CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke

Seventh Edition, 2020

Evidence Table: *Antiplatelet Therapy for Ischemic Stroke and Transient Ischemic Attack*

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on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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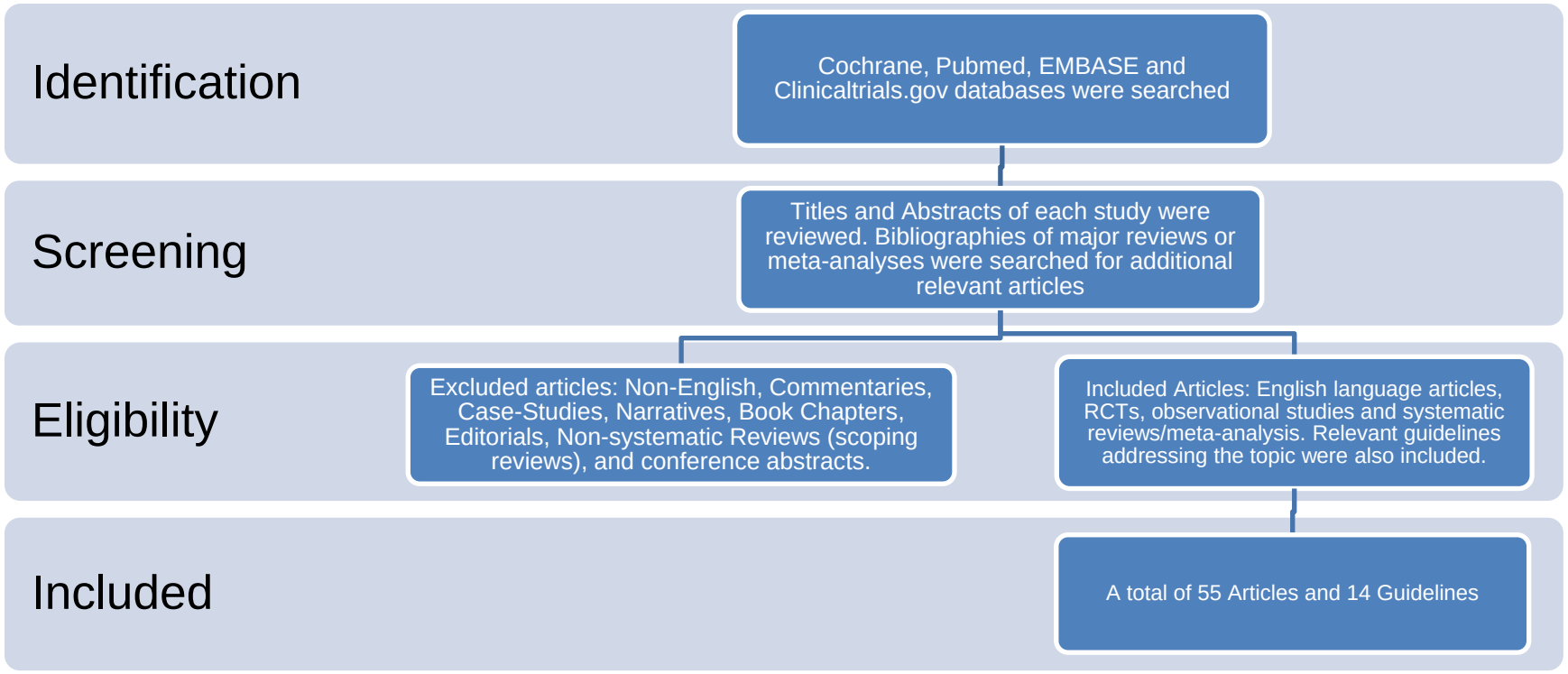
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases 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
Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. **2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** ***Circulation*. 2019;140:e596–e646**	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk. COE IIb Harm; LOE A 2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age. COE III Harm: LOE B-R 3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding. COE III Harm; LOE C-LD
Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. **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.** **(selected)**	**3.9 Antiplatelet Therapy** 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.
Prasad K, Siemieniuk R, Hao Q, et al. **Dual antiplatelet therapy with aspirin and**	We recommend dual antiplatelet therapy (clopidogrel + aspirin) over single agent therapy (aspirin). Start as soon as possible after index event. Strong recommendation. 19 fewer nonfatal recurrent strokes within 90 days (dual vs. mono antiplatelet). High-quality evidence. Dosing: clopidogrel-loading dose of 300 mg; aspirin, a daily dose between 75 mg and

Guideline	Recommendations
clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline. ***BMJ 2018;363:j656:k5130.***	81 mg. We recommend administering dual antiplatelet therapy for 10-21 days after the index event. Strong recommendation. 10 fewer (non-significant) nonfatal recurrent strokes (dual vs. mono antiplatelet). Moderate-quality evidence.
Wang Y, Liu M and Pu C. **2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack.** ***Int J Stroke* 2017; 12: 302–320.**	1. Antiplatelet treatment rather than anticoagulation treatment is recommended to patients with non-cardioembolic ischemic stroke or TIA for the purpose of preventing another stroke or cardiovascular events (Grade I recommendation, Class-A evidence). 2. The optimal dosage of aspirin is between 75 and 150 mg/dL. Both aspirin (25 mg) plus dipyridamole (timespan type) (200 mg, twice per day) or aspirin (25 mg) plus cilostazol (100 mg twice per day) are alternative treatment to aspirin or clopidogrel alone. 3. Using a combination of aspirin and clopidogrel for 21 days is recommended to patients with minor stroke (NIHSS ≤ 3) or high-risk TIA (ABCD2 ≥4) within 24 h of onset (Grade I recommendation, Class-A evidence). After 21 days, either aspirin or clopidogrel can be continued for long-term use (Grade I recommendation, Class A evidence). 4. For ischemic stroke or TIA patients with severe intracranial arterial stenosis (stenosis of 70% to 99%), a combination of aspirin and clopidogrel is recommended for 90 days (Grade II recommendation, Class B evidence). After 90 days, either aspirin or clopidogrel could be continued for long-term use (Grade I recommendation, Class-A evidence). 5. For ischemic stroke or TIA patients with atherosclerosis of aortic arch, antiplatelet drugs and statins are recommended (Grade II recommendation, Class-B evidence). The effect of anticoagulant drugs or a combination of aspirin and clopidogrel is unclear (Grade II recommendation, Class-B evidence). 6. For patients with non-cardioembolic ischemic stroke or TIA, long-term use of combined aspirin and clopidogrel for long time is not recommended (Grade I recommendation, Class-A evidence).
American Academy of Family Physicians (AAFP). Summary of recommendations for clinical preventive services. Leawood (KS), 2017	Aspirin Prevention, Adults Younger than Age 50 Years The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (2016) (Grade: I recommendation) Aspirin Prevention, Adults 50 to 59 Years The AAFP recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take lowdose aspirin daily for at least 10 years. (2016) (Grade: B recommendation) Aspirin Prevention, Adults 60 to 69 Years The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate

