Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Acute Antiplatelet Therapy

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ACUTE STROKE MANAGEMENT Writing Group

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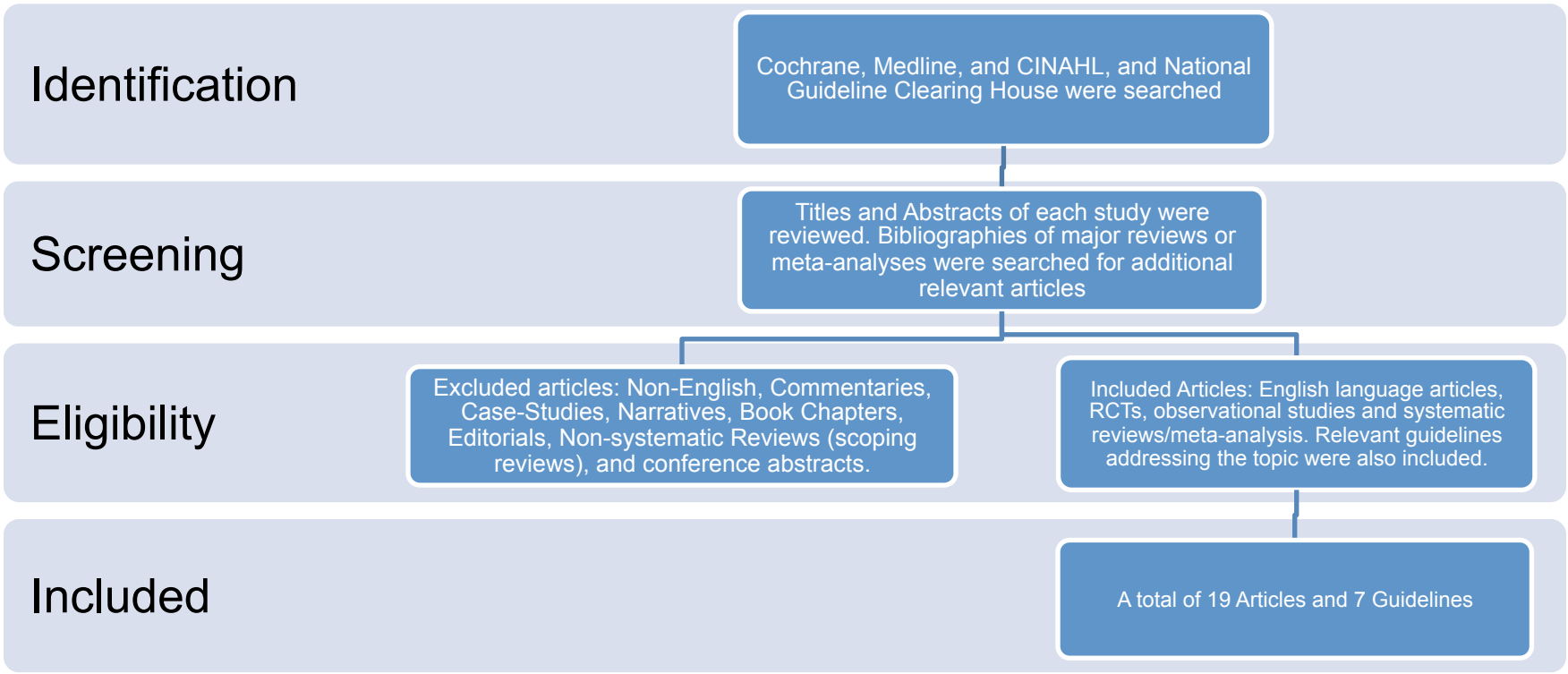
Search Strategy



Cochrane, Medline, and CINAHL, and National Guideline Clearing House were search using the medical subject headings (“Stroke” and “aspirin” or “Dipyridamole” and children or perinatal or neonatal). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 19 articles and 7 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke.* 2018; Mar;49(3):e46-e110**	3.9. Antiplatelet Treatment 1. Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk. Class I; LOE A. 2. Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy. Class III: No Benefit; LOE B-R. 3. The efficacy of IV tirofiban and eptifibatide is not well established. Further clinical trials are needed. Class IIb; LOE B-R. 4. The administration of other glycoprotein IIb/IIIa receptor antagonists, including abciximab, in the treatment of AIS is potentially harmful and should not be performed. Further research testing the safety and efficacy of these medications in patients with AIS is required. Class III: Harm; LOE B-R. 5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset. Class IIa; LOE B-R. 6. Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor stroke. Class III: No Benefit; LOE B-R.
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation.	Strong Recommendation Patients with ischaemic stroke who are not receiving reperfusion therapy should receive antiplatelet therapy as soon as brain imaging has excluded haemorrhage Strong Recommendation AGAINST Acute antiplatelet therapy should not be given within 24 hours of alteplase administration Weak recommendation New Aspirin plus clopidogrel may be used in the short term (first three weeks) in high-risk patients with minor ischaemic stroke or TIA to prevent stroke recurrence.
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	Patients with acute ischaemic stroke should be given aspirin 300mg as soon as possible within 24 hours (unless contraindicated): − orally if they are not dysphagic; − rectally or by enteral tube if they are dysphagic. Thereafter aspirin 300 mg daily should be continued until 2 weeks after the onset of stroke at which time long-term antithrombotic treatment should be initiated. Patients being transferred to care at home before 2 weeks should be started on long-term treatment earlier. Patients with acute ischaemic stroke reporting previous dyspepsia with an antiplatelet agent should be given a proton pump

