



TITLE: Lipid Lowering Agents for Stroke Prevention: A Review of the Clinical Evidence, Safety and Guidelines

DATE: 8 March 2012

CONTEXT AND POLICY ISSUES

In 2005, there were approximately 17.5 million deaths globally due to cardiovascular disease (CVD) and of these deaths, 7.6 million were due to coronary heart disease (CHD) and 5.7 million to stroke.¹ 14 000 Canadians die from stroke every year, accounting for the third leading cause of death in Canada.² CVD is the leading cause of mortality in elderly patients³ and although CHD mortality has decreased over the past 25 years, the percentage reduction for the elderly is nearly 50% lower than that for the general adult population, underscoring the importance for primary and secondary prevention in this population.³

Dyslipidemia, a risk factor for developing CVD, is characterized by an abnormal amount of lipids in the blood and can be managed by several lipid lowering agents including fibrates, nicotinic acid, ezetimibe, and statins.⁴ The most effective and commonly prescribed lipid lowering agents to date are HMG-CoA reductase inhibitors or statins.⁵ Current Canadian best practice recommendations for stroke care regarding lipid management recommend that patients who have had an ischemic stroke or transient ischemic attack (TIA) have their serum lipid levels assessed and aggressively managed using statin agents.²

Statins have been found to be cost-effective if administered in a wider population than is routinely treated.⁶ An economic model of simvastatin found that gains in life expectancy and cost savings decreased with increasing age.⁶

Lipid lowering agents have been prescribed in decreasing frequency in older adults due to a perceived lack of evidence for benefit and safety concerns.^{1,5} Since the CVD burden is so great in this population, there is substantial potential for lipid lowering treatments to provide benefit in this population. This review evaluates the efficacy and safety of lipid lowering agents for stroke prevention in elderly patients to provide an evidence base to formulate guidelines.

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

RESEARCH QUESTIONS

1. What are the evidence-based guidelines and recommendations regarding the use of lipid lowering agents for stroke prevention in frail elderly patients?
2. What is the clinical effectiveness of lipid lowering agents for stroke prevention in frail elderly patients?
3. What is the clinical evidence on the safety and harms of using lipid lowering agents for stroke prevention in frail elderly patients?
4. What is the clinical evidence on the safety and harms of discontinuing lipid lowering agents in frail elderly patients?

KEY MESSAGE

There is evidence to suggest that statins are safe and effective in reducing the risk of stroke in elderly patients. Discontinuation of statin therapy was an independent predictor of one-year all-cause mortality.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies containing safety data, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and February 08, 2012. Internet links were provided, where available.

Selection Criteria and Methods

Two reviewers split the screening of citations to identify health technology assessments, systematic reviews, meta-analyses, randomized and non-randomized studies regarding the use of lipid lowering agents for stroke prevention in frail elderly patients. Potentially relevant articles were ordered based on titles and abstracts, where available. One reviewer considered full-text articles for inclusion according to the selection criteria listed in Table 1. In cases of uncertainty, discrepancies were discussed with a secondary reviewer until consensus was reached.

Table 1: Selection Criteria

Population	Frail elderly geriatric patients, residents in long term care
Intervention	Lipid lowering agents such as statins, fibrates, nicotinic acid and ezetimibe
Comparator	Placebo, active comparator
Outcomes	Mortality, cardiovascular outcomes (stroke, myocardial infarction, cardiovascular death, hospitalization, revascularization), number needed to treat (NNT) to prevent one stroke, adverse events
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, if they were already reported in one or more included systematic reviews, health technology assessments or meta-analyses, had incomplete methods, or were narrative reviews or editorials.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was performed based on study design. Systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) criteria.⁷ Randomized and non-randomized studies were assessed for quality using the Down's and Black instrument.⁸ Instead of calculating numeric scores, the strengths and limitations of each study were described. No evidence-based guidelines were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 634 citations. Upon screening titles and abstracts, 37 potentially relevant articles were retrieved for full-text review. Four potentially relevant reports were retrieved from grey literature and hand searching. Of the 41 potentially relevant reports, seven contained an irrelevant population, three contained an irrelevant intervention, five contained irrelevant outcomes, two were reported in included systematic reviews or meta-analyses, and 11 were narrative reviews or editorials. Of the 13 publications included in this review, 12 report on the clinical effectiveness of statins for stroke prevention in elderly patients,⁹⁻²⁰ seven report on the safety and harms of using statins in elderly patients,^{13-16,18-20} and one reported on the safety and harms of discontinuing statins in elderly patients.²¹ Overall, two systematic reviews,^{9,12} two meta-analyses,^{10,11} six RCTs,¹³⁻¹⁸ and three non-randomized studies¹⁹⁻²¹ were reviewed. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Evidence-based Guidelines on Lipid Lowering Agents for Stroke Prevention

No evidence-based guidelines were found regarding the use of lipid lowering agents for stroke prevention in elderly patients.

Clinical Effectiveness of Lipid Lowering Agents for Stroke Prevention

Summary of Study Characteristics

The clinical effectiveness of lipid lowering agents for stroke prevention was reported in two systematic reviews,^{9,12} two meta-analyses,^{10,11} six RCTs¹³⁻¹⁸ and two non-randomized studies^{19,20} published between 2002 and 2010. Five studies were secondary analyses of the double blind RCTs JUPITER, IDEAL, TNT, SPARCL and CARDS (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, Incremental Decrease through Aggressive Lipid lowering, Treating to New Targets, Stroke Prevention by Aggressive Reduction of Cholesterol Levels and Collaborative Atorvastatin Diabetes Study, respectively).^{13,15-18} A prospective, randomized open-label blinded end point evaluation (PROBE),¹⁴ a cohort analysis of the Japan Lipid Intervention Trial,¹⁹ and a prospective observational cohort were also selected for review.²⁰ Studies were conducted internationally in at least 26 countries, including the United States, Canada, the Netherlands, the United Kingdom, Ireland, Italy, Denmark, Finland, Iceland, Norway, Sweden, and Japan.⁹⁻²⁰ Summaries of study characteristics, critical appraisal and study findings can be found in Appendices 2, 3, and 4, respectively. A summary of the clinical evidence on the effectiveness and safety of using lipid lowering agents in elderly patients and the safety and harms of discontinuing statins can be found in Table 2.

Systematic reviews and meta-analyses

Systematic reviews contained up to 135 studies and meta-analyses up to 18 RCTs.^{9,10} Two systematic reviews^{9,12} included a subgroup analysis of elderly patients aged 65 years or older while two meta-analyses^{10,11} focused solely on elderly patients. Specific patient populations included those with CHD;¹⁰ those with or at risk for CHD;¹² and those with acute coronary syndrome (ACS), revascularization patients, patients with atherosclerosis.⁹ All systematic reviews and meta-analyses compared statin therapy with placebo. One systematic review⁹ also looked at fixed-dose combination products containing a statin and one meta-analysis¹¹ specifically looked at statin monotherapy. All systematic reviews and meta-analyses reported all-cause mortality, CHD mortality, myocardial infarction (MI), and stroke outcomes.

