CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables
Antiplatelet Therapy

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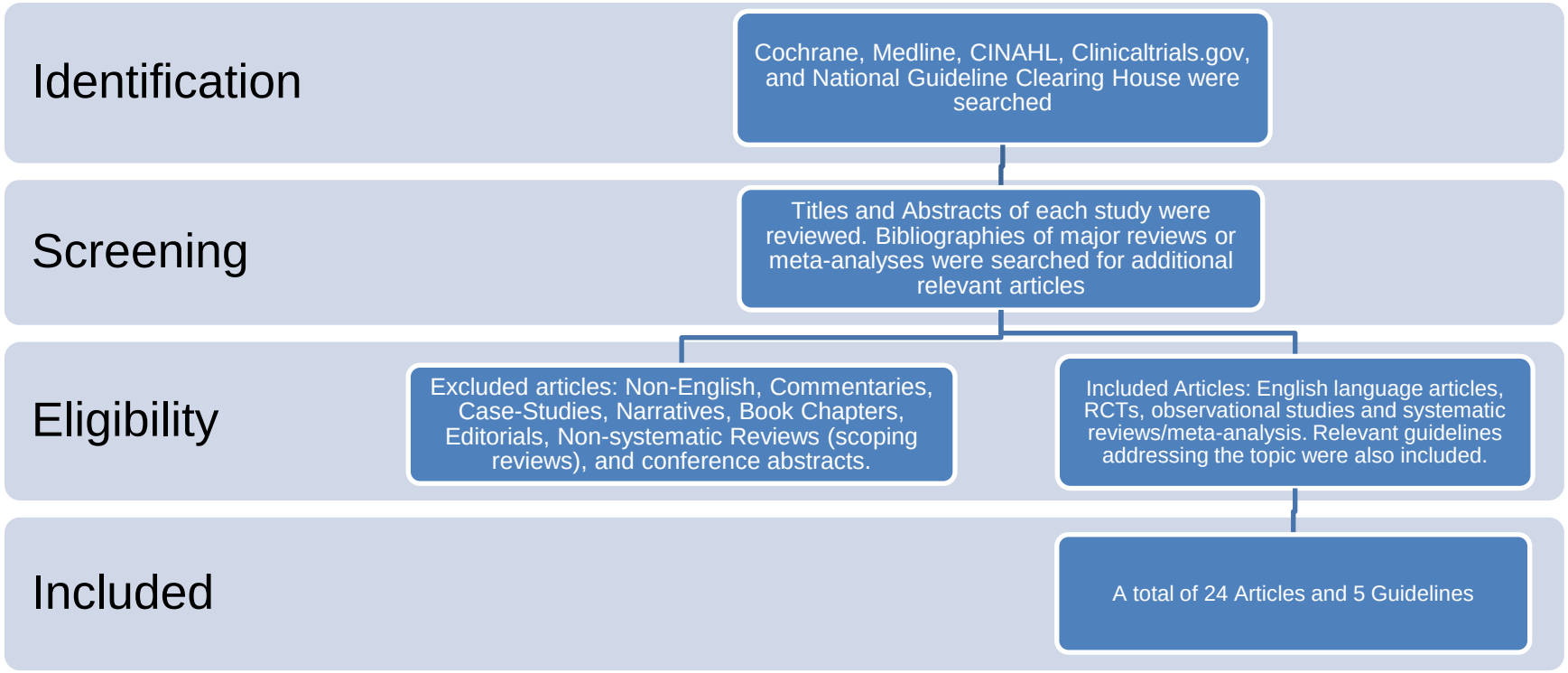
Search Strategy



Cochrane, Medline, CINAHL, National Guideline Clearing House and clinicaltrials.gov were search using the terms (“stroke” AND “dipyridamole” OR “antiplatelet” OR “clopidogrel” OR “blood platelets”). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review.

Published Guidelines

Guideline	Recommendations
National Clinical guidelines for stroke. 5th Edition 2016; Intercollegiate Stroke Working Party. Royal College of Physicians.	A-For long-term vascular prevention in people with ischaemic stroke or TIA without paroxysmal or permanent atrial fibrillation: − clopidogrel 75mg daily should be the standard antithrombotic treatment; − aspirin 75 mg daily with modified-release dipyridamole 200 mg twice daily should be used for those who are unable to tolerate clopidogrel; − aspirin 75mg daily should be used if both clopidogrel and modified-release dipyridamole are contraindicated or not tolerated; − modified-release dipyridamole 200 mg twice daily should be used if both clopidogrel and aspirin are contraindicated or not tolerated. The combination of aspirin and clopidogrel is not recommended unless there is another indication e.g. acute coronary syndrome, recent coronary stent. B- People with ischaemic stroke with haemorrhagic transformation should be treated with long-term antiplatelet therapy unless the clinician considers that the risks outweigh the benefits.
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	**Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Oral Anticoagulant and Antiplatelet Therapies)** • For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I; Level of Evidence A). • Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. (Revised recommendation) • Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Class IIa; Level of Evidence B). This recommendation also applies to patients who are allergic to aspirin. • The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Class I; Level of Evidence C). • The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (Class IIb; Level of Evidence B). (New • recommendation) • The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA (Class III; Level of Evidence A). • For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C)*. • For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA

