CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke
Seventh Edition, 2020
Evidence Table: *Lipid Management*

Gladstone D, Poppe A (Writing Group Chairs)
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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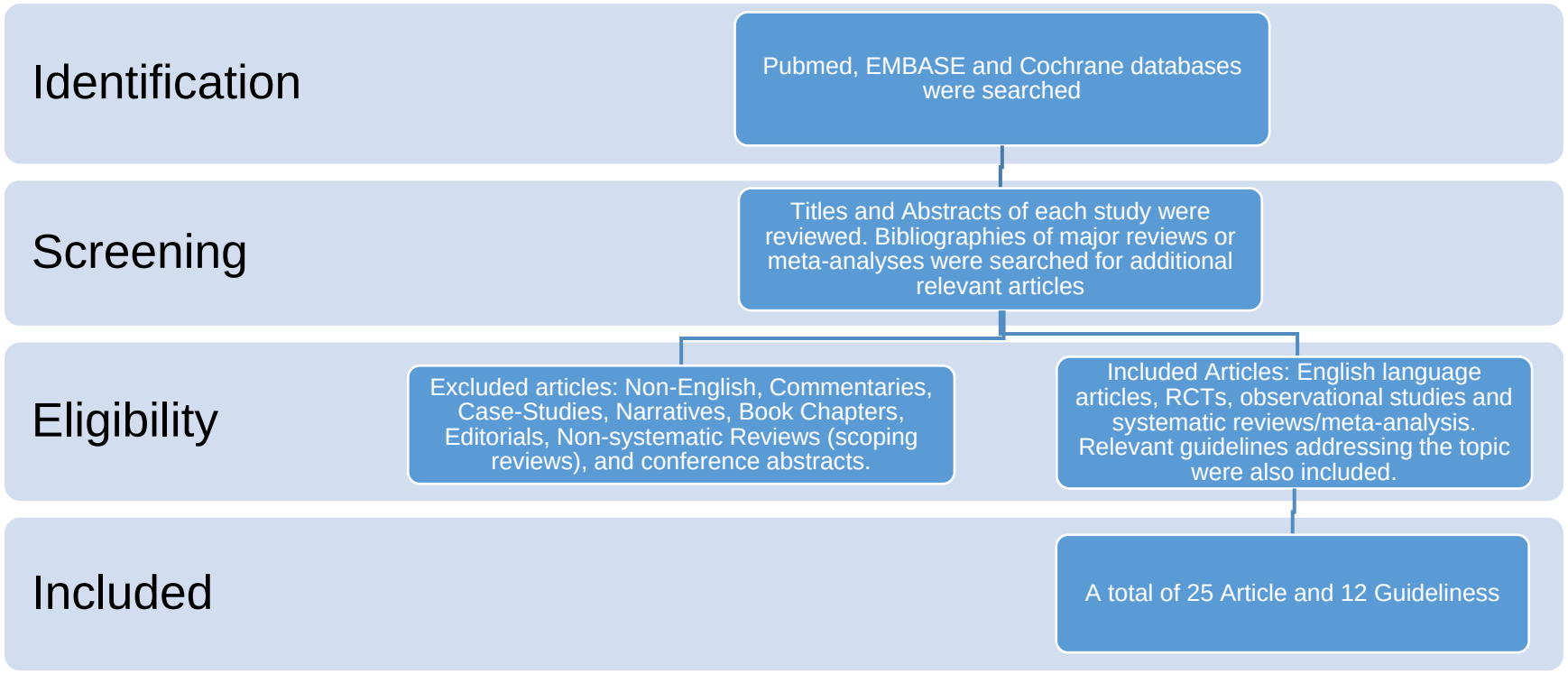
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“stroke” and Cholesterol, LDL/ or *Lipids/ or *Cholesterol). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 25 articles and 12 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Sagris D, Ntaios G, Georgiopoulos G, Kakaletsis N, Elisaf M, Katsiki N, Korompoki E, Kypreos KE, Boutari C, Bilianou H, Makaritsis K, Nomikos T, Papavasileiou V, Pitsavos C, Plomaritoglou A, Spengos K, Tziomalos K, Tselepis A, Vemmos K, Liberopoulos E, Milionis H. **Recommendations for lipid modification in patients with ischemic stroke or transient ischemic attack: A clinical guide by the Hellenic Stroke Organization and the Hellenic Atherosclerosis Society.** ***International Journal of Stroke*; 0: 1747493020971970.**	• Patients with ischemic stroke or transient ischemic attack should receive lipid-modifying treatment with high-intensity statin Level of evidence/Grade of evidence 1A • Patients with ischemic stroke or transient ischemic attack should be treated with an LDL-C target <55 mg/dL (1.4 mmol/L) and at least 50% reduction of baseline LDL-C levels. LDL-C levels should be monitored to reach the target after six to eight weeks 1B • In patients with previous ischemic stroke or transient ischemic attack who do not achieve the recommended LDL-C targets under the highest tolerated statin dose, ezetimibe should be added 1A • In patients with ischemic stroke or transient ischemic attack who do not achieve the recommended LDL-C targets under the highest tolerated dosage of statin and ezetimibe, a PCSK9-inhibitor should be added 1A • Patients with previous ischemic stroke or transient ischemic attack attributed to a specific cause that is not related to cardiovascular risk factors (such as cervical artery dissection, paradoxical embolism, infective or marantic endocarditis, atrial myxoma, and others) should not be a priori considered as very high-risk patients for future stroke and cardiovascular morbidity and mortality. Lipid modification treatment should be based on an individualized 10-year risk of new cardiovascular events, estimated by the calibrated country-specific SCORE 1B • Patients with ischemic stroke or transient ischemic attack should be monitored for statin-related adverse effects. If a patient develops statin-related adverse effects, another statin regimen (lower dose of the same statin or another statin or alternate statin administration) should be used. If the adverse effects recur following change of statin regimen, statin therapy should be permanently discontinued and ezetimibe and/or a PCSK9 inhibitor should be prescribed 2C • Elderly patients with ischemic stroke or transient ischemic attack should be treated similar to younger patients, since the cardiovascular benefit in this population is comparable to younger patients 2C • The association between very low LDL levels and the risk of ICH seems weak. This putative small risk of ICH does not seem adequate to outweigh the cardiovascular benefits of lipid-modification treatment 2B • For patients with acute ischemic stroke or transient ischemic attack, it is suggested that treatment with high-intensity statins should be initiated during hospitalization as early as possible 1C • In patients with ischemic stroke or transient ischemic attack, lipid-modification treatment aiming to achieve the recommended LDL-C targets should be continued lifelong 1B • The coadministration of statins with drugs metabolized by CYP450 should be avoided due to the increased risk of adverse effects and an alternative regimen should be used 1B
Liu L, Chen W, Zhou H, et al. **Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases.** ***Stroke and Vascular Neurology* 2020; 5(2): 159-176.**	High-intensity statins should be started or continued as a first-line treatment in females and ≤75 years of age males with ASCVD, unless there are contraindications (class I, level of evidence A). In patients with atherosclerotic ischaemic stroke who have already optimised statins, measuring blood cholesterol levels may help identify those who can benefit from proprotein convertase subtilisin/kexin type 9 (PCSK9) treatment (class IIb, level of evidence B). For patients with poor lipid-lowering effect or intolerable of statins, lipid-lowering treatment can be combined with ezetimibe but regular monitoring of transaminase and physical examination should be done (class IIb, level of evidence B). Patients with ASCVD with ischaemic stroke and other complications should be managed through lifestyle improvements, dietary advice and drug treatment (class I, level of evidence A).

Guideline	Recommendations
(selected)	For patients with ASCVD, it was originally intended to be treated with high-intensity statins. But when patients have contraindications or possible adverse reactions to statins, moderate-intensity statins should be used as a second option (class I, level of evidence A). For patients over 75 years of age with clinical ASCVD, the benefits of reducing ASCVD risk, adverse drug reactions, drug-drug interactions and patient's wishes should be evaluated when initiating moderate intensity or high-intensity statins. It is reasonable to continue statins in patients who can tolerate (class IIb, level of evidence C).
Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM. **2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS).** ***European Heart Journal*. 2020 Jan 1;41(1):111-88.** **(selected)**	In secondary prevention for patients at very-high risk, an LDL-C reduction of >_50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended. Class I, Level A. Patients with a history of ischaemic stroke or TIA are at very-high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy. Class I, Level A
Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, Sandset EC, Ntaios G, Charidimou A, Toni D, Pristipino C. **Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13 November 2018.** **European Stroke Journal. 2019 Dec;4(4):307-17.**	1. We recommend that statins be used as a part of standard secondary prophylactic treatment after an ischaemic stroke or a transient ischaemic attack (TIA). Most benefit was observed with atorvastatin 80 mg (Grade A). Aggressive Intensive lipid lowering therapy with statins plus/minus ezetimibe reduces the risk of stroke in stroke survivors in a LDL-C dependent manner (Grade A). 2. PCSK9 inhibitors represent a therapeutic option on top of statin plus/minus ezetimibe therapy to achieve very low LDL cholesterol target levels (Grade B). The addition of evolocumab was shown to reduce the risk of ischaemic stroke in patients with stabilized cardiovascular disease and the addition of alirocumab reduced the risk of ischaemic stroke in patients with acute coronary syndrome (Grade A). Evolocumab has been reported to reduce atherosclerotic vascular disease (AVD) risk in patients with a previous history of stroke (Grade B). 3. The use of statins in secondary prevention of ischaemic stroke caused by less frequent nonatherosclerotic aetiologies such as arterial dissection and PFO requires further investigations.