Guideline	Recommendations
	inhibitor in addition to aspirin. Patients with acute ischaemic stroke who are allergic to or intolerant of aspirin should be given an alternative antiplatelet agent (e.g. clopidogrel).
Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA. **Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines.** ***Chest 2012* Feb;141(2 Suppl):e601S-36S**	Aspirin in Acute Ischemic Stroke In patients with acute ischemic stroke or transient ischemic attack (TIA), the expert panel recommends early (within 48 hours) aspirin therapy at a dose of 160 to 325 mg over no aspirin therapy (Grade 1A). Anticoagulation in Acute Ischemic Stroke In patients with acute ischemic stroke or TIA, the expert panel recommends early (within 48 hours) aspirin therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A). **No recs made for antiplatelet use in pregnancy**
Singapore Ministry of Health. Stroke and transient ischaemic attacks. Assessment, investigation, immediate management and secondary prevention. Singapore: Singapore Ministry of Health; 2009 Jul. 64 p.	A - Antiplatelet therapy, normally aspirin, should be prescribed immediately for patients who have sustained an ischaemic stroke. (Grade A, Level 1+) **No recs made for antiplatelet use in pregnancy**
National Collaborating Centre for Chronic Conditions. Stroke. Diagnosis and initial management of acute stroke and transient ischaemic attack (TIA). London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Jul. 37 p. (Clinical guideline; no. 68).	Aspirin and Anticoagulant Treatment People with Acute Ischaemic Stroke All people presenting with acute stroke who have had a diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given: • Aspirin 300 mg orally if they are not dysphagic • Aspirin 300 mg rectally or by enteral tube if they are dysphagic Thereafter, aspirin 300 mg should be continued until 2 weeks after the onset of stroke symptoms, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatment earlier. Any person with acute ischaemic stroke for whom previous dyspepsia associated with aspirin is reported should be given a proton pump inhibitor in addition to aspirin.

Guideline	Recommendations
	Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin* should be given an alternative antiplatelet agent. *Note: Aspirin intolerance is defined in the NICE technology appraisal guidance 90, 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events,' as either of the following: • Proven hypersensitivity to aspirin-containing medicines • History of severe dyspepsia induced by low-dose aspirin Anticoagulation treatment should not be used routinely for the treatment of acute stroke. (There may be a subgroup of people for whom the risk of venous thromboembolism outweighs the risk of haemorrhagic transformation. People considered to be at particularly high risk of venous thromboembolism include anyone with complete paralysis of the leg, a previous history of venous thromboembolism, dehydration or comorbidities [such as malignant disease], or who is a current or recent smoker. Such people should be kept under regular review if they are given prophylactic anticoagulation. Further details are included in the NICE clinical guideline CG92, 'Venous thromboembolism: reducing the risk'). People with Acute Venous Stroke People diagnosed with cerebral venous sinus thrombosis (including those with secondary cerebral haemorrhage) should be given full-dose anticoagulation treatment (initially full-dose heparin and then warfarin [international normalized ratio (INR) 2–3]) unless there are comorbidities that preclude its use. People with Stroke Associated with Arterial Dissection People with stroke secondary to acute arterial dissection should be treated with either anticoagulants or antiplatelet agents, preferably as part of a randomised controlled trial to compare the effects of the two treatments. People with Acute Ischaemic Stroke Associated with Antiphospholipid Syndrome People with antiphospholipid syndrome who have an acute ischaemic stroke should be managed in same way as people with acute ischaemic stroke without antiphospholipid syndrome. (There was insufficient evidence to support any recommendation on the safety and efficacy of anticoagulants versus antiplatelets for the treatment of people with acute ischaemic stroke associated with antiphospholipid syndrome.) In people with prosthetic valves who have disabling cerebral infarction and who are at significant risk of haemorrhagic transformation, anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted. People with ischaemic stroke and symptomatic proximal deep vein thrombosis or pulmonary embolism should receive anticoagulation treatment in preference to treatment with aspirin unless there are other contraindications to anticoagulation. People with haemorrhagic stroke and symptomatic deep vein thrombosis or pulmonary embolism should have treatment to prevent the development of further pulmonary emboli using either anticoagulation or a caval filter.