Guideline	Recommendations
	therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events *(Class IIb; Level of Evidence C)*. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant DAPT/VKA therapy. (New recommendation)
Clinical Guidelines for Stroke Management 2010. National Stroke Foundation, Melbourne, Australia	**Antiplatelet therapy** • Long-term antiplatelet therapy should be prescribed to all people with ischaemic stroke or TIA who are not prescribed anticoagulation therapy. (Grade A) • Low-dose aspirin and modified release dipyridamole or clopidogrel alone should be prescribed to all people with ischeamic stroke or TIA, taking into consideration patient co-morbidities. (Grade A) • Aspirin alone can be used, particularly in people who do not tolerate aspiring plus dipyridamole or clopidogrel (Grade A) • The combination of aspirin plus clopidogrel is NOT recommended for the secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent. (Grade A)
"Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A national clinical guideline" December 2008 **(Scottish Intercollegiate Guidelines Network)**	**Patients with ischaemic stroke or TIA** **Combination Therapy** • Low-dose aspirin (75 mg daily) and dipyridamole (200 mg modified release twice daily) should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events. (Grade A) • Dose titration of dipyridamole may help to reduce the incidence of headache (Grade B) • Clopidogrel (75mg daily) monotherapy should be considered as an alternative to combination aspirin and dipyridamole after ischaemic stroke or TIA for secondary prevention of vascular events. (Grade A) • The combination of aspirin and clopidogrel is not recommended for long term secondary prevention of ischaemic stroke or TIA. (Grade A) **Patients with primary intracerebral haemorrhage** Antiplatelet Agents • The use of aspirin following ICH is not recommended to prevent further vascular events when the risk of recurrence is low. (Grade B) • The use of aspirin following ICH may be considered when there is a high risk of cardiac ischaemic events. (Grade C)
New Zealand **"New Zealand Clinical Guidelines for Stroke Management 2010"** **(Stroke Foundation of New Zealand)**	**Antiplatelet therapy** • Long-term antiplatelet therapy should be prescribed to all people with ischaemic stroke or TIA who are not prescribed anticoagulation therapy (Antithrombotic Trialists, 2002). (Grade A) • Low dose aspirin and modified release dipyridamole or clopidogrel alone should be prescribed to all people with ischaemic stroke or TIA taking into consideration patient comorbidities (Sacco et al, 2008). (Grade B) • Aspirin alone can also be used, particularly in patients who do not tolerate aspirin plus dipyridamole or clopidogrel (Antithrombotic Trialists, 2002). (Grade A) • The combination of aspirin plus clopidogrel is NOT recommended for the secondary prevention of cerebrovascular disease in patients who do not have acute coronary disease or recent coronary stent (Diener et al, 2004; Bhatt et al, 2006). (Grade A)
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **'Guidelines for Management of Ischaemic Stroke and Transient Ischaemic**	**Antithrombotic Therapy** • It is recommended that patients receive antithrombotic therapy (Class I, Level A) • It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A) • The combination of aspirin and clopidogrel is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment should be given for up to 9 months

Guideline	Recommendations
Attack 2008" ***Cerebrovasc Dis* 2008;25:457–507**	after the event (Class I, Level A) • It is recommended that patients who have a stroke on antiplatelet therapy should be re-evaluated for pathophysiology and risk factors (Class IV, GCP) • It is recommended that combined low-dose aspirin and dipyridamole should be given if oral anticoagulation is contraindicated (Class IV, GCP)

Evidence Tables

Aspirin Monotherapy for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Primary & Secondary Prevention					
Baigent et al. 2009 ***Antithrombotic Trialists' Collaborative (ATTC)*** **UK** **Systematic review & meta-analysis (update to 2002)**	NA	18 RCTs examining aspirin therapy for primary (n=6 with 95,456 subjects) and secondary (n=16) prevention of vascular events. In the 3 of the primary prevention trials, participants were at higher risk for coronary heart disease. Trials recruited men only (n=3), women only (n=1) and included both sexes (n=2). Similar details for participants in the secondary prevention trials were not provided.	Aspirin regimens (mg/day) in the primary prevention trials included 75 (n=2), 100 (n=2), 375 (n=1) and 500 (n=1) that was provided for at least 2 years. Persons in the control group received placebo in 3 trials. The mean duration of follow-up ranged from 3.7 to 10 years. Similar details for treatments in the secondary prevention trials were not provided	Any major coronary event (nonfatal MI, CHD death), any stroke, any vascular death.	**Primary Prevention Trials** There was a significant reduction in risk of any serious vascular event associated with aspirin therapy (RR=0.88, 95% CI 0.82-0.94, p=0.0001), representing a difference of an average of 0.51% vs. 0.57% vascular events per year. There was no significant reduction in the risk of any stroke (RR=0.95, 95% CI 0.85-1.06, p=0.40), fatal stroke (RR=1.21, 95% CI 0.84-1.74) or nonfatal stroke (RR=0.92, 95% CI 0.79-1.07). **Secondary Prevention Trials** There was a reduced risk of any subsequent stroke (RR=0.81, 95% CI 0.68-0.96) and stroke of unknown cause (RR=0.77, 95% CI 0.62-0.96). **Primary & Secondary Prevention Trials Combined** There was a significant increase in the risk of ICH (RR=1.39, 95% CI 1.08-1.78, p=0.01) and fatal ICH (RR=1.74, 95% CI 1.20-2.53, p=0.004) associated with aspirin use. Aspirin use was associated with a significant reduction in the risk of ischemic stroke (RR=0.83, 95% CI 0.73-0.95, p=0.005), but not any fatal stroke (RR=1.15, 95% CI 0.94-1.14, p=0.20). The risk of major gastrointestinal and other extracranial bleeds was significantly increased in persons taking aspirin (RR=1.54, 95% CI 1.30-1.82, p<0.0001).
Antithrombotic	NA	287 RCTs (n=135,000)	In 9 of these trials, long-	Any vascular event (MI,	In the trials that included persons with previous

