Drug Use Research & Management Program
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Month/Year of Review: November 2013 **Date of Last Review:** March 2012
PDL Classes: Statins **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: ATORVASTATIN, SIMVASTATIN, LOVASTATIN, PRAVASTATIN
- Non-Preferred Agents: FLUVASTATIN, FLUVASTATIN XL, ROSUVASTATIN (CRESTOR®), LOVASTATIN ER (ALTOPREV®), PITAVASTATIN (LIVALO®), NIACIN/LOVASTATIN (ADVICOR®), EZETIMIBE/SIMVASTATIN (VYTORIN®), AMLODIPINE/ATORVASTATIN (CADUET®), SITAGLIPTIN/SIMVASTATIN (JUVISYNC®)

Key Questions:

- Is there any new evidence about the comparative effectiveness of different statins, reducing long term cardiovascular or cerebrovascular outcomes?
- Is there any new evidence about comparative harms of different statins in patients being treated for the primary or secondary prevention of cardiovascular disease?
- Are there any subpopulations of patients for which one statin is more effective or associate with less harm?

PA Criteria: The standard non-preferred drugs in select PDL classes prior authorization criteria is in place for statins and combinations to ensure that non-preferred drugs are used for an above the line condition.

Conclusions:

- 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%, major coronary events by 32-37%, and all-cause mortality by 22% in patients over 65 years of age. [1]
- There is more evidence supporting the use of statins for the primary prevention of cardiovascular disease (CVD) with a demonstrated reduction in all-cause mortality (R 0.86, 95% CI 0.79-0.94, NNT 96), fatal CVD events (RR 0.83, 95% CI 0.72-0.96), and fatal coronary heart disease (RR 0.82, 95% CI 0.70-0.96).[2]
- There is moderate quality evidence of an increased risk of developing diabetes mellitus (RR 1.18, 95% CI 1.01-1.39)[2] with statin therapy compared to placebo, with different types and doses of statins having different potentials to increase the incidence of diabetes mellitus.[3]
- There is evidence that statin therapy is not associated with an increased risk of cancer (RR 1.16, 95% CI 0.87-1.54). [2]

Recommendations:

- There is insufficient comparative evidence on long term clinical outcomes or evidence that one agent is safer than another.
- Evaluate comparative costs in executive session.

Previous Conclusions and Recommendation:

- Reductions in cardiovascular (CV) and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. Evidence supports the ability of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin to improve coronary heart disease clinical outcomes.
- There is no comparative effectiveness data that pitvastatin is more effective or safer than other lipid-lowering agents for managing the risk of CV events in patients with hypercholesterolemia. Make it non-preferred.
- Due to safety concerns, simvastatin 80mg should not be initiated in new patients; implement a prospective dose limit.

Background:

Nine statins have been approved by the FDA since 1987.[4] Reducing high cholesterol is a primary way to reduce the risk of cardiovascular events.[2] There is strong evidence supporting the use of statins for the secondary prevention of cardiovascular events in patients with dyslipidemia. Statins have also been shown to reduce the risk of a first event in individuals at high risk of cardiovascular disease (primary prevention) but selecting appropriate patients for primary prevention is not clearly defined and the potential for harm has also been evaluated.[2] Reductions in cardiovascular and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available medications. There is limited evidence of comparative effectiveness and relative safety among the different statin medications. Head to head studies have shown that a higher dose of a more potent statin reduces lipid levels more than a lower dose of a less potent statin. However, differences in clinical outcomes such as deaths or major coronary events have not been consistently demonstrated between the statins. All statins have also been shown to be generally safe. Simvastatin has shown to have a greater myopathy risk at very high doses. [4]

Methods:

A Medline OVID search for randomized controlled trials (RCTs) was conducted using terms for included drugs. The search was limited to English language articles of controlled trials conducted on humans published from 2012 to October week one 2013. The Cochrane Collection, Agency for Health Care Research and Quality (AHRQ), National Institute for Clinical Evidence (NICE), Canadian Agency for Drugs and Technology in Health (CADTH), Dynamed and Medline OVID were searched for high quality systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.[5,6] The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

Agency for Healthcare Research and Quality:

At the time of this review, a draft AHRQ review comparing the benefits and harms of combination of statin and other lipid-modifying medication to intensification of statin monotherapy was available, including studies through January 2013.[7] Studies in adults with moderate or high cardiovascular disease (CVD) risk were included. Fifty-eight RCTs were included in the analysis. The strength of evidence was overall variable across comparisons. Only one comparison had high strength of evidence for serious adverse events and nine comparisons had moderate strength of evidence for LDL and HDL outcomes. All other comparisons and outcomes had low or insufficient evidence, including clinical outcomes of mortality, acute coronary events, and revascularization procedures. Other conclusions related to LDL and HDL outcomes are defined below:

Bile acid sequestrants plus statin therapy

- There is moderate quality evidence that combination therapy with bile acid sequestrants and low potency statin therapy lowers LDL cholesterol up to 14% more compared to intensification of statin monotherapy.
- There was insufficient evidence to compare combined bile acid sequestrant and statin therapy with statin monotherapy on the rates of serious adverse events.