Guideline	Recommendations
	4. Lipid lowering treatment with statins in combination with lifestyle changes is recommended is the mainstay for primary prevention of ischaemic stroke in patients who have high 10-year risk for cardiovascular events. The patients with diabetes and patients with multiple risk factors appear to benefit the most (Grade A). The drug-class and the intensity of the lipid-lowering treatment as well as the treatment goals are thus dependent on patient characteristics (Grade A). 5. Statins should be used with caution in patients with previous spontaneous ICH (Grade C). Using highdose statin regimens in patients with ICH should be decided on an individual patient basis. In a subgroup of patients with CAA-related lobar ICH, statin use should probably be reserved for compelling indications (Grade C). 6. There is no evidence from Randomized controlled trials (RCTs) to support the routine use of statins in the acute phase of stroke (first two weeks). However, observational studies do not show an increase in symptomatic ICH in patients previously treated with statins or to whom statin was given within three days after stroke. Statin treatment is thus recommended to start before discharge from hospital after an AIS or at least during follow-up (Grade C).
Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO	Management of dyslipidaemia at mid-life may be offered to reduce the risk of cognitive decline and dementia. Quality of evidence: low Strength of the recommendation: conditional
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** **(selected)**	In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk), statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended COE I; LOE A In intermediate risk (≥7.5% to <20% 10-year ASCVD risk) patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in patients at high risk (≥20% 10-year ASCVD risk), levels should be reduced by 50% or more. COE I; LOE A.
Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, et al.	**4.1 Secondary atherosclerotic cardiovascular disease (ASCVD) Prevention** In patients who are 75 years of age or younger with clinical ASCVD, high intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. COR 1; LOE A

Guideline	Recommendations
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. ***Journal of the American College of Cardiology.* Jun 18;139(25):e1082-e1143** **(selected)**	In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. COR 1; LOE A. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. COR 1; LOW B-NR In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non–HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost. COR IIa; LOE A In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy. COR IIa; LOE B-R In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences. COE IIa; LOE B-R In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL (≥1.8 mmol/L) or higher, it may be reasonable to add ezetimibe. COE IIb; LOE B-R
American Academy of Family Physicians (AAFP). Summary of recommendations for clinical preventive services. 2017.	*Adults 40-75 Years with no symptoms or history of CVD and a calculated 10-year CVD event risk of 10% or greater* The AAFP recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40 to 75 years. (2016) (Grade: B recommendation) *Adults 40-75 Years with no symptoms or history of CVD and a 10-year CVD event risk of 7.5%-10%* Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10- year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%. (2016) (Grade: C recommendation)
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation. Section 4 Secondary Prevention	Strong Recommendation All patients with ischaemic stroke or TIA with possible atherosclerotic contribution and reasonable life expectancy should be prescribed a high-potency statin, regardless of baseline lipid levels. Weak Recommendation AGAINST Statins should not be used routinely for intracerebral haemorrhage.

Guideline	Recommendations
	Weak Recommendation AGAINST Fibrates should not be used routinely for the secondary prevention of stroke
Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest Jr J, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GBJ, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R, **2016 Canadian Cardiovascular Society Guidelines for the management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult** ***Can J Cardiol* 2016;32(11): 1263–1282.** **(selected)**	RISK ASSESSMENT FOR PRIMARY PREVENTION 1. We recommend that a cardiovascular risk assessment be completed every 5 years for men and women age 40 to 75 using the modified Framingham risk score or Cardiovascular Life Expectancy Model to guide therapy to reduce major cardiovascular events. A risk assessment may also be completed whenever a patient's expected risk status changes. (Strong Recommendation, High Quality Evidence) 2. We recommend sharing the results of the risk assessment with the patient to support shared decision making and improve the likelihood that patients will reach lipid targets. (Strong Recommendation, High Quality Evidence) HOW TO SCREEN: FASTING OR NON-FASTING LIPID DETERMINATION 1. We recommend non-fasting lipid and lipoprotein testing which can be performed in adults in whom screening is indicated as part of a comprehensive risk assessment to reduce CVD events (Strong Recommendation, High Quality Evidence). 2. We suggest that for individuals with a history of triglyceride levels > 4.5 mmol/L that lipid and lipoprotein levels be measured fasting (Conditional Recommendation, Low Quality Evidence). PRIMARY AND SECONDARY LIPOPROTEIN DETERMINANTS We recommend that non-HDL-C and apo B should continue to be considered alternate targets to LDL-C to evaluate risk in adults (Strong Recommendation, High Quality Evidence). Values and preferences: As clinicians are most familiar with LDL-C we continue to recommend its use as the primary target, but anticipate a shift to preferential use of non HDLC or apo B in the future. WHEN TO CONSIDER PHARMACOLOGICAL TREATMENT IN RISK MANAGEMENT 1. Statin indicated conditions: We recommend management that includes statin therapy in high risk conditions including clinical atherosclerosis, abdominal aortic aneurysm, most diabetes mellitus, chronic kidney disease (age > 50 years) and those with LDL-C ≥ 5.0 mmol/L to lower the risk of CVD events and mortality (Strong Recommendation, High Quality Evidence). Primary prevention: a. We recommend management that does not include statin therapy for individuals at low risk (modified FRS < 10 %) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence). b. We recommend management that includes statin therapy for individuals at high risk (modified FRS ≥ 20%) to lower the risk of CVD events (Strong Recommendation, High Quality Evidence) c. We recommend management that includes statin therapy for individuals at intermediate risk (modified FRS 10-19%) with LDL-C ≥ 3.5 mmol/L to lower the risk of CVD events. Statin therapy should also be considered for intermediate risk persons with LDL-C MONITORING, SURVEILLANCE AND TARGETS 1. We recommend a treat-to-target approach in the management of dyslipidemia to mitigate CVD risk. (Strong Recommendation, Moderate Quality Evidence). Statin indicated conditions 1. We recommend a target LDL-C consistently 50% reduction of LDLC for individuals for whom treatment is initiated to lower the risk of CVD events and mortality (Strong Recommendation, Moderate-Quality Evidence). Alternative target variables are apoB 50% reduction of LDL-C for patients with

Guideline	Recommendations
	LDL-C > 5.0 mmol/L in individuals for whom treatment is initiated to decrease the risk of CVD events and mortality (Strong Recommendation, Moderate Quality evidence). Primary prevention conditions warranting therapy: All risk groups: 3. We recommend a target LDL-C consistently 50% reduction of LDLC in individuals for whom treatment is initiated to lower the risk of CVD events (Strong Recommendation, Moderate Quality Evidence). Alternative target variables are apoB
2016 ESC/EAS Guidelines for the Management of Dyslipidaemias The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) ***Eur Heart J* 2016;37: 2999–3058** **(selected)**	**Recommendations for the pharmacological treatment of hypercholesterolaemia** Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal. Class I; Level of evidence (LOE) A. In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered. Class IIa; LOE C If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered. Class IIa; LOE B If the goal is not reached, statin combination with a bile acid sequestrant may be considered. Class IIb; LOE C In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered. Class IIb; LOE C
National Clinical guidelines for stroke" 5th Edition 2016; Intercollegiate Stroke Working Party. Royal College of Physicians	A-People with ischaemic stroke or TIA should be offered advice on lifestyle factors that may modify lipid levels, including diet, physical activity, weight, alcohol and smoking. B- People with ischaemic stroke or TIA should be offered treatment with a statin drug unless contraindicated. Treatment should: − begin with a high intensity statin such as atorvastatin 20-80mg daily; − be with an alternative statin at the maximum tolerated dose if a high intensity statin is unsuitable or not tolerated; − aim for a greater than 40% reduction in non-HDL cholesterol. If this is not achieved within 3 months, the prescriber should: − discuss adherence and timing of dose; − optimise dietary and lifestyle measures; − consider increasing to a higher dose if this was not prescribed from the outset. C- People with ischaemic stroke or TIA should not be prescribed fibrates, bile acid sequestrants, nicotinic acid or omega-3 fatty acid compounds for secondary vascular prevention. Ezetimibe should be used only in people who also have familial hypercholesterolaemia. D- People with primary intracerebral haemorrhage should avoid statin treatment unless it is required for other indications.

Evidence Tables

Pharmacological Treatment with Statins for Primary Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Major Clinical Trials					
Yusef et al. 2016 a) **Canada** **RCT** ***Heart Outcomes Prevention Evaluation-3 (HOPE-3) (statin arm)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	12,705 men ≥55 and women ≥65 years with at least one cardiovascular risk factor (women ≥60 years with at least 2 risk factors were also eligible), but without known cardiovascular (CV) disease. Persons with an absolute indication for, or contraindication to any of the study medications were excluded. Participants were recruited from 228 centers in 21 countries. Mean age was 65.7 years, 46% were male, 47% of participants had 2 CV risk factors, 24% had ≥3.	2 x 2 factorial design (blood pressure and statin arms). During a 4-week run in period participants took both active study medications. Those who were compliant with treatment and did not suffer adverse events were randomized to receive 10 mg/day rosuvastatin or placebo for the duration of the trial.	**Primary outcomes:** i) Composite of death from CVD, or nonfatal MI or nonfatal stroke ii) i) +resuscitated cardiac arrest, heart failure or revascularization **Secondary outcomes:** primary outcome ii) + angina + evidence of ischemia **Additional outcomes:** Death from any cause, components of the primary and secondary outcomes, new onset diabetes, hospitalizations	Baseline chol levels were similar in each group (statin vs. placebo) Total chol 201.5 vs. 201.3 mg/dL LDL: 127.8 vs. 127.9 mg/dL HDL: 44.7 vs. 44.9 mg/dL TGs: 128.8 vs. 126.5 mg/dL The median duration of follow-up was 5.6 years. At the end of follow-up, the mean LDL-chol and apoproteinB-100 were significantly lower in the statin group by 26.5% and 22.0%, respectively. The risk of the first primary outcome was significantly lower in the statin group (3.7% vs. 4.8%, HR=0.76, 95% CI 0.64-0.91, p=0.02). The risk of the second primary outcome was significantly lower in the statin group (4.4% vs. 5.7%, HR=0.75, 95% CI 0.64-0.88, p<0.001) The risk of the secondary outcome was significantly lower in the statin group (4.8% vs. 6.2%, HR=0.77, 95% CI 0.66-0.89, p<0.001). The risk of stroke was significantly lower in the statin group (1.1% vs. 1.6%, HR=0.70, 95% CI 0.52-0.95). The risk of hospitalization for CV causes was significantly lower in the statin group (4.4% vs. 5.8%, HR=0.75, 95% CI 0.64-0.88, p<0.001). The results did not vary significantly in subgroup analyses based on baseline CV risk, lipid level, C-