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
***Trialists' Collaborative* 2002** **UK** **Systematic review & meta-analysis**		examining any antiplatelet therapy for the prevention of vascular events in high-risk patients.	term aspirin monotherapy was examined in patients who had experienced a previous stroke or TIA	stroke or vascular death)	stroke, fewer patients receiving aspirin therapy experienced a vascular event (8.2% vs. 9.1%) representing an 11% odds reduction. In 65 trials examining aspirin monotherapy, the reduction in the odds of any vascular event, for a given dose were: 500-1,500 mg:19% (data from 34 studies) 160-325 mg: 26% (data from 19 studies) 75-150 mg: 32% (data from 12 studies) <75 mg: 13% (data from 3 studies) Any aspirin: 23% For aspirin doses <325 mg, the risk of a major extracranial bleed was not increased relative to the control group (OR=1.7, 95% CI 0.8-3.3)
ii) Secondary Prevention					
Thompson et al. 2015 **UK** **Meta-analysis**	NA	The results from 3 trials were included- International Stroke Trial, Chinese Acute Stroke Trial and Multicentre Acute Stroke Trial (n=39,166)	Aspirin vs. placebo following acute ischemic stroke using individual patient-level data. Analysis to determine if patients at higher risk or thrombosis, lower risk of hemorrhage and higher risk of poor functional outcome, would all have a lower risk of poor functional outcome, if treated with aspirin, compared to an "average" patient.	**Primary outcomes:** Prediction of early thrombotic events including MI, ischemic stroke, DVT and pulmonary embolism (PE) and hemorrhage at 14 days, poor functional outcome (mRS 3-6) at 6 months	Overall, the absolute reduction in thrombotic events associated with aspirin therapy was 6/1000 (95% CI 3-10, p=0.0004), the increased risk of hemorrhage was 5/1000 (95% CI 3-7, p<0.0001) and the reduction in poor outcome at 6 months was 12/1000 (95% CI 2-21, p=0.0135). Independent predictors of thrombosis within 14 days of event were increased age (/10 years, OR=1.21, 95% CI 1.07-1.38, p=0.0027), and visible infarction evident on CT (OR=1.52, 95% CI 1.17-1.98, p=0.0019). There were no independent predictors of hemorrhage at 14 days. Both models performed poorly. Discrimination between patients with and without thrombosis and hemorrhage, after adjustment for all baseline variables was just above chance. Independent predictors of poor outcome at 6 months were younger age, lower blood pressure, female sex, drowsy/coma at randomization and an increasing number of stroke-related impairments. This model performed well (AUC 0.77, 95% CI 0.76-0.78)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					In analysis of outcome based on predicted risk of thrombosis and hemorrhage using tertiles, there was no evidence of increased harm or benefit associated with aspirin. In the analysis of predicted risk of poor outcome, using deciles, there was no evidence of increased harm or benefit associated with aspirin.
Chinese Acute Stroke Trial (CAST) Collaborative Group 1997 **China** **RCT (factorial)**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	21,106 patients with acute ischemic stroke onset 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, within 48 hours of stroke onset	**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).

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

Clopidogrel vs. Aspirin for the Prevention of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Gent et al. 1996 **International** **RCT** ***Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE*)**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	19,185 patients who had experienced an ischemic stroke (n= 6,431), thought to be of atherothrombotic origin, with onset ≥1 week or ≤6 months previously, or who had experienced MI (n=6,302) or had peripheral artery disease (PAD) (n=6,452). Mean age at baseline was 62.5 years. 72% of patients were male. Among patients in the stroke subgroup, mean time from stroke onset to randomization was 53 days.	Patients were randomized to receive 75 mg tablets of clopidogrel + aspirin placebo or 325 mg tablets of aspirin plus clopidogrel placebo, daily for 1-3 years.	**Primary outcome:** First occurrence of ischemic stroke, MI or vascular death. **Secondary outcomes:** Amputations	Mean duration of follow-up was 1.91 years. Clopidogrel was associated with a reduced risk of the primary outcome (event rate/year 5.32% vs. 5.83%, RRR=8.7%, 95% CI 0.3%-16.5%, p=0.043). Among the subgroup of patients with a history of stroke, there was no significant reduction in the risk of the primary outcome (event rate/year 7.15% vs. 7.71%, RRR=7.3%, 95% CI -5.7%-18.7%, p=0.26). Patients in the peripheral arterial disease subgroup taking clopidogrel experienced the greatest risk reduction in the primary outcome. There were 44 losses to follow-up and 0 withdrawals. There were more cases of nonfatal primary intracranial hemorrhage or hemorrhagic death or hemorrhagic death among patients in the aspirin group (0.53% vs. 0.39%).

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

Ticagrelor vs. Aspirin for the Prevention of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Johnston et al. 2016 **USA/International** **RCT** ***Acute Stroke or***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	13,199 patients ≥40 years, recruited from 674 sites in 33 countries who had suffered a minor acute ischemic stroke (NIHSS score of ≤5) or high-risk TIA (ABCD^2	Patients were randomized to receive either ticagrelor (n=6,589; loading dose of 180 mg, followed by 180 mg daily for days 2-90 + aspirin placebo) or	**Primary outcome:** First occurrence of any event from the composite of stroke (ischemic or hemorrhagic), MI, or death **Secondary outcome:**	By 90 days, the primary endpoint occurred in 6.7% of patients in the ticagrelor group vs. 7.5% in the aspirin group (HR=0.89, 95% CI 0.78-1.01, p=0.07). By 90 days there were fewer occurrence of both ischemic stroke and all stroke in the ticagrelor

