CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Lipid Management

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PREVENTION of STROKE Writing Group

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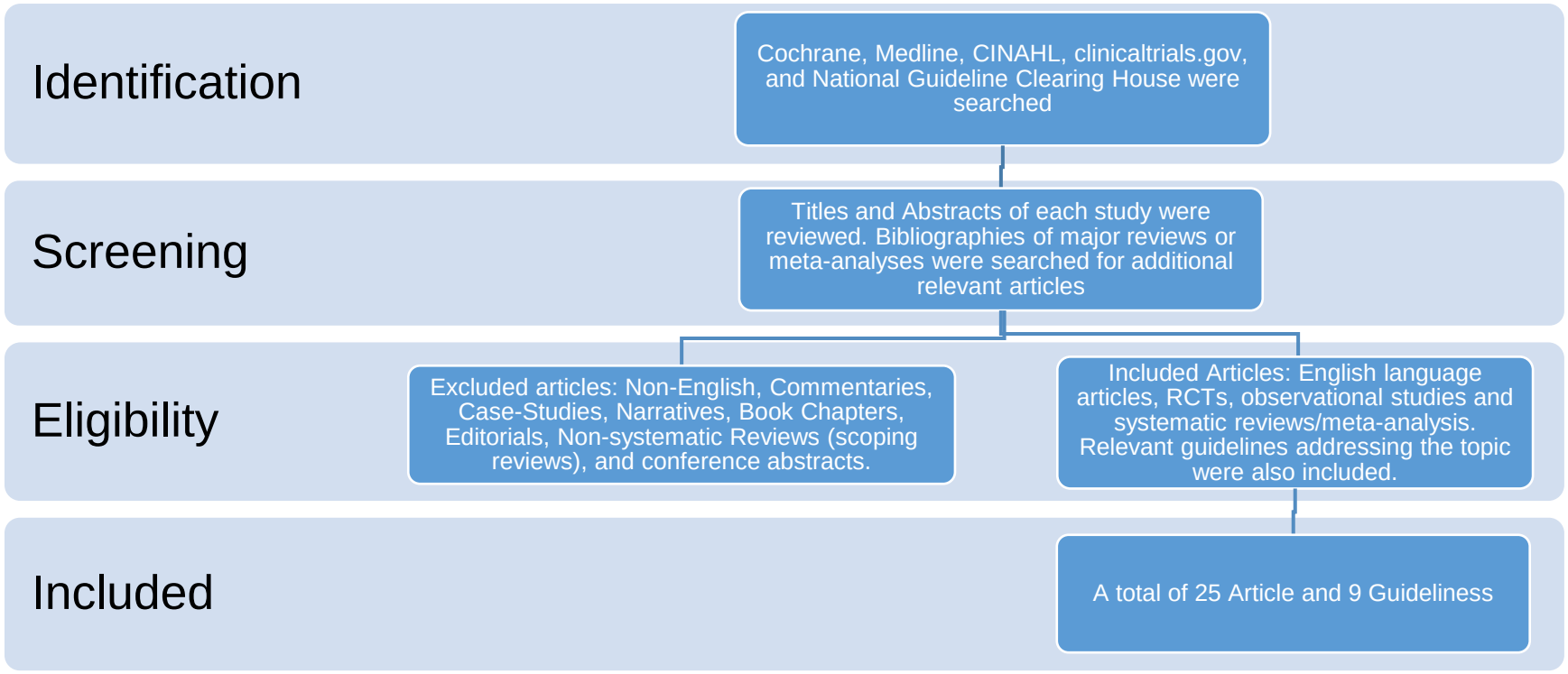
Search Strategy



Cochrane, Medline, CINAHL, National Guideline Clearing House and clinicaltrials.gov 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 9 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
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 LDL-C > 5.0 mmol/L in individuals for whom treatment is initiated to decrease the risk of CVD events and mortality (Strong

Guideline	Recommendations
	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
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.
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association.** ***Stroke 2014*;45:2160-2236.**	• Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other ASCVD (Class I; Level of Evidence B). • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD (Class I; Level of Evidence C). • Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the ACC/AHA 2013 guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations (Class I; Level of Evidence A).
Stone N, Robinson J, Lichtenstein A et al. **2013 ACC/AHA Guideline on the**	**Targets** The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD (atherosclerotic cardiovascular disease). **Statin Treatment-Secondary Prevention**