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					reactive protein level, blood pressure, and race or ethnic group. At 5 years, 75.5% of patients in the statin group were taking their prescribed medication compared with 73.2% in the placebo group. Significantly more participants in the statin group reported muscle pain or weakness (5.8% vs. 4.7%, p=0.005).
Yusef et al. 2016 b) **Canada** **RCT** ***Heart Outcomes Prevention Evaluation-3 (HOPE-3) (statin + blood pressure lowering arms)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	12,705 men ≥55 and women ≥65 years with at least one cardiovascular risk factor (women ≥60 years with at least 2 risk factors were also eligible), but without known cardiovascular (CV) disease. Persons with an absolute indication for, or contraindication to any of the study medications were excluded. Participants were recruited from 228 centers in 21 countries. Mean age was 65.7 years, 46% were male, 47% of participants had 2 CV risk factors, 24% had ≥3.	2 x 2 factorial design (blood pressure and statin arms). During a 4-week run in period participants took both active study medications. Those who were compliant with treatment and did not suffer adverse events were randomized to receive 16 mg/day candesartan +12.5 mg hydrochlorothiazide (HCTZ) or placebo and to 10 mg/day rosuvastatin or placebo for the duration of the trial. The outcomes of [participants assigned to active combination therapy (n=3,180) were compared with those who received dual placebo (n=3,168)	**Primary outcomes:** i) Composite of death from CVD, or nonfatal MI or nonfatal stroke ii) i) + resuscitated cardiac arrest, heart failure or revascularization **Secondary outcomes:** primary outcome ii) + angina + evidence of ischemia **Additional outcomes:** Death from any cause, components of the primary and secondary outcomes, new onset diabetes, hospitalizations	The median duration of follow-up was 5.6 years. Mean baseline blood pressure was similar between groups (combination therapy vs. dual placebo) SBP: 138.2 vs. 137.9 mm Hg DBP: 81.9 vs. 81.8 mm Hg Over the course of the trial mean SBP and DBP were 6.2 and 3.2 mm Hg lower, respectively in the combination therapy group. The risk of the first primary outcome was significantly lower in the combination therapy group (3.6% vs. 5.0%, HR=0.72, 95% CI 0.57-0.90, p=0.005). NNT=72 The risk of the second primary outcome was significantly lower in the combination therapy group (4.6% vs. 6.5%, HR=0.71, 95% CI 0.57-0.87, p=0.003). NNT=63 The risk of the secondary outcome was significantly lower in the combination therapy group (4.8% vs. 6.2%, HR=0.77, 95% CI 0.66-0.89, p<0.001). The risk of fatal or nonfatal stroke was significantly lower in the combination therapy group (1.0% vs. 1.7%, HR=0.56, 95% CI 0.36-0.87). The risk of hospitalization for CV causes was significantly lower in the combination therapy group