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES)		score of ≥4) or symptomatic intracranial or extracranial arterial stenosis) and could undergo randomization within 24 hours after symptom onset. Patients were not eligible if other antiplatelet or anticoagulation therapy was planned, or if revascularization procedures were planned that would require halting study treatment within 7 days after randomization. Mean age was 65.9 years, 41.5% were male. The qualifying events were ischemic stroke (73% and TIA (27%). Approx. 35% of patients were taking aspirin or clopidogrel prior to randomization	aspirin (n=6,610; loading dose of 300 mg, followed by 300 mg daily for days 2-90+ ticagrelor placebo)	Ischemic stroke, composite of ischemic stroke, MI or cardiovascular death, all stroke, disabling stroke, fatal stroke, MI death, cardiovascular death **Safety outcomes:** Major bleeding, fatal or life-threatening bleeding, ICH	group (5.8% vs. 6.7%, HR=0.87, 95% CI 0.76-1.00, p=.046 and 5.9% vs. 6.8%, HR=0.86, 95% CI 0.75-0.99, p=0.03, respectively). *The p values were not considered significant per their statistical plan.* There were no significant differences between groups in the risk of disabling stroke, fatal stroke, MI, death or cardiovascular death. The incidences of major bleeding events were 0.5% in the ticagrelor groups vs. 0.6% in the aspirin group (HR=0.83, 95%CI 0.52-1.34, p=0.45). The incidences of major, fatal or life-threatening bleeding events were 0.3% in the ticagrelor groups vs. 0.4% in the aspirin group (p=0.45). The incidences of major or minor bleeding events were 1.6% in the ticagrelor groups vs. 1.2% in the aspirin group (p=0.45). There were no significant differences between groups in sub group analyses of age, sex, race, weight, BMI, region, type of qualifying event, comorbidities, time from event to randomization, previous stroke/TIA previous antiplatelet therapy, previous MI or CAD