Guideline	Recommendations
Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines ***J Am Coll Cardiol 2014*;63:2889–934.**	High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD*, unless contraindicated (Strong recommendation). In individuals with clinical ASCVD* in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Strong recommendation). In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it (expert opinion).
Australia **"Clinical Guidelines for Stroke Management 2010"** **(National Stroke Foundation)**	• Therapy with a statin should be used for all patients with ischemic stroke or TIA (Grade A) • Statins should NOT be used routinely for haemorrhagic stroke (Grade B)
New Zealand **"New Zealand Clinical Guidelines for Stroke Management 2010"** **(Stroke Foundation of New Zealand)**	**Cholesterol Lowering** • Therapy with a statin should be considered for all patients with ischaemic stroke or TIA). (Grade A) • Statins should NOT be used routinely for patients with intracerebral haemorrhage (Grade B)
Ireland **"National Clinical Guidelines and Recommendations for the Care of People with Stroke and transient Ischemic Attack" March 2010** **(Irish Heart Foundation: Council for Stroke)**	**Choice of Statin and Monitoring suggestions** • Whilst all statins reduce total and LDL cholesterol to varying extents, their action in secondary prevention following TIA or ischaemic stroke may extend beyond their lipid-lowering properties. At the time of guideline publication, only one trial with a specific statin, Atorvastatin, has been shown to reduce the risk of recurrent ischaemic stroke and other vascular events in patients with ischaemic cerebrovascular disease. Other statins, especially Simvastatin 40 mg daily, may also be considered as cholesterol-lowering therapies. Simvastatin reduced the risk of major vascular events in ischaemic cerebrovascular disease patients between 40 - 80 years of age in the Heart Protection Study. • Individual physicians should choose a statin depending on the patient's medical status, co-morbidities and co-existing medication • The SPARCL and HPS Trials did not titrate the statin dose in patients with ischaemic cerebrovascular disease to achieve specific lipid targets, and further evidence regarding lipid target-adjusted lipid-lowering therapy following TIA or stroke is awaited. • Physician-directed lipid goals, which require further clarification in ischaemic cerebrovascular disease, should be aimed for in conjunction with lifestyle modification and adherence to evidence-based nutrition guidelines. • It is recommended to start with a low dose e.g. Atorvastatin 10 mg – 20 mg nocte, and titrate in increments up to 80 mg nocte, as tolerated, to achieve physician-directed lipid targets depending on initial lipid profile. • Patients should be monitored for adverse effects of statins, especially older patients, or patients on multiple other medications. Regular monitoring of CPK and LFTs and lipid profile and lipid profile is recommended. • If statins are contraindicated, not tolerated or have inadequate lipid-lowering effects at good therapeutic doses,

Guideline	Recommendations
	replacement with, or addition of alternative lipid-lowering agents should be considered. • In some cases, referral to a specialist Lipid Clinic is advised e.g. where lipid targets are not met or where first line lipid lowering agents are not tolerated **Statins in Primary Intracerebral Haemorrhage** • Statins should be avoided after primary intracerebral haemorrhage, unless risk of further ischaemic events outweighs the risk of recurrent haemorrhage.
"Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A national clinical guideline" December 2008 **(Scottish Intercollegiate Guidelines Network)**	**Statins** • A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol level. (grade A) • Atorvastatin (80 mg) should be considered for patients with TIA or ischaemic stroke. (Grade A) • other statins (such as simvastatin 40 mg) may also be considered as they reduce the risk of major vascular events. (Grade A) • statin therapy for prevention of further vascular events post-haemorrhagic stroke is not recommended routinely unless the risk of further vascular events outweighs the risk of further haemorrhage (Grade A) **Patients with primary intracerebral haemorrhage** • Statin therapy after haemorrhagic stroke is not routinely recommended unless the risk of further vascular events outweighs the risk of further haemorrhage (Grade A)
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**	• Blood cholesterol should be checked regularly. It is recommended that high blood cholesterol (e.g. LDL >150 mg/dl; 3.9 mol/L) should be managed with lifestyle modification (Class IV, Level C) and a statin (Class I, Level A)

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-reactive protein level, blood pressure, and race or

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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 (4.4% vs. 6.0%, HR=0.73, 95% CI 0.59-0.91, p=0.005).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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.
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.
Probstfield et al. 2002	CA: ☑	10,355 persons previously enrolled in the	In the LLT arm of the trial, participants were	**Primary outcome:** All-cause mortality.	The mean duration of follow-up was 4.8 years. Maximum follow-up was 7.8 years.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Margolis et al. 2013 (Long-term follow-up) **USA/Canada** **RCT** ***Antihypertensive & Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)***	Blinding: Patient: ☒ Assessor ☒ ITT: ☑	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.	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.	**Secondary outcomes:** Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers and Q-wave MI.	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. 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***	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-

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Rosuvastatin (JUPITER)					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, 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-