Ezetimibe plus statin therapy

- There is moderate quality evidence that combination therapy with ezetimibe in combination with mid potency statin improves LDL-c compared to high potency statin monotherapy and low quality evidence that it improves HDL-c compared with statin monotherapy.
- There is high quality evidence that high potency statin m monotherapy produces fewer serious adverse events than combination of mid potency statin with ezetimibe.
- In patients with preexisting coronary heart disease and in patients with diabetes, there is moderate quality evidence that ezetimibe in combination with mid potency statin more effectively lowers LDL and low quality evidence for raising HDL as compared to high potency statin monotherapy.

Fibrate plus statin therapy

- There is moderate quality evidence that high potency statin monotherapy lowers LDL up to 15% more than mid potency statin in combination with fibrate.
- Moderate quality evidence demonstrates that mid potency statin in combination with fibrate raises HDL up to 10% more than high potency statin monotherapy.
- There is insufficient evidence to compare fibrate plus statin combination therapy to statin monotherapy on the rates of serious adverse events.

Niacin plus statin therapy

- There is low quality evidence that high potency statin monotherapy lowers LDL up to 12% more than mid potency statin in combination with niacin.
- There is low quality evidence that mid potency statin in combination with niacin raises HDL more than high potency statin monotherapy.
- There is insufficient evidence to compare the combination of niacin and statin to statin monotherapy on the rates of serious adverse events.

Omega-3 Fatty Acid plus statin therapy

- There is insufficient evidence to compare the benefits or serious adverse events of combined lipid-modifying therapy with an omega-3 fatty acid and statin to statin monotherapy on LDL-c and HDL-c, regardless of statin potency.

The authors concluded that the evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL levels, including bile acid sequestrants and ezetimibe. However, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL lowering in comparison to combination therapy with fibrates or niacin. There is insufficient evidence to address whether LDL lowering benefits achieved with these medications leads to decreased rates of CV disease. The evidence suggests that providers should tailor therapy based on individual patient needs and concerns for adverse events.

Author: M. Herink, Pharm.D. Date: September 2013

Canadian Agency for Drugs and Technologies in Health (CADTH)

In 2012, CADTH produced a rapid response evaluating the clinical evidence, safety and guidelines of lipid lowering agents for stroke prevention in elderly patients.[1] A literature search was done to identify evidence in geriatric patients on clinical outcomes of mortality, CV outcomes, NNT to prevent on stroke, and adverse events. Overall, two systematic reviews, two meta-analyses, six RCTs, and three non-randomized studies were reviewed. Main conclusions are as followed:

- Evidence suggests statins reduce the risk of all-cause mortality by 22% stroke by 25-47% in patients ≥ 65 years.
- Rosuvastatin reduces the incidence of major coronary events in healthy older persons without hyperlipidemia but with elevated high-sensisitivity CRP levels.
- Evidence suggests atorvastatin reduces the risk of cerebrovascular events and major coronary events (NNT 21 over 4 years).
- Simvastatin therapy in older patients was as safe and effective as younger patients.
- There was no significant difference between rosuvastatin and placebo in serious adverse events among elderly (RR 1.05, 95% CI 0.93 to 1.17).
- The safety profile of atorvastatin was similar between young and older recipients.
- Simvastatin related adverse events were similar between older and younger patients. Renal dysfunction was slightly higher in older patients than younger patients (0.32% vs. 0.14%, respectively; p<0.01).
- 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).

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%, major coronary events by 32-37%, and all-cause mortality by 22% in patients over 65 years of age. Safety profiles were similar, with the most common being muscle weakness, bleeding events, diabetes, and renal, gastrointestinal or hepatic disorders.

Cochrane Collaboration:

A recent Cochrane review assessed the benefits and harms of statins for the primary prevention of CVD.[2] Randomized controlled trials of at least 12 months in duration were included in the analysis. A total of 27 papers reporting on 14 trials were included in the original report and 56 articles on 4 new trials were included in this update. Overall, the 18 included trials involved 56,934 participants with outcomes observed from 1 to 5.3 years. The mean age of the population was 57 years and 60.3% were male. In general, there was low risk of bias although all trials were either fully or partially funded by pharmaceutical companies. Overall, trials showed reductions in all-cause mortality, composite CVD, fatal and non-fatal CVD events, total and LDL cholesterol, and revascularisations. No significant excess of combined adverse events, cancers, myopathy, rhabdomyolysis, liver enzyme elevation, renal dysfunction were found. A slight increased risk of incident diabetes was found in two trials.

Thirteen trials reported on all-cause mortality and overall 4.4% died in the statin group compared with 5.1% in the placebo group (NNT 96, 95% CI 64-244). Only the JUPITER trial showed strong evidence of a reduction in total mortality. Pooled data using a fixed-effect model favored statin treatment (OR 0.86, 95% CI 0.79-0.94). A risk reduction in fatal coronary heart disease (CHD) (1.1% vs. 1.3%; RR 0.82, 95% CI 0.70-0.96), reduction in risk of fatal CVD events (17.4% vs. 20.8%, RR 0.83, 95% CI 0.72-0.96), and non-fatal CVD events (3% vs. 4%, RR 0.77, 95% CI 0.62-0.96) was observed favoring the statin group compared to placebo. A significant risk reduction was also seen in fatal stroke events (17% vs. 22%, RR 0.78, 95% CI 0.68-0.89) and non-fatal strokes (1.3% vs. 2%, RR .69; 95% CI 0.58-0.83) in the statin group compared to placebo group.