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

Dual vs. Monotherapy with Clopidogrel for the Prevention of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Clopidogrel + aspirin vs. aspirin alone					
Ge et al. 2016	NA	9 RCTs (n=21,923 patients) comparing dual	Treatments included aspirin + clopidogrel vs.	Stroke or TIA recurrence	DAPT was associated with a significantly reduced risk of ischemic stroke (RR=0.79, 95% CI 0.66-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
China **Systematic review & meta-analysis**		antiplatelet therapy (DAPT) vs. monotherapy. Trials with follow-up of <7 days and high-dose aspirin were excluded. Mean age was 64 years	aspirin (n=8) and aspirin +clopidogrel vs. clopidogrel (n=1). Target doses of aspirin ranged from 75-162 mg daily and 75 mg clopidogrel daily. Duration of treatment ranged from 7 days to 3.4 years		0.94, p=0.008) and major vascular events (RR=0.85, 95% CI0.78- 0.92, p<0.0001), but an increased risk of major bleeding and intracranial hemorrhage (RR=1.83, 95% CI 1.38- 2.43, p<0.001 and RR=1.54, 95% CI 1.09- 2.19, p=0.02). In a stratified analysis comparing short-term use (≤3 months) with long-term use (≥1 year), short-term use (n=6 trials) was associated with a significant reduction in the risk of stroke recurrence and major vascular events, but without a significant increase in the risk of intracranial hemorrhage. Long-term DAPT was not associated with a significantly reduced risk of ischemic stroke and major vascular events, but increased the risks of major bleeding (RR= 1.90; 95% CI 1.46–2.48; and intracranial hemorrhage (RR= 1.61; 95% CI 1.09–2.37).
Palacio et al. 2015 **USA** **Systematic review & meta-analysis**	NA	13 RCTs (90,433 patients) that compared clopidogrel + aspirin vs. aspirin. Mean age was 63 yrs, 63% were male.	3 groups of trials were assembled: including patients with stable vascular disease (n=5), patients with vascular events occurring within previous ≤30 days (n=5) and patients that had undergone perioperative or percutaneous interventions (n=3)	**Primary outcome:** All stroke **Secondary outcomes:** Stroke sub types, major hemorrhage	Mean follow-up was 1.0 years. Overall, the use of clopidogrel+ aspirin was associated with significantly reduced odds of any stroke (OR=0.81, 95% CI 0.74-0.89). The odds were reduced for patients with stable vascular disease (OR=0.82, 95% CI 0.69-0.97) and for patients with a recent vascular event (OR=0.84, 95% CI 0.72-0.98). The use of dual therapy was associated with a significant reduction in the odds of ischemic stroke (overall: RR=0.77, 95% CI 0.70-0.85) with similar reductions in patients with stable vascular disease and recent vascular events. The use of dual therapy was associated with a non-significant increase in the odds of ICH (OR=1.12, 95% CI 0.86-1.46). Results from 10 RCTs included.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The use of dual therapy was associated with a significant increase in the odds of major hemorrhage (OR=1.40, 95% CI 1.26-1.55). Results from 13 RCTs included. Among 4 RCTs that included patients with recent ischemic stroke (CARESS, CHARISMA, CLAIR, FASTER), the odds of all stroke and ischemic/unknown stroke were significantly reduced (OR=0.67, 95% CI 0.46-0.97 and OR=0.64, 95% CI 0.43-0.94, respectively). The odds of major hemorrhage were not significantly increased (OR=0.91, 95% CI 0.40-2.07).
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.
Wong et al. 2013 **China** **Systematic review & meta-analysis**	NA	5 RCTs examined the risk of stroke recurrence associated with clopidogrel + aspirin vs. aspirin alone. The 5 included trials (CARESS, CHAISMA,	Most of the trials compared a daily dose of clopidogrel 75 mg clopidogrel (with an initial loading dose of 300 mg) + 75-160 mg aspirin vs. aspirin alone. Treatment periods were 7 days	Risk of recurrent stroke, composite outcome of stroke, TIA, acute coronary syndrome, death from all causes	Fewer patients receiving dual therapy experienced a recurrent stroke (RR=0.70, 95% CI 0.59-0.82, p<0.001) as well as the composite outcome of vascular events/death (RR=0.71, 95% CI 0.62-0.82, p<0.001) with no significant increase in major bleeding events (RR=1.24, 95% CI 0.51-3.00, p=0.63).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		FASTER, CLAIR and CHANCE) are described above.	(n=2), 90 days (n=2) and 28 months.		The risk of the composite outcome was significantly reduced in studies in which patients received dual therapy (RR=0.71, 95% CI 0.62-0.82, p<0.0001).
Benavente et al. 2012 **Canada** **RCT** ***Secondary Prevention of Small Subcortical Strokes (SPS3) Trial (antiplatelet arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3020 participants, mean age of 63 years, who had sustained a confirmed lacunar stroke within the previous 180 days. Participants with disabling stroke, or previous ICH or cortical stroke, were excluded.	Patients were randomized to receive 325 mg of enteric coated aspirin + 75 mg clopidogrel daily or aspirin + placebo for the duration of the study	**Primary outcome:** Recurrent stroke **Secondary outcomes:** Myocardial infarction and death	Mean duration of follow-up was 3.4 years. Clopidogrel + aspirin therapy was not associated with significant reductions in any of the study outcomes. All stroke: HR=0.92, 95% CI 0.72-1.16, p=0.48 Disabling or fatal stroke: HR=1.06, 95% CI 0.69-1.64, p=0.79 MI: HR=0.84, 95% CI 0.52-1.35, p=0.47 Death (vascular cause): HR=1.46, 95% CI 0.81-2.64, p=0.20 Clopidogrel + aspirin was associated with a significant increase in death from any cause: HR=1.52, 95% CI 1.14-2.04, p=0.004). In subgroup analysis examining age, sex, history of diabetes, race, region of residence and aspirin use at the time of index event, no significant interactions were reported. The risk of all major hemorrhages was increased significantly in the active dual therapy group.
Cote et al. 2014 **Subgroup analysis of SPS3 Trial** **Canada** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	838 patients who were on aspirin therapy at the time of the qualifying event (i.e., aspirin failures). Mean age:66 years, 65% men	Patients were randomized to receive 325 mg of enteric coated aspirin + 75 mg clopidogrel daily or aspirin + placebo for the duration of the study	**Primary outcome:** Recurrent stroke **Secondary outcomes:** Myocardial infarction and death	The median time from qualifying event to randomization was 77 days. Patients taking ASA prior to the index event were older, and a greater proportion had vascular risk factors. Clopidogrel + aspirin therapy was not associated with significant reductions in stroke (HR=0.91, 95% CI 0.61-1.37, p=0.66) or MI (HR=0.99, 95% CI 0.49-2.04, p=0.99) Clopidogrel + aspirin was associated with a significant increase in death from any cause and vascular death.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Comparing the cohort of patients who had not been taking aspirin at the time of the qualifying event (n=2151), those taking aspirin were at higher risk for ICH. There were no significant differences between groups in the risks of all stroke, major bleeding, MI, or death.
Wong et al. 2010 **International** **RCT** ***Clopidogrel plus Aspirin versus Aspirin alone for Reducing embolization in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis (CLAIR)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☒	100 patients ≥18 years with a clinical diagnosis of acute ischemic stroke or TIA (symptom onset within 7 days) who had symptomatic large artery stenosis in the cerebral or carotid arteries and microembolic signals detected by transcranial doppler. Mean age at baseline was 58 years. 78% of patients were men.	Patients were randomized to receive dual therapy with clopidogrel (300 mg day 1, followed by 75 mg thereafter) + 75-160 mg aspirin or 75-160 mg aspirin only, for 7 days.	**Primary outcome:** Proportion of patients with at least one microembolic signal detected on day 2. **Secondary outcomes:** The number of microembolic signals on days 2 and 7, proportion of patients with at least one microembolic signal on day 7, number of new acute infarctions, NIHSS score at day 7, modified Rankin scale score at day 7 and mortality at day 7.	There were significantly fewer patients with at least one microembolic signal on day 2 in the group treated with combination therapy (31% vs. 54%, RRR=42.4%, 95% CI 4.6%-65.2%, p=0.025) and at day 7 (23% vs. 51%, RRR=54.4%, 95% CI 16.4%-75.1%, p=0.006). There were no between-group differences on any of the secondary outcomes. There were no deaths during the study. There were 5 adverse events reported in patients in the monotherapy group vs. 9 (1 severe) in the dual therapy group.
Connolly et al. 2009 **International** **RCT** ***Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE A)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	7554 patients with atrial fibrillation +at least one other stroke risk factor (eg. ≥75 yrs, hypertension, previous stroke or TIA). Patients at increased risk for hemorrhage were excluded. Mean age was 71 yrs, 58% were male. 13.2% had experienced a previous stroke or TIA	All patients received 75-100 mg aspirin daily Patients were randomized to receive 75 mg clopidogrel (n=3722) or placebo (n=3782) for the duration of the study	**Primary outcome:** Major vascular events **Secondary outcome:** Stroke, individual components of the primary outcome and composite of primary outcome and major hemorrhage	Mean follow-up was 3.6 years. At one year 39% and 37% of patients had discontinued the active treatment and placebo, respectively. The risk of the primary outcome was decreased significantly among patients in the active treatment group (6.8% vs. 7.6% events/year; RR=0.89, 95% CI 0.91-0.98, p<0.01). The risk of any stroke was decreased significantly among patients in the active treatment group (1.6% vs. 2.1% events/year; RR=0.74, 95% CI 0.62-0.89, p<0.001). The risk of disabling or fatal stroke was decreased significantly among patients in the active treatment group (2.4% vs. 3.3% events/year; RR=0.72, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					CI 0.62-0.83, p<0.001). Active intervention was not associated with significant reductions in the risk of death from vascular causes or death from any cause (RR=1.00, 95% CI 0.89-1.12, p=0.97 and RR=0.98, 95% CI 0.89-1.08, p=0.69). The risks of major bleeding and severe bleeding were increased significantly among patients receiving active intervention (RR=1.57, 95% CI 1.29-1.92, p<0.001 and RR=1.57, 95% CI 1.25-1.98, p<0.001, respectively). 43 patients were lost to follow up.
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 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 iv) double placebo.	**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 patients withdrew consent.
Bhatt et al. 2006 **International** **RCT** ***Clopidogrel for High Atherothrombotic***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	15,603 patients, ≥45 years with either established cardiovascular disease or multiple risk factors. Mean age at baseline was 64 years. 70% of	Patients were randomized to receive 75 mg clopidogrel + 75-162 mg aspirin (n=7,802) daily or matching clopidogrel placebo + 75-162 mg/day aspirin (n=7,801) for the duration	**Primary outcome:** A composite of MI, stroke or death from cardiovascular causes **Secondary outcomes:** Combined first occurrence of MI, stroke or cardiovascular	Median duration of follow-up was 28 months. There was a non-significant reduction in the risk of the primary outcome associated with dual therapy (6.8% vs. 7.3%, RR=0.93, 95% CI 0.83-1.05, p=0.22). There were non-significant reductions in death