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(4.4% vs. 6.0%, HR=0.73, 95% CI 0.59-0.91, p=0.005). The results did not vary significantly in subgroup analyses based on baseline CV risk, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. At the end of the trial, 74.6% of patients in the combination therapy group were taking their prescribed medication compared with 71.8% in the placebo/placebo group.
Probstfield et al. 2002 **Margolis et al. 2013 (Long-term follow-up)** **USA/Canada** **RCT** ***Antihypertensive & Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)***	CA: ☑ Blinding: Patient: ☒ Assessor ☒ ITT: ☑	10,355 persons previously enrolled in the 4-armed ALLHAT study (eligibility included ≥55 years with stage 1 or 2 hypertension with at least 1 additional CHD risk factor) and fasting LDL-C level of 3.1 to 4.9 mmol/L for those with no known CHD, or 2.6 to 3.3 mmol/L for those with known CHD and fasting triglyceride levels lower than 3.9 mmol/L. Mean age at baseline was 67 years. 49% of participants were women. 14% had a history of CHD and 35% had DM.	In the LLT arm of the trial, participants were randomized to receive 40 mg/day pravastatin (n=3,313) or usual care, where vigorous cholesterol-lowering therapy was discouraged unless warranted (n=3,325) for approximately 4 to 8 years. All participants were advised to follow the NCEP Step I diet.	**Primary outcome:** All-cause mortality. **Secondary outcomes:** Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers and Q-wave MI.	The mean duration of follow-up was 4.8 years. Maximum follow-up was 7.8 years. At 6 years, persons taking pravastatin had reduced LDL-chol from a mean of 3.75-2.69 mmol/L. Persons in the usual care group experienced a mean reduction from 3.75-3.13 mmol/L There was no significant reduction in risk associated with pravastatin treatment for any of the outcomes. All-cause mortality: RR=0.99, 95% CI 0.89-1.11, p=0.88 CV mortality: RR=0.99, 95% CI 0.84-1.16, p=0.91 Fatal stroke: RR=0.95, 95% CI 0.66-1.39, p=0.81. Fatal or nonfatal stroke: RR=0.91, 95% CI 0.75-1.09, p=0.31. 114 persons in the pravastatin group were lost to follow-up, with 139 lost to follow-up in the usual care group. **Long-term follow-up (Margolis et al. 2013)** The mean follow-up was 8.8 years. Maximum follow-up was 12.7 years. There was no significant reduction in risk associated with pravastatin treatment for any of the outcomes.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					All-cause mortality: HR=0.96, 95% CI 0.89-1.03, p=0.24 CV mortality: HR=0.93, 95% CI 0.84-1.04, p=0.19 Fatal stroke: HR=1.02, 95% CI 0.78-1.33, p=0.89. Fatal or non-fatal stroke: HR=0.90, 95% CI 0.77-1.05, p=0.18.
Ridker et al. 2008 **International** **RCT** ***Justification for the Use of Statins in Prevention Trial Evaluating Rosuvastatin (JUPITER)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	17,802 men (≥50 years) and women (≥60 years) without a history of CV disease, with LDL-chol levels <3.4 mmol/L and a C-reactive protein level of ≥2.0mg/L. Mean age of participants was 66 ye4ars. 38% were women.	After a 4-week run-in period, participants were randomized to receive 20 mg/day rosuvastatin (n=8,901) or placebo (n=8,901). Follow-up visits were scheduled for 13 weeks, 6, 12, 18, 24, 30, 42, 48, 54 and 60 months.	**Primary outcome:** First major cardiovascular event (nonfatal MI or stroke, hospitalization for unstable angina, arterial revascularization procedure or death resulting from CVD) **Secondary outcomes:** Individual components or primary outcome	The study was terminated early (median follow-up 1.9 years). At termination, significantly more patients in the placebo group had reached the primary end point (251 vs. 142). The associated HR was 0.56, 95% CI 0.46-0.58, p<0.0001. Significantly more strokes (any and nonfatal) had occurred in the placebo group (64 vs. 33 and 58 vs. 30). The associated HRs were 0.52, 95% CI 0.34-0.79, p=0.002 and 0.52, 95% CI 0.33-0.80, p=0.003. Treatment with rosuvastatin was equally effective across all subgroups examined (sex, age, smoking status, geographic location, HTN, family history of CHD, BMI, CV risk score) Total number of serious adverse events were similar between groups (1,352 vs. 1,377).
Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca (GISSI) **Investigators 2008** **Italy** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,631 patients ≥18 years with chronic heart failure (NY Heart Assoc class II-IV). Mean age was 68 years, 22% were female. 4.5% of patients had suffered a previous stroke	Participants were randomized to receive 10 mg rosuvastatin/d (n=2,314) or placebo (n=2, 317) for the duration of the study.	**Primary outcomes:** Time to death, time to death or hospital admission for cardiovascular causes **Secondary outcomes:** Cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death	Median duration of follow-up was 3.9 years. The risks of death or the combined outcome of all-cause mortality or admission to hospital for CVD were not significantly reduced for patients in the statin group (HR=1.00, 95% CI 0.90-1.12, p=0.94 and HR=1.01, 95% CI 0.91-1.12, p=0.90, respectively). The risk of fatal or non-fatal stroke was not significantly reduced in the statin group (3.6% vs. 2.9%, HR=1.23, 95% CI 0.89-1.70, p=0.211). In sub group analysis, based on age, left ventricular ejection fraction, heart failure class,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					diabetes, heart failure cause or cholesterol level, the risk of death or admission to hospital was not significantly reduced among patients in the statin group
Kjekshus et al. 2007 **International** **RCT** ***Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,011 participants, ≥60 years with chronic ischemic heart failure (New York Heart Association class II-IV) and an ejection fraction of ≤40%. The mean age at baseline was 73 years. 24% of participants were female. 12% had experienced a previous stroke.	Participants were randomized to receive 10 mg rosuvastatin/d (n=2,514) or placebo (n=2, 497) for the duration of the study.	**Primary outcome:** Cardiovascular death or non-fatal MI or non-fatal stroke **Secondary outcomes:** Total mortality, any coronary event, death from any CVD and total number of hospitalizations for cardiovascular causes Patients were evaluated at 6 weeks and every 3 months thereafter	The median duration of follow-up was 32.8 months. At 3 months, LDL-chol levels had fallen from a mean of 3.54 to 1.96 mmol/L among participants in the statin group, but did not change for those in the control group (3.52-3.57 mmol/L). There was no significant reduction in risk associated with rosuvastatin for any of the outcomes: Primary outcome: HR=0.92, 95% CI 0.83-1.02, p=0.12. Death from any cardiovascular cause: HR=0.97, 95% CI 0.87-1.09, p=0.60 Death from any cause: HR=0.95, 95% CI 0.86-1.03, p=0.31 There were 32 stroke events in the placebo group and 35 in the rosuvastatin group (no HR for the separate outcome of stroke reported). There were no interaction effects identified in subgroup analysis for the primary outcome (age, sex, class of heart disease, SBP, DBP, chol levels, diabetes) There was no difference in the number of serious adverse events between groups. More persons in the placebo group discontinued study drugs compared with those in the rosuvastatin group (21% vs. 19.5%, p=0.03).
***Heart Protection Study (HPS*)** **2002** **UK** **RCT**	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	20,536 adults, 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/Land considered to be at high-risk of death from coronary disease within	Following a run-in treatment (4 weeks of placebo, then 4–6 weeks of a fixed dose of 40 mg simvastatin daily) participants were randomized to receive 40	**Primary outcome:** All-cause mortality, mortality associated with CHD. **Secondary outcomes:** Non-coronary causes of death, major coronary events,	The mean duration of follow-up was 5 years. During the study, the average compliance for persons in the simvastatin group was 85%. The average non-study use of statins in the placebo group was 17%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		the next 5 years due to a history of existing coronary disease, or occlusive disease of non-coronary arteries, or diabetes or treated hypertension.	mg of simvastatin or placebo for 5 years.	major vascular events and coronary or non-coronary revascularizations and non-fatal or fatal strokes of any type	The average difference in LDL-chol levels between groups over the study period was -1.0 mmol/L (2.3 vs. 3.3 mmol/L). Treatment with simvastatin was associated with reduction in risk of any vascular death (7.6% vs. 9.1%, Rate ratio=0.83, 95% CI 0.75-0.91, p<0.0001). Treatment with simvastatin was associated with reduction in risk of any stroke (RR=0.75, 95% CI 0.66-0.85, p<0.0001) and nonfatal stroke (3.6% vs. 4.9%), but not fatal stroke (0.9% vs. 1.2%). The protective effect was significant for ischemic, (2.8% vs. 4.0%) but not hemorrhagic stroke (0.5% vs. 0.5%) and for mild and moderate stroke, but not severe or fatal stroke. There was a total of 67 losses to follow-up. There was no difference between groups in the number of persons whose medication was stopped due to muscle symptoms (0.5% vs. 0.5%). The annual excess risk of myopathy associated with active treatment was about 0.01%.
Shepherd et al. 2002 **International** **RCT** ***PRospective Study of Pravastatin in the Elderly at Risk (PROSPER)***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	5,804 patients aged 70-82 years with a history of cardiovascular disease or at high risk with total chol of 4.0-9.0 mmol/L, excluding those with MMSE scores <24. Mean age was 75 years. Mean chol was 5.7 mmol, 11% had previous stroke or TIA.	Patients were randomized to receive 40 mg/day of pravastatin (n=2,891) or placebo (n=2,913) for the duration of the trial.	**Primary outcome:** Composite of CHD, non-fatal MI, non-fatal or fatal stroke **Secondary outcomes:** Individual components of composite outcome	Mean duration of follow-up was 3.2 years. LDL chol was 2.5 mmol/L, 34% lower than control group. The risk of the primary outcome was significantly reduced in the pravastatin group (HR=0.85, 95% CI 0.74-0.97, p=0.014) The risk of fatal or non-fatal stroke was not reduced in the pravastatin group (HR=1.03, 95% CI 0.81-1.31, p=0.81). The risk of TIA was non-significantly reduced in the pravastatin group (HR=0.75, 95% CI 0.55-1.0, p=0.51).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The risk of non-fatal stroke was not reduced in the pravastatin group (HR=0.98, 95% CI 0.76-1.26, p=0.85). The risk of fatal stroke was not reduced in the pravastatin group (HR=1.57, 95% CI 0.80-3.08, p=0.19). The risk of a new cancer diagnosis was significantly higher in the pravastatin group (HR=1.26, 95% CI 1.04-1.51, p=0.02).
ii) Systematic Reviews & Meta-Analyses					
Willeit et al. 2018 Lipoprotein(a) Studies Collaboration **Austria** **Patient-level meta-analysis**	NA	Data from AFCAPS, CARDS,4D, JUPITER, LIPID, MIRACL, and 4S trials, which assayed lipoprotein(a) concentration at baseline and follow-up, were included (n= 29,069). Mean age was 62 years, 72% were men. 52% had previous cardiovascular disease.	The association between lipoprotein(a) and cardiovascular disease risk, was examined. 14,536 patients were randomly allocated to statin treatment. The outcomes of patients with Apo (a) levels of <15 mg/dL were compared with those ≥15 to <30 mg/dL, 30 to <50 mg/dL, and ≥50 mg/dL.	**Primary outcome:** Cardiovascular events, including fatal or non-fatal coronary heart disease, stroke, or revascularisation procedures	Median duration of follow-up was 5.1 years. Median baseline level of lipoprotein(a) was 11 mg/dL for baseline and on statin treatment. There were 5,751 events during 95,576 person-years at risk. LDL cholesterol was reduced by a mean of 39% (95% CI –43% to –35%) without a significant change in lipoprotein(a) (mean percentage change following statin therapy was –0·4% (95% CI –7% to 7%). Compared with levels <15 mg/dL, the risk of cardiovascular events increased with increasing lipoprotein(a) levels. Baseline (adjusted for age and sex) 15 to <30 mg/dL: HR=1·04, 95% CI 0·91–1·18, p=0·59 30 to <50: HR=1·11, 95% CI 1·00–1·22, p=0·047 ≥50 mg/dL: HR=1·31, 95% CI 1·08–1·58, p=0·005 On Statin treatment (adjusted for age and sex) Baseline (adjusted for age and sex) 15 to <30 mg/dL: HR=0.94, 95% CI 0·81–1·10, p=0·45 30 to <50: HR=1·06, 95% CI 0.94-1.12, p=0·33 ≥50 mg/dL: HR=1·43, 95% CI 1·15–1·76, p=0·001.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Lipoprotein(a) concentration during follow-up (≥50 mg/dL vs. < 50 mg/dL) was associated more strongly with risk for cardiovascular disease in patients assigned statins compared with those in the placebo group (HR= 1·48, 95% CI 1·23–1·78 vs. HR=1·23, 95% CI 1·04–1·45, after adjusting for age and sex, p for interaction=0.010). The authors concluded there is an approximately linear relation between cardiovascular risk and concentrations of lipoprotein(a), which become evident at levels ≥ 30 mg/dL and pronounced at concentrations of ≥50 mg/dL, which persists despite statin treatment.
Cholesterol Treatment Trialists (CTT) (Fulcher et al. 2015, Armitage et al. 2019) **UK** **Systematic review & meta-analysis**	NA	27 RCTS (n=186,854) in which the treatment aim was solely the reduction of LDL cholesterol, sample sizes of at least 1,000 were used and treatment was continued for at least 2 years. Trials in which patients were at low risk of vascular disease were included. All included trials included both men and women.	Evaluation of more intensive vs. less intensive regimens of statin therapy (5 trials, n=39,612) and the effectiveness of statin therapy vs. control condition (22 trials, n=134,537) The effectiveness of statin treatment between men and women was compared.	**Primary outcome:** Major vascular events (nonfatal MI, coronary death, stroke, coronary revascularization).	Median duration of follow-up was 4.9 years. 26.8% of participants were women. Their mean age was 65.1 years. 73.2% of participants were men. Their mean age was 61.8 years. Women were more likely to have diabetes (23.6% vs. 17.8%) and have HTN (60% vs. 47.5%), but were less likely to be a current smoker (20.4% vs. 16.3%). Overall, statins reduced the risk of the primary outcome by 21% per each 1.0 mmol/L reduction in LDL-chol (RR=0.79, 95% CI 0.77-0.81, p<0.0001). There was no interaction reported for sex. Both groups benefited from treatment Women: RR=0.84, 99% CI 0.78-0.91 Men: RR=0.78, 99% CI 0.75-0.81 The risk of any stroke was reduced significantly with statin therapy (RR=0.85, 95% CI 0.80-0.89, p<0.00001). Men benefited from treatment more than women. For each 1 mmol/L decrease in LDL chol the risk of stroke was: Women: RR=0.90, 99% CI 0.78-1.04