RCTs and non-randomized studies

The six RCTs¹³⁻¹⁸ included in this review have sample sizes ranging from 290¹⁴ to 5695,¹³ while non-randomized studies ranged from 529²⁰ to 42,360.¹⁹ Patient populations were diverse, including patients without CVD or diabetes,¹³ patients with¹⁶ and without CHD,¹⁹ patients with prior MI,^{14,15} prior stroke,¹⁷ and diabetes.^{18,20} One RCT compared rosuvastatin to placebo,¹³ while five RCTs reported on the use of atorvastatin (80 mg/d) compared to placebo,^{17,18} conventional care,¹⁴ low-dose atorvastatin (10 mg/d),¹⁶ or simvastatin.¹⁵ One non-randomized study compared simvastatin (5-10 mg/d) use in elderly versus younger patients,¹⁹ while the other compared statin use versus no statin use in diabetic patients.²⁰ Four RCTs reported on cerebrovascular events (CVE) or major coronary events (MCE), a compound outcome, including MI, revascularization, unstable angina (UA), stroke, and death,^{13-16,18} and four studies reported stroke independently.^{17,19,20}

Summary of Critical Appraisal

Systematic Reviews and Meta-Analyses

All systematic reviews and meta-analyses⁹⁻¹² performed a literature search based on clear pre-defined criteria. Study selection was performed by two or more independent reviewers in all but one review.¹² Data extraction was verified by a second reviewer in all but one review.⁹ One meta-analysis¹¹ only searched one database for articles. A list of excluded studies was only provided in one systematic review.⁹ Publication bias was not assessed in any of the systematic reviews and meta-analyses.

Pooled analysis of studies was not performed in the elderly subgroup analysis by Smith et al.⁹ because the identified studies were all meta-analyses themselves. It was also not performed in the Ward et al.¹² review due to a mix of primary and secondary prevention in the included statin trials.

RCTs and non-randomized studies

All studies clearly described their research questions, eligibility criteria, interventions and outcomes.¹³⁻²⁰ Five of six RCTs were post-hoc secondary analyses of the elderly population contained in a double blind RCT, where randomization was not stratified by age and outcomes were no longer blind.^{13,15,16,18,20} One RCT was independently designed and conducted by the investigators without industry support or funding,¹⁴ and one non-randomized study did not report a source of funding.²⁰ Of the five industry-sponsored RCTs,^{13,15,16,18,20} the sponsor was responsible for data analysis in two trials.^{16,20} Findings of Neil et al.¹⁸ excluded patients over the age of 75 years, and may not be representative of the full range of elderly patients. While the non-randomized observational cohorts suffer from inherent potential for selection bias, the participants were representative of the entire population from which they were recruited.^{19,20}

Summary of Findings

Systematic reviews and meta-analyses

In the systematic review by Smith et al,⁹ one included meta-analysis analyzed 5 trials and found that the risk of major cardiac events was similar between patients over 65 years of age (32%; 95% Confidence Interval [CI] 23 to 39) and patients under 65 years of age (31%; 95% CI 24 to 36). Another included meta-analysis found that statins reduced all-cause mortality (Relative Risk [RR] 0.78; 95% CI 0.65 to 0.89) in elderly patients when compared with placebo.

In the systematic review by Ward et al,¹² subgroup analysis of elderly patients identified three placebo-controlled trials evaluating efficacy of statin therapy and found that statins in patients over 65 years of age were associated with statistically significant reductions of total stroke, but not to a greater extent than younger patients.

In the two meta-analyses looking at the efficacy of statin therapy in patients over 65 years of age with CHD¹⁰ and in patients over 60 years of age,¹¹ statins were found to reduce the incidence of stroke by 25% (RR 0.75, 95% CI 0.56 to 0.94) and 24% (RR 0.76, 95% CI 0.65 to 0.90, P = 0.001), respectively. Analysis of patients over 65 years in the meta-analysis performed by Roberts et al.¹¹ showed a reduction of 19% in stroke incidence in statin recipients.

Randomized controlled trials (RCTs)

Rosuvastatin

Secondary analysis of JUPITER in patients older than 70 years showed that rosuvastatin reduces the incidence of CVE in healthy older individuals without hyperlipidemia but with high-sensitivity C-reactive protein.¹³ Thirty two percent of participants over 70 years of age had 49% of the CVE. Rates of CVE ($P < 0.001$) and all-cause mortality ($P = 0.09$) per 100 person-years were lower in rosuvastatin recipients compared to placebo. Absolute reductions in event rates associated with rosuvastatin were 48% greater in older versus younger persons (0.77 versus 0.52 events per 100 person-years, respectively). The number needed to treat for 4 years to prevent one CVE in older patients was 24 (95% CI 15 to 57) compared with 36 (95% CI 23 to 77) in younger patients.¹³

Atorvastatin

Secondary analysis of CARDS showed that both young and elderly diabetics benefit from stroke prevention with atorvastatin.¹⁸ Atorvastatin reduced the relative risk (RR) of MCE by 38% (95% CI -51 to -8; $P = 0.017$) in older patients and 37% (95% CI -57 to -7; $P = 0.019$) in younger patients. Twenty-one and 33 people, respectively would need to be treated for 4 years to prevent one event.¹⁸

Secondary analysis of SPARCL showed that both young and elderly stroke survivors benefit from stroke prevention with atorvastatin.¹⁷ The risk of stroke was reduced by 26% (Hazard Ratio [HR] 0.74, 95% CI 0.57 to 0.96; $P = 0.02$) in younger patients and by 10% (HR 0.90, 95% CI 0.73 to 1.11; $P = 0.33$) in elderly patients. Heterogeneity for treatment-age interaction was not significant ($P = 0.52$). The risk of stroke or TIA (HR 0.79; $P = 0.01$), MCE (HR 0.68; $P = 0.035$), CHD events (HR 0.61; $P = 0.0006$) and revascularization (HR 0.55; $P = 0.0005$) was reduced in elderly patients with a low rate of serious side effects.¹⁷

The Italian PROBE study showed that full-dose atorvastatin (80 mg/d) reduces ischemic recurrences after NSTEMI in patients with severe, diffuse non-revascularisable CAD.¹⁴ Within 12 months, a CVE occurred in 16% of atorvastatin (80 mg) recipients and 27% of patients receiving conventional medical treatment (HR 0.56; 95% CI 0.33 to 0.93; $P = 0.027$).¹⁴

Secondary analysis of TNT showed that in patients older than 65 years of age, high-dose atorvastatin reduces the absolute risk of CVE by 2.3% without persistent elevation of creatine kinase.¹⁶ Patients randomly assigned to 80 mg/d or 10 mg/d achieved average LDL cholesterol levels of 70 mg/dL and 100 mg/dL, respectively. Fewer high dose atorvastatin users had CVE than low-dose recipients (10.3% versus 12.6%). Thirty five patients would need to be treated with high-dose atorvastatin to prevent one CVE over 4.5 years.¹⁶ Eight patients (0.4%) who received 80 mg and 15 patients (0.8%) who received 10 mg had hemorrhagic stroke causing three deaths in each group. While not statistically significant, the rate of fatal and nonfatal stroke in patients older than 65 was lower in the 80 mg group than the 10 mg group. The risk for a cardiovascular events ($P < 0.001$), MCE ($P < 0.128$), a CVE ($P = 0.010$), and hospitalization for CHF ($P = 0.008$) was lower in the high-dose group.¹⁶ It is unclear whether benefits were due to the higher statin dose, lower cholesterol levels, or both.¹⁶

Secondary analysis of IDEAL comparing atorvastatin to simvastatin in persons less than and greater than 65 years of age showed that significant reductions in outcomes were observed only

in younger patients with the exception of CVE.¹⁵ While atorvastatin was associated with a 20% decrease in risk of MCE in patients <65 years (HR 0.80, 95% CI 0.66 to 0.98, with similarly significant reductions in secondary composite end points, corresponding reductions in risk in the group >65 years were 4% and 12%, and statistical significance was only achieved for CVE in older patients (HR 0.88, 95% CI 0.79 to 0.99).¹⁵

Simvastatin

Post-hoc subgroup analysis of the Japan Lipid Intervention Trial showed that simvastatin treatment in older individuals was as safe and effective as in younger patients.¹⁹ Rates of MCE were 1.30 per 1000 patient-years in elderly patients and 0.8 per 1000 patient-years in younger patients.¹⁹ Absolute risk of MCE in older patients was higher than younger patients, while RR increased by 1.7% with elevation of each 1 mg/dL LDL-C level in both groups.¹⁹ Rates of CVE were 2.61 per 1000 patient-years in older patients and 1.29 per 1000 patient-years in younger patients ($P < 0.001$).