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)		patients were male. 27% of patients had experienced a stroke within the previous 5 years, and 10%, a TIA.	of the study. In addition, all patients received additional medications (e.g. statins, anti-hypertensive agents) at the discretion of treating physicians.	death, hospitalization for unstable angina, TIA, or revascularization procedure.	from any cause (RR=0.99, 95% CI 0.86-1.14, p=0.90), death from cardiovascular causes (RR=1.04, 95% CI 0.87-1.25, p=0.68) and non-fatal MI (0.94, 95% CI 0.75-1.18, p=0.59) associated with dual therapy. There was a significant reduction in the risk of all nonfatal stroke (1.9% vs. 2.4%, RR=0.79, 95% CI 0.64-0.98, p=0.03), but not nonfatal ischemic stroke (1.7% vs. 2.1%, RR=0.81, RR=0.64-1.02, p=0.07). There was a significant reduction in the risk of the secondary outcome associated with dual therapy (16.7% vs. 17.9%, RR=0.92, 95% CI 0.86-0.995, p=0.04). More patients in the dual therapy group experienced moderate bleeding (2.1% vs. 1.3%, p<0.001) but there was no difference between groups in other adverse events (severe and fatal bleeding and ICH). 4.8% of patients in the dual therapy group discontinued treatment due to an adverse event vs. 4.9% in the aspirin group.
Markus et al. 2005 **UK & Europe** **RCT** ***Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	107 patients >18 years, with ≥50% carotid stenosis, who had experienced an ipsilateral carotid territory TIA or stroke within the last 3 months and with microembolic signals (MES) detected by transcranial doppler. Mean age at baseline was 65 years. 69% of patients were male.	Patients were randomized to receive dual therapy with clopidogrel (300 mg day 1, followed by 75 mg thereafter) + 75 mg aspirin or 75 mg aspirin only, for 7 days.	**Primary outcome:** Proportion of patients with MES on day 7. **Secondary outcomes:** Mean MES frequency/hour at day 7 and 2.	The qualifying events were TIA (61.7%) and stroke (38.3%). There were significantly fewer patients with at least one MES on day 7 in the group treated with dual therapy 44% vs. 73%, RRR=39.8%, 95% CI 13.8%-58%, p=0.005), and a non-significant reduction at day 2 (56% vs. 74%, RRR=24.4%, 95% CI -1.2%-43.5%, p=0.065). MES frequency/hour was significantly reduced at both days 7 and 2 among patients in the dual therapy group (1.8 vs. 5.9, Embolization Rate Reduction=61.4%, 95% CI 31.6%-78.2%, p=0.001 and 3.3 vs. 9.5, ERR=61.6%, 95% CI 34.9%-77.4%, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					There were no differences between groups in major or minor bleeds. 12 patients in the monotherapy group experienced an ischemic stroke or TIA compared with 5 in the dual therapy group. There were no dropouts.
ii) Clopidogrel + aspirin vs. clopidogrel alone					
Deiner et al. 2004 **International** **RCT** ***Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	7,599 patients who experienced an ischemic stroke or TIA within 3 months and who had at least one of previous myocardial infarction, angina pectoris, diabetes mellitus or symptomatic peripheral artery disease (PAD) within the previous 3 years. Mean age at baseline was 66 years. 63% of patients were male. The majority of previous strokes were due to small -vessel occlusion (53%).	All patients received 75 mg of clopidogrel daily. In addition, patients were randomized to receive 75 mg aspirin daily or placebo, daily for 18 months.	**Primary outcome:** First occurrence of ischemic stroke, MI, vascular death or re-hospitalization for acute ischemic event. **Secondary outcomes:** Components of the primary outcome, any death and any stroke.	The addition of aspirin did not reduce the occurrence of the primary outcome (16% vs. 17%, Absolute Risk Reduction=6.4%, 95% CI -4.6%-16.3%, p=0.244), or the incidence of fatal/nonfatal stroke and vascular death (11% vs. 11%, ARR=0.75%, 95% CI -0.7%-2.2%, p=0.324) or any stroke (9% vs. 9%, ARR=0.20%, 95% CI -1.1%-1.55, p=0.79). 270 patients in each group discontinued study medication. 13 patients in total were lost to follow-up. The incidents of life-threatening bleeding, major bleeding and minor bleeding were all significantly higher in the dual therapy group (all p<0.0001)

