CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Acute Stroke Management Evidence Tables

Seventh Edition, Update 2022

Section 6: Acute Antithrombotic Therapy

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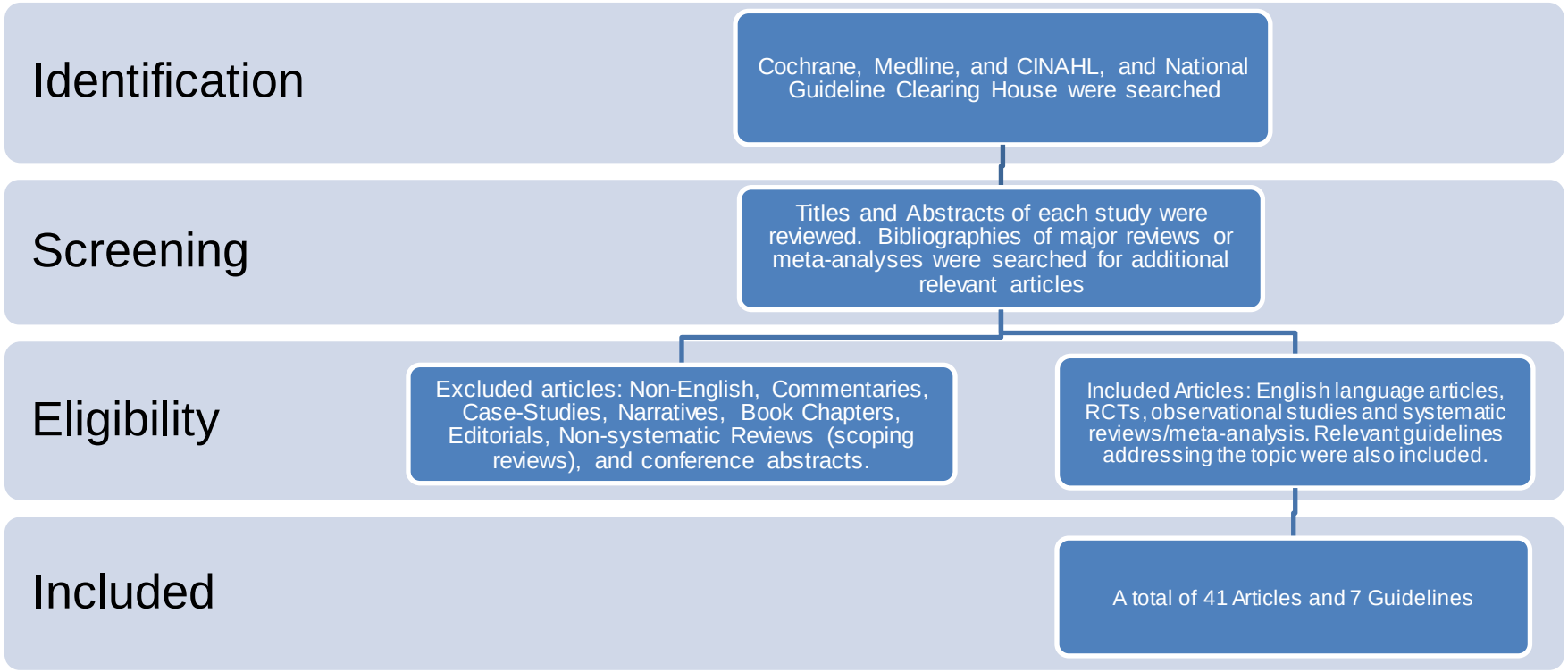
Search Strategy