General Statin Use

An American prospective observational cohort study suggests that statins are associated with a 37% significant, independent, reduction in new coronary events and a 47% significant, independent reduction in new stroke in older patients with diabetes, prior MI and serum LDL > 125 mg/d.²⁰ Elderly diabetics with prior MI and increased serum LDL cholesterol should be treated with statins.²⁰

Clinical Evidence on Safety and Harms of Lipid Lowering Agents for Stroke Prevention

Rosuvastatin

Secondary analysis of JUPITER showed the relative rate of severe adverse events (SAE) among older persons in rosuvastatin versus placebo was 1.05 (95% CI 0.93 to 1.17).¹³ Rates of muscle weakness, stiffness, bleeding, diabetes, and gastrointestinal or gastrointestinal disorder were higher in the rosuvastatin group but not statistically significant ($P > 0.1$) for each.¹³

Atorvastatin

Secondary analysis of CARDS showed that both young and elderly diabetics benefit from stroke prevention with atorvastatin.¹⁸ The safety profile was similar between age groups. Secondary analysis of SPARCL showed that both young and elderly stroke survivors benefit from stroke prevention with atorvastatin.¹⁷ Elderly patients maintained LDL reductions with a low rate of serious side effects.

The Italian PROBE study reported that full dose atorvastatin therapy provides greater protection against ischemic recurrences after NSTEMI in patients with severe CAD than conventional treatment.¹⁴ Atorvastatin was withdrawn in two atorvastatin recipients after persistent muscle pain and rise in total serum creatinine kinase. One person receiving conventional treatment and two people in the atorvastatin group had elevated alanine aminotransferase levels.¹⁴ Secondary analysis of the TNT study showed that high-dose atorvastatin reduces the risk of CVE without persistent elevation of creatinine kinase.¹⁶

Secondary analysis of IDEAL showed no difference in the number of atorvastatin and simvastatin patients who reported a SAE, but the percentage reporting events was higher in patients >65 years in both treatment groups. In the younger group, 40% of atorvastatin recipients and 41% of simvastatin recipients reported SAE while in the older group, 55% and 56% reported SAE, respectively.¹⁵ Regardless of age, more patients receiving atorvastatin than simvastatin had dose reductions and temporary or permanent discontinuations due to AE. In patients >65 years, 11.8% of atorvastatin recipients and 4.1% of simvastatin recipients permanently discontinued therapy due to AE while 7.9% and 4.2% of patients <65 years discontinued, respectively. Rates of death due to malignancy were similar in younger patients and lower in the atorvastatin versus simvastatin group in older patients, but this difference was not statistically significant (HR 0.82, 95% CI 0.58 to 1.15).¹⁵

Simvastatin

Post-hoc subanalysis of the Japan Lipid Intervention Trial showed that simvastatin treatment in older patients was as safe and effective as in younger patients.¹⁹ Drug related AEs were observed in 3.18% of older patients and 3.19% of younger patients (P = 0.99). Hepatic dysfunction (0.99% in older patients, 1.02% in younger patients, P = 0.79) and musculoskeletal disorders (0.81% and 0.91%, P = 0.4, respectively) were most frequently observed. No rhabdomyolysis occurred in either group. Renal dysfunction was slightly higher in older patients (0.32%) than younger patients (0.14%; P < 0.01).¹⁹

Clinical Evidence on Safety and Harms of Discontinuing Lipid Lowering Agents

Summary of Study Characteristics

Study design, population, intervention and outcomes

One Italian cohort study published in 2007 was selected for review.²¹ The study included 631 consecutive stroke survivors with a mean age of 70 years. All patients were discharged on statin therapy (78% on atorvastatin, 22% on simvastatin) and followed for 12 months following acute ischemic stroke. The primary endpoint of the study was death from any cause within 12 months of discharge.²¹

Summary of Critical Appraisal

The study had a clearly defined research question, eligibility criteria, interventions and outcomes.²¹ The patient population was clearly described but the potential for selection bias is inherent in single-centre studies. Patients with congestive heart failure, valvular dysfunction, cardiomyopathy and atrial fibrillation were excluded, limiting the generalizability of these results. While adherence to prescribed therapies was assessed by telephone interview, self-reported adherence and actual adherence may differ.²¹

Summary of Findings

Within 12 months of discharge, 246 patients (39%) discontinued statin therapy and 14% switched from the prescribed statin to another statin.²¹ The mean time from discharge to discontinuation was 49 ± 55 days. Discontinuation rates were similar for atorvastatin and simvastatin. Patients discontinuing statins were significantly older (71.4 ± 7.1 versus 69.5 ± 7.7 yr; P = 0.002) and typically female (138/246 versus 171/386; P = 0.004). Patients were less

likely to discontinue if they had diabetes ($P = 0.001$) or had previous stroke ($P = 0.038$). During follow-up, 116 patients died (1 yr probability of death 0.18; 95% CI 0.15 to 0.21). After adjusting for confounders, statin therapy discontinuation was determined to be an independent predictor of all-cause one year mortality (HR 2.78; 95% CI, 1.96 to 3.72; $P = 0.003$).²¹ Patients were more likely to die during follow-up if they were older (74 ± 5.0 versus 69.4 ± 7.8 years; $P = 0.0001$), diabetic (52/116 versus 176/511; $P = 0.03$), or had prior stroke (21/116 versus 57/515; $P = 0.037$).

Table 2. Summary of the Clinical Effectiveness, Safety and Harms of Statins for Stroke Prevention and the Safety of Discontinuing Statin Therapy in Elderly Patients

Intervention	Evidence	Results
Clinical Effectiveness of Statin Therapy for Preventing Stroke in the Elderly		
General Statin Use	2 Systematic reviews, ^{9,12} 2 Meta-analyses, ^{10,11} cohort study ²⁰	<ul style="list-style-type: none"> Evidence suggests statins reduce the risk of all-cause mortality by 22%,¹⁰ MCE by 32-37%,^{9,20} and stroke by 25-47%^{10,11,20} in patients ≥ 65 years.
Rosuvastatin	Secondary analysis of JUPITER ¹³	<ul style="list-style-type: none"> Rosuvastatin reduces the incidence of MCE in healthy older persons without hyperlipidemia but with elevated high-sensitivity CRP levels.¹³
Atorvastatin	Secondary analysis of IDEAL, ¹⁵ TNT, ¹⁶ SPARCL, ¹⁷ CARDS, ¹⁸ PROBE ¹⁴	<ul style="list-style-type: none"> Evidence suggests atorvastatin reduces the risk of CVE,¹⁴⁻¹⁷ and MCE.¹⁸ Twenty-one people need to be treated with atorvastatin to prevent one MCE over 4 years.¹⁸ The NNT for benefit for atorvastatin 80 mg versus 10 mg was 35 to prevent one CVE over 4.5 years.¹⁶
Simvastatin	Cohort ¹⁹	<ul style="list-style-type: none"> Simvastatin therapy in older patients was as safe and effective as in younger patients.¹⁹ Rates of CVE were 2.61 per 1000 patient-years in older patients and 1.29 per 1000 patient-years in younger patients ($P < 0.001$).¹⁹
Safety and Harms of Statin Therapy for Preventing Stroke in the Elderly		
Rosuvastatin	Secondary analysis of JUPITER ¹³	<ul style="list-style-type: none"> RR of SAE among elderly in the rosuvastatin versus placebo group was 1.05 (95% CI 0.93 to 1.17).¹³ Among older patients, rates of muscle weakness, renal disorder, bleeding events, diabetes, gastrointestinal and hepatic disorders were higher in the rosuvastatin group, but none was statistically significant ($P > 0.10$, each).¹³
Atorvastatin	Secondary analysis of IDEAL, ¹⁵ TNT, ¹⁶ SPARCL, ¹⁷ CARDS, ¹⁸ PROBE ¹⁴	<ul style="list-style-type: none"> The safety profile was similar between young and older atorvastatin recipients. In patients >65 years, 12% of atorvastatin recipients and 4% of simvastatin recipients discontinued therapy due to AE, while 8% and 4% of younger patients discontinued, respectively.¹⁵
Simvastatin	Cohort ¹⁹	<ul style="list-style-type: none"> Drug related AEs were similar between older and younger patients.¹⁹ Hepatic dysfunction and musculoskeletal disorders were most frequently observed. Renal dysfunction was slightly higher in older patients (0.32%) than younger patients (0.14%; $P < 0.01$).¹⁹
Safety and Harms of Discontinuing Statin Therapy in the Elderly		
Discontinuing Statin Therapy	Prospective single-centre	<ul style="list-style-type: none"> 39% of stroke survivors discontinued statin therapy within 12 months of discharge.