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

Dual vs. Monotherapy with Dipyridamole for the Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dipyridamole + aspirin vs. aspirin					
Wong et al. 2013 **China**	NA	3 RCTs examined the risk of stroke recurrence associated with dipyridamole + aspirin vs.	The treatment contrast in the included studies were 200 mg dipyridamole +25-75 mg aspirin bid vs. aspirin alone.	Risk of recurrent stroke, composite outcome of stroke, TIA, acute coronary syndrome, death from all	There was a non-significant reduction in the risk of stroke recurrence associated with dual therapy (RR=0.64, 95% CI 0.37-1.10, p=0.80).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & meta-analysis		aspirin alone. The included trials (ESP-2, ESPRIT & EARLY)	Treatment duration was 90 days-3.5 years.	causes	There was no significant risk associated with dual therapy for major bleeding events (RR=0.92, 95% CI 0.06-14.61, p=0.95).
Dengler et al. 2010 **Germany** **RCT** ***Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☒	548 patients aged ≥18 years who had experienced an acute ischemic stroke (NIHSS score ≤ 20) within 24 hours.	Patients were randomized to receive 25 mg aspirin + 200 mg extended-release dipyridamole bid within 24 hours of stroke or TIA and for 90 days, or 100 mg aspirin daily for 7 days and 25 mg aspirin+ 200 mg ER dipyridamole bid days 8-90 (late initiation)	**Primary outcome:** Functional status at day 90 (assessed by the TelemRS) **Secondary outcomes:** Nonfatal stroke, TIA, nonfatal MI	There was no difference between groups in the number patients who experienced a favourable outcome (TelemRS 0-1 at day 90, 56.4% vs. 52.4%, absolute difference=4.1%, 95% CI -4.5%-12.6%, p=0.45). There was a non-significant reduction in the number of nonfatal strokes among patients in the early group (5.6% vs. 10.0%, p=0.15) There was no between group difference in the number of patients who experienced an adverse event (75% vs. 68%, p=0.063). Non-serious drug-related adverse events were more common in the early group (38% vs. 21%, p<0.0001). 13 patients withdrew or were lost to follow-up in the early group compared with 22 in the late group.
Halkes et al. 2006 **International** **RCT** ***European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☒	2,763 patients who had experienced a TIA or minor stroke (mRS≤3) within the previous 6 months. Mean age at baseline was 63 years. 66% of patients were male. Qualifying events were TIA (35%) and minor stroke (65%)	Patient were randomized to receive extended-release dipyridamole (200 mg bid) + aspirin (30 to 325 mg/d-mean dose, 75 mg, n=1,363) or aspirin (as above) alone (n=1,376), for the duration of the study.	**Primary outcome:** Composite of vascular death, nonfatal stroke, nonfatal MI or major bleeding complication **Secondary outcomes:** Death from all causes, death from all vascular causes, nonfatal stroke or nonfatal MI.	Mean follow-up was 3.5 years. Fewer patients in the dual therapy group experienced the primary outcome (12.7% vs. 15.7%, HR=0.80, 95% CI 0.66-0.98). Fewer patients in the dual therapy group experienced all-cause mortality or nonfatal stroke (9.7% vs. 12.47%, HR=0.78, 95% CI 0.62-0.97). 34% of patients receiving dual therapy stopped taking study medication due to adverse effects (mainly due to headache) compared with 26% of patients taking monotherapy. 57 patients were lost to follow-up in the dual therapy group compared with 49 in the

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					monotherapy group.
Diener et al. 1996 ***European Stroke Prevention Trial-2 (ESPS-2)*** **Belgium** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	6,602 patients aged ≥18 years who had experienced an ischemic stroke or TIA within the previous 3 months. Mean age of patients was 67 years. 58% of patients were male. Approximately 75% of the qualifying events were stroke, and 25%, TIA.	Patients were randomized to receive: i) 25 mg aspirin bid, ii) 200 mg modified release dipyridamole bid, iii) regimen i +ii, iv) placebo, to be taken for 2 years.	**Primary outcome:** Stroke, death or the combined of stroke/death **Secondary outcomes:** TIA, MI, ischemic events and vascular events.	At 24 months, there were a total of 824 stroke events (734 nonfatal, 96 fatal) The stroke rate in each treatment group was: Aspirin: 12.9% Dipyridamole: 13.2% Dipyridamole + aspirin: 9.9% Placebo: 15.8%. Compared with placebo treatment, the lowest risk of stroke was associated with dual therapy: OR=0.59, 95% CI 0.48-0.73 Stroke risk was reduced by 18% with aspirin, 16% with dipyridamole alone and 37% with dual therapy compared to placebo. In pairwise comparisons, examining the outcome of stroke, all treatment groups were superior to placebo, dual therapy was superior to aspirin (RRR=23.1%, p=0.006) and dual therapy was superior to dipyridamole (RRR=24.7%, p=0.002) Compared with placebo, the lowest risk of death or stroke was associated with dual therapy: OR=0.71, 95% CI 0.59-0.84). There were no differences among treatment groups in the number of deaths. The number of patients who discontinued study medication that was attributed to an adverse event was: 15.9% in the dual therapy group, compared with 7.7% in the placebo group, 8.5% in the aspirin group and 15.1% in the dipyridamole group (p<0.001). <1.0% of patients were lost to follow-up.