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					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 the next 5 years due to a history of existing coronary disease, or occlusive disease of non-coronary arteries, or diabetes or treated hypertension.	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 mg of simvastatin or placebo for 5 years.	**Primary outcome:** All-cause mortality, mortality associated with CHD. **Secondary outcomes:** Non-coronary causes of death, major coronary events, major vascular events and coronary or non-coronary revascularizations and non-fatal or fatal strokes of any type	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%. 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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					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). 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					
Cholesterol Treatment Trialists (CTT) (Fulcher et al. 2015) **UK** **Systematic review & meta-**	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	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)	Major vascular events (nonfatal MI, coronary death, stroke, coronary revascularization).	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%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
analysis		included. All included trials included both men and women.	The effectiveness of statin treatment between men and women was compared.		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 Men: RR=0.83, 99% CI 0.76-0.90
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)	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	NA	26 RCTS in which the	Evaluation of more	Cause-specific mortality,	**More vs. less intensive statin therapy**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Treatment Trialists (CTT) (Baigent et al. 2010) **UK** **Systematic review & meta-analysis**		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.	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, 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	major coronary event (coronary death or non-fatal myocardial infarction), coronary revascularization (angioplasty or bypass grafting), or stroke	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. 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)	**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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			and 2,000 mg (n=1). Estrogen dose was 1.25-2.5 mg/d in one trial.		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** **Systematic review & meta-analysis**	NA	42 RCTs (n=121,285) examining statin therapy for all-stroke prevention. 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	Study drugs and mean doses included in the trial included: atorvastatin (n=8, 10-80 mg), 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)	**Primary outcome:** All-cause mortality, stroke **Secondary outcomes:** Cardiovascular death, ischemic stroke, non-hemorrhagic stroke, fatal stroke	The mean duration of follow-up ranged from 1.0 to 6.1 years. 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.

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

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

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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		years, 30% were women.	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.	**Secondary outcomes:** All-cause mortality, adverse events	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 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 ***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,	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	**Primary outcome:** Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. **Secondary outcome:** Composite of cardiovascular	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. The risk of the primary outcome was significantly lower for patients in the evolocumab group

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA/International **RCT**		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	placebo, for the duration of the trial.	death, myocardial infarction, or stroke.	(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). 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 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 ***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*** **USA/International**	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.

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

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 ***Study of the Effectiveness of additional Reductions in Cholesterol & Homocysteine (SEARCH) Collaborative Group*** **UK** **RCT**	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).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
LaRosa et al. 2005 **International** **RCT** ***Treating to New Targets (TNT)***	CA: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	10,001 participants, 35-75 years with clinically evident CHD and LDL-chol of <3.4 mmol/L. At baseline, mean age was 61 years. 81% were male, 54% had systemic hypertension.	Following a washout period of 1-8 weeks, participants were randomized to 80 vs. 10 mg/day of atorvastatin for the duration of the study.	**Primary outcome:** Occurrence of first major cardiovascular event (death from CHD, non-fatal, non-procedural related MI, 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	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). 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 rhabdomyolysis (80 mg, n=2; 10 mg, n=3). There was a total of 87 drop-outs/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

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					adverse events (9.6% vs. 4.2%, p<0.001). 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

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

Pharmacological Treatment with Statins for Secondary Prevention of Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Amarenco et al. 2006 **International** **RCT** ***Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL)***	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. The mean age at baseline was 63 years. 60% were male.	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 procedure, or any cardiovascular event	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 risk reduction was HR=0.84, 95% CI 0.71-0.99, p=0.03. 10.4% of persons in the atorvastatin had

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

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

Pharmacological Treatment with Statins for Secondary Prevention of Stroke in the Young

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Putaala et al. 2011 **Finland**	NA	215 patients, aged 15-49 years (mean 39.1 years) with first-ever ischemic stroke of unknown etiology admitted to a	Data, obtained from chart review and direct contact with the patient, were used to examine differences in outcome	**Primary outcomes:** Composite outcome of stroke, myocardial infarction, other arterial thrombosis, revascularization, or vascular	No patient who had received stain therapy continuously experienced the primary outcome. Among non-statin and non-continuous statin users, the numbers who reached the primary end point were significantly higher (20% and 11%,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Retrospective study		single site between 1994 and 2007.	among 3 groups: patients who had never been on a statin (n=143), continuous statin use (n=36) and non-continuous statin use (n=36)	death.	respectively, p=0.037). Patients aged >40 were at highest risk of recurrent stroke. Following adjustment for age, sex, dyslipidemia, hypertension, antihypertensive medication, stroke year, and propensity score, any statin use was associated with reduced risk of the primary outcome (HR=0.23, 95% CI 0.08-0.66, p=0.006).

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