Guideline	Recommendations
	low-dose aspirin. (2016) (Grade: C recommendation) Aspirin Prevention, Adults 70 Years and Older The AAFP concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (2016) (Grade: I recommendation)
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	**Strong Recommendation** Long-term antiplatelet therapy (low-dose aspirin, clopidogrel or combined low-dose aspirin and modified release dipyridamole) should be prescribed to all people with ischaemic stroke or TIA who are not prescribed anticoagulation therapy, taking into consideration patient co-morbidities. **Strong Recommendation** All ischaemic stroke and TIA patients should have antiplatelet therapy commenced as soon as possible once brain imaging has excluded haemorrhage unless thrombolysis has been administered, in which case antiplatelet therapy can commence after 24-hour brain imaging has excluded major haemorrhagic transformation. **Weak Recommendation** For high risk patients with minor ischaemic stroke or TIA, aspirin plus clopidogrel may be used in the short term (first three weeks) to prevent stroke recurrence **Strong Recommendation AGAINST** The combination of aspirin plus clopidogrel should not be used for the long-term secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent. **Strong Recommendation AGAINST** Antiplatelet agents should not be used for stroke prevention in patients with atrial fibrillation.
Bibbins-Domingo K. **Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement.** ***Ann Intern Med*. 2016;164(12):836-45.**	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation) The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation) The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement) The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

Guideline	Recommendations
Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I. **2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).** ***Eur Heart J.* 2016 May 23;37(29):2315-81.** **(selected)**	**Antiplatelet therapy in individuals with cardiovascular or cerebrovascular disease** In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended. Class 1; Level A **Antiplatelet therapy in individuals without cardiovascular disease** Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding. Class III; Level B
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	**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).

Guideline	Recommendations
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.**	• 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 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)
Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MSV, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Hypertension. **Guidelines for the primary prevention of stroke: a statement for healthcare**	1. The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is reasonable for people whose risk is sufficiently high (10-year risk >10%) for the benefits to outweigh the risks associated with treatment. (Class IIa; Level of Evidence A). 2. Aspirin (81 mg daily or 100 mg every other day) can be useful for the prevention of a first stroke among women, including those with diabetes mellitus, whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa; Level of Evidence B). 3. Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (ie, estimated glomerular filtration rate <45 mL/min/1.73 m^2) (Class IIb; Level of Evidence C). This recommendation does not apply to severe kidney disease (stage 4 or 5; estimated glomerular filtration rate <30 mL/min/1.73 m^2). 4. Cilostazol may be reasonable for the prevention of a first stroke in people with peripheral arterial disease (Class IIb; Level of Evidence B). 5. Aspirin is not useful for preventing a first stroke in low-risk individuals (Class III; Level of Evidence A).

Guideline	Recommendations
professionals from the American Heart Association/American Stroke Association. ***Stroke.* 2014;45:3754–3832.**	6. Aspirin is not useful for preventing a first stroke in people with diabetes mellitus in the absence of other high-risk conditions (Class III; Level of Evidence A). 7. Aspirin is not useful for preventing a first stroke in people with diabetes mellitus and asymptomatic peripheral artery disease (defined as asymptomatic in the presence of an ankle brachial index ≤0.99) (Class III; Level of Evidence B). 8. The use of aspirin for other specific situations (eg, AF,carotid artery stenosis) is discussed in the relevant sections of this statement. 9. As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for the prevention of a first stroke (Class III; Level of Evidence C).
Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, Akl EA, Lansberg MG, Guyatt GH, Spencer FA. **Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines.** ***Chest*. 2012 Feb 1;141(2):e637S-68S. (selected)**	2.1. For persons aged 50 years or older without symptomatic cardiovascular disease, we suggest low-dose aspirin 75 to 100 mg daily over no aspirin therapy (Grade 2B).
Bell AD, Roussin A, Cartier R, Chan WS, Douketis JD, Gupta A, Kraw ME, Lindsay TF, Love MP, Pannu N, Rabasa-Lhoret R. **The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines.** ***Can J Cardiol.* 2011 May 1;27(3):S1-59.** **(selected)**	For men and women without evidence of manifest vascular disease, the use of ASA at any dose is not recommended for routine use to prevent ischemic vascular events (Class III, Level A). For men and women without evidence of manifest vascular disease, the use of clopidogrel 75 mg daily plus ASA at any dose is not recommended to prevent ischemic vascular events (Class III, Level B). In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk is low, ASA 75-162 mg daily may be considered (Class IIb, Level C). There is currently no evidence to recommend routine use of ASA at any dose for the primary prevention of vascular ischemic events in patients with diabetes (Class III, Level A). For patients with diabetes aged > 40 years and at low risk for major bleeding, low-dose ASA (75-162 mg daily) may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class IIb, Level B).