Evidence Tables

Aspirin (Antiplatelet)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Rothwell et al. 2016 **UK** **Systematic review & patient-level meta-analysis**	NA	12 RCTs including 15,778 participants with acute ischemic stroke or TIA	Among the included trials, 3 included a comparison of aspirin vs. placebo initiated within 48 hours of stroke onset (IST, 1997, CAST 1997 and Rödén-Jüllig et al. 2003),	**Primary outcome:** Recurrent stroke within 14 days, stratified by stroke severity	Aspirin use reduced the risk of stroke among patients presenting with mild and moderate stroke (OR=0.51, 95% CI 0.34-0.75, p=0.0007 and OR=0.65, 95% CI 0.44-0.98, p=0.04, respectively), but not severe stroke (OR=1.10, 95% CI 0.77-1.58, p=0.60). Among patients with mild and moderate strokes, the risk of recurrent stroke given aspirin therapy was not reduced significantly at 24 hours, but was significantly reduced from days 2 to 14.
Su et al. 2016 **Taiwan** **Retrospective study**	NA	3,802 patients admitted to the ERs of a single hospital system from 2008-2012, ≥20 years with acute ischemic stroke (within 48 hours of symptom onset). Mean age was 68.2 years, 61.5% were male	The outcomes of patients who had received high-dose aspirin (160-325 mg) vs. low-dose aspirin (<160 mg), as a loading dose in the ER, were compared. Propensity matching (3:1) was used to balance baseline differences between groups.	**Primary Outcomes:** Favourable outcome (mRS score ≤1 at hospital discharge **Secondary Outcomes:** In-hospital mortality, stroke progression during hospitalization (≤4 points on NIHSS), major and minor bleeding events	The mean loading doses of aspirin in the groups were high-dose: 211.4 mg (n=3,052) and 100.0 mg (n=750), respectively. After propensity matching, and further adjustment for age, baseline NIHSS, GCS score, DM, HTN, previous stroke, smoking, initial heart rate and fasting glucose level, the risk of the primary outcome was increased significantly for patients in the high-dose group (OR=1.54, 95% CI 1.23-1.93, p<0.01). High-dose aspirin was not associated with a significantly reduced risk of stroke progression or in-hospital mortality (OR=0.82, 95% CI 0.54-1.24, p=0.35 and OR=0.60, 95% CI 0.28-1.27, p=0.18, respectively). High-dose aspirin was associated with a significantly increased risk of minor bleeding events (OR=2.16, 95% CI 1.23-3.78, p<0.01), but not major bleeding events (OR=1.10, 95% CI 0.44-2.72, p=0.83).
Xian et al. 2016 **USA**	NA	85,072 patients included in the Get with the Guidelines Stroke	The clinical outcomes of patients who had received antiplatelet	**Primary outcome:** Symptomatic ICH (sICH) within 36 hours, in-hospital	38,844 (45.7%) were receiving antiplatelet therapy. Patients receiving antiplatelet therapy before