Pubmed, EMBASE and the Cochrane Database were search using the search terms or MESH headings “stroke” and “aspirin” or “dipyridamole” or “acetylsalicylic acid” or “dual antiplatelet therapy”. 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 41 articles and 7 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Kleindorfer DO, Towfighi A, Chaturvedi S, et al. **2021 Guideline for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline from the American Heart Association/American Stroke Association.** ***Stroke* 2021; 52: e364-e467.**	5.19. Use of Antithrombotic Medications in Secondary Stroke Prevention 1. In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events while minimizing the risk of bleeding. COR 1, LOE A 2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325 mg daily, clopidogrel 75 mg, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated for secondary prevention of ischemic stroke. COR 1, LOE A 3. For patients with recent minor (NIHSS score ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12–24 hours of symptom onset and at least within 7 days of onset) and continued for 21 to 90 days, followed by SAPT, to reduce the risk of recurrent ischemic stroke. COR 1, LOE A (systematic review) 4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS score ≤5), high-risk TIA (ABCD2 score ≥6), or symptomatic intracranial or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH. COR 2b, LOE B-R 5. For patients already taking aspirin at the time of noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established. COR 2b, LOE B-R 6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage. COR 3 (harm), LOE A (systematic review)
Dawson J, Merwick Á, Webb A, Dennis M, Ferrari J, Fonseca AC, European Stroke Organisation. **European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA.** ***Eur Stroke J* 2021; Vol. 6(2) CLXXXVII–CXCI.**	PICO 1. In people with a non-cardioembolic minor ischaemic stroke or high-risk TIA, does early initiation of dual antiplatelet therapy with aspirin and clopidogrel, compared to aspirin monotherapy, reduce the risk of stroke recurrence? In people with a non-cardioembolic minor ischaemic stroke (NIHSS score of 3 or less) or high-risk TIA (ABCD2 score of 4 or more) in the past 24 hours, we recommend 21-days of dual antiplatelet therapy with aspirin and clopidogrel, followed by antiplatelet monotherapy thereafter. Quality of evidence: High ⊗⊗⊗⊗, Strength of recommendation: Strong for intervention ↑↑ PICO 2. In people with a non-cardioembolic mild to moderate ischaemic stroke or high-risk TIA, does early initiation of dual antiplatelet therapy with aspirin and ticagrelor, compared to aspirin monotherapy, reduce the risk of stroke recurrence? In people with non-cardioembolic mild to moderate ischaemic stroke (NIHSS of 5 or less) or high-risk TIA (ABCD2 score of 6 or more or other high-risk features*) in the past 24 hours, we suggest 30-days of dual antiplatelet therapy with aspirin and ticagrelor followed by antiplatelet monotherapy thereafter. *defined as either intracranial atherosclerotic disease or at least 50% stenosis in an internal carotid artery that could account for the presentation. Quality of evidence: Moderate ⊗⊗⊗, Strength of recommendation: Weak for intervention ↑?

Guideline	Recommendations
	Expert consensus statement: In people with acute non-cardioembolic low risk TIA or in whom the diagnosis is uncertain, 11/11 experts voted against use of dual antiplatelet therapy over monotherapy.
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2):159-176.**	**Single drug antiplatelet aggregation therapy Recommendations** 1. Aspirin is recommended for patients with AIS within 24–48hours after onset. For patients treated with IV rtPA, aspirin is usually delayed until 24hours later (class I, level of evidence A). 2. Aspirin (50–325mg/day) or clopidogrel (75mg/day) alone can be used as primary antiplatelet drug therapy (class I, level of evidence A). 3. Aspirin therapy is not recommended as an alternative therapy for patients with AIS who are suitable for IV rt-PA thrombolysis or mechanical thrombectomy (class III, level of evidence B). 4. Ticagrelor (instead of aspirin) is not recommended for acute mild stroke (class III, level of evidence B). 5. Cilostazol can be used in patients with AIS as an alternative to aspirin if aspirin or clopidogrel is not available (class IIa, level of evidence A). 6. For high risk of aspirin intolerance (gastrointestinal adverse reactions or allergies, etc) in patients with ischaemic stroke, indobufen (100mg per time, twice a day) is feasible (class IIb, level of evidence B). **Dual antiplatelet aggregation therapy** 1. For patients with mild stroke and high-risk TIA who did not receive IV thrombolysis, dual antiplatelet therapy (aspirin 100mg/day, clopidogrel 75mg/day (first day load dose 300mg)) was initiated within 24hours of onset and lasted for 21 days, then clopidogrel 75mg/ day which could significantly reduce stroke recurrence for 90 days (class I, level of evidence A). 2. The efficacy of dipyridamole alone or dipyridamole combined with aspirin for preventing the recurrence of ischaemic stroke still needs RCTs to confirm (class IIb, level of evidence B). **Triple antiplatelet aggregation therapy** 1. Triple antiplatelet aggregation therapy (aspirin, clopidogrel and dipyridamole) are not recommended for the treatment of acute non-cardiogenic stroke and TIA (class III, level of evidence B).
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K; on behalf of the American Heart Association Stroke Council. **Guidelines for the early management of patients with acute ischemic stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association** ***Stroke.* 2019;50:e344–e418.**	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. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset. Class I: LOE A 4. Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor stroke. Class III: No Benefit; LOE B-R.