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Men: RR=0.83, 99% CI 0.76-0.90 **2019 (examination of older age)** 14,483 (8%) of participants were ≥75 years at randomization. Statins significantly reduced the risk of a major vascular event and vascular death across all age groups per each 1.0 mmol reduction in LDL-chol (≤55 years, >55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, >70 to ≤75 years and >75 years). Statins significantly reduced the risk of a major vascular event across all age groups per each 1.0 mmol reduction in LDL-chol in those with and without vascular disease at study entry. Statins significantly reduced the risk of any stroke across all age groups per each 1.0 mmol reduction in LDL-chol (≤55 years,>55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, >70 to ≤75 years), except for persons aged >75 years (RR= 0·89, 95% CI 0·71–1·10).
Taylor et al. 2013 **UK** **Cochrane review**	In general, trials were considered to have a low risk of bias	18 RCTs (n= 56,934) including persons ≥18 years. Less than 10% of participants had pre-existing cardiovascular disease. Mean age was 57 years. 60.3% were men. Mean Baseline total cholesterol levels ranged from 4.81 to 6.97 mmol/L, mean LDL cholesterol from 2.8 to 4.95 mm/L. 14 trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, or microalbuminuria).	Trials compared treatment with statins for ≥ 12 months with placebo or usual care, with length of follow-up ≥ 6 months. Doses ranged from 10-80 mg.	**Primary outcomes:** Death from all causes, fatal and non-fatal CHD, CVD and stroke events; combined endpoint (fatal and non-fatal CHD, CHD and stroke events), change in blood total and low-density lipoprotein (LDL) cholesterol concentration	The odds of all-cause mortality were significantly reduced with statin therapy (4.4% vs. 5.1%; OR= 0.86, 95% CI 0.79 to 0.94). Data from 13 trials included. The risks of fatal and nonfatal CHD and CVD events were reduced significantly with statin therapy (RR= 0.73, 95% CI 0.67 to 0.80 and RR=0.75, 95% CI 0.70 to 0.81, respectively). Data from 14 and 9 trials included. The risk of fatal or nonfatal stroke was reduced significantly with statin therapy (RR=0.78, 95% CI 0.68 to 0.89). Data from 10 trials included. There were significant reductions in mean total chol and LDL chol (-1.05, 95% CI -1.35 to -0.76 mmol/L and -1.00, 95% CI -1.16 to -0.85 mmol/L).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cholesterol Treatment Trialists (CTT) (Mihaylova et al. 2012) **UK** **Systematic review & meta-analysis**	NA	27 RCTS in which the treatment aim was solely the reduction of LDL cholesterol, sample sizes of at least 1,000 were used and treatment was continued for at least 2 years. Trials in which patients were at low risk of vascular disease were included.	Evaluation of more intensive vs. less intensive regimens of statin therapy (5 trials, n=39,612) and the effectiveness of statin therapy vs. control condition (22 trials, n=134,537) Patients were classified into one of 5 groups, based on 5-year risk of major vascular events associated with control therapy (i.e placebo or low statin therapy)	**Primary outcomes:** Major vascular events (nonfatal MI, coronary death, stroke, coronary revascularization).	Median duration of follow was 4.8 years (control vs. statin) and 5.1 years (more vs. less intense therapy). Overall, statins reduced the risk of the primary outcome by 21% per each 1.0 mmol/L reduction in LDL-chol (RR=0.79, 95% CI 0.77-0.81, p<0.0001). The risk of the primary outcome among patients with and without a history of vascular disease was significantly lower given statin therapy. For each 1 mmol/L reduction in LDL chol the risks were: Previous history: RR=0.80, 95% CI 0.77-0.82, p<0.0001 No previous history: RR=0.75, 95% CI 0.70-0.80, p<0.0001) The risk of any stroke was reduced significantly with statin therapy (RR=0.85, 95% CI 0.80-0.89, p<0.00001). Across risk groups, each 1 mmol/L decrease in LDL chol was associated with a decreased risk of stroke: <5%: HR=0.74, 95% CI 0.46-1.19 ≥5%to<10%: HR=0.77, 95% CI 0.68-0.98 ≥10% to <20%: HR=0.86, 95% CI 0.75-0.98 ≥20% to<30%: HR=0.86, 95% CI 0.75-0.97 ≥30%: HR=0.86, 95% CI 0.75-0.99
Cholesterol Treatment Trialists (CTT) (Baigent et al. 2010) **UK** **Systematic review & meta-analysis**	NA	26 RCTS in which the treatment aim was solely the reduction of LDL cholesterol, sample sizes of at least 1,000 were used and treatment was continued for at least 2 years. All trials included both men and women. In 14 trials, none of the participants had prior vascular diseases.	Evaluation of more intensive vs. less intensive regimens of statin therapy (5 trials, n=39,612) and the effectiveness of statin therapy vs. control condition (21 trials, n=129,536) Treatment contrasts (dose of statin) in the more vs. less intensive trials were: 80 vs. 40 mg,	**Primary outcomes:** Cause-specific mortality, major coronary event (coronary death or non-fatal myocardial infarction), coronary revascularization (angioplasty or bypass grafting), or stroke	**More vs. less intensive statin therapy** Median duration of follow-up in the more vs. less intensive trials was 5.1 years (n=5 trials). The mean reduction in LDL cholesterol was 0.51 mmol/L. There was a significant reduction in the risk of stroke (RR=0.72, 95% CI 0.66-0.78, p<0.0001). **Statin vs. Control** Median duration of follow-up in the 21 statin vs. control trials was 4.8 years (n=21 trials). The mean reduction in LDL cholesterol was 1.07 mmol/L.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			80 vs. 20 mg, 80-10 mg, 40-80 mg vs. 20-40 mg Treatment contrasts in the statin vs. control trials ranged from 10-80 mg statin. Control conditions were placebo, usual care and no treatment		The rate ratios (RR) associated with each 1 mmol/L reduction in LDL-chol, for the outcomes of interest were: Any major vascular event: RR=0.79, 95% CI 0.77-0.81, p<0.0001. Ischemic stroke: RR=0.80, 95% CI 0.73-0.88 Hemorrhagic stroke: RR=1.10, 95% CI 0.86-1.42 Any stroke: RR=0.85, 95% CI 0.80-0.90, p< 0.001 Overall, using the results from 26 trials, a 1 mmol/L reduction in LDL-chol was associated with a significantly decreased risk of any major vascular event (RR=0.78, 95% CI 0.76-0.80, p<0.0001), but was not associated with reductions in stroke mortality (RR=0.96, 95% CI 0.84-1.09).
Manktelow & Potter 2009 **UK** **Cochrane review**	NA	8 RCTs (n=10,000) including participants aged ≥18 years with a history of stroke or TIA. The age ranges for eligibility varied widely across included trials (up to > 70 years). 2 trials included only males. The percentages of males in the remaining trails ranged from 53%-86%.	The interventions included those designed to reduce serum lipids: statins (n=5), clofibrate (n=2) and estrogen (n=1). All included trials were placebo controlled. The daily statin doses were 40 mg (n=4 trials) and 80 mg (n=1 trial). The daily clorfibrate doses ranged from 1,000 to 4,000 mg/day depending on sex (n=1) and 2,000 mg (n=1). Estrogen dose was 1.25-2.5 mg/d in one trial.	**Primary outcome**: Ischemic or hemorrhagic strokes **Secondary outcomes:** Fatal and disabling stroke events, all-cause mortality, serious vascular events (non-fatal stroke, non-fatal, MI and vascular death), all cardiovascular events (fatal and non-fatal MI, congestive cardiac failure, symptomatic peripheral vascular disease).	Duration of follow-up ranged from 90 days to 6 years. In 7 trials that included persons with a history of stroke or TIA, and reported results for all stroke and treatment types, there was no reduction in the risk of recurrent stroke (OR= 0.92, 95% CI 0.81, 1.04, p=0.16); however, statin therapy was associated with a reduction in the risk of recurrent stroke (OR= 0.88, 95% CI 0.77-1.00, p=0.05). Results from 5 trials included. Based on the results from 2 trials (SPARCL & HPS) statin therapy was associated with a reduction in the risk of ischemic stroke and an increase in the risk of hemorrhagic stroke (OR= 0.78, 95% CI 0.67- 0.92, p=0.002 and OR= 1.72, 95% CI 1.20- 2.46, p=0.0033, respectively). In trials that restricted inclusion of participants to those with a history of stroke only (i.e. excluding TIA) there was no reduction in the risk of recurrent stroke, regardless of drug or stroke type.
O'Reagan et al. 2008 **UK & Canada**	NA	42 RCTs (n=121,285) examining statin therapy for all-stroke prevention.	Study drugs and mean doses included in the trial included: atorvastatin (n=8, 10-80 mg),	**Primary outcome:** All-cause mortality, stroke **Secondary outcomes:**	The mean duration of follow-up ranged from 1.0 to 6.1 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & meta-analysis		Average age at baseline ranged from 47-75 years. 5 trials included men only. In the remaining trials, the percentage of women 8.3%-68% ranged from	lovastatin (n=5, 20-73 mg, fluvastatin (n=5, 40-80 mg), simvastatin (n=6, 20-40 mg) and pravastatin (n=18, 10-40 mg). Most studies were placebo controlled (5 trials used usual care as control condition)	Cardiovascular death, ischemic stroke, non-hemorrhagic stroke, fatal stroke	Using the results from 40 trials, there was a significant reduction in the risk of all-cause mortality associated with statin treatment (RR=0.88, 95% CI 0.83-0.93). In meta-regression, LDL-chol was the only predictor of effect size. Each unit increase was associated with a 0.3% increase in mortality risk (RR=1.003, 95% CI 1.005-1.006, p=0.02) Using the results from 42 trials, there was a significant reduction in the risk of all strokes associated with statin treatment (RR=0.84, 95% CI 0.79-0.91). Statin treatment was associated with a reduction in cardiovascular death and ischemic stroke, but not hemorrhagic or fatal stroke.

