%), warfarin +antiplatelet (8%), no treatment (12%). The risk of embolic events associated with the use of medications was: Stains: RR=0.39, 95% CI0.24-0.62, p<0.0001) Warfarin: RR=1.18, 95% CI 0.91-1.54, p=0.21) Antiplatelets (RR=0.77, 95% CI 0.51-1.15, p=0.20) **Matched –pair analysis:** Satins (150 matched pairs): The risk of embolic events was reduced significantly in patients taking statins (RR=0.30, 95% CI 0.20-0.60, p=0.0004, NNT=6) Warfarin (147 matched pairs): The risk of embolic events was not reduced significantly in patients taking warfarin (RR=0.70, 95% CI 0.40-1.20, p=0.26). Antiplatelets (167 matched pairs): The risk of embolic events was not reduced significantly in patients taking antiplatelets (RR=1.40, 95% CI 0.80-2.40, p=0.19)

Abbreviations

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

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