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Twelve trials reported on adverse events. Overall, there was no difference in event rates between the intervention and control groups (RR 1.00, 95% CI 0.97-1.03) and no differences were observed in the number of participants stopping statin treatment due to adverse events. Heterogeneity was observed in these analyses. Two trials reported new occurrences of type 2 diabetes and demonstrated a relative risk of developing diabetes of 1.18 (95% CI 1.01-1.39). This was driven by the JUPITER trial. There was no evidence of any excess risk of cancer and weak evidence for an increased risk of liver enzyme elevation (RR 1.16, 95% CI 0.87-1.54). There was insufficient data to evaluate patient quality of life. There was limited evidence suggesting that the use of statins for primary prevention is cost-effective.

The authors concluded that the evidence now supports the benefits of statins for primary prevention and further cost-effectiveness analyses are needed to guide the widespread use in these low risk populations.

Navarese et al.

With recent reports indicating that statins are associated with an increased risk for new-onset diabetes mellitus compared with placebo, this recent systematic review evaluated the impact of different types and doses of statins on new-onset diabetes.[3] A literature search was conducted through October 2012 and internal validity of the RCTs was assessed by 2 independent reviewers. Seventeen studies were included in the network meta-analysis. Nine studies evaluated new-onset DM in patients treated with high-dose statins compared with placebo. There were a total of 4,610 cases of new-onset DM (7.28%) in the high-dose statin group and 7.09% in the control group. Treatment with rosuvastatin 20mg/day was associated with a 25% relative increase in the risk for developing DM compared to placebo (OR 1.25, 95% CI 0.82-1.90). Therapy with pravastatin 40 mg/day was associated with the lowest risk (OR 1.07, 95% CI 0.86-1.30).

In patients treated with moderate-dose statins, 81.8% compared with 7.95% in the control group developed new-onset DM. Moderate dose rosuvastatin therapy still created the highest risk (RR 1.11, 95% CI 0.81-1.52) and pravastatin 10 mg/day was associated with a numerically lower risk of DM compared with placebo (RR 0.90, 95% CI 0.71-1.35). The risk was generally increased with higher dose statin regimens compared to moderate dose regimens and there was a gradient for the risk across different types and doses of statins. Numerically, pravastatin was associated with the lowest risk of new-onset DM and rosuvasatin was associated with the highest incidence of DM.

Naci et al.

A meta-analysis was done to determine the comparative effects of individual statins on major cerebrovascular events.[8] A medline search was done to identify literature between 1985 and 2011. Both open-label and double-blind RCTs comparing one statin to another in adults with cardiovascular disease were included. The primary outcome was major cerebrovascular events (defined as fatal- and non-fatal strokes and transient ischemic attacks). A total of 61 trials were identified. Overall, statin therapy was associated with a reduction in the risk of major cerebrovascular events (OR 0.82; 95% CI 0.77-0.87) when compared with control. Atorvastatin, pravastatin, and simvastatin were associated with a significant reduction in major cerebrovascular events compared with control, while fluvastatin, lovastatin and rosuvastatin were not.

There were 11 direct head-to-head studies that demonstrated no significant differences among statins in major cerebrovascular events. However, the evidence for some statins was much stronger and consistent compared to the evidence for others. In addition, a quality assessment of trials was not defined in the systematic review and open-label studies were included. Therefore, comparative results need to be interpreted with caution.

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Tolerability and Harms:

A recent meta-analysis was done to evaluate the comparative harms of individual statins.[9] Open-label and double-blind RCTs comparing one statin with another or with control for adults with, or at risk of developing, CV disease were included. A total of 135 trials were included (n=246,955). The overall methodological quality of included trials was moderate, although it was unclear how quality was assessed in this analysis. Results showed that there was no difference in discontinuations because of adverse events between statins as a class and control (OR 0.95, 95% CI 0.83 to 1.08; I^2=21.9%). Simvastatin was significantly more tolerable than atorvastatin (OR 0.61, 95% CI 0.42-0.89; I2=71.9%) and rosuvastatin (OR 0.49; 95% CI 0.27-0.88; I2=0.0%). The network meta-analysis demonstrated that those randomized to pravastatin (OR 1.46, 95% CI 1.10-1.92) and simvastatin (OR 1.34, 95% CI 1.06-1.69) were significantly less likely to stop treatment because of adverse events compared to those randomized to atorvastatin. There was also no overall difference between statins and control in myalgia (OR 1.07; 95% CI 0.89-1.29; I2=22.2%) and those on simvastatin had lower odds of myalagia compared to atorvastatin (OR 0.56, 95% CI 0.42-0.75; I2=0.0%). There was no significant difference in cancer occurrences between statins and control or between individual statins, which a higher incidence of diabetes mellitus with statins compared to control (OR 1.09; 95% CI 1.02-1.16; I2=2.8%). There were no statistically detectable differences between individual statins in terms of diabetes mellitus incidence. The authors concluded that overall, statins as a class are associated with an increased risk of diabetes mellitus and hepatic transaminase elevations, with no statistically significant difference in myalgia, myopathy, rhabomyolysis, and cancer. When compared head-to-head in network meta-analysis, simvastatin and pravastatin are likely to be superior in their safety profile compared to the other agents.