Intervention	Evidence	Results
	observational cohort study ²¹	<ul style="list-style-type: none"> • Older female patients were more likely to discontinue statins while patients with diabetes or prior stroke were less likely to discontinue therapy. • Discontinuation of statin therapy was an independent predictor of all cause one year mortality (HR 2.78; 95% CI 1.96 to 3.72; P = 0.003).²¹ • Patients were more likely to die during follow-up if they were older, diabetic or had prior stroke.

AE: adverse event; CRP: C-reactive protein; CVE: cerebrovascular event; MCE: major cardiovascular event; RR: relative risk

Limitations

The evidence included in this review has inherent limitations that limit its usefulness in drawing conclusions regarding the safety and effectiveness of using lipid lowering agents for stroke prevention in the frail elderly. While the populations within the included studies were diverse, including patients without cardiovascular disease (CVD) or diabetes,¹³ patients with¹⁶ and without coronary heart disease (CHD),¹⁹ patients with prior MI,^{14,15} prior stroke,²⁰ and diabetes,^{18,20} no study specifically identified a population as frail and elderly. The findings of the secondary analysis of CARDS hold limited generalizability as they are not directly applicable to the very elderly because patients older than 75 years at randomization were excluded from study.¹⁸ There was some overlap in the studies described in included systematic reviews, in particular the PROSPER and CARE trials which were included in all reviews. This may give undue weight to particular studies, however this is mitigated by the quantity of statin research available for review. No studies were found regarding the safety and effectiveness of lipid lowering agents other than statins. Not all studies reported stroke as an independent outcome. Four RCTs reported on CVE or CME, a compound outcome, including myocardial infarction (MI), revascularization, unstable angina (UA), stroke, and death.^{13-16,18} Five of six RCTs were post-hoc secondary analyses of the elderly population contained in an RCT, where randomization was not stratified by age and outcomes were no longer blind, leading to potential selection bias.^{13,15,16,18,20}

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

While no evidence based guidelines were found regarding lipid lowering agents for stroke prevention in frail elderly patients, there is evidence to suggest that statins reduce the risk of stroke by 25-47%,^{10,11,20} MCE by 32-37%,^{9,20} and all-cause mortality by 22%¹⁰ in a variety of patients over 65 years of age. One would need to treat 24 elderly patients with rosuvastatin to prevent one CVE over four years.¹³ The NNT to gain benefit of atorvastatin 80 mg versus 10 mg was 35 to prevent one CVE over four years.¹⁶ Safety profiles were similar between older and younger patients receiving statins.^{18,19} The most common AEs included muscle weakness, bleeding events, diabetes, and renal, gastrointestinal or hepatic disorders.^{13,19} While 39% of stroke survivors discontinue statin therapy within 12 months of discharge, discontinuation of statin therapy was an independent predictor of one year all-cause mortality.²¹