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		Registry who had been admitted to one of 1,545 registry hospitals from 2009-2015, who received iv t-PA within 4.5 hours of symptom onset.	therapy within 7 days of stroke were compared with patients not taking antiplatelet agents. Antiplatelet therapy was classified as: aspirin alone, a combination of aspirin and dipyridamole, clopidogrel alone, and dual antiplatelet therapy with aspirin and clopidogrel.	mortality, discharge ambulatory status and mRS score 0-1 and 0-2 **Secondary outcomes:** Life-threatening or serious systemic hemorrhage within 36 hours, any tPA complication within 36 hours and discharge destination Analyses were adjusted for baseline prognostic factors	admission were older (median age, 76 vs 68), had a greater prevalence of cardiovascular risk factors, and were more likely to receive antihypertensives or medications to lower cholesterol or glucose levels but were less likely to receive anticoagulants before admission (p < .001 for all). Patients receiving prior antiplatelets were significantly more likely to experience sICH (5.0 vs. 3.7%, adj OR=1.18, 95% CI 1.10-1.28, p<0.001). A significantly higher proportion of patients had mRS scores of 0-1 and 0-2 at hospital discharge (OR=1.14, 95% CI 1.07-1.22, p<0.001 and OR=1.16, 95% CI 1.09-1.24, p<0.001, respectively). There was no difference between groups in the odds of in-hospital mortality. Patients taking antiplatelets had higher odds of experiencing a life-threatening or serious systemic hemorrhage or any t-PA complication. **Aspirin only** In the sub group of patients taking aspirin prior to stroke, the odds of sICH were increased significantly (4.6% vs. 3.3%, adj OR=1.19, 95% CI 1.06-1.34), as were the odds of being independent in ambulation (adj OR=1.09, 95% CI 1.03-1.15) and having a mRS score of 0-1 and 0-2 at hospital discharge (OR=1.16, 95% CI 1.07-1.26 and OR=1.16, 95% CI 1.08-1.2, respectively).
Sandercock et al. 2014 **UK** **Cochrane Review**	NA	8 RCTs (n=41,483 patients) of any age or sex with presumed ischaemic stroke. In 4 of the trials, patients were recruited within 48 hrs of stroke. In the remaining trials, patients were	Trials compared either a single oral antiplatelet agent or a combination of antiplatelet agents with control (placebo or no treatment). Treatment contrasts	**Primary Outcomes:** Death or dependency, at least 1-month post stroke. **Secondary Outcomes:** Death (during treatment or at scheduled follow-up, evidence of DVT, evidence of	Two trials testing aspirin, started within 48 hours of onset, contributed 98% of the data (CAST 1997, IST 1997). Antiplatelet therapy was associated with a significant reduction in the odds of being dead or dependent at final follow-up (OR=0.95, 95% CI 0.91 to 0.99, p= 0.01). Results from 8 trials included.