Statin Use in Patients with Chronic Kidney Disease:

A systematic review and meta-analysis was done to evaluate the effects of statins on major clinical outcomes in patients with chronic kidney disease (CKD).[10] A literature search for prospective, RCTs through November 2011 identified 31 included trials (n=48,429). The Jadad scale was used to assess trial quality; 13 trials had a score of 4 and all others had a score of 3 or less. Overall, statin therapy produced a reduction in the risk of CV events (RR 0.77, 95% CI 0.70-0.85, P<0.001) with evidence of heterogeneity in the individual trials. A reduction in CV events was seen when evaluated based on CKD stage, including CKD stage 5 (RR 0.92, 95% CI 0.85-0.99; p=0.031; ARR 2.2%; NNT 46), CKD stage 4 (RR 0.78, 95% CI 0.63-0.96; p=0.017; ARR 2.8%; NNT 36), and CKD stage 3 or stage 2 (RR 0.69, 95% CI 0.63-0.77; p<0.001; ARR 4.2%; NNT 24), with a more pronounced effect in lower CKD stages demonstrating that statin effect was modified by kidney function. There was no significant difference seen in CKD stage 5 – non-dialysis patients (RR 0.82, 95% CI 0.60-1.11), and overall there was a larger benefit in patients not on dialysis (RR 0.70, 95% CI 0.63-0.99) than those on dialysis (RR 0.92, 95% CI 0.85-0.99). Overall, there was no effect of statin therapy on the risk of stroke (RR 0.79, 95% CI 0.56-1.12) with evidence of heterogeneity between trials. Statin therapy also reduced all-cause death (RR 0.92, 95% CI 0.85-0.99) and cardiovascular death (RR 0.91, 95% CI 0.84-0.99). Based on 6 trials, there was no evidence that statins reduced the risk of kidney failure (RR 0.95, 95% CI 0.90-1.01). A subgroup analysis demonstrated that the effect of statin therapy on major CV events was modified by the average baseline kidney function of the subjects in the trials with a progressively smaller relative risk reduction with a lower estimated glomerular filtration rate (GFR). There was no significant difference in the risk of hepatic impairment, muscle pain, increased creatinine kinase level, cancer morbidity, and severe adverse events in the statin-treated groups compared to control. This review combined data from RCTs with data from CKD subgroups which lowers the strength of this review.

A systematic review and meta-analysis by Palmer et al. also evaluated the benefits and harms of statin therapy for adults with CKD.[11] A literature search through February 2012 identified 80 randomized trials comparing the effects of statins with placebo, no treatment, or another statin on mortality and CV outcomes. Two or more authors independently evaluated the trials for quality and evidence was rated using the GRADE method for each outcome.. Many of the included trials reported 1 or more risks of bias. The evidence showed a statistically significantly different treatment effect on mortality according to the stage of CKD (p=0.009). Moderate-to-high quality evidence indicated that stain treatment reduced all-cause mortality (RR 0.81, 95% CI 0.74 to 0.88) and cardiovascular mortality (RR 0.78, 95% CI 0.68 to 0.89) in persons not receiving dialysis but had little or no effect in persons receiving dialysis (RR 0.96, 95% CI 0.88 to 1.04 and RR 0.94, 95%

CI 0.82 to 1.07, respectively). There was low-quality evidence that treatment effects of mortality were uncertain in kidney transplant pateints (RR 1.05, 95% CI 0.84 to 1.31). Strong evidence demonstrated that treatment effects on major CV events were statistically significantly different between the subgroups showing a prevention in major CV events in persons receiving dialysis (RR 0.76, 95% CI 0.73 to 0.80), but little effect in persons receiving dialysis (RR 0.95, 95% CI 0.87 to 1.03). Overall, there was no difference in fatal or nonfatal stroke (RR 0.86, 95% CI 0.62 to 1.20). The authors concluded that the benfits of stain therapy for mortality and CV outcomes differ depending on stage of CKD. Moderate to high quality evidence indicates that statins reduce all-cause and CV mortality and major CV events in persons not receiving dialysis, while having little or no effect in persons receiving dialysis, despite decrease in serum cholesterol levels. There remains insufficient evidence for the use of statins in kidney transplant recipients. This analysis also included data from post hoc analysis of larger trials, which may be less reliable data.

A third systematic review was conducted by Updahyay et al examining the effect of lipid-lowering therapy on clinical outcomes in persons with CKD.[12] A literature search from January 2000 through November 2011 identified 18 RCTs (n=36,528). Lipid lowering agents in addition to statins were included in this review, such as ezetimibe, niacin, colestipol, and cholestyramine. However, 16 of the 18 RCTs evaluated various statins. Overall, there was moderate evidence that lipid lowering therapy was beneficial on all-cause mortality (RR 0.91, 95% CI 0.83 to 0.99; p=0.031), with the upper limit of the 95% CI close to 1.0 and studies having significant heterogeneity. The subgroup of patients with CKD not receiving dialysis was the only subgroup of patients with a statistically significant rate ratio. Trials included participants with different stages of CKD and different baseline risks. The four trials reporting on CV mortality did not show lipid-lowering therapy to be beneficial (RR 0.96, 95% CI 0.87 to 1.06; p=0.41). The authors concluded that the benefit in all-cause mortality was limited to studies in patients with CKD not receiving dialysis and the results were highly heterogeneous. This review also showed that stroke was not prevented by lipid-lowering therapy in patients with CKD.