Guideline	Recommendations
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 Strong Recommendation AGAINST Routine use of anticoagulation in patients without cardioembolism (e.g. atrial fibrillation) following TIA/stroke is not recommended Strong Recommendation Aspirin plus clopidogrel should be commenced within 24 hours and used in the short term (first three weeks) in patients with minor ischaemic stroke or high-risk 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 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, et al. **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**

Evidence Tables

Oral Antiplatelet Monotherapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Minhas et al. 2022 **UK** **Cochrane review** **(update to Sandercock et al. 2014-see below)**	Using the Risk of Bias 1 (RoB1) tool, bias was low in all trials	11 studies including 42,226 participants with acute presumed or definitive ischemic stroke. Most patients were >70 years, approximately 50% were men.	Patients were randomized to receive antiplatelet therapy vs. placebo or no treatment. IST (1997) and CAST (1997) contributed 96% of the data. Patients in IST were randomized patients to 300 mg aspirin once daily, for 14 days starting within 48 hours of stroke onset. Patients in CAST were randomized to receive 160 mg aspirin once daily for 4 weeks, initiated within 48 hours of symptom onset. In the other trials, antiplatelet regimens included aspirin, ticlopidine, PF-03049423 and clopidogrel. One trial used dual antiplatelet therapy. In all trials, patients were randomized within 72 hours. Duration of treatment ranged from 5 days to 3 months. Duration of follow-up ranged from 10 days to 6 months.	**Primary outcome:** Death or dependence at the end of follow-up **Secondary outcomes:** Death, recurrent ischemic stroke, symptomatic ICH	The odds of death at the end of follow-up were significantly lower in the antiplatelet group (OR=0.93, 95% CI 0.87 to 0.98; 10 trials, n=41,929) GRADE: very low-certainty evidence, for every 1,000 people treated 9 would avoid death (NNTB=108). The odds of recurrent ischemic stroke at the end of follow-up were significantly lower in the antiplatelet group (OR=0.79, 95% CI 0.70 to 0.88; 9 trials, n=41,652) GRADE: very low-certainty evidence, for every 1,000 people treated 7 would avoid a recurrent stroke (NNTB=140). The odds of symptomatic ICH during the treatment period were not significantly increased in the antiplatelet group (OR=1.18, 95% CI .970 to 1.44; 9 trials, n=41,652) GRADE: very low-certainty evidence, for every 1,000 people treated 2 would have a symptomatic ICH (NNTH=574).
Rothwell et al. 2016 **UK** **Systematic**	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	**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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
review & patient-level meta-analysis			and Rödén-Jüllig et al. 2003),		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** **Retrospective study**	NA	85,072 patients included in the Get with the Guidelines Stroke 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.	The clinical outcomes of patients who had received antiplatelet 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	**Primary outcome:** Symptomatic ICH (sICH) within 36 hours, in-hospital 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	38,844 (45.7%) were receiving antiplatelet therapy. Patients receiving antiplatelet therapy before 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			clopidogrel.	Analyses were adjusted for baseline prognostic factors	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 subgroup 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 recruited an average of 72 hrs, (n=1), 6 days (n=1) and 4 weeks (n=2) following stroke onset.	Trials compared either a single oral antiplatelet agent or a combination of antiplatelet agents with control (placebo or no treatment). Treatment contrasts 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	**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 pulmonary embolus, recurrence of stroke (combined and by stroke type), and complete recovery (post-hoc analysis), ICH.	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. 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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			months following stroke. Follow-up periods were 10 days, 3 weeks (n=2), 4 weeks, 3 months (n=2) and 6 months (n=2)		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, 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	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	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		Scandinavian Stroke Scale score (SSS) at admission was 13		months, discharge destination, ambulatory status	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%
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 4 weeks during hospitalization or until death or discharge.	**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).
Intravenous Antiplatelet					

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

Trials of Dual Antiplatelet Therapy (DAPT)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Clopidogrel + aspirin vs. aspirin					
Johnston et al. 2018, 2019 **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 onset.	**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 efficacy and an excess of major hemorrhage. 93.4% of patients completed the 90-day trial visit or died. Significantly fewer patients in the clopidogrel-aspirin 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-aspirin group (4.6% vs. 6.3%; HR=0.72, 95% 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-aspirin 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+aspirin during a period of 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result. There were no significant interaction terms of the primary outcome including age, sex, race, time to randomization, baseline NIHSS score, or

