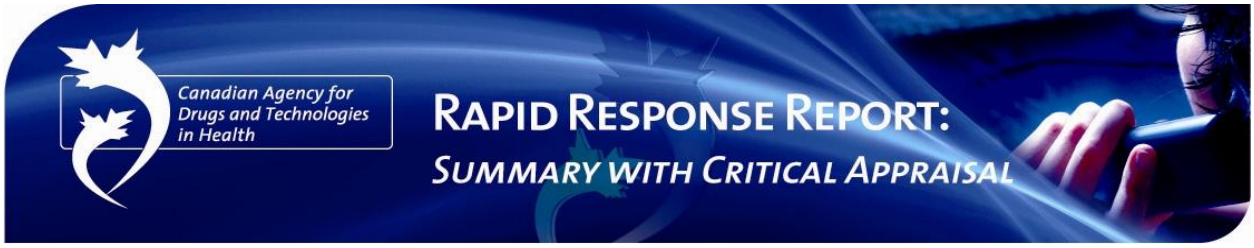

TITLE: Comparative Effectiveness of Rosuvastatin Versus Other Statins: A Review of Clinical Effectiveness

DATE: 15 February 2011

CONTEXT AND POLICY ISSUES

Statins work by inhibiting HMG-CoA reductase, the rate limiting step in the endogenous cholesterol production pathway and are the most potent low-density lipoprotein (LDL) cholesterol lowering agents.[1] Treatment with statins has demonstrated significant reductions in cardiovascular disease morbidity, cardiovascular disease mortality and total mortality in both primary and secondary prevention.[2,3] There are six statins currently available in Canada, including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin.[1]

Statins are one of the top prescribed cardiovascular drugs, accounting for the highest proportion of Canadian drug program spending on seniors.[4] In May 2010, generic atorvastatin was approved by Health Canada making it the fifth statin to be genericized.[5] Currently, rosuvastatin is only available as the brand name product Crestor®.[6] Generic atorvastatin is priced considerably lower than Pfizer's brand name product Lipitor®, [7] offering millions of dollars in savings to Provincial drug programs. Despite the significantly lower prices of generic statins, there is has been increased prescribing of higher priced rosuvastatin.

This report will review the evidence on the comparative effectiveness and safety of rosuvastatin versus other statins. This will help determine if rosuvastatin has advantages over other available statins to justify its price premium compared to other agents.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of rosuvastatin versus other statins?

2. What is the comparative safety of rosuvastatin versus other statins?

KEY MESSAGE

Evidence suggests that rosuvastatin has the most potent per milligram LDL lowering effect but with appropriate dosage adjustments different statins can provide equivalent LDL reductions. Data suggests similar effects on HDL, TG and CRP with rosuvastatin compared with other statins. Based on the identified literature, there is no significant difference in rates of adverse events between rosuvastatin and other statins.

METHODS

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2011), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2001 and January 17, 2011. Filters were applied to limit the retrieval type by systematic reviews, health technology assessments, meta-analyses, randomized controlled trials and non-randomized studies with safety only.

SUMMARY OF FINDINGS

The literature search identified nine relevant systematic reviews and meta-analyses; five comparing the effects of different statins on lipid parameters,[8-12] one examining the impact of statins in heart failure,[13] and three evaluating the effects of statins on insulin sensitivity and incidence of diabetes.[14-16] Forty-four relevant randomized controlled trials (RCTs) were identified, 36 of which were either included in the above meta-analyses or were post-hoc analyses of previously published RCTs. The remaining eight RCTs are reviewed in this report.[17-24] Three non-randomized studies evaluating the safety of statins were identified.[25-27] No relevant health technology assessment reports were identified. Additional articles of interest are found in the appendix.

Systematic reviews and meta-analyses

Effects of Statins on Lipid Parameters

The characteristics of the five meta-analyses evaluating the effects of different statins on lipid parameters are summarized in Table 1. All five meta-analyses included only RCTs. The number of trials included ranged from 37 to 164. The patient populations in all of the meta-analyses were heterogeneous including both primary and secondary prevention patients. Three meta-analyses analyzed data on five or more different statins.[8,10,12] The remaining two limited their included studies to those that compared rosuvastatin with atorvastatin or simvastatin.[9,11] All five meta-analyses reported on low density lipoprotein (LDL) lowering.