Guidelines:

In 2012, The Endocrine Society updated the clinical guidelines for the treatment of hypertriglyceridemia.[13] The guidelines recommend that statins not be used as monotherapy for severe or very severe hypertriglyceridemia. However, statins may be useful for the treatment of moderate hypertriglyceridemia when indicated to modify CV risk.

In 2012, the National Heart, Lung, and Blood Institute (NHLBI) expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents was updated.[14] Evidence was graded A-D based on the study design (A from RCTs, D from expert opinion). Statements were given a definition and included: Strong Recommendation, Recommendation, Optional, and No Recommendation. Statins are generally recommended in children ages 11-21 years with elevated LDL-C levels but not specific recommendations are given preferring one statin over another. Although some of the recommendations were based on Grade A evidence, the majority of the evidence is based on efficacy trials evaluating changes in lipid profiles and vascular markers. There is very limited evidence based on reducing the rate of cardiovascular disease events.

New drugs:

None

New Formulations/Indications:

FDA approved a new fixed dose combination product of atorvastatin and ezetimibe (Liptruzet®) in May 2013 for the treatment of hyperlipidemia.

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Approval was based on two unpublished RCTs demonstrating that atorvastatin/ezetimibe was equivalent in terms of LDL-C reduction compared to the co-administration of ezetimibe 10mg with atorvastatin 20mg and 40mg.[15] Both studies were similar in design; one evaluated the combination with atorvastatin 20mg, the other with atorvastatin 40mg. Subjects included adults with primary hypercholesterolemia at low, moderate, or moderately high CV risk. The primary objective of the studies was LDL-C lowering efficacy. A total of 406 and 328 subjects were included in each study. The population was mostly Caucasian, 60% female, mean age of 55, and average BMI of 30 kg/m2. The mean baseline LDL-C was 162 mg/dl. The 95% confidence intervals for the changes in LDL-C were within the predefined ± 4%, and therefore the combination tablets were considered pharmacodynamically equivalent to the co-administered tablets.

New FDA safety alerts:
None

New Trials:

The initial literature search resulted in 313 citations. After reviewing abstracts, a total of 8 potentially relevant RCTs were identified and are briefly described in Table 1. Two of these trials were evaluating long term clinical outcomes[16], [17] and the others are head to head trials evaluating lipid lowering outcomes. The abstracts of these trials are included in Appendix 1.

Table 1: Description of Relevant Randomized Controlled Trials

Study	Comparison	Population	Primary Outcome	Results
Mulders et al.[16] RCT, DB, PC	Atorvastatin 20mg vs. placebo	Positive family history for CAD and coronary calcium scoring above the 80th percentile	Cardiovascular events	Cardiovascular Event Ator: 7.2% Pla: 12.5% HR 0.55, 95% CI 0.31-0.97; p=0.04, NNT 19 Cardiovascular Event w/o family history: Ator: 6.6% Pla: 6.8% HR 1.04, 95% CI 0.51-2.13; p=0.912
Ridker et al.[17] Secondary analysis of JUPITER	Rosuvastatin 20 mg vs. placebo	Stratified on the basis of having none or at least one of four major risk factors for developing diabetes	MI, stroke, admission to hospital for unstable angina, arterial revascularization, or CV death	Those with one or more major diabetes risk factor were at higher risk of developing diabetes than those without.
Backes et al.[18]	Rosuvastatin 80mg once	Adults with dyslipidemia	Lipid Changes	Changes in HDL, triglycerides,

RCT, DB	weekly vs. atorvastatin 10 mg daily (n=20)			and CRP were nosignificant and similar between groups.
Hing Ling et al.[19] RCT, DB	Switching to Ezetimibe/simvastatin 10/40 mg vs. atorvastatin 40 mg (doubling dose) (n=250)	Adults at high CV risk with uncontrolled hypercholesterolemia already on atorvastatin 20 mg or its equivalent	Percent change from baseline in LDL-C	<u>Change in LDL-C at 6 weeks:</u> Ezet/Sim: -26.8% Ator 40: -11.8% Treatment Difference = -15.0%, 95% CI -21.15, -8.84% P<0.001
Lee et al.[20] RCT, open-label	Atorvastatin 20mg/day vs. rosuvastatin 10mg/day (n=350)	Statin-naïve auldts with clinically indicated percutaneous coronary intervention	Percent change in total theroma volume (TAV)	<u>Percentage change in TAV:</u> Ator: -3.9% Rosu: -7.4% p=0.018 Usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naïve patients, with a greater decrease in favor of rosuvastatin
Lee et al.[21] RCT, open=label	Atorvastatin 20 mg vs. atorvastatin/ezetimibe 5 mg/5 mg (n=78)	Adults with combined hyperlipidemia	Percentage changes in levels of fasting and postprandial TG from baseline to week 8	<u>Change in fasting TG</u> Ator/ez: -30% Ator: -18% P=0.07 <u>Change in postprandial TG</u> Ator/ez: -34% Ator: -13% P=0.03
Pitt et al.[22] Open-label	Rosuvastatin 20 mg vs. rosuvastatin 40 mg vs. atorvastatin 80 mg (n=825)	Adults with acute coronary syndrome	LDL lowering over 6 to 12 weeks	<u>LDL lowering</u> Ros 40: 46.8% Ator 80: 42.7% P=0.02 Ros 20mg was similar to ator 80mg.