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

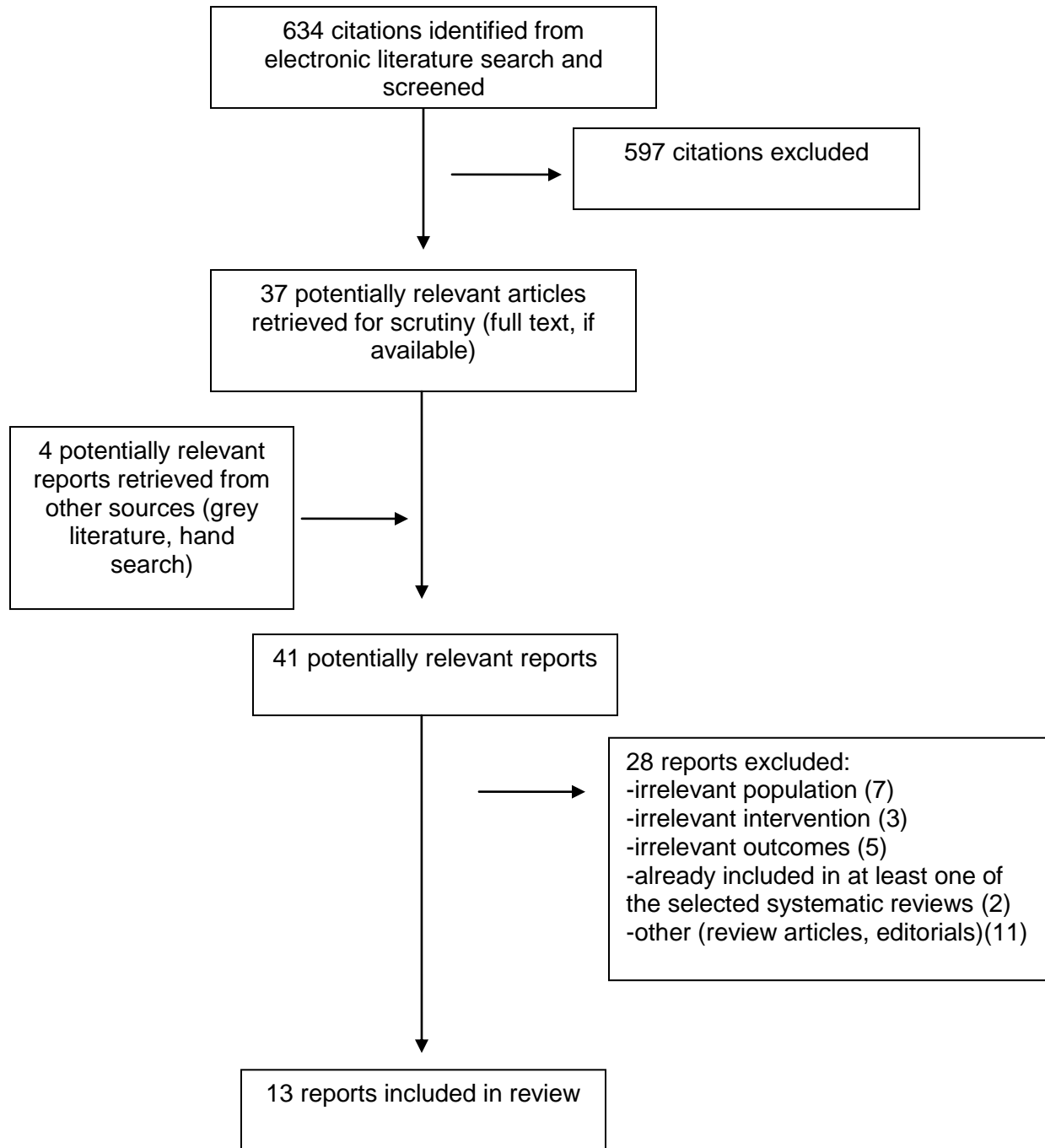
REFERENCES

1. Thomas JE, Tershakovec AM, Jones-Burton C, Sayeed RA, Foody JM. Lipid lowering for secondary prevention of cardiovascular disease in older adults. *Drugs Aging*. 2010 Dec 1;27(12):959-72.
2. Lindsay MP, Gubitz G, Bayley M, Hill MD, Davies-Schinkel C, Singh S, et al. Canadian best practice recommendations for stroke care (update 2010) [Internet]. Ottawa (ON): Canadian Stroke Network; 2010 Dec 8. [cited 2012 Feb 8]. Available from: http://www.strokebestpractices.ca/wp-content/uploads/2011/04/2010BPR_ENG.pdf
3. Maroo BP, Lavie CJ, Milani RV. Secondary prevention of coronary heart disease in elderly patients following myocardial infarction: are all HMG-CoA reductase inhibitors alike? *Drugs Aging*. 2008;25(8):649-64.
4. Institute for Clinical Systems Improvement (ICSI). Health care guideline: lipid management in adults [Internet]. 12th ed. Bloomington (MN): ICSI; 2011 Oct. [cited 2012 Feb 8]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html
5. Walker DB, Jacobson TA. Initiating statins in the elderly: the evolving challenge. *Curr Opin Endocrinol Diabetes Obes*. 2008 Apr;15(2):182-7.
6. Heart Protection Study Collaborative, Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, et al. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *BMJ* [Internet]. 2006 Dec 2 [cited 2012 Feb 8];333(7579):1145. Available from: http://www.bmj.com/highwire/filestream/395193/field_highwire_article_pdf/0.pdf
7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2012 Feb 7];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998 Jun;52(6):377-84.
9. Smith MEB, Lee NJ, Haney E, Carson S. Drug class review: HMG-CoA Reductase Inhibitors (Statins) and fixed-dose combination products containing a statin: final report update 5 [Internet]. Portland (OR): Oregon Health & Science University; 2009 Nov. [cited 2012 Feb 8]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK47273/pdf/TOC.pdf>

10. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol*. 2008 Jan 1;51(1):37-45.
11. Roberts CG, Guallar E, Rodriguez A. Efficacy and safety of statin monotherapy in older adults: a meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2007 Aug;62(8):879-87.
12. Ward S, Lloyd JM, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess [Internet]*. 2007 Apr [cited 2012 Feb 8];11(14):1-iv. Available from: <http://www.hta.ac.uk/fullmono/mon1114.pdf> (copy and paste link into URL bar).
13. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med*. 2010 Apr 20;152(8):488-96, W174.
14. Colivicchi F, Tubaro M, Mocini D, Genovesi EA, Strano S, Melina G, et al. Full-dose atorvastatin versus conventional medical therapy after non-ST-elevation acute myocardial infarction in patients with advanced non-revascularisable coronary artery disease. *Curr Med Res Opin*. 2010 Jun;26(6):1277-84.
15. Tikkanen MJ, Holme I, Cater NB, Szarek M, Faergeman O, Kastelein JJ, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus ≥65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study). *Am J Cardiol*. 2009 Mar 1;103(5):577-82.
16. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK, Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med*. 2007 Jul 3;147(1):1-9.
17. Chaturvedi S, Zivin J, Breazna A, Amarenco P, Callahan A, Goldstein LB, et al. Effect of atorvastatin in elderly patients with a recent stroke or transient ischemic attack. *Neurology*. 2009 Feb 24;72(8):688-94.
18. Neil HA, DeMicco DA, Luo D, Betteridge DJ, Colhoun HM, Durrington PN, et al. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care [Internet]*. 2006 Nov [cited 2012 Feb 8];29(11):2378-84. Available from: <http://care.diabetesjournals.org/content/29/11/2378.full.pdf+html>
19. Horiuchi H, Kita T, Mabuchi H, Matsuzaki M, Matsuzawa Y, Nakaya N, et al. Primary cardiovascular events and serum lipid levels in elderly Japanese with

- hypercholesterolemia undergoing 6-year simvastatin treatment: a subanalysis of the Japan lipid intervention trial. *J Am Geriatr Soc*. 2004 Dec;52(12):1981-7.
20. Aronow WS, Ahn C, Gutstein H. Reduction of new coronary events and new atherothrombotic brain infarction in older persons with diabetes mellitus, prior myocardial infarction, and serum low-density lipoprotein cholesterol ≥ 125 mg/dl treated with statins. *J Gerontol A Biol Sci Med Sci*. 2002 Nov;57(11):M747-M750.
21. Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. *Stroke* [Internet]. 2007 Oct [cited 2012 Feb 8];38(10):2652-7. Available from: <http://stroke.ahajournals.org/content/38/10/2652.full.pdf+html>

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Clinical Effectiveness and Safety of Statins for Stroke Prevention					
<i>Systematic Reviews and Meta-analyses</i>					
Smith ⁹ 2009 United States	Systematic review 135 included studies: 74 RCTs, 38 observational, 8 systematic reviews, 15 other)	ACS patients, revascularization patients, or outpatients targeted for primary/secondary prevention of CHD or atherosclerosis	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) Fixed-dose combination products containing a statin (lovastatin + niacin, simvastatin + ezetimibe, simvastatin + niacin)	Active comparator or placebo	All-cause mortality, CHD, CHD mortality, revascularization, MI, stroke
Afilalo ¹⁰ 2008 Canada and The Netherlands	Meta-analysis (Hierarchical Bayesian) 9 RCTs	Elderly patients ≥65 years with CHD	Statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	Placebo	All-cause mortality, CHD mortality, MI, revascularization, stroke
Roberts ¹¹ 2007 United States	Meta-analysis 18 RCTs	Patients ≥60 years	Statins monotherapy (atorvastatin, simvastatin, pravastatin, rosuvastatin, fluvastatin, lovastatin)	Placebo	All-cause mortality, CHD mortality, fatal and nonfatal MI, fatal and nonfatal stroke
Ward ¹² 2007 United Kingdom	Systematic review, meta-analysis and economic evaluation 31 RCTs	Patients >18 years with, or at risk of, CHD	Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin)	Placebo	All-cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, QoL, cost
<i>Randomized Controlled Trials (RCTs)</i>					
Glynn ¹³ 2010	Secondary analysis of DB	Patients without CVD or diabetes	Rosuvastatin (20 mg/d)	Placebo (n=8901)	CVE (MI, stroke,