Guideline	Recommendations
	Low-dose ASA therapy (75-162 mg daily) may be considered for secondary prevention in patients with diabetes and manifest vascular disease for which its benefits are established (Class I, Level A). Clopidogrel 75 mg daily may be considered for secondary prevention in patients with diabetes who are unable to tolerate ASA (Class IIa, Level B).
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** ***Cerebrovasc Dis* 2008;25:457–507**	**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 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Primary Prevention					
Huang et al. 2019 **Taiwan** **Systematic review & meta-analysis**	In 3 trials, participants were not blinded to treatment group. 3 trials had attrition bias due to incomplete outcome data.	13 RCTs (n= 134,446) that included persons without preexisting symptomatic cardiovascular diseases (eg, coronary heart disease, stroke, or peripheral artery disease). Mean age ranged from 42.9 to 74.0 years. Percentage of men ranged from 10% to 100%.	Trials compared low-dose aspirin (≤100 mg/day, for ≥6 months) vs. placebo, or no treatment. Daily doses in active treatment arm were 75 mg (n=2), 81 mg (n=1), 100 mg (n=8), 100 mg every other day (n=1) and 81 or 100 mg (n=1)	**Primary outcome:** Any intracranial hemorrhage **Secondary outcomes**: Intracerebral hemorrhage, subdural or extradural hemorrhage, and subarachnoid hemorrhage (SAH)	Mean duration of follow-up ranged from 2.3 to 8.2 years. Aspirin was associated with a significantly increased risk of any intracranial bleeding (RR=1.37, 95% CI, 1.13-1.66; n=8 trials; 2 additional intracranial hemorrhages in 1,000 people). In a sensitivity analysis, excluding the results from ASPREE, which included elderly people, the risk became non-significant (RR=1.28, 95% CI, 0.99-1.65). Aspirin was not associated with a significantly increased risk of intracerebral hemorrhage (RR=1.23, 95% CI, 0.98- 1.54, n=10 trials) or SAH (RR= 1.13, 95% CI, 0.70-1.83, n=5 trials) Aspirin was associated with a significantly increased risk of subdural or extradural hemorrhage (RR=1.53, 95% CI, 1.08-2.18, n=4 trials, 1 additional event in 1,000 people). In subgroup analysis, Asians and persons with a BMI <25 taking aspirin were at significantly higher risk for intracerebral hemorrhage
Mahmoud et al. 2019 **USA** **Systematic review & meta-analysis**	1 trial had high risk of selection bias, 5 had high risk of performance bias, 3 had high risk of attrition bias	11 RCTs (n=157,248) that included persons without prior history of atherosclerosis (including peripheral arterial disease, coronary artery disease, prior MI, prior stroke or TIA, prior percutaneous coronary intervention, prior	Trials compared aspirin vs. placebo, or no treatment	**Primary outcome:** All-cause mortality **Safety outcome:** Major bleeding	Mean duration of follow-up was 6.6 years. The use of aspirin was not associated with a lower incidence of all-cause mortality (4.6% vs. 4.7%; RR= 0.98, 95% CI 0.93–1.02; p = 0.30). The risk of ischemic stroke was not reduced significantly with aspirin (1.7% vs. 1.8%; RR=0.94, 95% CI 0.86-1.04, p=0.24)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		coronary artery bypass grafting), and which enrolled ≥500 patients. Mean age was 61.3 years, 48% were men.			Aspirin was associated with an increased incidence of major bleeding (1.8% vs. 1.2%; RR=1.47, 95% CI 1.31–1.65; P < 0.0001) and intracranial haemorrhage (0.4% vs. 0.3%; RR= 1.33, 95% CI 1.13–1.58; P = 0.001).
Zheng & Roddick 2019 **UK** **Systematic review &meta-analysis**	4 open-label trials were deemed to be at high risk of bias.	13 RCTs (n=164,225), which enrolled at least 1,000 participants with no known cardiovascular disease and a follow-up of at least 12 months.	Trials compared aspirin vs. placebo, or no treatment. Doses ranged from 75 to 500 mg per day. 100 mg was the most common dose.	**Primary outcomes:** *Cardiovascular outcome* A composite of cardiovascular mortality, nonfatal MI, and nonfatal stroke, **Bleeding outcomes:** Major bleeding events, intracranial bleeding, GI bleeding	The use of aspirin was associated with a significant reduction in the cardiovascular outcome (HR=0.89 [95% CrI, 0.84-0.95]; ARR, 0.38% [95% CI, 0.20%-0.55%]; NNT= 265), and ischemic stroke (HR=0.81 [95% CrI, 0.76-0.87]; ARR, 0.16% [95% CI 0.06 to 0.30]; NNT=540). The use of aspirin was associated with an increased rate of major bleeding (HR=1.43 [95% CrI, 1.30-1.56]; ARI, 0.47% [95% CI, 0.34%-0.62%]; NNH= 210), intracranial bleeding and GI bleeding. The risk of the cardiovascular outcome was reduced significantly in persons at high and low cardiovascular risk, and those with diabetes. Bleeding risk was also significantly increased in these groups.
Gaziano et al. 2018 **International** **RCT** ***Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	12,546 patients recruited primarily from primary care centres in 7 countries (Germany, Italy, Ireland, Poland, Spain, UK, and USA). Eligible men were ≥ 55 years and had 2-4 cardiovascular risk factors; eligible women were ≥60 years and had 3-5 risk factors. Persons with a significant cardiovascular history and those with a history of bleeding were excluded. Mean age was 63.9 years, 70.4% were men. Mean estimated ACC/AHA 10-year	Participants were randomized 1:1 to receive 100 mg aspirin or placebo daily for the duration of the trial	**Primary outcome:** Composite of time to first occurrence of confirmed MI, stroke, cardiovascular death, unstable angina, or TIA **Safety outcomes:** Hemorrhagic events	Median duration of follow-up was 5.1 years. 29.6% of patients terminated the study early. In the intention- to- treat analysis, the risk of the primary outcome and its component parts were not reduced significantly with aspirin therapy. Primary outcome: HR=0·96, 95% CI 0·81–1·13, p=0·6038 Fatal/nonfatal MI: HR=0·85, 95% CI 0·64–1·11, p=0·2325 Fatal/nonfatal stroke: HR=1.12, 95% CI 0·80–1·55, p=0·5072 Cardiovascular death: HR=0·97, 95% CI 0·62–1·52, p=0·9010 TIA: HR=0·93, 95% CI 0·61–1·42, p=0·7455 The risk of serious adverse events was similar between groups (20.19% vs. 20.89%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		ASCVD risk score at baseline was 17.3%			The overall incidence of treatment-related adverse events was significantly higher in the aspirin group (16.75% vs. 13.54%, p<0·0001). The authors suggested that the reason for the apparent lack of benefit of aspirin was due to the lower than expected event rate (1,500 expected, 500 actual), which was attributed to aggressive prevention measures, particularly, the treatment of hypertension).
ASCEND Study Collaborative Group 2018 (Bowman et al) **UK** **RCT** ***A Study of Cardiovascular Events in Diabetes***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	15,480 participants >40 years, with diabetes with no known CVD. Mean age was 63 years, 63% were men, 36% had taken aspirin previously. Median duration of diabetes was 7 years. 83% of participants had low or moderate vascular risk scores.	Participants were randomized 1:1 to receive 100 mg aspirin or placebo daily for the duration of the trial	**Primary outcome:** First serious vascular event (MI, stroke, TIA or cardiovascular death) **Secondary outcome:** Gastrointestinal tract cancers **Safety outcomes:** Hemorrhagic events	Mean duration of follow-up was 7.4 years. Estimated mean adherence was 70% in both groups. The risk of the primary outcome was significantly lower in the aspirin group (8.5% vs, 9.6%, RR=0.88, 95% CI, 0.79 to 0.97; p=0.01). The risk of any major bleeding was significantly increased in the aspirin group (4.1% vs. 3.2%, RR=1.29, 95% CI 1.09-1.52, p=0.003). There was no significant difference between groups in the risk of GI cancer (2% vs. 2%, RR=0.99, 95% CI 0.80–1.24).
McNeil et al. 2018 **Australia** **RCT** ***Aspirin in Reducing Events in the Elderly (ASPREE) trial***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	19,114 persons ≥70 years (or ≥65 years of age among blacks and Hispanics in the United States) without cardiovascular disease, dementia, or disability, recruited from Australia and the US between 2010 and 2014. Median age was 74 years, 44% were men. 14% had used NSAIDS regularly.	Participants were randomly assigned (1:1) to receive 100 mg of enteric-coated aspirin or placebo.	**Primary outcome:** CVD (fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure). **Safety outcomes:** Major bleeding events	Median duration of follow-up was 4.7 years. In the final 12 months of the trial, 62% of the participants in the aspirin group and 64% of those in the placebo group were still taking the assigned trial intervention. The number of CVD events did not differ significantly between groups (10.7 vs. 11.3/1,000-person years, HR=0.95, 95% CI 0.83–1.08), nor did the number of ischemic strokes (3.5 vs. 3.9/1,000 person-years follow-up; HR=0.89, 95% CI 0.71–1.11). The risk of major bleeding events was significantly increased in the aspirin group (8.6 vs. 6.2/1,000-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					person years; HR=1.38, 95% CI 1.18–1.62, p<0.001). The risk of fatal hemorrhagic stroke was not significantly increased with aspirin therapy (0.3 vs. 03/1,000-person years; HR=1.01, 95% CI 0.47–2.17).
ii) 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	**Primary outcome:** 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 Trialists' Collaborative	NA	287 RCTs (n=135,000) examining any antiplatelet therapy for	In 9 of these trials, long-term aspirin monotherapy was examined in patients	**Primary outcome:** Any vascular event (MI, stroke or vascular death)	In the trials that included persons with previous stroke, fewer patients receiving aspirin therapy experienced a vascular event (8.2% vs. 9.1%)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
(2002) **UK** **Systematic review & meta-analysis**		the prevention of vascular events in high-risk patients because of evidence of pre-existing disease (previous occlusive event or predisposing condition).	who had experienced a previous stroke or TIA		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)
iii) Secondary Prevention (short-term use following acute stroke)					
Rothwell et al. 2016 **UK** **Systematic review & patient-level meta-analysis**	NA	12 RCTs including 15,778 participants with acute ischemic stroke or TIA	Among the included trials, 3 included a comparison of aspirin vs. placebo initiated within 48 hours of stroke onset (IST, 1997, CAST 1997 and Rödén-Jüllig et al. 2003).	**Primary outcome:** Recurrent stroke within 14 days, stratified by stroke severity	Aspirin use reduced the risk of stroke among patients presenting with mild and moderate stroke (OR=0.51, 95% CI 0.34-0.75, p=0.0007 and OR=0.65, 95% CI 0.44-0.98, p=0.04, respectively), but not severe stroke (OR=1.10, 95% CI 0.77-1.58, p=0.60). Among patients with mild and moderate strokes, the risk of recurrent stroke given aspirin therapy was not reduced significantly at 24 hours, but was significantly reduced from days 2 to 14.
Thompson et al. 2015 **UK** **Meta-analysis**	NA	The results from 3 trials (n=39,166) were included-International Stroke Trial (1997), Chinese Acute Stroke Trial (1997) and Multicentre Acute Stroke Trial (MAST 1995)	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”	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			patient.		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) 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.
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 months following stroke. Follow-up periods were 10 days, 3 weeks (n=2), 4 weeks, 3 months (n=2) and 6 months (n=2)	**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). All results represent only aspirin vs placebo trails. Aspirin 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). For every 1,000-people treated, 13 fewer people would avoid death or dependency (NNTB 79) Aspirin was associated with a marginally significant reduction in death during follow-up (OR=0.92, 95% CI 0.87 to 0.98). For every 1,000-people treated, 9 fewer people would avoid death (NNTB 108). Aspirin was associated with significantly reduced odds of recurrent stroke during treatment (OR=0.77, 95% CI 0.69-0.87) and marginally increased odds of intracranial hemorrhage (OR=1.22, 95% CI 1.00-1.50 Aspirin was associated with a decreased risk of PE (OR=0.71, 95% CI 0.53 to 0.76) and increased odds of complete stroke recovery (OR=1.06, 95% CI 1.01 to 1.11, p=0.02).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Roden-Jullig et al. 2003 **Sweden** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	441 patients admitted to one of 4 hospitals with acute ischemic stroke. Included patients had not been treated with antiplatelet drugs within the 72 hours preceding stroke onset. Mean age was 74 years. The mean Scandinavian Stroke Scale score at admission was 13	Patients were randomized to receive 325 mg aspirin (n=220) or placebo (n=221), initiated 48 hours post onset and continuing for 5 consecutive days	**Primary Outcomes:** Progression of stroke symptoms (decrease of ≥2 points on the SSS scale) within the 5-day treatment period. **Secondary Outcomes:** SSS at discharge and at 3 months, discharge destination, ambulatory status	Aspirin therapy did not significantly reduce the risk of stroke progression (15.9% vs. 16.7%, OR=0.95, 95% CI 0.62-1.45) during the treatment period. At the point of discharge there were no significant differences between groups (aspirin vs. placebo) % discharged home: 60.6% vs. 64.1% % able to walk without aid: 51.9% vs. 58.4% Mean SSS score: 10.9 vs.10.2 Death: 2.7% vs. 3.2% At 3 months, there were no significant differences between groups (aspirin vs. placebo) % able to walk without aid: 60.2% vs. 64.8% % living at home: 80.3% vs. 84.0% Death: 6.8% vs. 5.4%
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