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		recruited an average of 72 hrs, (n=1), 6 days (n=1) and 4 weeks (n=2) following stroke onset.	included: 160-325 mg aspirin daily vs. placebo (n=3), aspirin + dipyridamole and/or heparin vs. placebo (n=2), ticlopidine vs. placebo (n=2) and ticlopidine vs. no treatment (n=1). Treatment duration ranged from 5 days to 3 months following stroke. Follow-up periods were 10 days, 3 weeks (n=2), 4 weeks, 3 months (n=2) and 6 months (n=2)	pulmonary embolus, recurrence of stroke (combined and by stroke type), and complete recovery (post-hoc analysis), ICH.	For aspirin, for every 1,000-people treated, 13 fewer people would avoid death or dependency (NNTB 79) Treatment was associated with a marginally significant reduction in death during treatment at the end of the treatment period (OR= 0.92, 95% CI 0.85 to 1.00, p=0.05). Results from 8 trials included. For aspirin, for every 1,000-people treated, 9 fewer people would avoid death (NNTB 108). Treatment was associated with a significant reduction in the odds of death at a final follow-up (OR=0.92, 95% CI 0.87 to 0.99, p=0.01). NNTB=108. Results from 8 trials included. Treatment was not associated with a decreased risk of DVT: OR=0.78, 95% CI 0.36 to 1.67, p>0.05. Results from 2 trials included. Treatment was associated with a decreased risk of PE (OR=0.71, 95% CI 0.53 to 0.96, p=0.03. NNTB=693. Results from 7 trials included. Treatment was associated with a decreased risk of recurrent ischemic/unknown stroke: OR=0.77, 95% CI 0.69 to 0.87, p<0.0001. NNTB=140. Results from 7 trials included. Treatment was associated with an increased risk of recurrent ICH: OR=1.23, 95% CI 1.00 to 1.50, p=0.04. NNTH=574. Results from 7 trials included. Treatment was associated with reduced risk of any recurrent stroke (net reduction): OR=0.88, 95% CI 0.79 to 0.97, p=0.01. NNTB=200. NNTB=200. Results from 7 trials included. Major extracranial hemorrhage: OR=1.69, 95% CI 1.35 to 2.11, p<0.001. NNTH=245. Results from 7 trials included. Complete recovery: OR=1.06, 95% CI 1.01 to 1.11,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					p=0.02. NNTB=89. Results from 2 trials included.
Roden-Jullig et al. 2003 **Sweden** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	441 patients admitted to one of 4 hospitals with acute ischemic stroke. Included patients had not been treated with antiplatelet drugs within the 72 hours preceding stroke onset. Mean age was 74 years. The mean Scandinavian Stroke Scale score at admission was 13	Patients were randomized to receive 325 mg aspirin (n=220) or placebo (n=221), initiated 48 hours post onset and continuing for 5 consecutive days	**Primary Outcomes:** Progression of stroke symptoms (decrease of ≥2 points on the SSS scale) within the 5-day treatment period. **Secondary Outcomes:** SSS at discharge and at 3 months, discharge destination, ambulatory status	Aspirin therapy did not significantly reduce the risk of stroke progression (15.9% vs. 16.7%, OR=0.95, 95% CI 0.62-1.45) during the treatment period. At the point of discharge there were no significant differences between groups (aspirin vs. placebo) % discharged home: 60.6% vs. 64.1% % able to walk without aid: 51.9% vs. 58.4% Mean SSS score: 10.9 vs. 10.2 Death: 2.7% vs. 3.2% At 3 months, there were no significant differences between groups (aspirin vs. placebo) % able to walk without aid: 60.2% vs. 64.8% % living at home: 80.3% vs. 84.0% Death: 6.8% vs. 5.4%
Berge & Sandercock 2002 **UK** **Cochrane Review**	NA	4 RCTs (n=16,558) including patients with confirmed ischemic stroke. All patients were randomized within 48 hrs. of stroke onset. Studies that included primarily patients with hemorrhagic strokes or TIAs were excluded. Studies that investigated agents with multiple modes of action (e.g., piracetam) were also excluded.	Treatment contrasts included: UHF vs 300 mg aspirin daily (n=1), LMWH vs. 160 mg aspirin daily (n=1), UHF vs. 333 mg aspirin +LMWH daily (n=1) and hi vs. low dose LMWH vs. 300 mg aspirin (n=1). Treatment duration was 10 (n=2) or 14 (n=2) days.	**Primary Outcome:** Death or dependency (defined as dependence on other for ADLs or mRS>2), at least one-month post stroke **Secondary Outcomes:** Death (during treatment or at scheduled follow-up, evidence of DVT, evidence of pulmonary embolus, progression of symptoms, and recurrent stroke (combined and by stroke type).	**Anticoagulant vs. Antiplatelet:** Death or dependency: OR=1.07, 95% CI 0.99 to 1.15, p=0.085 (all patients). Results from 3 trials included; OR=1.10, 95% CI 0.90 to 1.35, p>0.05 (patients with atrial fibrillation). Death: OR=1.10, 95% CI 1.01 to 1.21, p=0.035. NNTH=20 (at follow-up); OR=1.04, 95% CI 0.92 to 1.19, p=0.54 (during the treatment period). Deep vein thrombosis: OR=1.03, 95% CI 0.31 to 3.40, p=0.97 (asymptomatic or symptomatic); OR=0.19, 95% CI 0.07 to 0.58, p=0.0031, NNTB=10 (symptomatic only) Pulmonary embolism: OR=0.85, 95% CI 0.55 to 1.32, p=0.47. Recurrent ischemic/unknown stroke: OR=1.09, 95% CI 0.89 to 1.33, p>0.05. Recurrent intracerebral hemorrhage: OR=2.27, 95% CI 1.49 to 3.46, p<0.05, NNTH=10 (significantly greater risk in trials using high dose anticoagulants).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Any recurrent stroke (net reduction): OR=1.20, 95% CI 0.99 to 1.46, p>0.05 (low and high dose UFH); OR=1.38, 95% CI 1.05 to 1.82, p<0.05 (high dose only) Major extracranial hemorrhage: OR=1.94, 95% CI 1.20 to 3.12, p<0.05, NNTH=5.
Chen et al. 1997 ***Chinese Acute Stroke Trial (CAST)*** **China** **RCT (factorial)**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	21,106 patients with acute ischemic stroke onset (<48 hours) with no contraindications for treatment with aspirin. Mean age at baseline was 63 years. 72% of patients were male.	Patients were randomized to receive 160 mg/day of aspirin (n=10,554) or placebo (n=10,552) for 14 days.	**Primary outcome:** Death from any cause **Secondary outcomes:** Fatal/nonfatal recurrent stroke events	There were significantly fewer deaths among patients in the aspirin group (3.3% vs. 3.9%, p=0.04), corresponding to an absolute benefit 5.4/1,000 fewer deaths. There was a non-significant reduction in the number of deaths due to recurrent stroke among patients in the aspirin group (1.0% vs. 1.2% (absolute benefit of 0.9/1,000, p>0.10). There was a non-significant reduction in the number of all strokes among patients in the aspirin group (3.2% vs. 3.4% (absolute benefit of 1.6/1,000, p>0.10). There was a significant reduction in the number of ischemic strokes among patients in the aspirin group (1.6% vs. 2.1% (absolute benefit of 4.7/1,000, p<0.01). There was a significant reduction in the number of deaths/nonfatal strokes among patients in the aspirin group (5.3% vs. 5.9%, absolute benefit of 6.8/1,000, p=0.03). At hospital discharge, there was no difference between groups in the number of patients who were dead or dependent (mRS≥3) (30.5% vs. 31.6%, p=0.08). Aspirin therapy was associated with a significant excess of 2.7/1,000 transfused or fatal extracranial bleeds during the treatment period (0.8% vs. 0.6%, p=0.02).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Intravenous Antiplatelet					
Zinkstok et al. 2012 **Netherlands** ***Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke (ARTIS) Trial***	Concealed Allocation: ☑ Blinding: Assessor ☑ ITT: ☑	642 patients with acute ischemic stroke undergoing alteplase treatment (protocol sample size = 800).	Participants were randomized to receive 300mg of aspirin intravenously within 90 min. of alteplase treatment (n=322) or standard treatment (n=320). All patients received aspirin therapy 24 hours following alteplase treatment. The trial was terminated due to excess symptomatic intercranial hemorrhage (SICH) and lack of benefit in the intervention group.	**Primary Outcomes:** Favourable outcome (mRS=0-2) at 3-months. **Secondary Outcomes:** Mortality at 3 months, NIHSS at 7-10 days, SICH, and severe systemic bleeding.	At the three-month follow-up, 54% of patients in the intervention group achieved a good outcome, as compared to 57.2% of patients in the control group (adj. OR=0.91, 95% CI 0.66 to 1.26, p>0.05). A non-significant tread was reported comparing the 3-month mortality rate in the aspirin group (11.2%) and the control group (9.7%, p=0.54). 4.3% of patients receiving early aspirin therapy experienced a symptomatic ICH compared to 1.6% in the control group (RR=2.78, 95% CI 1.01 to 7.63, p=0.04).