First Author, Publication Year Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
International (1315 sites, 26 countries)	RCT JUPITER assessing efficacy in patients >70 yr; 2 yr follow-up	(M>50 yr; F>60 y) Of 17802 participants assigned LDLs<130 mg/dL) and CRP levels of 2.0 mg/L, 5695 were >70 y	(n=8901)		revascularization, hospitalization for UA, or death)
Colivicchi ¹⁴ 2010 Italy	PROBE 12 months	Patients with NSTEMI and CAD not amenable to revascularization; (n=290, mean age: 75 yr)	Atorvastatin (80 mg/d) (n=144)	Conventional medical treatment (n=146)	CVE (CV death, MI, stroke)
Tikkanen ¹⁵ 2009 Denmark, Finland, Iceland, The Netherlands, Norway, Sweden	Secondary analysis of IDEAL comparing efficacy in patients <65 yr versus >65 yr	Patients <80 yr (n=8888 with previous MI: n= 5129), 58%<65 yr, mean=55 yr; 3759, 42% 65-80 yr, mean=71 yr)	Atorvastatin (80 mg/d) 13% of younger group, 10% of older group	Simvastatin 20-40mg/d) 51% of younger group, 49% of older group	CVE (MCE, stroke revascularization, UA, CHF, PAD)
Wenger ¹⁶ 2007 International (356 sites, 14 countries)	Secondary analysis of TNT to assess efficacy and safety of high-dose atorvastatin in patients >65 yr; 4.9 yr	Patients >65 yr with CHD and LDL <130 mg/dL (n=3809; 38% >65 yr, mean=70 yr)	Atorvastatin (80 mg) (n=1937)	Atorvastatin (10 mg) (n=1872)	CVE (CHD death, nonfatal MI, resuscitated cardiac arrest, stroke)
Chaturvedi ¹⁷ 2008 International (205 centres)	Secondary analysis of DB RCT SPARCL to compare the effect of atorvastatin in patients >65 yr to <65 yr.	Recent stroke or TIA survivors (n=4,731; n=2249 > 65 yr, mean: 72 yr, LDL: 62 mg/dL; n=2482 < 65 yr, mean: 54 yr, LDL: 59 mg/dL)	Atorvastatin (80 mg/d) (n=2365)	Placebo (n=2366)	Stroke
Neil ¹⁸ 2006 UK and Ireland	Secondary analysis of DB RCT CARDS to compare efficacy and safety of atorvastatin in patients aged 65-75 yr	Type 2 diabetes patients (65-75 yr) LDL<160 mg/dL; 3.9 years (n=1428)	Atorvastatin (10 mg/d) (n=572)	Placebo (n=557)	CHD event, revascularization, stroke

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
<i>Non-Randomized Studies</i>					
Horiuchi ¹⁹ 2004 Japan	Cohort analysis of Japan Lipid Intervention Trial; 6 yr	Japanese patients without CHD, men (35-70 yr), women <70 yr with TC < 220 mg/dL (n=42,360)	Simvastatin (5-10 mg/d) treated patients aged 65-70 yr (n=9,860; mean: 67 yr)	Simvastatin (5-10 mg) treated patients <65 yr (n=32,500; mean: 55 yr)	MCE (MI, cardiac death, angina, stroke)
Aronow ²⁰ 2002 United States	Observational prospective cohort; 2 yr	Diabetic patients with prior MI and LDL > 125 mg/dL living in long term care (n=529, range: 62-100 yr, mean: 79 yr)	Statin use (n=279)	No statin use (n=250)	MCE, stroke, death
Safety and Harms of Discontinuing Statin Therapy					
Colivicchi ²¹ 2007 Italy	Cohort	Stroke survivors; 78% atorvastatin (10-20 mg/d), 22% simvastatin (20-40 mg/d) (n=631; 51% M; 70 yr)	Discharged on statin therapy and followed 12 months after ischemic stroke	NA	Death

CARDS: Collaborative Atorvastatin Diabetes Study; CHD: coronary heart disease; CVD: cardiovascular disease; CRE: cardiorenal event; CVE: cardiovascular event; CHF: congestive heart failure; CRP: C-reactive protein; DB: double blind; F: female; IDEAL: Incremental Decrease through Aggressive Lipid lowering; JUPITER: Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL: low-density lipoprotein; M: male; MCE: major coronary event; MI: myocardial infarction; PAD: peripheral artery disease; PROBE: prospective, randomized open-label blinded end point evaluation; QoL: quality of life; RCT: randomized controlled trial; RF: renal failure; RVD: renovascular disease; SPARCL: Stroke Prevention by Aggressive Reduction of Cholesterol Levels; TC: total cholesterol; TNT: Treating to New Targets; UA: unstable angina; United Kingdom: yr: year

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Clinical Effectiveness and Safety of Statins for Stroke Prevention		
<i>Systematic Reviews and Meta-Analyses</i>		
Smith ⁹ 2009	<ul style="list-style-type: none"> • Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • Article selection process was well documented including a list of included and excluded studies • Conflict of interest statement 	<ul style="list-style-type: none"> • Search restricted to English language articles • Study type inclusion criteria not clearly defined • Unclear if data extraction was performed in duplicate • Characteristics of included studies not provided in detail • Publication bias not assessed
Afilalo ¹⁰ 2008	<ul style="list-style-type: none"> • Comprehensive literature search based on pre-defined criteria • Study selection was performed by three independent reviewers • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate and well reported 	<ul style="list-style-type: none"> • List of excluded studies not provided • Publication bias not assessed • No conflict of interest statement provided
Roberts ¹¹ 2007	<ul style="list-style-type: none"> • Literature search based on pre-defined criteria • Study selection and data extraction was performed by two independent reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate and well reported • Conflict of interest statement 	<ul style="list-style-type: none"> • Only one database (PubMed) searched • Grey literature was not included in the literature search • List of excluded studies not provided • Scientific quality of included studies not well documented
Ward ¹² 2007	<ul style="list-style-type: none"> • Comprehensive literature search based on pre-defined criteria • Data extraction was performed by one reviewer and checked by another reviewer • Methods of pooling studies were appropriate and well reported • Article selection process was well documented including a list of included and excluded studies • Conflict of interest statement 	<ul style="list-style-type: none"> • Unclear if study selection was performed by two independent reviewers • Characteristics of included studies not provided in detail, only subgroup analysis performed and outcomes analyzed • Publication bias not assessed

First Author, Publication Year	Strengths	Limitations
Clinical Effectiveness and Safety of Statins for Stroke Prevention		
<i>Randomized Controlled Trials (RCTs)</i>		
Glynn ¹³ 2010	<ul style="list-style-type: none"> Clearly described the research question, eligibility criteria, intervention and outcomes Patients were randomized to rosuvastatin or placebo and number lost to follow-up were reported 	<ul style="list-style-type: none"> Secondary analysis and randomization was not stratified by age The study was stopped early so long-term outcomes are not reported Industry funded
Colivicchi ¹⁴ 2010	<ul style="list-style-type: none"> Clearly described research question, eligibility criteria, intervention and outcomes Sample size calculations and intent to treat analysis Independently designed and conducted by the investigators without industry support or funding 	<ul style="list-style-type: none"> Possible bias in assessment of clinical outcomes as the study was not blinded
Tikkanen ¹⁵ 2009	<ul style="list-style-type: none"> Clearly described the research question, eligibility criteria, intervention and outcomes 	<ul style="list-style-type: none"> Prospective open-label randomized blind endpoint trial. Patients were switched at randomization without washout or run in, resembling clinical practice Adherence to treatment was lower in older patients Industry funded
Wenger ¹⁶ 2007	<ul style="list-style-type: none"> An independent end point committee that was blinded to treatment assignment adjudicated all primary and secondary outcomes 	<ul style="list-style-type: none"> Data was analyzed by the funding source according to the statistical analysis plan approved by a steering committee. Industry sponsored
Chaturvedi ¹⁷ 2008	<ul style="list-style-type: none"> Clearly described research question, eligibility criteria, intervention and outcomes Patients were randomized to atorvastatin or placebo 	<ul style="list-style-type: none"> Secondary analysis and randomization was not stratified by age Sponsor responsible for data and analysis Industry sponsored
Neil ¹⁸ 2006	<ul style="list-style-type: none"> Clearly described research question, eligibility criteria, intervention and outcomes Patients were randomized to atorvastatin or placebo 	<ul style="list-style-type: none"> Secondary analysis and randomization was not stratified by age Findings are not directly applicable to the very elderly as patients >75 years at randomization were excluded