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

Systematic Reviews

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Antiplatelet Therapy for Secondary Prevention					
Chiarito et al. 2020 **Italy**	Risk of bias was assessed as low in 3 of the trials. There were some concerns in the remaining 6 trials	9 RCTs (n=42,108) with established atherosclerosis with coronary, or peripheral artery disease or cerebrovascular event. Mean age ranged from 59.2 to 66.7 years, 46.5% to 84.9% were men.	Participants were randomized to receive a $P2Y_{12}$ inhibitor (n=21,043) or aspirin (n=21,065). $P2Y_{12}$ agents included ticlopidine (n=3,250 mg 2x/day), clopidogrel (n=3, 75 mg 2/day) and ticagrelor (n=3, 90 mg, 2x/day). Aspirin doses ranged from 80 mg 2x/day to 650 mg 2x/day. Duration of follow-up ranged from 3 to 36 months.	**Primary outcomes:** MI and stroke. **Secondary outcomes:** All-cause death and vascular death	The risk of MI was significantly lower in patients in the P2Y12 group (OR= 0·81, 95% CI 95% CI 0·66–0·99). The NNT to prevent one MI with P2Y12 inhibitor monotherapy was 244 patients. The risks of stroke (OR=0·93, 95% CI 0·82–1·06), all-cause death (OR=0·98, 95% CI 0·89–1·08]) and vascular death (OR=0·97, 95% CI 0·86–1·09) were not significantly lower in the P2Y12 group. The risk of major bleeding was not significantly higher in the P2Y12 group (OR=0·90, 95% CI 0·74–1·10).
Greving et al. 2019 **The Netherlands** **Patient-level network meta-analysis**	Risk of bias was assessed as low in all trials	6 RCTs (CAPRIE, ESPS-2, MATCH, CHARISMA, ESPRIT, and PRoFESS, n=48,023) examining mono or dual antiplatelet therapy in long-term (i.e.> 30 days) secondary prevention	Treatment contrasts included: 1) aspirin vs. clopidogrel; 2) aspirin vs. aspirin + dipyridamole (n=2); 3) aspirin vs. aspirin + clopidogrel; 4) clopidogrel vs. aspirin + dipyridamole; clopidogrel vs. aspirin + clopidogrel;	**Primary outcomes:** Serious vascular events (composite of stroke, MI, or vascular death) and ischemic events (composite of ischemic stroke, MI, or vascular death) **Safety outcomes:** Major (including fatal)	The median time to randomization was 21 days. Aspirin/dipyridamole combination significantly reduced the risk of serious vascular events compared with aspirin (RR= 0.83; 95% CI, 0.74–0.94), as did clopidogrel (RR= 0.88; 95% CI, 0.78–0.98), and aspirin/clopidogrel combination (RR=0.83; 95% CI, 0.71–0.96). Only the combination of aspirin + dipyridamole

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		after a non-cardioembolic TIA or ischemic stroke. Trials of aspirin vs. placebo were excluded. Mean age was 65 years, 36% were female. 90% of qualifying events were strokes.	and aspirin + dipyridamole vs. aspirin + clopidogrel	bleeding and primary ICH Analyses were adjusted for age, sex, hypertension, diabetes mellitus, current smoking, qualifying diagnosis (stroke vs TIA).	significantly reduced the risk of recurrent ischemic stroke (RR=0.86, 95% CI 0.76–0.97). Clopidogrel led to significantly less major bleeding and intracranial hemorrhage compared with aspirin. Compared with clopidogrel alone, treatment with aspirin + dipyridamole and aspirin + clopidogrel led to significantly higher risks of major bleeding and ICH. Compared with aspirin + dipyridamole, treatment with aspirin + clopidogrel was associated with a significantly higher risk of major bleeding (but not ICH). Combining safety and efficacy outcomes, the highest-ranking net clinical benefit outcome (serious vascular events or major bleeding) profile was achieved by clopidogrel and aspirin/dipyridamole combination (RR=0.89; 95% CI 0.82–0.96 and RR=0.87; 95% CI 0.80–0.95, respectively.)
Dual vs. Mono Antiplatelet Therapy					
Rahman et al. 2019 **USA** **Systematic review & meta-analysis**	All trials were considered to be of low risk of bias. 3 trials were open label.	10 RCTs (15,434 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	The association between 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.	**Primary outcomes:** Recurrent stroke, major bleeding **Secondary outcomes:** Major adverse cardiovascular events (composite of stroke, MI, and cardiovascular mortality) and all-cause mortality	Dual therapy significantly reduced the risk of 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		mean age was 64.0 years, 61.1% were men.			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). Treatment duration ranged from 14 days to 42 months	**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 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	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-

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

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

Mono Antiplatelet Therapy with Clopidogrel (Non Acute)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Gent et al. 1996 **International** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑	19,185 patients who had experienced an ischemic stroke (n= 6,431), thought to be of atherothrombotic origin, with onset ≥1 week or ≤6	Patients were randomized to receive 75 mg tablets of clopidogrel + aspirin placebo or 325 mg tablets of aspirin plus clopidogrel	**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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE)	ITT: ☑	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.	placebo, daily for 1-3 years.		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%).