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

Dipyridamole vs. Clopidogrel for the Prevention of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sacco et al. 2008 **Belgium** **RCT** ***Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	20,332 patients aged ≥55 years, who had experienced an ischemic stroke within the previous 90 days. Mean age at baseline was 66 years. 64% of patients were male. 52% of qualifying stroke events were lacunar, 29% were large-artery atherosclerosis.	Patients were randomized to receive 25 mg aspirin + 200 mg ER Dipyridamole (ERDP) bid. or 75 mg clopidogrel daily.	**Primary outcome:** Any recurrent stroke **Secondary outcomes:** Composite of stroke, MI or death from vascular causes	Mean duration of follow-up was 2.5 years. There was no difference in the number of recurrent strokes between groups (9.0% in ERDP vs. 8.8% dipyridamole, HR=1.01, 95% CI 0.92-1.11). There was no difference in the number of patients who experienced stroke, MI or vascular death between group (13.1% in each group, HR=0.99, 95% CI 0.92-1.07). There were no differences between groups in the tertiary outcomes of MI, death from vascular causes, death from any cause, new or worsening CHF, or other vascular event. More patients in the ERDP group experienced a major hemorrhagic event (life-threatening and non-life-threatening combined) (4.1% vs. 3.6%, HR=1.15, 95% CI 1.00-1.32) and an intracranial hemorrhage (including fatal and nonfatal ICH (0.9% vs. 0.5%, HR=1.08, 95% CI 1.11-1.83). More patients in the ERDP group discontinued study medication (29.1% vs. 22.6%, p<0.001). 0.6% of patients in both groups were lost to follow-up.

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

Triple Antiplatelet Therapy for the Prevention of Recurrent Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Triple Antiplatelets for	CA: ☑	3,096 patients, ≥50 years, with TIA (31%) or	Patients are randomized to receive Intensive	**Primary outcome:** Any recurrent stroke within	TBA

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
***Reducing Dependency after Ischaemic Stroke (TARDIS) trial Investigators* 2015** **International** **RCT**	Blinding: Patient: ☒ Assessor ☑ ITT: ☑	mild ischemic stroke (69%) occurring within the previous 48 hours. Mean age was 69 years, 63% were men	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)	90 days, severity of stroke (mRS) **Secondary outcomes:** Composite of stroke, MI or death from vascular causes, assessed at 7 and 35 days	

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

Bleeding Risk Associated with Long-term Antiplatelets Use

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Li et al. 2017 **UK** **Prospective study**	NA	3,166 patients, presenting with MI (n=1094, 35%), and cerebrovascular events (n=2,072, 65%) treated with antiplatelet drugs (ie, started anew or continued), who were included in the Oxford Vascular Study (OXVASC) from 2002 to 2012, with follow-up until 2013, who were not routinely prescribed proton pump inhibitors. 1,582 patients (50%) were aged ≥75 years and 577 (18%) were ≥ 85 years.	Demographics and vascular risk factors were obtained at initial assessment, as were risk factors for bleeding, including alcohol use, anaemia, history of peptic ulcer, renal failure, chronic liver disease, history of cancer, and weight. All medications taken before the event, at discharge, and at follow-up were recorded. In patients with TIA and ischaemic stroke, long-term recommended antiplatelet treatment was aspirin (75	**Primary outcome:** Bleeding events	During 13,509 patient-years follow-up, there were 405 first bleeding events (n=218 gastrointestinal, n=45 intracranial, and n=142 other). The risk of all bleeds was significantly increased for patients ≥75 years (HR=1.76, 95% CI 1.44-2.14, p<0.0001). The 10-year risk of fatal, but not major, non-fatal intracranial hemorrhage was significantly increased among patients aged ≥75 years (HR= 0.79, 95% CI 0.33‑1.90, p=0.60). The average annual risk of bleeding was 3.36%, (95% CI 3.04-3.70) and 1.46%, 95% CI 1.26-1.68 for major bleeds.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			mg daily) plus dipyridamole (200 mg twice daily). No PPI or other gastric protection strategies were routinely co-prescribed. Patients were followed up face to face at 30 days, 6 months, and years 1, 5, and 10.		

Clopidogrel in Pediatric Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Soman et al. 2006 **Canada** **Prospective study**	NA	17 children, aged 1 month to 18 years admitted from 2000-2004 with an arterial ischemic stroke, who received antiplatelet therapy with clopidogrel (failed or intolerant to aspirin). Mean age was 8.8 years	Children received 1 mg/kg/day clopidogrel (goal), with a maximum dose of 75 mg/day. Follow-up visits were scheduled every 3-6 months	Risks and complications related to clopidogrel therapy	9 patients received aspirin in addition to clopidogrel. Patients were followed for 2-3 years (n=9), 1-1.5 years (n=3) and 4 months (n=1) after initiation of therapy. Four patients discontinued use after 6 months or 1 year. There were no cases of stroke recurrence. No patient receiving monotherapy with clopidogrel reported any major complications. Two patients reported minor complications (hand numbness and headache) that were not thought to be medication related. There were 2 cases of intracranial bleeding in patients on clopidogrel + aspirin

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