Dual & Triple Antiplatelet Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dual Antiplatelet Therapy					
Johnston et al. 2018 **USA/ International** ***Platelet-Oriented Inhibition in New TIA & Minor Ischemic Stroke (POINT) Trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,881 patients from 269 sites, ≥ 18 years, with high-risk TIAs ($ABCD^2$ score ≥4), or minor ischemic stroke (NIHSS ≤3), randomized within 12 hours of the time last known free of new ischemic symptoms. Mean age was 65 years, 55% were men. Qualifying events: minor stroke 57%; TIA 43%.	Patients were randomized 1:1 to receive 75 mg/day clopidogrel (loading dose of 600 mg) for 90 days vs. placebo. Patients in both groups received open-label aspirin (a dose of 162 mg daily for 5 days, followed by 81 mg daily dose). The first dose of study medication was given no later than 12 hours from symptom	**Primary outcome:** New ischemic vascular events (ischemic stroke, MI or ischemic vascular death) at 90 days. **Secondary outcome:** Each component of the primary outcome **Primary Safety outcome:** Major hemorrhage	The trial was halted after 84% of patients were recruited because of an excess of major hemorrhage and also efficacy. 93.4% of patients completed the 90-day trial visit or died. Significantly fewer patients in the clopidogrel group had a new vascular event (5% vs. 6.5%, HR=0.75, 95% CI 0.59–0.95, p=0.02). The risks of ischemic and hemorrhagic and ischemic stroke were significantly lower in the clopidogrel group (4.6% vs. 6.3%; HR=0.72, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			onset.		CI 0.56–0.92, p= 0.01 and 4.8% vs. 6.4%; HR=0.74, 95% CI 0.58–0.94, p=0.01, respectively). There were no significant differences between groups in the risks of MI or ischemic vascular death. There were significantly more cases of major hemorrhage in the clopidogrel group (0.9% vs. 0.4%, HR=2.32, 95% CI 1.10–4.87, p= 0.02). There were no significant differences between groups in hemorrhagic stroke or symptomatic ICH. The authors estimated that for every 1000 patients treated with clopidogrel plus aspirin during a period of 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result.
Wang et al. 2013 **China** **RCT** ***Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,170 patients ≥40 years diagnosed with of minor ischemic stroke (NIHSS score of ≤3) or high-risk TIA (ABCD score ≥4) within 24 hours. Median age at baseline was 62 years. 66% of patients were male. 20% of patients had a previous stroke, 3.5% had suffered a TIA.	Patients were randomized to receive clopidogrel (300 mg on day 1, and then 75 mg daily for the duration of the study) +75 mg aspirin for the first 21 days (and placebo for days 22-90) or placebo clopidogrel +75 mg aspirin for 90 days.	**Primary outcome:** Any stroke within 90 days **Secondary outcome:** MI, stroke or vascular death, combined, ischemic stroke, ICH, MI, death from any cause and TIA	Significantly fewer patients in the clopidogrel + aspirin group experienced a stroke within 90 days: Any stroke: 8.2% vs. 11.7%, HR=0.68, 95% CI 0.0.57-0.81, p<0.001 Ischemic stroke: 7.9% vs. 11.4%, HR=0.67, 95% CI 0.56-0.81, p<0.001. Fatal or disabling stroke 5.2% vs. 6.8%, HR=0.75, 95% CI 0.60-0.94, p=0.01 Significantly fewer patients in the clopidogrel + aspirin group experienced an MI, stroke or vascular death stroke within 90 days (8.4% vs. 11.9%, HR=0.69, 95% CI 0.58- 0.82, p<0.001). There was no difference in (any) bleeding events between groups (2.3% vs. 1.6%, p=0.09). A total of 36 patients were lost to follow-up. 5.6% of patients in the aspirin group discontinued the study medication compared with 6.4% in the dual therapy group.
He at al. 2015	CA: ☒	690 patients ≥40 years with	Patients were	**Primary outcomes:**	647 patients completed the trial.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
China **RCT**	Blinding: Patient: ☒ Assessor ☒ ITT: ☒	minor stroke (NIHSS ≤7) or TIA within the previous 72 hours, not of cardioembolic etiology. Mean age was 62 years, 57% were men. 94% of qualifying events were minor stroke.	randomized (1:1) to receive aspirin alone (300 mg/day) or clopidogrel (300 mg for the first day, 75 mg/day thereafter) plus aspirin (100 mg/day) for 2 weeks	Neurological deterioration (defined as an increase of ≥2 points on NIHSS), recurrent stroke, and development of stroke in patients with TIA within 14 days after admission.	9 patients in the monotherapy group experienced a worsening of their stroke, compared with 19 in the monotherapy group. Stroke occurred after TIA in one patient in the dual therapy group and 3 patients in the monotherapy group
Geeganage et al. 2012 **UK** **Systematic review & meta-analysis**	NA	12 RCTs, including patients ≥18 years, who had sustained a noncardioembolic stroke or TIA within the previous 72 hours.	Trials compared dual vs. mono antiplatelet therapy. Treatment contrasts included aspirin + clopidogrel vs. aspirin (4 trials, 731 patients); aspirin + clopidogrel vs. clopidogrel (1 trial, 491 patients); aspirin + dipyridamole vs. aspirin (5 trials, 964 patients); aspirin + dipyridamole vs. dipyridamole (2 trials, 220 patients); and aspirin + dipyridamole vs. clopidogrel	**Primary outcome:** Stroke recurrence **Secondary outcomes:** Combination of stroke, TIA, acute coronary syndrome, and death, composite of nonfatal stroke, nonfatal MI, and vascular death; MI (fatal or nonfatal); and severe stroke (mRS 2– 6)	Based on the results from all trials, dual therapy was associated with significantly reduced risks of recurrent stroke (RR=0.67, 95% CI 0.49-0.93, p=0.02), composite of stroke, MI and vascular death (RR= 0.75; 95% CI, 0.56 – 0.99, p=0.04). Dual therapy was not associated with reduced risks of severe stroke, fatal stroke, or vascular death.
Kennedy et al. 2007 **International** **RCT (factorial)** ***Fast Assessment of Stroke and TIA to prevent Stroke Recurrence (FASTER)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	392 patients ≥40 years, diagnosed with minor stroke (NIHSS score of ≤3) or TIA within previous 24 hours. Mean age was 68 years. 53% of patients were male. <10% of patients had experienced a previous stroke.	All patients received 81 mg aspirin within 24 hours of the qualifying event and then daily for the duration of the 90-day study. Patients were randomized receive: i) clopidogrel (300 mg loading dose, then 75 mg daily thereafter) + placebo, ii) simvastatin (40 mg daily) + clopidogrel, iii) simvastatin, + placebo or	**Primary outcome:** 90-day risk for total stroke **Secondary outcome:** 90-day risk for MI, stroke, & vascular death, combined.	The trial was stopped early because of a failure to recruit. There was a non-significant reduction in the risk of stroke associated with clopidogrel use (7.1% vs. 10.8%, RR=0.7, 95% CI 0.3-1.2, p=0.19). There was a non-significant reduction in the risk of the secondary outcome associated with clopidogrel use (RR=0.7, 95% CI 0.4-1.3, p=0.28). There was a significant 3% increase in risk (p=0.03) for symptomatic bleeding events in the groups allocated to clopidogrel. There was a total of 7 losses to follow-up and 4