Monoclonal Antibodies to Inhibit Proprotein Convertase Subtilisin–Kexin Type 9 (PCSK9)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Schwartz et al. 2018, Jukema et al. 2019 **USA** **RCT** ***ODYSSEY OUTCOMES Trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	18,924 persons recruited from 57 countries, ≥40 years who had been hospitalized with an acute coronary syndrome (MI or unstable angina) 1 to 12 months previously with an LDL cholesterol level ≥ 70 mg/dL (1.8 mmol/L), a non−high-density lipoprotein (HDL) cholesterol level of ≥100 mg/dL, or an apolipoprotein B level ≥ 80 mg/dL, who were already receiving maximum tolerated statin dose. The qualifying event was MI in 83% of cases. Mean age was 58.6 years, 74.8% were men.	Patients were randomized 1:1 to receive 75 mg alirocumab subcutaneously or matching placebo every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg/dL.	**Primary outcome:** A composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. **Secondary outcomes:** Any coronary heart disease event including (death from coronary heart disease, nonfatal MI, unstable angina requiring hospitalization, or an ischemia-driven coronary revascularization procedure); major coronary heart disease event (death from coronary heart disease	Median duration of follow-up was 2.8 years. The risk of the composite outcome was significantly lower in the alirocumab group (9.5% vs. 11.1%, HR=0.85, 95% CI 0.78 to 0.93, p<0.001). The risk of any coronary heart disease event was significantly lower in the alirocumab group (12.7% vs. 14.3%, HR=0.88, 95% CI 0.81 to 0.95, p=0.001). The risks of a major coronary heart disease event, any cardiovascular disease event and a composite of death from any cause, nonfatal MI or nonfatal ischemic stroke, were also significantly reduced in the alirocumab group. The risk of fatal or nonfatal ischemic stroke was reduced significantly in the alirocumab group

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				or nonfatal MI); any cardiovascular event (death from cardiovascular causes, nonfatal ischemic stroke, nonfatal MI, unstable angina requiring hospitalization, or an ischemia-driven coronary revascularization procedure); a composite of death from any cause, nonfatal MI, or nonfatal ischemic stroke; death from coronary heart disease; death from cardiovascular causes; and death from any cause	(1.2% vs. 1.6%, HR= 0.73, 95% CI 0.57–0.93). The risk of hemorrhagic stroke was not increased significantly with (HR= 0.83, 95% CI, 0.42−1.65). The effect of alirocumab on stroke was similar among 5.0% of patients with a history of previous cerebrovascular disease (vs. no previous CVD) and among those with varying levels of baseline LDL-C, although patients with a baseline LDL-C of ≥100 mg/dL derived the greatest benefit from treatment with alirocumab. The risk of adverse events was similar between groups.
Schmidt et al. 2017 **UK** **Cochrane Review**	NA	20 RCTs including participants ≥18 years, with or without a prior history of CVD, with normal lipid levels or with hypercholesterolemia. Median age was 61 years, 30% were women.	Participants were randomized to receive a PCSK9 inhibitor (alirocumab, n=12, bococizumab n=3, RG7652, n=1 and evolocumab, n=4) vs. placebo, statins, or ezetimibe, or a combination of these drugs for a minimum of 24 weeks. In 13 trials, PCSK9 inhibitors were compared with placebo, in 2 trials PCSK9 inhibitors were compared with ezetimibe and in 5 trials, a PCSK9 inhibitor was compared with ezetimibe or statins, or both ezetimibe and statins.	**Primary outcomes:** Lipid parameters, Composite endpoint of CVD, defined as urgent coronary revascularisation, unstable angina pectoris, non-fatal and fatal MI, non-fatal and fatal stroke, and CHD death **Secondary outcomes:** All-cause mortality, adverse events	***PCSK9 inhibitors vs. placebo*** At 6 months, compared with placebo, treatment with PCSK9 inhibitors was associated with a mean 53.9% reduction in LDL-chol from baseline (95% CI -58.6 to -49.1%; 8 studies; 4782 participants). At maximum follow-up (6-36 months), treatment with PCSK-9 inhibitor was associated with a significantly reduced risk of any cardiovascular events (OR=0.86, 95% CI 0.80 to 0.92; 8 studies; 59,294 participants. At maximum follow-up (6-36 months), treatment with PCSK-9 inhibitor was associated with significantly reduced risks of any stroke or MI (OR=0.77, 95% CI 0.69 to 0.85, and OR= 0.76,95% CI 0.65 to 0.89, respectively). The risk of any adverse event was significantly higher in the PCSK-9 inhibitor group, compared with placebo (OR=1.08, 95% CI 1.04-1.12). ***PCSK9 inhibitors vs. ezetimibe*** At 6 months, compared with ezetimibe, treatment with PCSK9 inhibitors was associated with a

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					mean reduction of LDL-C by 30.2% (95% CI 34.18 to 26.23; 2 studies; 823 participants) ***PCSK9 inhibitors vs. ezetimibe and statins*** At 6 months, treatment with PCSK9 inhibitors was associated with a mean reduction of -39.20% in LDL-C, from baseline (95% CI -56.15 to -22.26; 5 studies; 5376 participants). The risk of any CVD event associated with PCSK9 inhibitors was reduced significantly, (OR=0.45, 95% CI 0.27 to 0.75; 3 studies; 4770 participants). The risk of any adverse event was significantly higher with ezetimibe and statins, compared with PCSK-9 inhibitors (OR=1.18, 95% CI 1.05-1.34).
Sabatine et al. 2017 **USA/ International** **RCT** ***Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	27,564 patients from 49 countries, aged 40-85 years, with established atherosclerotic cardiovascular disease and a fasting LDL cholesterol level of ≥1.8 mmol/L, or HDL chol level of ≥2.6 mmol/L, who were also receiving ≥20 mg/day of a statin. Mean age was 63 years, 24.6% of the patients were women. 81.1% of the patients had a history of MI, 19.4% had a previous nonhemorrhagic stroke. Median baseline LDL level was 2.4 mmol/L	Patients were randomized 1:1 to receive evolocumab (either 140 mg every 2 weeks or 420 mg every month, by subcutaneous injection, according to patient preference) or placebo, for the duration of the trial.	**Primary outcome:** Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. **Secondary outcome:** Composite of cardiovascular death, myocardial infarction, or stroke.	Median duration of follow-up was 2.2 years. At 48 weeks, the mean absolute reduction associated with evolocumab was 1.45 mmol/L (95% CI,1.43 to 1.47). The median reduction was 0.78 mmol/L. Overall, the risk of the primary outcome was significantly lower for patients in the evolocumab group (9.8% vs. 11.3%, HR=0.85, 95% CI 0.79-0.92, p<0.001). The risk of the secondary outcome was significantly lower for patients in the evolocumab group 5.9% vs. 7.4%, HR=0.80, 95% CI 0.73-0.88, p<0.001). Overall, the risk of any stroke was significantly lower for patients in the evolocumab group (1.5% vs. 1.9%, HR=0.79, 95% CI 0.66-0.95, p<0.01). The risk of ischemic stroke or TIA was significantly lower for patients in the evolocumab

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					group (1.7% vs. 2.1%, HR=0.77, 95% CI 0.65-0.92, p=0.003). There was no significant reduction in the risk of cardiovascular death (1.8% vs. 1.7%, HR= 1.05, 95% CI 0.88-1.25, p=0.62). There were no significant differences between groups in the numbers of adverse events, serious adverse events, or adverse events thought to be related to the study agent, leading to discontinuation of the study.
Robinson et al. 2015 **USA/ International** **RCT** ***Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	2,341patients ≥18 years, with established atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia and a fasting LDL cholesterol level of ≥1.8 mmol/L, who were on high-dose statin therapy. Mean age was 60 years, 37.8% of the patients were women. Median baseline LDL level was 3.2 mmol/L	Patients were randomly assigned 2:1, to receive alirocumab (150 mg, n=1,553) or placebo (n=788) subcutaneously, every 2 weeks for 78 weeks, in addition to statin therapy, with or without other lipid-lowering therapy.	**Primary outcome:** Percentage change in calculated LDL cholesterol level from baseline to week 24.	The mean percentage change in calculated LDL cholesterol level from baseline to week 24 was significantly greater with alirocumab (−61.0% vs.0.8%, mean difference= −61.9% points, p<0.001). The mean absolute LDL cholesterol level at week 24 was significantly lower in the alirocumab group (1.2 vs. 3.1 mmo/L). At week 78, the mean calculated LDL chol level was significantly lower in the alirocumab group (1.5 vs. 3.2 mmo/L). The mean percentage change in calculated LDL cholesterol level from baseline to week 78 was −57.9% with alirocumab vs. 3.6% with placebo. The percentage of patients with any adverse event was similar between groups (81.0% with alirocumab and 82.5% with placebo). The percentage of patients with fatal or nonfatal ischemic stroke was similar between groups (0.6% vs. 0.3%, p=0.35).