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					hypertension, among others. **2019 (Assessing time course for benefit and risk)** Day 21 was identified as the cut-point for prevention of major ischemic events. Within the first 21 days, the risk of a major ischemic event was significantly lower in the clopidogrel-aspirin group (HR=0.65, 95% CI 0.50–0.85, p=0.0015). From 22-90 days, the risk of a major ischemic event was not significantly lower in the clopidogrel-aspirin group (HR=1.38, 95% CI 0.81–2.35, p=0.24). Within the first 21 days, major hemorrhage occurred in 5 patients (0.2%) in the aspirin group and in 10 patients (0.4%) in the clopidogrel-aspirin group with a nonsignificant absolute risk difference of –0.21% (95% CI, –0.52% to 0.10%). For 90-day treatment, the difference was –0.54% (95% CI, –1.00% to –0.08%). The benefit of clopidogrel-aspirin was greatest when initiated within 12 hours of symptom onset, but remained consistently beneficial even when started 72 hours after onset.
Wang et al. 2013, Pan et al. 2017 **China** **RCT** ***Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events***	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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(CHANCE)					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. **Time course analysis (2017)** Of 204 new ischemic strokes that occurred in the clopidogrel + aspirin group, 145 (71.1%) occurred within the first week, 13 (6.4%) during the second week, with decreasing cases occurring in weeks 3-90 days. Of the 60 bleeding (any) events, 38.3% occurred during the first week, 25% during the second week and 15% during the third week. Of 295 new ischemic strokes that occurred in the aspirin group, 223 (75.6%) occurred within the first week, 19 (6.4%) during the second week, with decreasing cases occurring in weeks 3-90 days. Of the 41 bleeding (any) events, 36.6% occurred during the first week, 19.5% during the second week and 17.3% during the third week. The authors suggested that the risk of bleeding events may outweigh the benefits of ischemic stroke reduction if dual antiplatelet treatment is given beyond 2 weeks.
Hong et al. 2016 **Korea** **RCT** ***Combination of Clopidogrel and Aspirin for Prevention of Recurrence in Acute***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	358 patients ≥30 years, with acute ischemic stroke and arterial stenosis >30% (i.e., presumed source was large artery atherosclerosis). Mean age was 66.1 years, 63% were men. Median baseline NIHSS was 3.	Patients were randomized 1:1 within 48 hours of the event to receive 75 mg clopidogrel once daily without load + 100 mg of aspirin daily (following a 300 mg loading dose) vs. aspirin (at same dose) only for 30 days	**Primary outcome:** Confirmed new ischemic lesions within 7 and 30 days **Secondary outcomes:** Disability (ordinal shift in distribution of mRS scores and proportion of patients with mRS 0-2), clinical stroke recurrence, and composite of stroke, myocardial infarction,	There was no significant difference between groups in the risk or recurrent stroke at 30 days (36.5% vs 35.9%, RR=1.02; 95% CI 0.77–1.35, p=0.91). There were no significant differences between groups in any of the secondary outcomes. There were no significant differences between groups in the risk of any bleeding events between groups (16.7% vs. 10.7%, RR= 1.59, 95% CI

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Atherothrombotic Stroke Study (COMPRESS)				and vascular death at 30 days **Safety outcomes:** Bleeding (life-threatening, major and minor)	0.91–2.68, p=0.11).
He at al. 2015 **China** **RCT**	CA: ☒ Blinding: Patient: ☒ Assessor ☒ ITT: ☒	690 patients ≥40 years with 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.	Patients were 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	**Primary outcomes:** 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.	647 patients completed the trial. 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
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.
Kennedy et al. 2007 **International** **RCT (factorial)** ***Fast Assessment of Stroke and TIA to prevent Stroke Recurrence***	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	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	**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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(FASTER)		stroke.	loading dose, then 75 mg daily thereafter) + placebo, ii) simvastatin (40 mg daily) + clopidogrel, iii) simvastatin, + placebo or iv) double placebo.		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.
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). 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) Ticagrelor + aspirin vs. aspirin					
Johnston et al. 2020, Amarenco et al. 2020 **USA** **RCT** ***Acute STroke or Transient***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	11,0161 patients (13,000 planned) from 450 sites globally, ≥40 years, with minor acute ischemic stroke (NIHSS score of ≤5) or high-risk TIA (ABCD^2 score of ≥6) or symptomatic intracranial or extracranial arterial	Patients were randomized 1:1 to receive 90 mg ticagrelor bid + 75-100 aspirin mg/day vs. 75-100 mg aspirin daily, within 5 days of stroke onset, for 30 days.	**Primary outcome:** Subsequent stroke or death within 30 days **Secondary outcome:** Ischemic stroke within 30 days, disability (mRS>1) at 30 days	The risk of the primary event was significantly lower in the ticagrelor–aspirin group (5.5% vs. 6.6%, HR=0.83, 95% CI 0.71-0.96, p=0.02). NNT=92 The risk of ischemic stroke was significantly lower in the ticagrelor–aspirin group (5.0% vs. 6.3%, HR=0.79, 95% CI 0.63-0.94, p=0.04).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death (THALES)		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 24 hours prior to randomization. Mean age was 65 years, 39% were women. Approx.20% had a previous stroke or TIA.	Loading doses of ticagrelor and aspirin were 180 mg and 300-325 mg, respectively	**Safety outcomes:** Major bleeding, fatal or life-threatening bleeding, ICH	Disability was 23.8% in the ticagrelor–aspirin group and 24.1% in the aspirin group (HR=0.98, 95% CI 0.89–1.07, p=0.61) The risk of severe bleeding and Intracranial hemorrhage or fatal bleeding were significantly higher in the ticagrelor–aspirin group (0.5% vs. 0.1%, HR=3.99, 95% CI 1.74–9.14, p=0.001 [NNTH=263] and 0.4% vs. 0.1%, HR=3.66, 95% CI 1.48–9.02, p=0.005, respectively). **Amarenco et al. 2020 (additional analysis)** The risk of death or disabling stroke (mRS>1) was significantly lower in the ticagrelor–aspirin group (4.0% vs. 4.7%, HR=0.83; 95% CI, 0.69-0.99, p= 0.04). NNT=133.
iii) Ticagrelor + aspirin vs. Clopidogrel + aspirin					
Wang et al. 2021 **China** **RCT** ***Clopidogrel with Aspirin in High-Risk Patients with Acute Non-disabling Cerebrovascular Events CHANCE-2)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	6,412 patients who presented to hospital within 24 hours after the onset of minor ischemic stroke or high-risk TIA and were carriers of *CYP2C19* loss-of-function (LOF) alleles. Median was 64.8 years, 33.8% were women. 80. 4% of the qualifying events were stroke.	Participants were randomly assigned 1:1 to receive ticagrelor (180mg loading dose on day 1, followed by 90mg twice daily on days 2–90) or clopidogrel (300mg loading dose on day 1, followed by 75mg daily on days 2–90). Both groups received 75 mg aspirin for the first 21 days.	**Primary outcome:** Recurrent ischemic or hemorrhagic stroke at 90 days **Secondary outcomes:** New stroke within 30 days, vascular event, or ischemic stroke at 90 days **Safety outcomes:** Severe or moderate bleeding, defined using the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria at 90 days, any bleeding	The risk of primary outcome was significantly lower in the ticagrelor–aspirin group (6.0% vs. 7.6%, HR=0.77, 95% CI 0.64–0.94). There were no significant differences between groups for any of the secondary outcomes. There were 0.3% of patients in both groups that sustained a severe or moderate bleeding event. The risk of any bleeding was significantly higher in the ticagrelor–aspirin group (5.3% vs. 2.5%, HR= 2.18, 95% CI 1.66–2.85).
iv) Dipyridamole + aspirin vs. aspirin					
Dengler et al. 2010	CA: ☑ Blinding:	548 patients aged ≥18 years who had experienced an acute ischemic stroke	Patients were randomized to receive 25 mg aspirin + 200 mg	**Primary outcome:** Functional status at day 90 (assessed by the TelemRS)	There was no difference between groups in the number patients who experienced a favourable outcome (TelemRS 0-1 at day 90, 56.4% vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **RCT** ***Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY)***	Patient: ☒ Assessor ☑ ITT: ☒	(NIHSS score ≤ 20) within 24 hours.	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)	**Secondary outcomes:** Nonfatal stroke, TIA, nonfatal MI	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.