Dual Antiplatelet Therapy with Clopidogrel

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Clopidogrel + aspirin vs. aspirin alone (Secondary prevention-acute)					
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 below). 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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).
Johnston et al. 2018, 2019, Tillman et al. 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 the trial had crossed the pre-specified safety threshold for major hemorrhage. 93.4% of patients completed the 90-day trial visit or died. Significantly fewer patients in the clopidogrel group had a new vascular event (5% vs. 6.5%, HR=0.75, 95% CI 0.59–0.95, p=0.02). The risks of ischemic and hemorrhagic and ischemic stroke were significantly lower in the clopidogrel group (4.6% vs. 6.3%; HR=0.72, 95% CI 0.56–0.92, p= 0.01 and 4.8% vs. 6.4%; HR=0.74, 95% CI 0.58–0.94, p=0.01, respectively). There were no significant differences between groups in the risks of MI or ischemic vascular death. There were significantly more cases of major hemorrhage in the clopidogrel group (0.9% vs. 0.4%, HR=2.32, 95% CI 1.10–4.87, p= 0.02). There were no significant differences between groups in hemorrhagic stroke or symptomatic ICH.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The authors estimated that for every 1000 patients treated with clopidogrel plus aspirin during a period of 90 days, 15 ischemic strokes would be prevented but 5 major hemorrhages would result. **Tillman et al. 2019 (secondary analysis)** In the on-treatment analysis, the risks of minor and major hemorrhage were significantly higher in the dual platelet group (HR=2.98, 95% CI 1.59-5.60 and 0.9% vs. 0.2%; HR=3.57, 95% CI 1.44-8.85, respectively). **Johnston et al. 2019** The absolute number of major ischemic events prevented by clopidogrel-aspirin treatment for 21 days exceeded the absolute number of major hemorrhage events caused. For every 1,000 patients treated, 20 major ischemic events would be prevented and 2 major hemorrhages would be expected. In contrast, treatment with dual antiplatelet therapy for 90 days would be expected to prevent 16 major ischemic events, but there would be 5 major hemorrhages expected.
Wang et al. 2013, 2018 **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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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. **Subgroup analysis** Included the results of 1,809 patients who had imaging completed during their hospital stay using MRI. The outcomes of patients with different infarct patterns were compared: multiple acute infarctions (MAIs), single acute infarction (SAI), and no acute infarction (NAI). The risks of recurrent stroke at 3-month follow-up were 14.2%, 8.7%, and 2.0% in patients with MAIs, SAI, and NAI, respectively. The risk of recurrent stroke at 3 months among patients with MAI who received dual antiplatelet therapy was significantly lower compared with MAI patients who received monotherapy (10.1% vs. 18.8%; adj HR=0.5, 95% CI 0.3-0.96, p=0.04). The same risk reduction pattern was not evident for patients with SAI or NAI who received dual vs. mono antiplatelet therapy.
Hong et al. 2016 **Korea** **RCT** ***Combination of Clopidogrel and Aspirin for Prevention of Recurrence in Acute Atherothrombotic Stroke Study (COMPRESS)***	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, and vascular death at 30 days **Safety outcomes:**	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 0.91–2.68, p=0.11).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Bleeding (life-threatening, major and minor)	
ii) Clopidogrel + aspirin vs. aspirin alone (Secondary prevention-non acute)					
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. Comparing the cohort of patients who had not

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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, respectively). 43 patients were lost to follow up.
Bhatt et al. 2006 **International**	CA: ☑ Blinding:	15,603 patients, ≥45 years with either established	Patients were randomized to receive 75 mg clopidogrel + 75-	**Primary outcome:** A composite of MI, stroke or death from cardiovascular	Median duration of follow-up was 28 months. There was a non-significant reduction in the risk of

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)***	Patient: ☑ Assessor ☑ ITT: ☑	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.	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.	causes **Secondary outcomes:** Combined first occurrence of MI, stroke or cardiovascular death, hospitalization for unstable angina, TIA, or revascularization procedure.	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.
iii) Clopidogrel + aspirin vs. clopidogrel alone (Secondary prevention)					
Deiner et al. 2004 **International** **RCT** ***Management of Atherothrombosis with Clopidogrel in High-risk***	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	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	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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Patients (MATCH)		(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%).		stroke.	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)

Antiplatelet Therapy with Ticagrelor (Acute)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ticagrelor vs. Aspirin					
Johnston et al. 2016 **USA/International** **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	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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		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			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
Ticagrelor + Aspirin vs. Aspirin					
Johnston et al. 2020, Amarenco et al. 2020 **USA** **RCT** ***Acute STroke or Transient IscHaemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death (THALES)***	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 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	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. Loading doses of ticagrelor and aspirin were 180 mg and 300-325 mg, respectively	**Primary outcome:** Subsequent stroke or death within 30 days **Secondary outcome:** Ischemic stroke within 30 days, disability (mRS>1) at 30 days **Safety outcomes:** Major bleeding, fatal or life-threatening bleeding, ICH	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). 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.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		previous stroke or TIA.			

Antiplatelet Therapy with Dipyridamole

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Dipyridamole + aspirin vs. aspirin (Secondary prevention-acute)					
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.
ii) Dipyridamole + aspirin vs. aspirin (Secondary prevention-non acute)					
Halkes et al. 2006 **International**	CA: ☑ Blinding: Patient: ☒	2,763 patients who had experienced a TIA or minor stroke (mRS≤3) within the previous 6	Patient were randomized to receive extended-release dipyridamole (200 mg bid) + aspirin (30 to 325 mg/d-mean	**Primary outcome:** Composite of vascular death, nonfatal stroke, nonfatal MI or major	Mean follow-up was 3.5 years. Fewer patients in the dual therapy group experienced the primary outcome (12.7% vs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)***	Assessor ☑ ITT: ☒	months. Mean age at baseline was 63 years. 66% of patients were male. Qualifying events were TIA (35%) and minor stroke (65%)	dose, 75 mg, n=1,363) or aspirin (as above) alone (n=1,376), for the duration of the study.	bleeding complication **Secondary outcomes:** Death from all causes, death from all vascular causes, nonfatal stroke or nonfatal MI.	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** ***European Stroke Prevention Trial-2 (ESPS-2)***	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.

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

Dipyridamole + Aspirin vs. Clopidogrel

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. Median time from qualifying event to randomization was 17 days.	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					medication (29.1% vs. 22.6%, p<0.001). 0.6% of patients in both groups were lost to follow-up.