Omega-3 Fatty Acids

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Bhatt et al. 2019 **USA/International** **RCT** ***Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	8,179 patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). Eligible patients had been receiving a stable dose of a statin for at least 4 weeks. Median age was 68 years, 28.8% were women. 70.7% were enrolled for secondary prevention.	Patients were randomized to receive 2 grams of icosapent ethyl twice daily or placebo for the duration of the study.	**Primary outcome:** A composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. **Secondary outcome:** A composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	Median duration of follow-up was 4.9 years. The risk of the primary outcome was significantly lower in the icosapent ethyl group (17.2% vs. 22%; HR=0.75, 95% CI 0.68-0.83, p<0.001, NNT=21). In subgroup analyses, patients <65 years and those with baseline TG ≥200 mg/dl and HDL cholesterol ≤35 mg/dl receiving icosapent ethyl had significantly lower risk. The risk of the secondary outcome was significantly lower in the icosapent ethyl group (11.2% vs. 14.8%; HR=0.74, 95% CI 0.65-0.83, p<0.001, NNT=28). In subgroup analyses there were no significant interactions. The risks of cardiovascular death or nonfatal MI, fatal or nonfatal MI, cardiovascular death, hospitalization for unstable angina, fatal of nonfatal stroke and death from any cause, nonfatal MI, or nonfatal stroke were all significantly lower in the icosapent ethyl group. Significantly more patients in the icosapent ethyl group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).
Aung et al. 2018 The Omega-3 Treatment Trialists' Collaboration **UK/International** **Systematic review & meta-analysis**	The risk of bias of the included trials was low, with the exception of the 2 trials that did not include a placebo group	10 RCTs (n=47, 803) including persons at high risk for cardiovascular events. Mean age was 64 years, 61.4% were men. 27.6% had a previous stroke. 83.4% had prior statin use.	Trials compared marine-derived very-long-chain omega-3 fatty acid supplements vs placebo or open-label control, with a sample size of at least 500 participants and a scheduled duration of treatment of at least 1 year. The daily doses of EPA varied from 226 to 1800	**Primary outcomes:** Nonfatal MI; death caused by CHD; ischemic, hemorrhagic, and unclassified stroke; coronary or noncoronary arterial revascularization events; major vascular events and all-cause mortality	Mean duration of follow-up was 4.4 years. Supplementation with omega-3 fatty acids was not associated with significant risks of any of the outcome. Nonfatal MI: RR=0.97, 95% CI 0.87-1.08 CHD death: RR=0.93, 95% CI 0.83-1.03 Ischemic stroke: RR= 1.03, 95% CI 0.88-1.21 Any stroke: RR=1.03, 95% CI 0.93-1.13 Any major vascular event: RR=0.97, 95% CI 0.93-1.01 All-cause mortality: RR=0.96; 95% CI, 0.92-1.01

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			mg/day, and DHA varied from 0 to 1700 mg/day		

Pharmacological Treatment with Statins (high dose vs. low dose) for Primary Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Armitage et al. 2010 **UK** **RCT** ***Study of the Effectiveness of additional Reductions in Cholesterol & Homocysteine (SEARCH) Collaborative Group***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	12,064 men and women 18–80 years with a history of previous myocardial infarction who were current statin users, (with a total cholesterol of at least 3.5 mmol/L) or in whom statin use was indicated (with a total cholesterol of 4.5 mmol/L).	Following a trial run-in period, participants were randomized to receive 80 mg (n=6,031) or 20 mg (n=6,033) simvastatin daily until study end. Participants were seen in study clinics at 2, 4, 8, and 12 months and then at 6-month intervals.	**Primary outcome:** Major vascular events including major coronary events (non-fatal MI, coronary death or coronary revascularisation), non-fatal or fatal stroke, or peripheral revascularization (peripheral artery angioplasty or arterial surgery, including amputations) **Secondary outcomes:** Major vascular events separated by year (1st vs. later years)	Mean duration of follow-up was 6.7 years. The mean difference in LDL-chol over the study period was -0.40, favouring the 80 mg group. Although more persons in the 20 mg group experienced a major vascular event (25.7% vs. 24.5%), the associated risk ratio was not statistically significant (RR= 0.94, 95% CI 0.88-1.01, p=0.10). There was no difference in risk reduction associated with treatment group between subgroups (sex, age, baseline chol, smoking status, treatment for hypertension) The reduction in the risk of stroke associated with 80 mg simvastatin was: Any stroke: RR=0.91, 95% CI 0.77-1.08, p=0.03. Non-fatal stroke: RR=0.91, 95% CI 0.75-1.10 Fatal stroke: RR=0.85, 950.60-1.21 Ischemic: RR=0.91, 95% CI 0.77-1.09 Losses to follow-up: 99% completion in both groups. Cases of definite myopathy were higher in the 80 mg group (53 vs. 2).
LaRosa et al. 2005 **International**	CA: ☑ Blinding: Patient: ☑ Assessor ☑	10,001 participants, 35-75 years with clinically evident CHD and LDL-chol of <3.4 mmol/L.	Following a washout period of 1-8 weeks, participants were randomized to 80 vs. 10	**Primary outcome:** Occurrence of first major cardiovascular event (death from CHD, non-fatal, non-procedural related MI,	Median duration of follow-up was 4.9 years. LDL chol levels were reduced from 2.6 to 2.0 mmol/L (80 mg group) and were unchanged in the 10 mg group (2.6-2.6 mmol/L).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT ***Treating to New Targets (TNT)***	ITT: ☑	At baseline, mean age was 61 years. 81% were male, 54% had systemic hypertension.	mg/day of atorvastatin for the duration of the study.	resuscitation after cardiac arrest and fatal/non-fatal stroke). **Secondary outcomes:** Major coronary event, stroke, hospitalization for congestive heart failure, peripheral-artery disease, death from any cause, any cardiovascular event and any coronary event	Fewer persons in the 80 mg group experienced the primary event (8.7% vs. 10.9%). The associated relative reduction in risk was 22%. HR=0.78, 95% CI 0.69-0.89, p<0.001. Fewer persons in the 80 mg group experienced a fatal or nonfatal stroke (2.3% vs. 3.1%). HR=0.75, 95% CI 0.59-0.96, p=0.02. Fewer persons in the 80 mg group experienced a fatal/non-fatal stroke or TIA (3.9% vs. 5.0%, HR=0.77, 95% CI 0.64-0.93, p=0.007). There were more treatment-related adverse events reported in persons in the 80 mg group (8.1% vs. 5.8%). There were 5 cases of rhabdomylosis (80 mg, n=2; 10 mg, n=3). There was a total of 87 dropouts/losses to follow-up.
Pedersen et al. 2005 **Norway** **RCT** ***Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)***	CA: ☑ Blinding: Patient: ☒ Assessor ☒ ITT: ☑	8,888 participants aged ≤80 years, with previous MI who were candidates for statin therapy. At baseline, mean age was 62 years, 81% of participants were male. Most patients had been taking statin therapy prior to randomization. The baseline LDL-chol level was 3.13 mmol/L in both groups.	Following dietary counseling, participants were randomized to receive 80 mg/day of atorvastatin or usual-dose simvastatin (20 mg/day) for study duration. If after 24 weeks, total chol was >5.0 mmol/L the dose of simvastatin could be increased to 40 mg/day and atorvastatin dose could be decreased if chol was <1.0 mmol/L	**Primary outcome:** Major coronary event (coronary death, hospitalization for non-fatal MI, cardiac arrest with resuscitation) **Secondary outcomes:** Primary outcome + stroke, any CHD event and cardiovascular event.	The median duration of follow-up was 4.8 years. There were 463 major coronary events in the simvastatin group and 411 in the atorvastatin group. The corresponding unadjusted HR=0.89, 95% CI 0.78-1.01, p=0.07. After adjusting for sex, age, statin use at randomization, duration since MI and chol, HR=0.87, 95% CI 0.76-0.99, p=0.04. There were 174 fatal/nonfatal stroke in the simvastatin group and 151 in the atorvastatin group (HR=0.87, 95% CI 0.70-1.08, p=0.20). The risk of death from all causes was similar between group (374 vs. 366, p=0.81). More participants in the atorvastatin group discontinued medication permanently due to adverse events (9.6% vs. 4.2%, p<0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					A total of 48 participants withdrew consent (20 and 28).
Cannon et al. 2004 **USA** **RCT** ***Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,162 patients ≥18 years, who had been hospitalized for an acute coronary syndrome (MI or unstable angina) in the previous 10 days, with a total chol of ≤240 mg/dL (6.21 mmol/L). Patients who had been receiving long-term lipid-lowering therapy had to have a total chol of ≤200 mg/dL (5.18 mmol/L). Mean age was 58 years, 78% were male	All patients received standard medical treatment including aspirin (75-325 mg/d and/or clopidogrel or warfarin). Patients were randomized to receive 40 mg pravastatin or 80 mg of atorvastatin daily for the study duration. Patients were also randomized to receive a 10-day course of gatifloxin or placebo	**Primary outcome:** Time from randomization until death from any cause, MI, unstable angina and stroke **Secondary outcomes:** Death from CHD, nonfatal MI	Mean duration of follow-up was 24 months. Over the study period, the primary outcome occurred in 26.3% of patients on standard therapy vs. 22.4% receiving higher dose therapy, representing a 16% reduction (95% C I5%-26%, p=0.005). Although statistically significant this difference did not reach the criteria for equivalency. There was no significant difference in the incidence of stroke between groups (1% vs. 1%). In sub group analysis, patients with a baseline chol level of ≥125 mg/dL benefitted more from higher dose therapy compared with a level <125 mg/dL

Pharmacological Treatment for Secondary Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Amarenco et al. 2020 a, b **France/South Korea** **RCT** ***Treat Stroke to Target trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	2,860 patients ≥18 years (>20 years in South Korea) who had sustained an ischemic stroke in the previous 3 months or a TIA within the previous 15 days, with confirmed atherosclerotic disease). Mean age at baseline was 66.5 years, 67.5% were men. Mean baseline LDL-chol level was 135 mg/dL (3.5 mmol per liter. 85.5% of qualifying events were stroke	Patients were randomized 1:1 to a target LDL cholesterol level of < 70 mg/dL (1.8 mmol/L, lower-target group) or to a target range of 90 -110 mg/dL (2.3 to 2.8 mmol/L, higher-target group) using a statin, ezetimibe, or both for the duration of the trial	**Primary outcome:** Composite of major cardiovascular events including ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes. **Secondary outcomes:** MI or urgent coronary revascularization, cerebral infarction or urgent revascularization of carotid or cerebral artery, cerebral infarction or TIA, any revascularization procedure,	Median duration of follow-up was 3.5 years. The trial was stopped prematurely for administrative reasons. At the end of follow-up, the mean LDL chol was 65 mg per deciliter (1.7 mmol per liter) in the lower-target group and 96 mg per deciliter (2.5 mmol per liter) in the higher-target group. The risk of the primary outcome was significantly lower in the lower-target group (8.5% vs. 10.9%, HR=0.78, 95% CI 0.61 to 0.98; p=0.04). The risks of all secondary outcomes, with 2 exceptions (ICH and diabetes) were lower in the low-target group, but none were statistically

