Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Cardiac Issues

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PREVENTION of STROKE Writing Group

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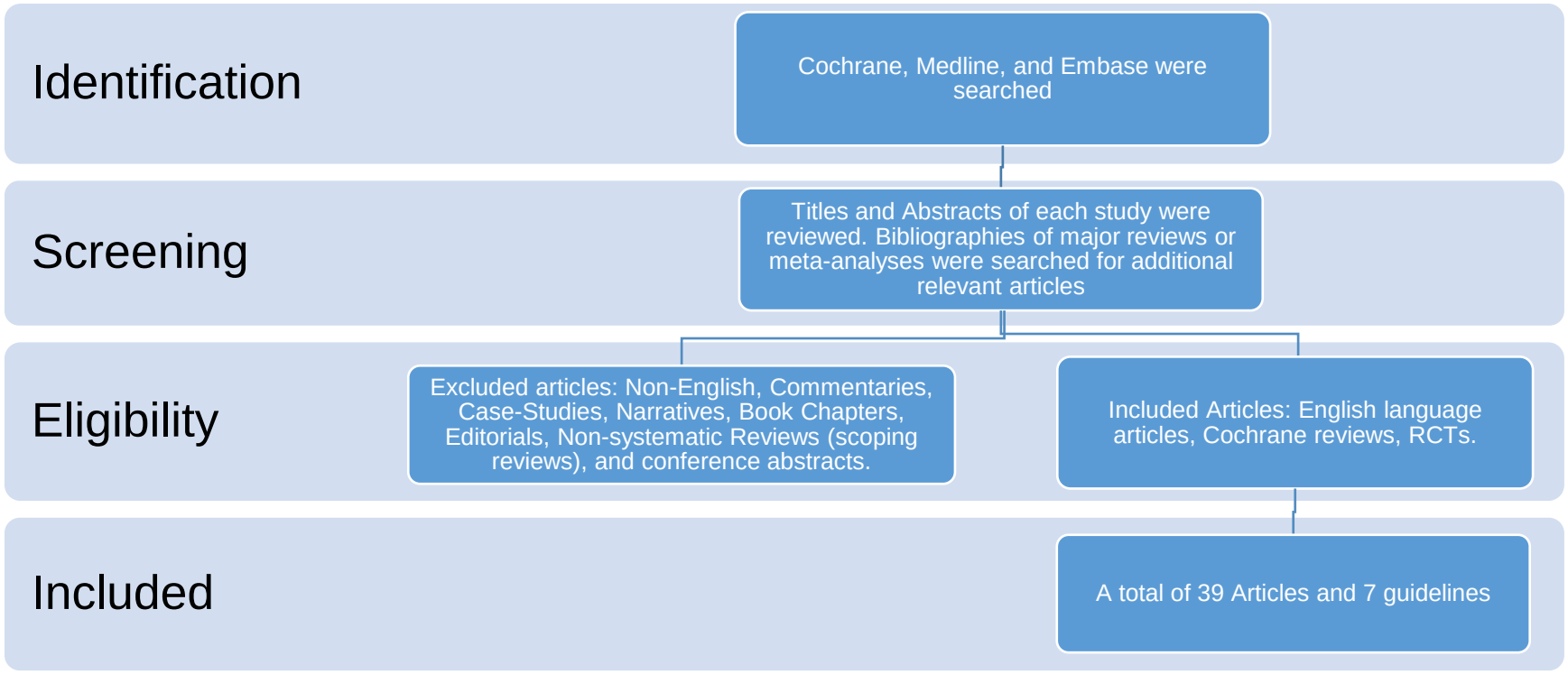
Search Strategy



Cochrane, Medline, and Embase 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 7 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
National Clinical Guideline for Stroke. 5th Edition. 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** 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**	**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)

Guideline	Recommendations
the American heart association/American stroke association. ***Stroke* 2014;45:2160-2236.**	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) 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**	**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

Guideline	Recommendations
Practice Guidelines. ***J Am Coll Cardiol* 014;63:2438–88.**	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. **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**	**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). 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**	**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).*"

Guideline	Recommendations
thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. ***CHEST Journal*, *141*(2_suppl), e601S-e636S.**	
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010. Melbourne Australia.	**5.9 Patent foramen ovale** a) All patients with ischaemic stroke or TIA, and a PFO should receive antiplatelet therapy as first choice [Grade C]. b) Anticoagulation therapy can also be considered taking into account other risk factors and the increased risk of harm [Grade C]. c) There is insufficient evidence to recommend PFO closure [Good Practice Point].
Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, 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**	**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) 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)