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

Aspirin vs. Novel oral anticoagulants (NOACs)

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NCT02295826		300 patients ≥18 years,	Patients were randomized	**Primary outcome:**	TBA

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Canada **Phase II RCT** ***Dabigatran Following Transient Ischemic Attack and Minor Stroke (DATAS II)***		with TIA or ischemic stroke (NIHSS score <9) with symptom onset within the previous 48 hours, and with a lesion volume <25 mL, confirmed by MRI with DWI.	1:1 to receive 150 mg dabigatran BID or 81 mg aspirin (loading dose of 325 mg) for 30 days	Symptomatic hemorrhagic transformation within 5 weeks of treatment initiation **Secondary outcome:** Symptomatic hemorrhagic transformation within 30 days	
Diener et al. 2019 **Germany/ International** **RCT** ***Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,390 patients ≥60 years, recruited from 564 sites with stroke of undetermined source, sustained within the previous 3 months, or, if there was at least one vascular risk factor identified within the previous 6 months. Mean age was 64.2 years, 36.9% were women. Median time from qualifying event to randomization was 44 days.	Patients were randomized 1:1 to receive 150 or 110 mg (in patients ≥75 years, or those who had an estimated creatinine clearance of 30 to 50 ml per minute) dabigatran twice daily or 100 mg plain aspirin once daily for the duration of the trial (planned for a minimum of 6 moths, maximum of 3.5 years)	**Primary efficacy outcome:** First recurrent stroke (ischemic, hemorrhagic, or undefined stroke) **Secondary efficacy outcomes:** Ischemic stroke and a composite of death from cardiovascular causes, nonfatal stroke and nonfatal MI, death from any cause, disabling stroke (mRS 4-5) at 3 months **Primary safety outcome:** Major bleeding at any site in the body **Secondary safety outcomes:** Clinically relevant nonmajor bleeding resulting in hospitalization, and a composite of major bleeding or clinically relevant nonmajor bleeding	Median duration of follow up was 19 months. The risk of recurrent stroke was not reduced significantly in the dabigatran group (4.1% vs. 6.6%, HR=0.85; 95% CI 0.69 to 1.03; p=0.10), nor was the risk of ischemic stroke (4.0% vs. 4.7% per year, HR=0.84, 95% CI 0.68–1.03), or the composite outcome (4.8% vs. 5.4% per year, HR=0.88, 95% CI 0.73–1.06). The risk of disabling stroke was significantly reduced in the dabigatran group (0.6% vs. 0.9% per year, HR=0.59, 95% CI 0.36–0.96). The risk of bleeding was not significantly higher in the dabigatran group (1.7% vs. 1.4% per year, HR= 1.19; 95% CI, 0.85 to 1.66). The risk of clinically relevant nonmajor bleeding was significantly higher in the dabigatran group (1.6% vs. 0.9% per year, HR= 1.73, 95% CI 1.17–2.54), as was the composite safety outcome (3.3% vs. 2.3% per year, HR=1.44, 95% CI 1.12–1.85).
Hart et al. 2018,	CA: ☑	7,213 patients ≥50 years,	Patients were randomized	**Primary efficacy**	The trial was terminated early due to an excess risk

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Healey et al. 2019, Ntaios et al. 2019, Veltkamp et al. 2020 **Canada/ International** **RCT** ***New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS)***	Blinding: Patient: ☑ Assessor ☑ ITT: ☑	recruited from 459 centers in 31 countries who had an ischemic, non-lacunar stroke of undetermined source, 7 days to 6 months previously, that was not associated with extracranial vessel atherosclerosis causing ≥50% stenosis in arteries supplying the area of ischemia or with an identified cardioembolic source. Mean age was 67 years, 62% were men. Median NIHSS score was 1.	1:1 to receive 15 mg rivaroxaban + aspirin placebo or 100 mg of enteric coated aspirin + rivaroxaban placebo for the duration of the trial.	**outcome:** First recurrent stroke (ischemic, hemorrhagic, or undefined stroke) or systemic embolism **Secondary efficacy outcomes:** A composite of death from cardiovascular causes, recurrent stroke, systemic embolism, and MI; death from any cause; disabling stroke (mRS 4-5) at hospital discharge) or fatal stroke, and individual components of the primary and secondary efficacy outcomes. **Primary safety outcome:** Major bleeding at any site in the body **Secondary safety outcomes:** Life-threatening or fatal bleeding, clinically relevant nonmajor bleeding, symptomatic intracranial hemorrhage	of bleeding among patients in the rivaroxaban group and an absence of benefit. The trial was planned to recruit until at least 450 events of the primary efficacy outcome had occurred. Median duration of follow-up was 11 months. The median time from the qualifying stroke to randomization was 37 days. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR=1.07; 95% CI, 0.87 to 1.33; p=0.52). There were no significant differences between groups in the risks of any of the secondary efficacy outcomes, except for a significantly increased risk of hemorrhagic stroke among patients in the rivaroxaban group (annual rate 0.4 vs. 0.1, HR=6.50, 95% CI 1.47–28.8). The risk of the primary safety outcome was significantly increased among patients in the rivaroxaban group (annual rate 1.8 vs. 0.7, HR=2.72, 95% CI 1.68–4.39, p <0.001). The risks of life-threatening and clinically relevant bleeding and intracerebral hemorrhage were significantly increased among patients in the rivaroxaban group. A total of 1% of the patients were lost to follow-up after a mean of 15 months, and an additional 1% of patients withdrew consent for follow-up after a mean of 5 months. **Healey et al. 2019 (secondary analysis)** 239 patients (3%) developed atrial fibrillation during follow-up.

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					Among a small subgroup of patients (n=361) with left atrial diameter of >4.6 cm, of whom 23 had atrial fibrillation, the risk of recurrent ischemic stroke was significantly reduced in the rivaroxaban group (3 [1.7%] vs. 11 [6.5%], HR=0.26, 95% CI 0.07-0.94, p for interaction=0.02). **Ntaios et al. 2019 (subgroup analysis based on presence of atherosclerosis)** Mild carotid atherosclerosis stenosis (20-49%) was identified in 10.5% of participants and carotid plaque (based on local definitions) was identified in 40.3% of participants. **Mild carotid stenosis** The rate of ischemic stroke recurrence during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (5.0 vs. 5.9 per 100 patient-years, HR=0.85; 95% CI, 0.39–1.87). For patients without carotid stenosis the rate of ischemic stroke during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (4.8 vs. 5.9 per 100 patient-years, HR=0.96; 95% CI, 0.72-1.87). There was no treatment interaction between rivaroxaban/aspirin and carotid stenosis status (P for interaction 0.78). The risk of major bleeding was not significantly increased in persons in the rivaroxaban treated group (HR=5.67, 95% CI 0.68–47.08, p= 0.11). **Carotid plaque** The rate of ischemic stroke recurrence during follow-up was not statistically different between rivaroxaban- and aspirin-treated patients (5.9 vs. 4.9 per 100 patient-years, respectively, HR=1.20; 95% CI, 0.86–1.68). The corresponding rates for patients without carotid plaque were 4.0 vs.4.5 per 100 patient-years, respectively, HR= 0.90; 95% CI, 0.67–1.2. There was no treatment interaction