First Author, Publication Year	Strengths	Limitations
Clinical Effectiveness and Safety of Statins for Stroke Prevention		
		<ul style="list-style-type: none"> • Industry sponsored
<i>Non-Randomized Studies</i>		
Horiuchi ¹⁹ 2004	<ul style="list-style-type: none"> • Clearly described research question, eligibility criteria, intervention and outcomes • Findings are representative of the entire population from which they were recruited 	<ul style="list-style-type: none"> • Non-randomized, non-blind, comparison of statin use in elderly versus younger patients • Industry sponsored
Aronow ²⁰ 2002	<ul style="list-style-type: none"> • Clearly described the research question, eligibility criteria, intervention and outcomes. Patients in long term care, events confirmed by cardiologist and neurologist • Participants were representative of the entire population from which they were recruited 	<ul style="list-style-type: none"> • Non-randomized, non-blind comparison of statin use versus no statin use in older diabetic patients with prior MI • Funding source not reported
Safety and Harms of Discontinuing Statin Therapy		
Colivicchi ²¹ 2007	<ul style="list-style-type: none"> • Clearly described research question, eligibility criteria, intervention, and outcomes. Efforts were made to obtain hospital records and death certificate 	<ul style="list-style-type: none"> • Potential selection bias is inherent in single-centre observational studies where patients are prospectively included by investigators. Patients with CHF, valvular dysfunction, cardiomyopathy, and AF were excluded from the study, limiting generalizability • Adherence to prescribed therapies was assessed by telephone interviews, daily compliance may differ • Funding source not reported

AF: atrial fibrillation; CHF: congestive heart failure; MI: myocardial infarction