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			iv) double placebo.		patients withdrew consent.
Triple Antiplatelet Therapy					
Bath et al. 2017 **UK/ International** **RCT** ***Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	3,096 patients, ≥50 years, with TIA (31%) or mild ischemic stroke (69%) occurring within the previous 48 hours. Mean age was 69 years, 63% were men. 72% of qualifying events were strokes.	Patients were randomized to receive Intensive antiplatelet therapy including Aspirin (50-150 mg od) +Dipyridamole (200 mg bid) + Clopidogrel (75 mg od) for 28-30 days vs. standard guideline therapy with one or two antiplatelet drugs (standard treatment)	**Primary outcome:** Any recurrent stroke within 90 days, severity of stroke (mRS 6; mRS 4-5; mRS 2-3; mRS 0-1) **Secondary outcomes:** Disability (Barthel Index), Mood (Zung Depression Scale) cognition or quality of Life, assessed at 90 days **Safety outcome:** Hemorrhage (fatal, major, moderate, minor and none)	Trial was stopped prematurely (recruitment of 4,100 patients planned), due to futility and safety concerns. There was no significant difference between groups in the incidence or severity of stroke or TIA, using ordinal analysis of mRS (6% intensive therapy vs. 7% guideline therapy, adj cHR=0.90, 95% CI 0.67-1.20, p=0.47). There was no significant difference between groups in 90-day mortality between groups (1% intensive therapy vs. <1% guideline therapy, adj cHR=1.92, 95% CI 0.76-4.84, p=0.17). There were no significant differences between groups on any of the secondary outcomes. The risk of bleeding events was significantly higher in the intensive therapy group (20% vs. 9%, adj cHR=2.54, 95% CI 2.05-3.16, p<0.0001)