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				death, cerebral infarction or intracranial hemorrhage, intracranial hemorrhage, newly diagnosed diabetes	significant. The risk of ICH or diabetes was not increased significantly in the low-target group. There were no interactions based on subgroup analyses (type of qualifying event, age, sex, baseline weight, BMI, HTN or diabetes at baseline, smoking status, atherogenic dyslipidemia at baseline, time in therapeutic range). **2020b) French cohort (n=1,073)** Median duration of follow-up was 5.3 years. The risk of the primary outcome was significantly lower in the lower-target group (9.6% vs. 12.9%, HR=0.74, 95% CI 0.57 to 0.94; p=0.019). The NNT to prevent one recurrent vascular event was 30.
Giugliano et al. 2020 **USA** **RCT (subgroup analysis)** ***Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	5,337 patients representing 19% of the original sample with prior ischemic stroke. The median time between prior stroke and randomization was 3.3 years. Median age was 65 years, 34.3% were women.	Patients were randomized (1:1) to receive subcutaneous evolocumab (either 140 mg every 2 weeks or 420 mg every 4 weeks per patients' preference) or matching placebo	**Primary outcomes:** Time to the first of any of the following events: cardiovascular death, MI, stroke (ischemic or hemorrhagic), hospitalization for unstable angina, or coronary revascularization. **Secondary outcomes:** Stroke (combined ischemic, hemorrhagic, and strokes of unknown type) and the composite of ischemic stroke or TIA	Median duration of follow-up was 2.1 years. There were significantly fewer patients in the evolocumab group who experienced a primary end point event (259 vs. 300; HR= 0.85, 95% CI 0.72–1.00, p=0.047). The risks for all other primary and secondary outcomes were not significantly lower for the evolocumab group except for the need for coronary revascularization (4.8% vs. 3.3%, HR=0.68, 95% CI 0.52–0.90).
Milionis et al. 2020 **Greece** **Systematic review & meta-analysis**	NA	4 primary prevention trials (HPS, MEGA, CARDS, JUPITER) and 4 secondary prevention trials (HPS, J-STARS, SPARCL, IMPROVE-IT)	Patients were randomized to receive a statin (n=7) or statin + ezetimibe (n=1) vs. placebo. Mean duration of follow-up ranged from 2 to 6 years.	**Primary outcome:** Ischemic stroke	Statin therapy was associated with a significantly lower risk of ischemic stroke in primary (RR= 0.70, 95% CI 0.60–0.82; p < 0.001) and in the secondary prevention trials (RR=0.80, 95% CI 0.70–0.90; p < 0.001).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					In the secondary prevention trials, the NNTs to prevent another ischemic stroke ranged from 13 (IMPROVE-IT) to 170 (J-STARS)
Cannon et al. 2015 **USA** **RCT** ***Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	18,144 patients ≥18 years, who had been hospitalized for an acute coronary syndrome (MI or unstable angina) in the previous 10 days, with a LDL chol of 50-125 mg/dL (1.3-2.3 mmol/L) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. Mean age was 63.6 years, 76% were male, 34% were taking statin drugs at the time of the event	Patients were randomized 1:1 to receive 40 mg simvastatin + 10 mg ezetimibe or 40 mg simvastatin + placebo for the study duration (minimum of 2.5 years).	**Primary outcome:** Composite of death from cardiovascular disease, a major coronary event (nonfatal MI, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke **Secondary outcomes:** i) a composite of death from any cause, major coronary event, or nonfatal stroke; ii) a composite of death from CHD, nonfatal MI, or urgent coronary revascularization 30 days or more after randomization; and iii) a composite of death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization 30 days or more after randomization, or nonfatal stroke **Tertiary outcomes:** Individual components of primary and secondary outcomes	Over the course of the trial, the median time-weighted average LDL cholesterol level was 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin monotherapy group and 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group. The risk of the primary outcome over 7 years was significantly lower in the dual-therapy group (32.7% vs. 34.7%; HR=0.936, 95% CI 0.89-0.99, p=0.016). The risks of the 3 secondary outcomes were all significantly lower in the dual therapy group. The risks of any stroke and ischemic stroke were significantly lower in the dual therapy group (HR=0.86, 95% CI 0.73-1.00, p=0.05 and HR=0.79, 95% CI 0.67-0.94, p=0.008, respectively). The risk of hemorrhagic stroke was not reduced significantly.
Hosomi et al. 2015, Kitagawa et al. 2018	CA: ☑ Blinding: Patient: ☒ Assessor ☑	1,589 patients aged 45 to 80 years with a history of non-cardioembolic ischemic stroke, sustained within the preceding one month to	Participants were randomized 1:1 to receive either 10 mg/day pravastatin (the approved dose for the nation) or	**Primary outcome:** Stroke and TIA **Secondary outcomes:** Onset of each stroke subtype, myocardial infarction,	Mean duration of follow-up was 4.9 years. During follow-up, mean total chol and LDL chol levels were significantly lower in the pravastatin group while HDL chol was significantly higher.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Japan **RCT** ***Japan Statin Treatment Against Recurrent Stroke (J-STARS)***	ITT: ☑	3 years were enrolled from 123 centers. Mean LDL chol ranged from 4.65 to 6.21 mmol/L at baseline, without the use of statins. Mean age was 66.2 years, 69% were men. 91% of persons were taking antiplatelets.	placebo for the duration of the study.	vascular accident, death and hospitalization,	The risk of recurrent stroke or TIA was not reduced significantly with pravastatin (2.56% vs. 2.65%/year, p=0.82, adjusted HR= 0.97, 95% CI 0.73 to 1.29). The risk of occurrence of atherothrombotic infarction was reduced significantly in the pravastatin group (0.21% vs. 0.65%/year, p=0.0047, adjusted HR= 0.33, 95%CI 0.15 to 0.74). There were no significant differences between groups in the risks of lacunar stroke, cardioembolic stroke or intracranial hemorrhages, not were there any differences in the risks of MI, vascular accidents, deaths or hospitalizations. **2018 Post Hoc analysis** Among persons in the statin group, where treatment was initiated within 6 months of the index event, the risk of the primary outcome was significantly reduced in those who achieved a LDL-chol level <120 mg/dL, compared with ≥120 mg/dL (adj HR=0.56, 95% CI 0.37-0.85, p=0.006), and those with C reactive protein <1 mg/L compared with ≥1 mg/L (adj HR=0.64, 95% CI 0.44-0.93, p=0.018). The lowest risk of the primary outcome was in persons on statin therapy who achieved an LDL-chol level of <120 md/dL and had a CRP<1 mg/L (adj HR=0.41, 95% CI 0.22-0.78, p=0.006).
Amarenco et al. 2006 **International** **RCT** ***Stroke Prevention by Aggressive Reduction in***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,732 individuals with previous stroke/TIA (ischemic or hemorrhagic) that occurred 1 – 6 months prior to enrolment, and with LDL between 2.6-4.9 mmoL/L and no known history of coronary heart disease.	Participants were randomly assigned to receive either 80 mg/day atorvastatin or matching placebo for the duration of the study. Patients were assessed at 1, 3 and 6 months then every 6 months thereafter.	**Primary outcome:** Fatal or nonfatal stroke events. **Secondary outcomes:** Stroke or TIA, major coronary event, major cardiovascular event, acute coronary event, any coronary event, revascularization	The median duration of follow-up was 4.9 years. LDL-chol was decreased from 3.43 to 1.58 mmol/L, for persons in the atorvastatin group but was unchanged for those in the placebo group (3.45 mmol/L). There were fewer fatal/nonfatal strokes among persons in the atorvastatin group (11.2% vs. 13.1%, p=0.05). The associated 5-year absolute

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cholesterol (SPARCL)		The mean age at baseline was 63 years. 60% were male.		procedure, or any cardiovascular event	risk reduction was HR=0.84, 95% CI 0.71-0.99, p=0.03. 10.4% of persons in the atorvastatin had experienced a nonfatal stroke compared with 11.8% in the placebo group (p=0.14). This difference was not associated with a significant reduction in risk (HR=0.87, 95% CI 0.73-1.03, p=0.11). There were fewer fatal strokes among persons in the atorvastatin group (1.0% vs. 1.7%, p=0.04). The associated risk reduction was HR=0.57, 95% CI 0.35-0.95, p=0.03. There were fewer strokes or TIAs among persons in the atorvastatin group (15.9% vs. 20.1%, p<0.001). The associated risk reduction was HR=0.77, 95% CI 0.67-0.88, p<0.001. When examined by stroke type, the treatment-associated risk reduction was significant for ischemic, but not hemorrhagic stroke (HR=0.78 (95% CI 0.66-0.94 and 1.66 95% CI 1.08-2.55, respectively. There was no difference between groups in the number of serious adverse events (41.8% vs. 41.2%). There were 93 drop-out/withdrawals in the active treatment group and 113 in the placebo group.

Abbreviations

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

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