Stender et al.[23] RCT, DB, non-inferiority	Pitavastatin (1, 2, and 4 mg) vs. pravastatin (10, 20, and 40 mg) (n=942)	Elderly patients (> or = 65 years) with primary hypercholesterolemia or mixed dyslipidemia	Mean percentage LDL-C reduction at 12 weeks	<u>Mean decrease in LDL:</u> Pitavastatin: 31.4%-44.3% Pravasatin: 22.4-34.0% P<0.001 for all dose comparisons

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Appendix 1: Randomized Controlled Trial Abstracts

- *Mulders, T. A., S. Sivapalaratnam, et al. (2012). "Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis Heart Study." Jacc: Cardiovascular Imaging 5(3): 252-260.*

OBJECTIVES: The goal of this study was to evaluate whether individuals with a positive family history for premature coronary artery disease (CAD) and coronary calcium scoring (CCS) above the 80th percentile might benefit from preventive treatment.
BACKGROUND: First-degree relatives of patients with premature CAD have an increased risk for cardiovascular disease (CVD), whereas events are poorly predicted in these individuals. Surrogate markers, such as CCS, might refine risk scoring. Nevertheless, the outcome of the St. Francis Heart trial, which investigated the effect of atorvastatin 20 mg/day in asymptomatic individuals with CCS above the 80th percentile, did not reach statistical significance.
METHODS: We performed a post hoc analysis on the database of the St. Francis trial to assess efficacy of treatment with atorvastatin 20 mg/day in those with CCS above the 80th percentile and presence (n = 543) or absence (n = 462) of a positive family history for premature CAD. All participants received aspirin 81 mg/day. Primary outcome included coronary death, myocardial infarction, coronary revascularization, stroke, and arterial surgery.
RESULTS: A total of 1,005 individuals, with a mean age of 59.0 +/- 5.9 years and a median absolute CCS of 370 Agatston units (interquartile range: 183 to 662) participated in the trial. After a follow-up of 4.3 (interquartile range: 3.5 to 4.5) years, 7.2% of the treated individuals with a positive family history had a cardiovascular event versus 12.5% of the placebo group (hazard ratio [HR]: 0.55; 95% confidence intervals [CI]: 0.31 to 0.97; p = 0.040). This is comparable with a number needed to treat of 18.9. In individuals without a family history, events were minimally reduced: 6.6% in the treated versus 6.8% in the placebo group (HR: 1.04; 95% CI: 0.51 to 2.13; p = 0.912).
CONCLUSIONS: The combination of a positive family history and CCS above the 80th percentile identifies a subgroup within the primary prevention population that receives greater benefit from statin treatment than the population at large. These results have important implications for future guidelines concerning individuals with a positive family history for premature CAD. Copyright 2012 American College of Cardiology Foundation.

- *Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012 Aug 11;380(9841):565-71. doi: 10.1016/S0140-6736(12)61190-8.*

BACKGROUND:
In view of evidence that statin therapy increases risk of diabetes, the balance of benefit and risk of these drugs in primary prevention has become controversial. We undertook an analysis of participants from the JUPITER trial to address the balance of vascular benefits and diabetes hazard of statin use.
METHODS:

In the randomised, double-blind JUPITER trial, 17,603 men and women without previous cardiovascular disease or diabetes were randomly assigned to rosuvastatin 20 mg or placebo and followed up for up to 5 years for the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death) and the protocol-prespecified secondary endpoints of venous thromboembolism, all-cause mortality, and incident physician-reported diabetes. In this analysis, participants were stratified on the basis of having none or at least one of four major risk

factors for developing diabetes: metabolic syndrome, impaired fasting glucose, body-mass index 30 kg/m(2) or higher, or glycated haemoglobin A(1c) greater than 6%. The trial is registered at ClinicalTrials.gov, NCT00239681.
FINDINGS:
Trial participants with one or more major diabetes risk factor (n=11,508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47-0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39-1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64-1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07-1·54, p=0·01). Thus, for those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33-0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21-1·03, p=0·05), a 22% reduction in total mortality (0·78, 0·59-1·03, p=0·08), and no increase in diabetes (0·99, 0·45-2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin vs 216 on placebo; HR 1·25, 95% CI 1·05-1·49, p=0·01), the point estimate of cardiovascular risk reduction associated with statin therapy (HR 0·63, 95% CI 0·25-1·60) was consistent with that for the trial as a whole (0·56, 0·46-0·69). By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin vs 89·7 [50·4] weeks on placebo).
INTERPRETATION:
In the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes.