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Clinical Effectiveness and Safety of Statins for Stroke Prevention		
<i>Systematic Reviews and Meta-Analyses</i>		
Smith ⁹ 2009	<p><u>Efficacy in elderly subgroup</u></p> <ul style="list-style-type: none"> • 4 meta-analyses suggest statins are equally efficacious in the elderly • One meta-analysis analyzed 5 trials and found that the risk reduction in MCE was 32% (95% CI, 23-39) for patients ≥65 years and 31% (95% CI, 24-36) in those younger than 65 years • One meta-analysis evaluating statins in the elderly pooled 9 placebo-controlled trials revealing a RR for all-cause mortality of 0.78 (95% CI, 0.65-0.89) and a reduction of stroke with statins compared with placebo 	Evidence suggests that the elderly benefit from statin therapy
Afilalo ¹⁰ 2008	<ul style="list-style-type: none"> • In patients ≥65 years, statins reduced the incidence of stroke by 25% (RR 0.75, 95% CI 0.58-0.94) over 5 years compared to placebo according to a pooled analysis of 5 RCTs (CARE, HPS, LIPID, PLAC I, PROSPER) • Statins reduced all-cause mortality by 22% (RR 0.78, 95% CI 0.65-0.89) over 5 years and CHD mortality by 30% (RR 0.70, 95% CI 0.53-0.83) over 5 years compared to placebo according to a pooled analysis of 9 RCTs 	Statins reduce all-cause mortality and stroke incidence in elderly patients
Roberts ¹¹ 2007	<ul style="list-style-type: none"> • In patients ≥60 years, the rate of fatal and nonfatal stroke was reduced by 24% in statin recipients (RR 0.76, 95% CI 0.65-0.90; P = 0.001) according to a pooled analysis of 11 RCTs • In patients ≥65 years, the rate of fatal and nonfatal stroke was reduced by 19% in statin recipients (RR 0.81, 95% CI 0.66-1.00; P = 0.05) according to a pooled analysis of 11 RCTs 	Statin therapy is effective in reducing cardiovascular outcomes, including stroke, in older adults
Ward ¹² 2007	<p><u>Subgroup analysis of elderly patients</u></p> <ul style="list-style-type: none"> • 3 placebo-controlled studies administered statin to elderly patients (PROSPER) or presented subgroup data (4S, CARE) • Statins in patients ≥65 years were associated with statistically significant reductions in RR of CHD mortality, total stroke, non-fatal MI, coronary revascularization, and CHD death • In the CARE study, NNT to prevent CHD death or non-fatal MI is substantially lower in patients ≥65 years than in younger patients 	<p>Results should be interpreted with caution due to small sample sizes</p> <p>There is no evidence that statins are more less effective in older people</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p><u>Cost-effectiveness</u> ICERs increase with age varying between £10,000 and £17,000 per QALY for ages 45 and 85, respectively</p>	
<i>Randomized Controlled Trials (RCTs)</i>		
Glynn ¹³ 2010	<ul style="list-style-type: none"> • 32% of participants >70 yr had 194/393 (49%) CVE • Rates of CVE were 1.22 and 1.99 per 100 person-yr of follow-up in rosuvastatin and placebo groups, respectively (HR: 0.61, 95% CI 0.46 to 0.82; P < 0.001) • All-cause mortality was 1.63 and 2.04 (HR: 0.80, 95% CI 0.62 to 1.04; P = 0.09). • Stroke rate was 0.35 and 0.64 (HR: 0.55, 95% CI 0.33 to 0.93; P = 0.023) • Absolute reductions in event rates associated with rosuvastatin were 48% greater in older persons compared to younger persons (0.77 versus 0.52 events/100 person-yr, respectively). • NNT for 4 yr to prevent 1 CVE in older patients was 24 (95% CI 15 to 57) compared with 36 (95% CI 23 to 77) in younger patients • The relative rate of SAE among older persons in rosuvastatin versus placebo was 1.05 (95% CI 0.93 to 1.17). <p><u>Safety</u></p> <ul style="list-style-type: none"> • The relative rate of SAE among older persons in rosuvastatin versus placebo was 1.05 (95% CI 0.93, 1.17). Rates of muscle weakness, stiffness, renal disorder, bleeding, GI disorder, hepatic disorder and diabetes were higher in rosuvastatin group but not statistically significant (P > 0.1) for each 	<p>“In apparently healthy older persons without hyperlipidemia but with elevated high-sensitivity CRP levels, rosuvastatin reduces the incidence of major CVE” (pg 488).¹³</p>
Colivicchi ¹⁴ 2010	<ul style="list-style-type: none"> • Within 12 months, a CVE occurred in 16% of atorvastatin (80 mg) recipients and 27% of patients receiving conventional medical treatment (HR 0.56; 95% CI 0.33 to 0.93; P = 0.027). <u>Safety</u> • Atrovastatin was withdrawn in two atorvastatin recipients after persistent muscle pain and rise in total serum CK. One medical management recipient and two people atorvastatin recipients had elevated alanine aminotransferase levels. 	<p>“When compared with conventional treatment, full-dose atrovastatin (80 mg/d) provides greater protection against ischemic recurrences after NSTEMI in patients with severe, diffuse, non-revascularisable CAD” (pg. 1277).¹⁴</p>
Tikkanen ¹⁵	<ul style="list-style-type: none"> • Magnitude of effectiveness of atorvastatin was 	<p>“Except for any CVE in</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
2009	<p>higher in younger versus older patients (MCE HR 0.80, 95% CI 0.66 to 0.98 and HR 0.96, 95% CI 0.80 to 1.15, respectively; CVE HR 0.80, 95% CI 0.71 to 0.89 and HR 0.88, 95% CI 0.79 to 0.99, respectively). Results likely influenced by lower adherence in older patients. Regardless of age, adherence to atorvastatin (89%) was lower than simvastation (95%; P < 0.0001).</p> <p><u>Safety</u></p> <ul style="list-style-type: none"> • SAEs rates were higher in older patients but didn't differ between groups. In the younger group, 40% of atorvastatin recipients and 41% of simvastatin recipients reported SAEs while in the older group, 55% and 56% reported SAE, respectively. • Regardless of age, more patients receiving atorvastatin than simvastatin had dose reductions, or temporary or permanent discontinuations due to AE. In patients >65 years, 11.8% of atorvastatin recipients and 4.1% of simvastatin recipients permanently discontinued therapy due to AE while 7.9% and 4.2% of patients <65 years discontinued, respectively. • Rates of death due to malignancy were similar in younger patients and numerically lowering in the atorvastatin versus simvastatin group in older patients (HR 0.82, 95% CI 0.58 to 1.15). 	<p>the older group, significant reductions in primary and secondary endpoints were observed only in patients <65 yr. The safety of atorvastatin (80 mg) and simvastatin (20-40 mg) was similar in patients <65 and >65 yr with stable coronary disease" (pg. 577).¹⁵</p>
Wenger ¹⁶ 2007	<ul style="list-style-type: none"> • In patients > 65 yr, absolute risk was reduced by 2.3% and RR by 19% for CVE in favor of high-dose atorvastatin (HR 0.81 95% CI, 0.67 to 0.98; P = 0.032). • CHD mortality, MI, and stroke were lower in older patients receiving high-dose atorvastatin though the difference was not statistically significant for individual components. • The NNT for benefit for 80 mg versus 10 mg was 35 to prevent 1 CVE over 4.5 yr. <p><u>Safety</u></p> <ul style="list-style-type: none"> • Improved clinical outcomes in patients >65 yr were not associated with persistent elevations creatinine kinase. 	<p>"Secondary analysis suggests that additional clinical benefit is achieved by treating older patients with CHD more aggressively to reduce LDL cholesterol levels to <100 mg/dL. Finding support intensive LDL cholesterol-lowering in high-risk persons with CHD" (pg. 1).¹⁶</p>
Chaturvedi ¹⁷ 2008	<ul style="list-style-type: none"> • Risk of stroke was reduced by 26% (HR 0.74, 0.57 to 0.96; P = 0.02) in younger patients and by 10% (HR 0.90, 0.73 to 1.11; P = 0.33) in elderly patients. Heterogeneity for treatment-age 	<p>"There was no heterogeneity in the stroke reduction seen with atorvastatin in the</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>interaction was not significant ($P = 0.52$). Risk of stroke or TIA (HR 0.79; $P = 0.01$), MCE (HR 0.68; $P = 0.035$), CHD event (HR 0.61; $P = 0.0006$) and revascularization (HR 0.55; $P = 0.0005$) was reduced in the elderly.</p> <p><u>Safety</u></p> <ul style="list-style-type: none"> Elevated liver enzymes were uncommon in atorvastatin treated groups (1.0% elderly versus 0.8% younger patients). Rate of myopathy was 0.3% in both elderly and younger patients. 	<p>elderly and younger subgroups treated with atorvastatin. The results support the use of atorvastatin in elderly patients with recent stroke or TIA" (pg. 688).¹⁷</p>
Neil ¹⁸ 2006	<ul style="list-style-type: none"> Atorvastatin reduced the RR of MCE by 38% (95% CI -58 to -8; $P = 0.017$) in older patients and 37% (-57 to -7; $P = 0.0019$) in younger patients. Absolute risk reductions were 0.39 and 2.7, respectively (difference 1.2% 95% CI -2.8 to 5.3; $P = 0.545$). The NNT for 4 years to avoid one event were 21 and 33, respectively. All-cause mortality was reduced non-significantly by 22% (95% CI -49 to 18; $P = 0.245$) and 37% (95% CI -64 to 9); $P = 0.98$), respectively. <p><u>Safety</u></p> <ul style="list-style-type: none"> The safety profile was similar between age groups. Treatment associated SAEs occurred in 1.2 % of atorvastatin treated patients and 1.6% of placebo treated patients > 65 yr. Corresponding values for younger patients were 0.9 and 0.8%, respectively. Myalgia was reported in 3.5% of atorvastatin recipients and 4.8% of placebo recipients in the elderly, and 4.3% and 4.7%, respectively in younger patients. 	<p>"Absolute and relative benefits of statin therapy in older patients with type 2 diabetes are substantial, and all patients warrant treatment unless specifically contraindicated" (pg. 2378).¹⁸</p>
<i>Non-Randomized Studies</i>		
Horiuchi ¹⁹ 2004	<ul style="list-style-type: none"> Rates of MCE were 1.30/1000 patient-years in elderly patients and 0.8/1000 patient-years in younger patients. Absolute risk of MCE in older patients was higher than younger patients, while RR increased by 1.7% with elevation of each 1 mg/dL LDL-C level in both groups. Rates of CVE were 2.61/1000 patient-years in older patients and 1.29/1000 patient-years in younger patients ($P < 0.001$). 	<p>"The LDL-C level dependent increase of relative risk of CHD was similar in elderly and younger patients, whereas the absolute risk at any LDL-C level in elderly patients was higher than in younger patients" (pg. 1981).¹⁹</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p><u>Safety</u></p> <ul style="list-style-type: none"> • Drug related AEs were observed in 3.18% of older patients and 3.19% of younger patients; P = 0.99. • Hepatic dysfunction (0.99% in older patients, 1.02% in younger patients, P = 0.79) and musculoskeletal disorders (0.81% and 0.91, P = 0.4, respectively) were most frequently observed. No rhabdomyolysis occurred in either group. • Renal dysfunction was slightly higher in older patients (0.32%) than younger patients (0.14%; P < 0.01). 	
Aronow ²⁰ 2002	<ul style="list-style-type: none"> • Controlling for other risk factors, statins were associated with a 37% significant independent reduction in the incidence of new coronary events and a 47% significant independent reduction in the incidence of new stroke. 	<p>“Statin use is associated with a 37% significant, independent, reduction in new coronary events and a 47% significant, independent reduction in new stroke in older men and women with diabetes, prior MI and serum LDL >125 mg/dL. Elderly diabetics with prior MI and increased serum LDL cholesterol should be treated with statins” (pg. 749).²⁰</p>
Safety and Harms of Discontinuing Statin Therapy		
Colivicchi ²¹ 2007	<ul style="list-style-type: none"> • Within 12 months of discharge, 246 (39%) patients discontinued statin therapy; mean time: 49 ± 55 days; 40% atorvastatin versus 37% simvastatin; P = 0.544). • Discontinuation (28%) was due to dyspepsia, fatigue, headache, myalgias, rise in liver enzymes, or kinase and unaccounted in 71%. • Patients discontinuing statins were significantly older (71.4 ± 7.1 versus 69.5 ± 7.7 yr, P = 0.002); typically female 138/246 versus 171/386, P = 0.004). • Patients were less likely to discontinue if they had diabetes (66/246 versus 162/386, P = 0.001) or prior stroke (22/246 versus 56/385, P = 0.038) • During follow-up, 116 patients died (1 yr probability of death 0.18; 95% CI, 0.15 to 0.21). Patients were more likely to die during follow-up if 	<p>“A large number of patients discontinue their use of statins early after acute stroke. Moreover, patients discontinuing statins have a significantly increased mortality during the first year after the acute CVE. These findings suggest patient care should be improved during transition from hospital to outpatient setting” (pg. 2652).²¹</p>

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	they were older (74 ± 5.0 versus 69.4 ± 7.8 years, $P = 0.0001$), diabetic (52/116 versus 176/511, $P = 0.03$), with a previous stroke (21/116 versus 57/515, $P = 0.037$).	

CARE: Cholesterol and Recurrent Events; CHD: coronary heart disease; CI: confidence interval; CRP: C-reactive protein; CVE: cerebrovascular event; HPS: Heart Protection Study; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LDL: low-density lipoprotein; LIPID: Long Term Intervention with Pravastatin in Ischemic Disease; MCE: major cardiac event; MI: myocardial infarction; NNT: number needed to treat; PLAC I: Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; QALY: quality adjusted life year; RR: relative risk; SAE: severe adverse events; TIA: transient ischemic attack