Table 1: Characteristics of systematic reviews and meta-analyses comparing effects of different statins on lipid parameters

Systematic Reviews and Meta-Analysis	Objectives	Search Strategy	Study Criteria	Studies Selected
Weng et al. (2010)[8]	"To compare the efficacy and safety profiles of different statins at different doses and determine the therapeutically equivalent doses of statins to achieve a specific level of LDL lowering"p.139	Trials published between 1996 and 2006 plus search from Jan 2005 to Apr 2006 of PubMed, Medline and EMBASE and Cochrane Controlled Trials Registry (first quarter of 2006)	English and Chinese RCTs conducted in patients age ≥18 using statin monotherapy for hyperlipidemia Only studies involving head-to-head comparisons between different statins, with a minimum duration of 4 weeks, were eligible	75 RCTs representing 140 paired statin comparisons (18 RCTs comparing rosuvastatin with another statin) 68% of studies met ≥3/4 quality criteria including: randomization, concealment, study blinding and similar attrition rates between groups
Wlodarczyk et al. (2008)[9]	To determine if rosuvastatin provides additional LDL lowering compared to atorvastatin without increased risk of short-term adverse events	Medline, EMBASE and Cochrane Clinical Trials Register was searched up till April 2005 (starting date not clear) Obtained unpublished RCTs data from AstraZeneca	RCTs comparing rosuvastatin versus atorvastatin No language restrictions	25 RCTs (n=19,621) resulting in: • 28 comparisons of 1:1 dose ratios • 20 comparisons of 1:2 dose ratios • 6 comparisons of 1:4 dose ratios of rosuvastatin vs. atorvastatin 10 of 25 trials were double blinded Mean study follow-up: 8.6 weeks
Law et al. (2003)[10]	To determine effects of statin drug, dose and duration on LDL lowering (Other study objectives not relevant)	Search of Medline, Cochrane Collaboration and Web of Science database (1982 to 2001) Unpublished data obtained from pharmaceutical companies	RCT, DB, fixed dose, placebo controlled trials	164 DB, RCTs (n=38,000) of different statins Mostly healthy patients aged 34 to 76 with median LDL 4.7mmol/L Median duration: 8 weeks

Systematic Reviews and Meta-Analysis	Objectives	Search Strategy	Study Criteria	Studies Selected
Nicholls et al. (2010)[11]	"To determine the relation between increasing dose of each individual statin and their incremental ability to lower levels of atherogenic lipid parameters and achieve established treatment goals" p.69	Cochrane Controlled Trials Registry, Medline & EMBASE (1999-2007), Citeline Trialtrove and collection of all published research on rosuvastatin	Fixed dose trials of rosuvastatin vs. atorvastatin or simvastatin with a minimum duration of 4 weeks Excluded observational or pharmacokinetic studies	37 RCTs (n=32,258) comparing rosuvastatin with either atorvastatin or simvastatin 13 of 37 trials were double blinded 57% of patients were at high risk of CVD Study duration range: 4 to 12 weeks
Edwards et al. (2003)[12]	To determine the effect of different statins on blood cholesterol	PubMed (Sept 2001), Cochrane Library (Issue 3, 2001) Pharmaceutical companies were contacted for references and unpublished data	RCT, DB, ≥12 weeks duration, with mean baseline TC ≥5mmol/L Excluded studies lacking baseline data, <20 patients per treatment group, combinations of statin plus another drug, trials examining patients with familial hypercholesterolemia, diabetes mellitus, renal or hepatic pathology	91 DB, RCTs (n=68,485) 87% had a Jadad quality score of ≥3/5 indicating good quality based on assessment of randomization, blinding and description of dropouts and withdrawals 4 RCTs (n=1,005) with rosuvastatin

CVD: cardiovascular disease; DB: double-blind; HDL: high-density lipoprotein; LDL: low-density lipoprotein cholesterol; RCT: randomized controlled trial; TC: total cholesterol; TG: triglycerides; ↓: reducing.

The results, conclusions, and limitations of the five meta-analyses evaluating the effects of different statins on lipid parameters are summarized in Table 2. Data from all five analyses suggests rosuvastatin has the most potent per milligram LDL lowering effect, followed by atorvastatin. One study found, when given at the same dose as atorvastatin, rosuvastatin reduces LDL by an additional 8.5%.[9] Similar results were reported in three other analyses.[10-12] However, the data does suggest that with appropriate dose adjustment other statins can be therapeutically equivalent in LDL lowering.[9-11] Based on data from three analyses atorvastatin given at twice the dose of rosuvastatin produces equivalent or marginally smaller LDL

reductions (1 to 4.5% less than rosuvastatin) and when given at four times the dose produces equivalent or slightly greater LDL reductions (0.7 to 7% greater than rosuvastatin).[9,11,12] Three analyses reported similar increases in high-density lipoprotein (HDL) cholesterol (0.07 to 0.1mmol/L) between different statins with no detectable dose effect.[8,10,12] Reductions in triglycerides (TG) were also similar between different statins at equivalent doses.[9] In terms of adverse effects, one analysis reported no significant difference in rates of myalgia, withdrawals or serious adverse events between rosuvastatin and atorvastatin.[9] Another analysis reported having insufficient data to evaluate differences in adverse events between various statins[8] and the remaining three meta-analyses did not report safety data.[10-12]

Table 2: Results, conclusion and limitations of systematic reviews and meta-analyses comparing effects of different statins on lipid parameters