Guideline	Recommendations
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)**	

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
Katsanos et al. 2014 **Greece** **Systematic review & Meta-analysis**	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 diagnosed using echocardiography or transcranial Doppler	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 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**	NA	588 participants ≥45 years recruited from the general population who were participants of the	Transesophageal echocardiography (including 2-dimensional, color flow, and Doppler	Prevalence of PFO	Of the 581 patients who underwent transesophageal echocardiography, 148 (25.6%) were found to have a PFO.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Prospective study		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.	imaging with biplane or multiplane transduces) was used to detect the presence of PFOs.		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 **US** **Prospective study**	NA	95 patients >39 years with first acute ischemic stroke.	Patients were examined by the study neurologist within one week of the index stroke event. Data was collected through in-person interview and hospital record review. Diagnosis of PFOs were based on findings from contrast studies.	Prevalence of PFOs	Of the 95 patients who underwent transesophageal echocardiography, 31 (33%) were found to have a PFO. 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).

Patent Foramen Ovale Closure vs. Medical Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Reviews & Meta-Analyses					
Li et al. 2015 **China** **Cochrane Review**	NA	3 RCTs (n=2,303) comparing percutaneous catheter-based PFO closure to medical therapy in patients with cryptogenic stroke or TIA.	Pooling or 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) **Secondary outcomes:** Composite of all-cause mortality or serious adverse events (atrial fibrillation, myocardial infarction and bleeding	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. 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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
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 or 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 **Systematic Review & Meta-analysis**	NA	3 RCTs (n=2,303) comparing transcatheter PFO closure to medical therapy for the prevention of stroke.	Pooling or results from RESPECT, PC Trial and Closure 1 trials. (all described below)	**Primary outcome:** Composite outcome of recurrent stroke, TIA, or death.	Across the 3 included trials, mean follow-up time was 2.5 years. 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 sub group analysis, there were no significant differences between groups based on the presence of atrial septal aneurysm, age or shunt size, but

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					males appeared to benefit preferentially form PFO closure (HR= 0.48, 95% CI 0.24-0.96, p= 0.04).
Major Trials					
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***	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	**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	**Primary outcome:** Fatal or nonfatal stroke **Secondary outcomes:** Composite of ischemic stroke, TIA, or systemic embolism; disabling stroke, ischemic stroke,	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)		septal aneurysm or large interatrial shunt. Mean age was 43 years, 58% were men.	receive oral anticoagulation alone **Group 2 (n=129)** 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	cerebral hemorrhage, TIA, systemic embolism, all-cause mortality, death from vascular-related causes, success of device implantation and success of PFO closure.	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 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)	CA: ☒ Blinding: Patient ☒ Assessor☑	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	Participants were randomized to receive medical therapy alone (n=481) or PFO closure + antiplatelet therapy with the Amplatzer PFO	**Primary outcome:** Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death following randomization (primary	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
US & Canada **RCT** ***Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT)***	ITT: ☑	PFO. Patients with mechanism of stroke other than paradoxical 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.	Occluder device (n=499). Medical therapy consisted of aspirin, warfarin, clopidogrel, or aspirin plus extended release dipyridamole.	endpoint: 45 days post-randomization or 30 days following PFO closure).	per 100-person years): HR= 0.49, 95% CI 0.22 to 1.11, p=0.08. 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. At baseline, all patients in the closure group