Systematic Reviews of Dual vs. Mono Antiplatelet Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pomero et al. 2022 **Italy** **Systematic review & meta-analysis**	The overall risk of bias, assessed using Cochrane Risk of Bias tool (RoB 2) was low in 2 trials, high in one and there were some concerns in the 4th.	4 RCTs (CHANCE, POINT, THALES and FASTER) including the results of 21,459 patients with acute stroke or TIA.	Patients were randomized to receive dual antiplatelet therapy with ticagrelor + aspirin vs. aspirin plus placebo (THALES trial) and clopidogrel + aspirin vs. aspirin + placebo in the other 3 RCTs (all trials described above)	**Primary outcome:** Fatal/nonfatal recurrent ischemic stroke **Primary safety outcome:** Major bleeding, defined using the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria **Secondary outcomes:** All-cause mortality, hemorrhagic stroke, intracranial hemorrhage,	Compared to aspirin alone, DAPT significantly reduced the risk of stroke recurrence (RR=0.74, 95% CI 0.67–0.82, absolute risk difference=2%, NNT=50). GRADE: high certainty of evidence The risk of major bleeding was significantly higher with DAPT compared with aspirin (RR=2.54, 95% CI 1.65 to 3.92, absolute risk difference= 0.4%, NNH=250). GRADE: high certainty of evidence. The risk of all-cause mortality was not increased significantly with DAPT (RR=1.30, 95% CI (0.90 to 1.89). GRADE: moderate certainty of evidence The risk of intracranial hemorrhagic was increased significantly with DAPT (RR=1.87, 95%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				minor bleeding, disabling stroke (mRS >2)	CI (1.18 to 2.97, NNH 500). GRADE: moderate certainty of evidence The risk of hemorrhagic stroke was not increased significantly with DAPT (RR=1.89, 95% CI (0.98 to 3.65). GRADE: moderate certainty of evidence The risk of minor bleeding was significantly higher with DAPT compared with aspirin (RR=2.22, 95% CI 1.66 to 2.97, NNH 71). GRADE: high certainty of evidence The risk of disabling stroke was reduced significantly with DAPT (RR=0.84, 95% CI 0.75 to 0.95).
Medranda et al. 2021 **USA** **Systematic review & meta-analysis**	NA	3 RCTs (CHANCE, POINT and THALES) including the results of 21,067 persons with acute ischemic stroke or TIA (12-24 hours).	Patients were randomized to receive dual antiplatelet therapy with either clopidogrel + aspirin or ticagrelor + aspirin vs. aspirin alone (as described in the trials above) for 30-90 days.	**Primary outcomes:** Ischemic stroke and all-cause mortality, severe bleeding	Dual antiplatelet therapy significantly reduced the risk of ischemic stroke (HR=0.73; 95% credible interval [CrI] 0.54, 0.97). The risk of severe bleeding was increased significantly with dual antiplatelet therapy (HR=2.48; 95% CrI: 1.07, 5.26). There was a non-significant trend towards increased mortality with dual antiplatelet therapy (HR=1.29; 95% CrI: 0.73, 2.23).
Trifan et al. 2021 **USA** **Systematic review & meta-analysis**	Risk of bias assessed using RoB2 was low in most trials.	17 RCTs including the results of 27,358 adult patients with mild to moderate noncardioembolic acute ischemic stroke or TIA (within 3 days of symptoms). Mean age was 65 years, 64% were men.	Patients were randomized to receive dual antiplatelet therapy (DAPT) or mono antiplatelet therapy (MAPT). Treatments included clopidogrel + aspirin vs. aspirin (n=9), aspirin vs. aspirin + dipyridamole (n=1), clopidogrel vs. aspirin + clopidogrel (n=1), aspirin vs aspirin + clopidogrel or clopidogrel + simvastatin (n=1), clopidogrel vs aspirin +	**Primary outcomes:** Stroke recurrence and the composite of stroke, TIA, acute coronary syndrome, and death from any cause. **Safety outcome:** Major hemorrhage	The risk of recurrent stroke was significantly low in the DAPT group (RR=0.71, 95% CI, 0.63–0.81). The absolute effect was 20 fewer strokes per 1,000 (95% CI 10–30) participants treated with DAPT. The risk of the composite outcome was reduced significantly with DAPT (RR=0.76, 95% CI 0.69–0.83). The absolute effect was 20 fewer strokes per 1,000 (95% CI 10–30) participants treated with DAPT. The risk of major hemorrhage was increased significantly with DAPT (RR= 2.17, 95% CI 1.45–3.25). The absolute effect was 3 additional major hemorrhages (95% CI, 2–5) per 1,000