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					between patients with and without carotid plaque (P for interaction =0.2). The risk of major bleeding was significantly increased in persons in the rivaroxaban treated group (HR=3.75, 95% CI 1.63–8.65, p<0.01). **Veltkamp et al. 2020 (Characteristics of patients with recurrent stroke)** 309 patients had an ischemic stroke during follow-up Of 270 classifiable ischemic strokes, 58% were ESUS and 42% were non-ESUS. Of the non-ESUS, 32% were cardioembolic, 23% were atherosclerotic, 31% were lacunar, and 14% were from other determined cause. Atrial fibrillation was found in 27 patients (9%) with recurrent ischemic stroke and was associated with higher morbidity and mortality (15% vs 1%) than other causes.
Eikelboom et al. 2017, Sharma 2019, Perera et al. 2019 Canada*l* International ***Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS)***	CA: ☑ Blinding: Patient ☑ Assessor ☑ ITT:☑	27,395 patients with coronary artery disease, peripheral arterial disease, or both. Mean age was 68.2 years, 22% were women. 3.8% of patients had a previous stroke. 90.6% and 27.3% of patients had a history of coronary artery disease, and peripheral arterial disease, respectively.	Patients were randomly assigned (1:1:1) to receive 2.5 mg rivaroxaban twice daily plus 100 mg aspirin once daily, 5 mg rivaroxaban twice daily with an aspirin-matched placebo once daily, or 100 mg aspirin once daily with a rivaroxaban matched placebo twice daily for the duration of the study	**Primary outcomes:** Composite of cardiovascular death, stroke, or MI **Secondary outcomes:** Ischemic stroke, MI, acute limb ischemia, or death from CHD	The dual therapy arm of the trial was stopped early due to superiority, after a mean of 23 months. The primary outcomes occurred in 4.1% of patients taking rivaroxaban plus aspirin, 4.9% on patients taking rivaroxaban and 5.4% in patients taking aspirin. The risk of the primary outcome was significantly lower for patients on dual therapy compared to aspirin alone (HR=0.76, 95% CI 0.66–0.86, p<0.001). The risk of the primary outcome was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (HR=0.90, 95% CI 0.79–1.03, p=0.12). The risk of any stroke was significantly lower for patients on dual therapy compared to aspirin alone

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					(0.9% vs.1.6%; HR=0.58, 95% CI 0.44-0.76, p<0.001). The risk of any stroke was non-significantly lower for patients taking rivaroxaban compared to aspirin alone (1.3% vs. 1.6%, HR=0.82, 95% CI 0.65–1.05, p=0.12). Major bleeding occurred in 3.1% of patients taking rivaroxaban plus aspirin, 2.8% on patients taking rivaroxaban and 1.9% in patients taking aspirin. **2019 (stroke outcomes)** The risk of ischemic stroke was significantly lower for patients on dual therapy compared to aspirin alone (0.7% vs.1.4%; HR=0.51, 95% CI 0.38-0.69, p<0.001), and was also reduced in the rivaroxaban group, compared with aspirin (0.9% vs. 1.4%, HR 0.66, 95% CI 0.50-0.88, p= 0.004). The risk of hemorrhagic stroke was significantly increased by rivaroxaban. compared with aspirin (0.3% vs. 0.1%, HR= 2.70, 95% CI 1.31-5.58, *p*=0.005) but not with dual therapy vs. aspirin alone (0.2% vs. 0.1%, HR= 1.49, 95% CI 0.67-3.31, *p*=0.33). The risk of fatal or disabling stroke (mRS 3-6) at day 7 or hospital discharge was significantly reduced in the dual therapy group compared with aspirin (0.3% vs. 0.6%, HR= 0.58, 95% CI 0.37-0.89, p< 0.01), but not in the rivaroxaban group vs aspirin group. However, significantly fewer patients in the dual therapy group were likely to have a good outcome (mRS 0-2) at 7 days compared to aspirin (0.6% vs. 1.0%, HR= 0.56, 95% CI 0.40-0.79), p<0.001). Independent predictors of stroke were increased age, increased SBP, HTN, diabetes, previous stroke and Asian race. **Perera et al. 2019 (Ischemic stroke subtypes)**

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					Of 291 ischemic strokes, 59 were cardioembolic, 54 were due to large artery atherosclerosis, 21 were lacunar strokes and 155 were due to stroke of undetermined cause, of which 42 were due to embolic stroke of undetermined source (ESUS) Compared with patients who received aspirin only, the risks of cardioembolic stroke, ESUS were all significantly lower among those who received rivaroxaban + aspirin (HR=0.40, 95% CI 0.20-0.78, p=0.005, HR=0.30, 95% CI 0.12-0.74, p<.006, respectively). The risk of lacunar stroke was not reduced significantly with rivaroxaban + aspirin.

Antiplatelet Therapy with Cilostazol

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
McHutchison et al. 2020 **UK** **Systematic review & meta-analysis**	Median score of 23.5 using CONSORT selection criteria (max score =37)	20 RCTs, including 10,505 participants with stroke (ischemic stroke, non-cardioembolic ischemic stroke, lacunar ischemic stroke, TIA), small vessel disease, mild cognitive impairment, or dementia.	Participants were randomized to treatment with cilostazol (100-200 mg 2x/day +/- additional antiplatelet therapy or to a control condition that included 75-300 mg daily aspirin, or 50 or 75 mg clopidogrel daily, placebo aspirin or no treatment. Treatment was initiated from within 7 days on index event to up to 4 years. Treatment duration ranged from 4 weeks to 5 years.	**Primary outcomes:** Any recurrent stroke, recurrent ischemic stroke, recurrent hemorrhagic stroke mortality and adverse events	Cilostazol significantly decreased any recurrent stroke (OR=0.61, 95% CI 0.52 to 0.72, p<0.00001), recurrent ischemic stroke (OR=0.68, 95% CI, 0.57 to 0.81, p<0.0009), recurrent hemorrhagic stroke (OR=0.43, 95% CI 0.29 to 0.64) and mortality (OR=0.64, 95% CI 0.49 to 0.83). The risk of headaches, dizziness, palpitations, tachycardia, diarrhea and nausea were significantly higher in the cilostazol group. Cilostazol reduced recurrent ischemic stroke to a greater extent when given longer periods (>6 months) and in trials with larger proportions (>40%) of lacunar stroke.
Kim et al 2019 **South Korea**	One trial was considered to be at high risk of bias	10 RCTs including persons recovering from noncardioembolic stroke	5 trials compared monotherapy using 200 mg/day cilostazol vs. 80,	**Primary outcomes:** Recurrent stroke, ischemic stroke,	**Monotherapy** The risks of recurrent stroke, ischemic stroke and hemorrhagic stroke were all significantly reduced