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	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)	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** **Retrospective**	NA	12,396 patients ≥18 years, included in the Registry of the Canadian Stroke Network (2003-2008) with acute ischemic stroke. Mean age was 72 years.	The outcomes of patients with heart failure were compared with patients without heart failure. Heart failure was defined as pre-existing, pulmonary edema	**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 of admission, compared with 360 (3.2%)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
study		65% of patients were admitted with mild strokes.	present at the time of arrival to hospital.		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). The 1-30-year risk ratio was 1.1, 95% CI 1.0-1.2.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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.
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. 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
Homma et al. 2012 **USA**	CA: ☑ Blinding: Patient ☑ Assessor☑	2,305 patients ≥18 years recruited from 168 centres in 11 countries, in normal sinus rhythm and a LVEF of ≤35%, mRS ≤4 and planned	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.	**Primary outcome:** Time to first event of composite outcome of ischemic stroke, ICH or death from any cause	Mean duration of follow-up was 3.5 years. Mean LVEF was 24.7%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF)***	ITT: ☑	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.	Follow-up was conducted by telephone, or in-person at the time of blood collection	**Secondary outcomes:** Composite endpoint of hospitalization for heart failure, myocardial infarction, ischemic stroke, intracerebral hemorrhage, or death.	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 (sub group 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, 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,	As per original trial + intracerebral hemorrhage (ICH)	Age and country of origin were the only sub groups 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) 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			WBC, serum sodium, hematocrit, and hemoglobin.		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** **RCT** ***Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial***	CA: ☑ Blinding: Patient ☑ (aspirin and clopidogrel groups) Assessor☑ ITT: ☑	1,587 patients recruited from 142 centres in US, Canada and the UK, ≥18 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%	Patients were randomized to receive 162 mg aspirin daily (n=523), 75 mg 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.	**Primary outcome:** Composite of all-cause mortality, nonfatal MI, and nonfatal stroke. **Secondary outcomes:** Components of the primary end point and hospitalizations for heart failure.	The mean duration of follow-up was 1.9 years. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		had suffered a prior stroke			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** **RCT** ***Heart Failure Long-term Antithrombotic (HELAS) Study***	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☒	197 patients aged 20-75 years with symptomatic HF, 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%.	Patients were randomized to receive 2.5-10 mg warfarin daily with a target 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).	**Primary outcome:** Any of the following: non-fatal stroke, peripheral or pulmonary embolism, myocardial (re)infarction, re-hospitalization, exacerbation of heart failure, or death from any cause	The mean duration of follow-up ranged from 18.5- 21.9 months across groups. 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)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			Patients with idiopathic dilated cardiomyopathy (DCM) received warfarin (n=38) or placebo (n=44).		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).

Antithrombotic Treatment for Atherosclerotic Vascular Disease

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Eikelboom et al. 2017 **Canada/ International** ***Cardiovascular Outcomes for People Using Anticoagulation***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	27,395 patients with coronary artery disease, peripheral arterial disease, or both. Mean age was 68.2 years, 22% were women. 3.8% of patients had a previous stroke. 90.6% and 27.3% of patients had a history of coronary artery disease, and peripheral	Patients were randomly assigned (1:1:1) to receive 2.5 mg rivaroxaban twice daily plus 100 mg aspirin once daily, 5 mg rivaroxaban twice daily with an aspirin-matched placebo once daily, or 100 mg aspirin once daily with a rivaroxaban matched	**Primary outcomes:** Composite of cardiovascular death, stroke, or MI **Secondary outcomes:** Ischemic stroke, MI, acute limb ischemia, or death from CHD	The dual therapy arm of the trial was stopped early due to superiority, after a mean of 23 months The primary outcomes occurred in 4.1% of patients taking rivaroxaban plus aspirin, 4.9% on patients taking rivaroxaban and 5.4% in patients taking aspirin.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Strategies (COMPASS)		arterial disease, respectively.	placebo twice daily for the duration of the study		The risk of the primary outcome was significantly lower for patients on dual therapy compared to aspirin alone (HR=0.76, 95% CI 0.66–0.86, p<0.001). The risk of the primary outcome was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (HR=0.90, 95% CI 0.79–1.03, p=0.12). The risk of any stroke was significantly lower for patients on dual therapy compared to aspirin alone (0.9% vs.1.6%; HR=0.58, 95% CI 0.44-0.76, p<0.001). The risk of any stroke was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (1.3% vs. 1.6%, HR=0.82, 95% CI 0.65–1.05, p=0.12). Major bleeding occurred in 3.1% of patients taking rivaroxaban plus aspirin, 2.8% on patients taking rivaroxaban and 1.9% in patients taking aspirin.

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***	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	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	**Primary outcome:** Composite of cerebral infarction, MI, peripheral embolism, vascular death, or intracranial hemorrhage. **Secondary outcomes:** Individual components of the primary outcome, + primary end	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hazard Trial (ARCH)		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.	stopped prematurely (planned recruitment was 372 patients/treatment arm)	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	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) were matched to another patient not taking medications.	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 + 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:**

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

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