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			extended-release dipyridamole (n=1), aspirin vs aspirin + extended-release dipyridamole (n=1), aspirin vs aspirin + cilostazol (n=2), aspirin vs ticagrelor + aspirin (n=1). Duration of treatment was ≤21 days (n=6), 30 days-3 months (n=7), ≥6 months (n=4).		participants treated with DAPT. The risk for major hemorrhage for aspirin + clopidogrel was comparable to monotherapy when used for ≤30 days (RR=1.52, 95% CI, 0.67–3.44).
Pan et al. 2019 **USA** **Patient-level meta-analysis**	Risk of bias was low in both trials	10,051 patients included in the POINT and CHANCE trials (both described above). Median age was 63.2 years, 60.8% were men. 64.7% had a minor stroke as the qualifying event, and 35.3% presented with TIA.	Patients were randomized to receive clopidogrel-aspirin or aspirin alone within 12 hours (POINT) or 24 hours (CHANCE) of symptom onset for 90 days.	**Primary outcome:** Major ischemic event (ischemic stroke, MI, or death from ischemic vascular causes) within 90 days **Primary safety outcome:** Major hemorrhage, hemorrhagic stroke	In the fully adjusted model, a major ischemic event occurred significantly less frequently in the dual antiplatelet group (6.5% vs. 9.1%. HR=0.70, 95% CI, 0.60-0.82, p <0 .001). The risks of ischemic stroke, disabling or fatal stroke and nondisabling stroke were all significantly lower in the dual antiplatelet group (6.3% vs. 8.9%, HR=0.69, 95% CI 0.59-0.81, p<.001; 4.6% vs. 6.1%, HR=0.69, 95% CI 0.59-0.81, p <0.001 and 1.9% vs. 3.0%, HR=0.63, 95% CI 0.47-0.84, p=0.002, respectively). The risks of major hemorrhage and hemorrhagic stroke were not increased significantly with dual antiplatelet therapy (0.6% vs. 0.4%, HR=1.20, 95% CI 0.61-2.39, p=0.60 and 0.3% vs. 0.2%, HR=0.77, 95% CI 0.30-1.95, p=0.58, respectively). The risk of a major ischemic event associated with dual antiplatelet therapy was reduced significantly from days 0-21 (5.2% vs. 7.8%, HR=0.66, 95% CI 0.56-0.77, p <.001). The risk was reduced significantly from days 0-10 (HR=0.65, 95% CI 0.55-0.77, p <0.001), but not from days 11-21 (0.5% vs. 0.8%, HR=0.72, 95% CI 0.43-1.22, p=0.22), or days 22-90 (1.4% vs. 1.5%, HR=0.94, 95% CI 0.67-1.32, p=0.72).
Rahman et al.	All trials were	10 RCTs (15,434	The association between	**Primary outcomes:**	Dual therapy significantly reduced the risk of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
2019 **USA** **Systematic review & meta-analysis**	considered to be of low risk of bias. 3 trials were open label.	patients) examining dual antiplatelet therapy (aspirin + clopidogrel) vs. monotherapy with aspirin in patients with TIA or noncardioembolic ischemic stroke. Treatment was initiated within 72 hours in 7 trials, within 7 days in one trial, within 30 days in one trial and within 180 days in one trial. The mean age was 64.0 years, 61.1% were men.	length of dual antiplatelet therapy and outcomes was examined. Analysis was based on the short- (≤1 month), intermediate- (≤3 month), and long-term (>3 month) A+C therapy.	Recurrent stroke, major bleeding **Secondary outcomes:** Major adverse cardiovascular events (composite of stroke, MI, and cardiovascular mortality) and all-cause mortality	recurrent ischemic stroke in both short-term (6.4% vs.10.0%; RR= 0.53; 95% CI, 0.37– 0.78) and intermediate-term (4.8% vs. 6.7%; RR= 0.72; 95% CI, 0.58–0.90 durations, but there was no difference between groups of long-term duration (6.3% vs. 7.7%; RR= 0.81; 95% CI, 0.63–1.04). The risk was not increased significantly during short-term use with dual therapy (0.4% vs. 0.2%; RR= 1.82; 95% CI, 0.91–3.62), but was increased with both intermediate and long-term use (1.1% vs. 0.4%; RR= 2.58; 95% CI, 1.19–5.60 and 6.6% vs. 3.4%; RR= 1.87; 95% CI, 1.36– 2.56, respectively). Major adverse cardiovascular events were significantly reduced by short-term dual therapy (RR= 0.68; 95% CI, 0.60–0.78) and intermediate-term dual therapy (R= 0.76; 95% CI, 0.61–0.94). The risk of all-cause mortality was significantly increased in trials of intermediate and long-term use of dual therapy, although the results were based on 3 trials.
Yang et al. 2018 **China** **Systematic review & meta-analysis**	The methodological quality of 15 of the trials was classified as "A".	18 RCTS (n=15,515) patients with acute non-cardioembolic ischemic stroke or TIA who were treated within 3 days of symptom onset	Treatment contrasts included: aspirin + clopidogrel vs. aspirin (9 trials; n=12,404); aspirin + clopidogrel vs. clopidogrel (1 trial; n=491); aspirin + dipyridamole vs. aspirin (5 trials; n=964); aspirin + dipyridamole vs dipyridamole (2 trials; n=220); aspirin + dipyridamole vs. clopidogrel (1 trial; 1,360) and cilostazol + aspirin vs. aspirin (1 trial; n=76).	**Primary outcomes:** Stroke recurrence, composite vascular events (stroke, TIA, MI and death from cardiovascular causes) and major bleeding.	Overall, dual antiplatelet therapy significantly reduced the risk of recurrent stroke (RR=0.69, 95% CI 0.61-0.78, p<0.0001). Results from 16 trials included. In the subgroup of 8 trials that compared aspirin + clopidogrel vs. aspirin, the risk of recurrent stroke was significantly reduced (RR=0.69, 95% CI 0.61-0.79, p<0.0001). There was no significant reduction in the risk of stroke in other subgroup analysis of other treatment contrasts. Dual antiplatelet therapy significantly reduced the risk of the composite vascular events (RR= 0.72, 95%CI 0.64 to 0.80; p<0.00). Results from 11 trials were included. Dual antiplatelet therapy was associated with an