- *Backes, J. M., C. A. Gibson, et al. (2012). "The high-dose rosuvastatin once weekly study (the HD-ROWS)." Journal of Clinical Lipidology 6(4): 362-367.*

BACKGROUND: Alternative dosing is often used clinically to address common barriers with statin therapy, such as intolerance and cost. Previous findings have demonstrated significant and clinically similar reductions in low-density lipoprotein (LDL) cholesterol to daily dosing, when comparing similar total weekly doses.
OBJECTIVE: To determine whether rosuvastatin 80 mg once weekly produced comparable lipid and high-sensitivity C-reactive protein (hsCRP) changes to atorvastatin 10 mg daily, when measured at key points after last dose.
METHODS: This was a randomized, double-blind, parallel group, 8-week pilot study. Eligible subjects, 18 to 65 years of age, had documented dyslipidemia with LDL cholesterol >100 mg/dL and triglycerides <200 mg/dL. Participants were randomized to receive either rosuvastatin 80 mg once weekly (n= 10) or atorvastatin 10 mg daily (n= 10), for 8 weeks. Lipid panels and hsCRP were measured at baseline and 1-4 and 5-8 days after the last dose.
RESULTS: Participants in each arm experienced significant and comparable reductions from baseline in total cholesterol, total cholesterol/high-density lipoprotein cholesterol ratio, non-high-density lipoprotein cholesterol, and overall LDL cholesterol (-29%). Changes in high-density lipoprotein cholesterol, triglycerides, and hsCRP were nonsignificant and similar between groups. Each regimen was well tolerated, with no major adverse events reported.
CONCLUSION: Rosuvastatin 80 mg once weekly produced comparable lipid changes to atorvastatin 10 mg daily when measured at specific points after the last dose. Our findings support previous data demonstrating a significant reduction in LDL-C with once weekly statin dosing.

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- *Hing Ling, P. K., F. Civeira, et al. (2012). "Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study." Lipids in Health & Disease 11: 18.*

BACKGROUND: A considerable number of patients with severely elevated LDL-C do not achieve recommended treatment targets, despite treatment with statins. Adults at high cardiovascular risk with hypercholesterolemia and LDL-C >= 2.59 and <= 4.14 mmol/L (N = 250), pretreated with atorvastatin 20 mg were randomized to ezetimibe/simvastatin 10/40 mg or atorvastatin 40 mg for 6 weeks. The percent change in LDL-C and other lipids was assessed using a constrained longitudinal data analysis method with terms for treatment, time, time-by-treatment interaction, stratum, and time-by-stratum interaction. Percentage of subjects achieving LDL-C < 1.81 mmol/L, < 2.00 mmol/L, or < 2.59 mmol/L was assessed using a logistic regression model with terms for treatment and stratum. Tolerability was assessed.
RESULTS: Switching to ezetimibe/simvastatin resulted in significantly greater changes in LDL-C (-26.81% vs.-11.81%), total cholesterol (-15.97% vs.-7.73%), non-HDL-C (-22.50% vs.-10.88%), Apo B (-17.23% vs.-9.53%), and Apo A-I (2.56%vs.-2.69%) vs. doubling the atorvastatin dose (all p <= 0.002), but not HDL-C, triglycerides, or hs-CRP. Significantly more subjects achieved LDL-C < 1.81 mmol/L (29% vs. 5%), < 2.00 mmol/L (38% vs. 9%) or < 2.59 mmol/L (69% vs. 41%) after switching to ezetimibe/simvastatin vs. doubling the atorvastatin dose (all p < 0.001). The overall safety profile appeared generally comparable between treatment groups.
CONCLUSIONS: In high cardiovascular risk subjects with hypercholesterolemia already treated with atorvastatin 20 mg but not at LDL-C < 2.59 mmol/L, switching to combination ezetimibe/simvastatin 10/40 mg provided significantly greater LDL-C lowering and greater achievement of LDL-C targets compared with doubling the atorvastatin dose to 40 mg. Both treatments were generally well-tolerated.

- *Lee, C. W., S.-J. Kang, et al. (2012). "Comparison of effects of atorvastatin (20 mg) versus rosuvastatin (10 mg) therapy on mild coronary atherosclerotic plaques (from the ARTMAP trial)." American Journal of Cardiology 109(12): 1700-1704.*

High-dose rosuvastatin induces regression of coronary atherosclerosis, but it remains uncertain whether usual-dose statin has similar effects. We compared the effects of atorvastatin 20 mg/day versus rosuvastatin 10 mg/day on mild coronary atherosclerotic plaques (20% to 50% luminal narrowing and lesion length >10 mm) using intravascular ultrasound (IVUS). Three hundred fifty statin-naive patients with mild coronary atherosclerotic plaques were randomized to receive atorvastatin 20 mg/day or rosuvastatin 10 mg/day. IVUS examinations were performed at baseline and 6-month follow-up. Primary end point was percent change in total atheroma volume (TAV) defined as (TAV at 6 months - TAV at baseline)/(TAV at baseline) x 100. Evaluable IVUS was obtained for 271 patients (atorvastatin in 143, rosuvastatin in 128). Clinical characteristics, lipid levels, and IVUS measurements at baseline were similar between the 2 groups. At 6-month follow-up, percent change in TAV was significantly less in the atorvastatin group than in the rosuvastatin group (-3.9 +/- 11.9% vs -7.4 +/- 10.6%, respectively, p = 0.018). In contrast, change in percent atheroma volume was not different between the 2 groups (-0.3 +/- 4.2 vs -1.1 +/- 3.5, respectively, p = 0.157). Compared to baseline, TAV and TAV at the most diseased 10-mm subsegment were significantly decreased in the 2 groups (p <0.001). Changes in lipid profiles at 6-month follow-up were similar between the 2 groups. In conclusion, usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naive patients, with a greater decrease in favor of rosuvastatin.