Pediatric Aspirin Therapy Published Guidelines

Guideline	Recommendations
Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, Vesely SK. **Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guielines.** ***Chest 2012*;141(2 Suppl):e737S-801S.**	Arterial Ischemic Stroke in Neonates 2.18. For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented, ongoing cardioembolic source, the expert panel suggests supportive care over anticoagulation or aspirin therapy (Grade 2C). 2.19 For neonates with a first AIS and a documented cardioembolic source, the expert panel suggests anticoagulation with UFH or LMWH (Grade 2C). 2.20 For neonates with recurrent AIS, the expert panel suggests anticoagulant or aspirin therapy (Grade 2C).

Guideline	Recommendations
	Children: 1.5. We suggest that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C).
Roach ES, Golomb MR, Adams R et al. **Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young.** ***Stroke* 2008;39:2644-2691.**	Perinatal stroke: no recommendations made Childhood & infant stroke: 1. Aspirin is a reasonable option for the secondary prevention of AIS in children whose infarction is not due to SCD and in children who are not known to have a high risk of recurrent embolism or a severe hypercoagulable disorder (Class IIa, Level of Evidence C). 2. A dose of 3 to 5 mg/kg per day is a reasonable initial aspirin dose for stroke prevention in children (Class IIa,Level of Evidence C). If dose-related side effects occur with this aspirin dose, a dose reduction to 1 to 3 mg/kg may be considered (Class IIb, Level of Evidence C).
Royal College of Physicians, London. Paediatric Stroke Working Group. Paediatric Stroke Working Group. Stroke in childhood: clinical guidelines for diagnosis, management and rehabilitation, 2004.	Aspirin (5 mg/kg/day) should be given once there is radiological confirmation of arterial ischaemic stroke, except in patients with evidence of intracranial haemorrhage on imaging and those with sickle cell disease. (Good practice point)

Pediatric Antithrombotics

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Strater et al. 2001 **Germany** **Controlled study**	NA	135 children aged ≥6 months, ≤18 years admitted to hospital with first occurrence of ischemic stroke. Median age was 7 yrs., 61% male.	Patients received antithrombotic treatment at the discretion of the treating physician. Treatments included aspirin (4 mg/kg/day, n=49) or low molecular weight heparin (enoxaparin 1-1.5 mg/kg/day, or dalteparin (75-125 anti-Xa U/kg/day, n=86) for 6-14 months	**Primary outcome:** Recurrent stroke Patients were followed for 4-48 months (median of 36 months)	Recurrent stroke was confirmed in 13 (9.6%) children. Timing of recurrent stroke ranged from 2-13 months (median of 5 months). Deaths occurred in 3/13 of cases. Of the children who experienced a second stroke, 4 had been treated with aspirin and 9 had been treated with LMWH. There was no significant difference between groups in the risk of subsequent stroke associated with LMWH compared with aspirin therapy (OR=1.3, 95% CI 0.4-4.5, p=0.76). No adverse events were reported for either treatment during the observation period.

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