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			Treatment duration ranged from 14 days to 42 months		increased risk of major bleeding (RR=1.77, 95%CI 1.09 to 2.87, p=0.02). When results from the POINT trial was excluded from the analysis, the risk was no longer statistically significant. (RR=1.46, 95%CI 0.77 to 2.75, p=0.25).
Ge et al. 2016 **China** **Systematic review & meta-analysis**	NA	9 RCTs (n=21,923 patients) comparing dual antiplatelet therapy (DAPT) vs. monotherapy. Trials with follow-up of <7 days and high-dose aspirin were excluded. Mean age of participants was 64 years.	Treatments included aspirin + clopidogrel vs. 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	**Primary outcome:** Stroke or TIA recurrence	DAPT was associated with a significantly reduced risk of ischemic stroke (RR=0.79, 95% CI 0.66-0.94, 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 years, 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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. 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).
Wong et al. 2013 **China** **Systematic review & meta-analysis**	NA	3 RCTs examined the risk of stroke recurrence associated with dipyridamole + aspirin vs. aspirin alone. (ESP-2, ESPRIT & EARLY) 5 RCTs examined the risk of stroke recurrence associated with clopidogrel + aspirin vs. aspirin alone. (CARESS, CHAISMA, FASTER, CLAIR and CHANCE) are described above.	Trials compared 200 mg dipyridamole +25-75 mg aspirin bid vs. aspirin alone. Treatment duration was 90 days-3.5 years. Most of the trials compared a daily dose of clopidogrel 75 mg (with an initial loading dose of 300 mg) + 75-160 mg aspirin vs. aspirin alone. Treatment periods were 7 days (n=2), 90 days (n=2) and 28 months.	**Primary outcomes:** Risk of recurrent stroke, composite outcome of stroke, TIA, acute coronary syndrome, death from all causes	**Dipyridamole** 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). 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). **Clopidogrel** 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). 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).