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Systematic review & meta-analysis	due to unblinded patients/assessors. The other trials were considered to be at low risk of bias.	or TIA who received either mono or dual antiplatelet therapy with cilostazol or cilostazol + aspirin. Timing of intervention varied from 48 hours to 6 months following stroke onset. Mean age ranged from 60.2 to 69.7 years. 35.3% to 74.9% were men.	100 or 300 mg/day aspirin (n=5,429) and 5 trials compared dual therapy using 200 mg/day cilostazol + 80, 100, or 300 mg/day aspirin vs. aspirin only. In one trial a portion of the patients received 50-75 mg of clopidogrel as the antiplatelet agent (n=2,456)	hemorrhagic stroke, and MI.	with cilostazol RR= (0.66; 95% CI, 0.66–0.78; HR=0.78, 95% CI 0.62- 0.97 and RR=0.36, 95% CI 0.21-0.61, respectively). Cilostazol did not reduce the risk of MI significantly. **Combination therapy** The risks of recurrent stroke and ischemic stroke were significantly reduced with cilostazol + aspirin (RR= (0.72; 95% CI, 0.54–0.81; HR=0.58, 95% CI 0.53- 0.65). Cilostazol did not reduce the risk of MI or hemorrhagic stroke significantly. The risk of recurrent stroke in patients who received a cilostazol combination was significantly lower than in the patients treated with cilostazol monotherapy (RR=0.72; 95% CI, 0.66–0.78). The risk of a recurrent stroke was lower in patients in the cilostazol mono and combination therapies compared with mono antiplatelet treatments when each intervention was initiated after the acute period and then administered for >6 months.
Toyoda et al. 2019 **Japan** **RCT** ***Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS)***	CA: ☑ Blinding: Patient: ☒ Assessor ☒ ITT: ☑	1,879 patients, aged 20-85 years, with a non-cardioembolic ischaemic stroke that occurred 8-180 previously, who were taking either aspirin or clopidogrel alone as antiplatelet therapy, who were considered to be at high risk of stroke recurrence (≥50% stenosis of a major intracranial or extracranial artery or two or more of the vascular risk factors). Mean age was 69.7 years, 70% were men. 100% of	Patients were randomized 1:1 to receive monotherapy with either oral aspirin (81 or 100 mg, once per day) or clopidogrel (50 or 75 mg, once per day) alone, or a combination of cilostazol (100 mg, twice per day) with aspirin or clopidogrel for the duration of the trial.	**Primary outcome:** First recurrence of symptomatic ischaemic stroke **Secondary outcomes:** Any stroke (ischaemic or hemorrhagic), haemorrhagic stroke (intracerebral or SAH, symptomatic), ischaemic stroke or TIA, death from any cause; a composite of stroke, MI and vascular death; and all vascular events, including stroke, MI, and other vascular events	The trial was stopped prematurely because of a delay in recruitment. Median duration of follow-up was 1.4 years. The risk of ischemic stroke was significantly lower in the dual therapy group (2.2% vs. 4.5% per year; HR=0·49, 95% CI 0·31–0·76, p=0·0010). The risk of severe or life-threatening bleeding was similar between groups (0·6% per year in the dual therapy group vs. 0·9% in the monotherapy group (HR= 0·66, 95% CI 0·27–1·60, p=0·35). The risks of any stroke, ischemic stroke or TIA and all vascular events were significantly lower in the dual therapy group, while th e risks of hemorrhagic stroke and death from any cause were not significantly lower in the dual therapy

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		patients were Asian. Median time from index event to randomization was 26 days.		**Safety outcomes:** severe or life-threatening bleeding	group. The risks of severe or life-threatening bleeding were not significantly higher in the dual therapy group.
Lee et al. 2018 **Korea** **RCT** ***Prevention of CArdiovascular Events in iSchemic Stroke Patients with High Risk of Cerebral HemOrrhage (PICASSO)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	1,534 patients ≥20 years, recruited from 67 hospitals in South Korea, China and the Philippines, who had a noncardioembolic ischaemic stroke or TIA within the previous 180 days, and who had a history of ICH (defined as clinical or radiological findings or the presence of ≥2 cerebral microbleeds). Patients with asymptomatic ICH, found incidentally on MRI, were also eligible. Patients who had sustained a hemorrhagic stroke within the previous 6 months, were excluded. Mean age was 66 years, 62% were men. 95% of qualifying events were stroke. Median time to randomization was 18 days.	Patients were randomized 1:1:1:1 to receive oral cilostazol (100 mg twice a day) + aspirin placebo, aspirin (100 mg once a day) + cilostazol placebo, cilostazol plus probucol (250 mg twice a day), or aspirin plus probucol until end of follow-up.	**Primary outcome:** Composite of stroke, MI, or vascular death (efficacy) and incidence of haemorrhagic stroke (safety) at end of follow-up **Secondary outcomes:** Stroke, ischemic stroke, MI, other vascular events and all-cause mortality	The median duration of follow-up was 1.9 years. 10 patients did not take any study medication and 12 patients were lost to follow-up. In the antiplatelet arm (cilostazol vs. aspirin), 63 patients in the cilostazol group and 80 patients in the aspirin group experienced composite vascular events. 4·27 vs. 5.33 per 100 person-years (HR=0·80, 95% CI 0·57−1·11; noninferiority p=0·0077; superiority p=0·18). 9 patients in the cilostazol group and 18 patients in the aspirin group experienced a hemorrhagic stroke. 0.61 vs. 1.02 per 100 person-years (HR= 0·51, 97·5% CI 0·20−1·27; superiority p=0·18). The risk of any stroke was significantly lower in the cilostazol group (48 vs. 73, HR=0·66, 95% CI 0·46−0·96, p=0·027), while the risk of ischemic stroke was not (40 vs. 55, HR=0·73, 95% CI 0·49−1·10, p=0·14). The risk of MI was significantly increased among patients in the cilostazol group (HR=4·59, 95% CI 0·99−21·24, p=0·0321). The risk of all-cause mortality did not differ between groups. In the antiplatelet + probucol arms, 60 patients in the probucol group and 83 patients in the non-probucol group experienced composite vascular events. 3.91 vs. 5.75 per 100-person years (HR=0·69, 95% CI 0·50−0·97, p=0.005 for non-inferiority; p=0·0316 for superior (p=0·0316) compared to cilostazol or aspirin alone.

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					11 patients in the probucol group and 16 patients in the non-probucol group experienced a hemorrhagic stroke. 0.71 vs. 1.10 per 100 person-years (HR= 0·65, 97.5% CI 0·27−1.57, p=0.55 for superiority). The risks of any stroke and ischemic stroke were significantly lower in the probucol arm (HR=0·59, 95% CI 0·41−0·85, p=0·0044 and HR=0·56, 95% CI 0·37−0·86, p=0·0063, respectively). The risk of all other secondary outcomes did not differ between groups. The number of patients who had serious adverse ranged from 31%-38% and did not differ significantly across groups. 18%-21% of patients across groups discontinued medication due to adverse events.
Shinohara et al. 2010 **Japan** **RCT** ***Cilostazol Stroke Prevention Study (CSPS)-2***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	2,757 patients aged 20–79 years, recruited from 278 sites who had had a cerebral infarction within the previous 26 weeks. Mean age was 63.5 years, 72% were men.	Patients were randomized 1:1 to receive 100 mg cilostazol twice daily or 81 mg aspirin once daily for 1–5 years.	**Primary outcome:** Any stroke (recurrent infarction, ICH of SAH) **Secondary outcomes:** Recurrent cerebral infarction, ischaemic cerebrovascular events (cerebral infarction or TIA), death from any cause, and the composite endpoint of: completed stroke (cerebral infarction, ICH or SAH), TIA, angina pectoris, MI, heart failure or any haemorrhage requiring hospital admission **Safety outcome:** Any (non-cerebral) hemorrhage requiring hospital admission	Mean duration of follow-up was 29 months. The primary outcome occurred less frequently in the cilostazol group (2.76%/person-years vs. 3.71%/person-years, HR= 0·743, 95% CI 0·564-0·981, p= 0·0357). There were no significant differences between groups for any of the secondary outcomes except for the composite endpoint (4.7%/person-years vs. 5.8%/person-years, HR= 0·80, 95% CI 0·64-0·99, p= 0·044). The risk of any major bleeding was significantly lower in the cilostazol group (0.77%/person-years vs. 1.78%/person-years, HR= 0·46, 95% CI 0·30-0·71, p= 0·0004); however, there were more adverse events reported including headache, diarrhea, palpitations, dizziness and increased blood pressure.

Bleeding Risk Associated with Long-term Antiplatelet 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 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,	**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
			and 10.		

Abbreviations

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

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