- *Lee, S.-H., S. Park, et al. (2012). "Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia." Journal of Cardiovascular Pharmacology & Therapeutics 17(1): 65-71.*

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Postprandial triglyceride (TG) levels are easy to measure and are associated with future cardiovascular risk. The aim of this study was to compare the effects of statin monotherapy and low-dose statin/ezetimibe on lipid parameters including fasting and postprandial TG. After a 4-week dietary run-in period, 78 patients with combined hyperlipidemia were randomized into 1 of 2 treatment groups for 8 weeks: atorvastatin 20 mg or atorvastatin/ezetimibe 5 mg/5 mg. An oral fat load test was performed before and after the drug-treatment period. The low-dose combination had a tendency to decrease fasting TG more than atorvastatin monotherapy. The combination regimen showed a greater reduction in postprandial TG (-13% +/- 42% and -34% +/- 30%, in the atorvastatin and combination groups, respectively, P = .03) and total cholesterol (TC; P = .03). The changes in low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) were not different between the 2 groups. The reduction in apo B/A1 was greater in the combination group (-32% +/- 19% and -42% +/- 13%, in the atorvastatin and combination groups, respectively, P = .02). In conclusion, these results demonstrated a potential beneficial effect of low-dose atorvastatin/ezetimibe combination treatment on postprandial TG control after comparable LDL-C lowering in patients with combined hyperlipidemia.

- *Pitt, B., J. Loscalzo, et al. (2012). "Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study)." American Journal of Cardiology 109(9): 1239-1246.*

Patients with acute coronary syndrome are recommended for early aggressive low-density lipoprotein (LDL) cholesterol-lowering therapy. The LUNAR study compared the efficacy of rosuvastatin with that of atorvastatin in decreasing LDL cholesterol in patients with acute coronary syndrome. Adult patients with coronary artery disease who were hospitalized for an acute coronary syndrome within 48 hours of first symptoms were randomized (n = 825) to an open-label, once-daily treatment with rosuvastatin 20 mg (RSV20), rosuvastatin 40 mg (RSV40), or atorvastatin 80 mg (ATV80) for 12 weeks. Patients were evaluated at weeks 2, 6, and 12. The primary end point was treatment efficacy in lowering LDL cholesterol averaged over 6 to 12 weeks. Changes in other lipoproteins, including high-density lipoprotein (HDL) cholesterol, and safety were evaluated. Analysis of covariance was used to compare least squares mean differences between each rosuvastatin treatment arm and the atorvastatin arm. The efficacy of RSV40 in lowering LDL cholesterol was significantly greater than that of ATV80 (46.8% vs 42.7% decrease, p = 0.02). LDL cholesterol lowering by RSV20 was similar to that by ATV80. Increases in HDL cholesterol were significantly greater with RSV40 (11.9%, p <0.001) and RSV20 (9.7%, p <0.01) than with ATV80 (5.6%). RSV40 was also significantly more effective than ATV80 in improving most other secondary efficacy variables, whereas the effects of RSV20 on these parameters were generally similar to those of ATV80. All 3 treatments were generally well tolerated over 12 weeks. In conclusion, results from the LUNAR study show that RSV40 more effectively decreased LDL cholesterol, increased HDL cholesterol, and improved other blood lipid parameters than ATV80 in patients with acute coronary syndrome.

12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia." European Journal of Preventive Cardiology 20(1): 40-53.
AIM: To compare the safety and efficacy of once-daily pitavastatin (1, 2, and 4 mg) and pravastatin (10, 20, and 40 mg) in elderly patients (>= 65 years of age) with primary hypercholesterolaemia or combined (mixed) dyslipidaemia.
DESIGN: After a 6-8-week washout/dietary period, patients were randomized to six treatment groups (1, 2, or 4 mg pitavastatin vs. 10, 20, or 40 mg pravastatin) in a 12-week multicentre double-blind study. Patients (n = 942; men, 44.3%; Caucasian, 99.3%; mean age, 70 years; age range, 65-89 years) in all groups were well matched for duration of disease and diagnosis.
RESULTS: Mean decreases in low-density lipoprotein cholesterol over 12 weeks were 31.4- 44.3% with pitavastatin 1-4 mg and 22.4-34.0% with pravastatin 10-40 mg (p < 0.001 for all dose comparisons). Compared with pravastatin, pitavastatin provided greater decreases in total cholesterol and apolipoprotein B in all dose groups (p < 0.001) and triglycerides in the low-dose (p = 0.001) and higher-dose (p = 0.016) groups, and greater increases in

high-density lipoprotein cholesterol in the intermediate-dose ($p = 0.013$) and higher-dose ($p = 0.023$) groups. The proportions of patients achieving the European Atherosclerosis Society target with pitavastatin and pravastatin, respectively, were: low doses, 59.9 and 37.9%; intermediate doses, 79.5 and 51.0%; higher doses, 88.1 and 65.7% ($p < 0.001$ for all comparisons). Both statins were well tolerated, with no reports of myopathy or rhabdomyolysis. CONCLUSION: Pitavastatin provides superior efficacy and comparable tolerability to pravastatin in elderly patients.

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