Ticagrelor vs. Aspirin

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Johnston et al. 2016 **USA** **RCT** ***Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES)***	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 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	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 aspirin (n=6,610; loading dose of 300 mg, followed by 300 mg daily for days 2-90+ ticagrelor placebo)	**Primary outcome:** First occurrence of any event from the composite of stroke (ischemic or hemorrhagic), MI, or death **Secondary outcome:** 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	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 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 subgroup 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.

Clopidogrel vs. Aspirin

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%).

Triple Antiplatelet Therapy

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bath et al. 2017 **UK/ International** **RCT** ***Triple Antiplatelets for Reducing***	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	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.	**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),	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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Dependency after Ischaemic Stroke (TARDIS) trial		strokes.	standard guideline therapy with one or two antiplatelet drugs (standard treatment)	Mood (Zung Depression Scale) cognition or quality of Life, assessed at 90 days **Safety outcome:** Hemorrhage (fatal, major, moderate, minor and none)	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)

Dual vs. Monotherapy (Secondary prevention-non acute)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Clopidogrel + aspirin vs. aspirin					
Benavente et al. 2012 **Canada** **RCT** ***Secondary Prevention of Small Subcortical Strokes (SPS3) Trial (antiplatelet arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	3,020 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 was 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.
Connolly et al. 2009 **International** **RCT** ***Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE A)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	7,554 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% 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,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					respectively). 43 patients were lost to follow up.
Bhatt et al. 2006 **International** **RCT** ***Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)***	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 male. 27% of patients had experienced a stroke within the previous 5 years, and 10%, a TIA.	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 of the study. In addition, all patients received additional medications (e.g. statins, anti-hypertensive agents) at the discretion of treating physicians.	**Primary outcome:** A composite of MI, stroke or death from cardiovascular causes **Secondary outcomes:** Combined first occurrence of MI, stroke or cardiovascular death, hospitalization for unstable angina, TIA, or revascularization procedure.	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 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.
ii) Clopidogrel + aspirin vs. clopidogrel					
Diener et al. 2004 **International**	CA: ☑ Blinding: Patient: ☑	7,599 patients who experienced an ischemic stroke or TIA within 3 months and	All patients received 75 mg of clopidogrel daily. In addition, patients were randomized to	**Primary outcome:** First occurrence of ischemic stroke, MI, vascular death or re-	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH)***	Assessor ☑ ITT: ☑	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%).	receive 75 mg aspirin daily or placebo, daily for 18 months.	hospitalization for acute ischemic event. **Secondary outcomes:** Components of the primary outcome, any death and any stroke.	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)
iii) Dipyridamole + aspirin vs. aspirin					
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 monotherapy group.
Diener et al. 1996 **Belgium** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑	6,602 patients aged ≥18 years who had experienced an ischemic stroke or TIA within the previous 3	Patients were randomized to receive: i) 25 mg aspirin bid, ii) 200 mg modified release dipyridamole	**Primary outcome:** Stroke, death or the combined of stroke/death **Secondary outcomes:**	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%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
European Stroke Prevention Trial-2 (ESPS-2)	ITT: ☑	months. Mean age of patients was 67 years. 58% of patients were male. Approximately 75% of the qualifying events were stroke, and 25%, TIA.	bid, iii) regimen i +ii, iv) placebo, to be taken for 2 years.	TIA, MI, ischemic events and vascular events.	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.

Abbreviations

CA: concealed allocation	CI: confidence interval	HR: hazard ratio
ITT: intention-to-treat	NA: not assessed	NNTB: number needed to benefit
NNTH: number needed to harm	OR: odds ratio	RoB2: Revised Cochrane risk of bias tool for randomized trials

RR: relative risk	RRR: relative risk reduction	

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