Systematic Reviews and Meta-Analysis	Results	Authors' Conclusions	Limitations
Weng et al. (2010)[8]	% LDL lowering achieved by different statins at various doses 20-30% — simvastatin 10mg, fluvastatin 40mg & lovastatin 10-20mg 30-40% — atorvastatin 10mg, simvastatin 20mg, fluvastatin 80mg & lovastatin 40-80mg >40% — rosuvastatin ≥10mg & atorvastatin ≥20mg Increase in HDL and reduction in TG similar between different statins at equivalent doses Overall rate of all muscle related symptoms was <10% and rates of alanine aminotranferease (ALT)/aspartate aminotransferase (AST) ≥3 times the upper limit of normal was <1%. Data was insufficient to evaluate differences between different statins.	With dose adjustment different statins can be therapeutically equivalent in reducing LDL Statins at equivalent doses provide similar effects on HDL and TG	Search methods not well described for trials between 1966 and 2006 Potential that relevant studies may have been missed by restricting to only English and Chinese studies
Wlodarczyk et al. (2008)[9]	When given at the same dose rosuvastatin resulted in larger LDL reductions than atorvastatin Mean Difference in Reduction of LDL 1 to 1 Dose ratio: -8.52% (-9.23 to-7.81) 1 to 2 Dose ratio: -3.24% (-4.10 to -2.38) 1 to 4 Dose ratio: 1.12% (-0.24 to 2.48) Rosuvastatin 5mg: 41% ↓LDL Rosuvastatin 40mg: 56% ↓LDL Atorvastatin 10mg: 37.2% ↓LDL Atorvastatin 80mg: 51.3% ↓LDL No significant difference in rates of myalgia, withdrawals or serious adverse events between rosuvastatin and atorvastatin at any dose ratio.	Rosuvastatin was more efficacious than the same dose of atorvastatin (1:1 dose ratio) or a 2 times higher dose (1:2 dose ratio) of atorvastatin	Potential bias due to pharmaceutical company involvement Potential information bias as 15 of 25 studies were open-label

<table>
<tr><th>Systematic Reviews and Meta-Analysis</th><th>Results</th><th>Authors' Conclusions</th><th>Limitations</th></tr>
<tr><td></td><td>Atorvastatin 80mg and rosuvastatin 40mg had the highest rates of ALT >3 times the upper limit of normal, with rates of 2.2/100 and 0.8/100 respectively.</td><td></td><td></td></tr>
<tr><td>Law et al. (2003)[10]</td><td>% reduction in serum LDL with various doses:
<table><tr><th></th><th colspan="5">Daily dose (mg)</th></tr><tr><th>Statin</th><th>5</th><th>10</th><th>20</th><th>40</th><th>80</th></tr><tr><td>Atorvastatin</td><td>31</td><td>37</td><td>43</td><td>49</td><td>55</td></tr><tr><td>Fluvastatin</td><td>10</td><td>15</td><td>21</td><td>27</td><td>33</td></tr><tr><td>Lovastatin</td><td>--</td><td>21</td><td>29</td><td>37</td><td>45</td></tr><tr><td>Pravastatin</td><td>15</td><td>20</td><td>24</td><td>29</td><td>33</td></tr><tr><td>Rosuvastatin</td><td>38</td><td>43</td><td>48</td><td>53</td><td>58</td></tr><tr><td>Simvastatin</td><td>23</td><td>27</td><td>32</td><td>37</td><td>42</td></tr></table>
Average increase in HDL for statins was 0.07mmol/L with no detectable dose effect

No comparative safety data between different statins was analyzed</td><td>Statins can lower LDL cholesterol by an average of 1.8mmol/L

It may be prudent to use moderate doses of commonly used older drugs</td><td>Details of study selection and process of review were not well described

EMBASE was not search thus European studies may have been missed

Validity of included trials not reported</td></tr>
<tr><td>Nicholls et al. (2010)[11]</td><td>% reduction in serum LDL with various doses:
<table><tr><th></th><th colspan="5">Daily dose (mg)</th></tr><tr><th>Statin</th><th>5</th><th>10</th><th>20</th><th>40</th><th>80</th></tr><tr><td>Rosuvastatin</td><td>39</td><td>44</td><td>49.5</td><td>54.7</td><td>---</td></tr><tr><td>Atorvastatin</td><td>---</td><td>35.5</td><td>41.4</td><td>46.2</td><td>50.2</td></tr><tr><td>Simvastatin</td><td>---</td><td>27.4</td><td>33</td><td>38.9</td><td>45</td></tr></table>Doubling dose of each statin results in additional 5-7% reduction in serum LDL

% reductions in serum TG with various doses:
<table><tr><th></th><th colspan="5">Daily dose (mg)</th></tr><tr><th>Statin</th><th>5</th><th>10</th><th>20</th><th>40</th><th>80</th></tr><tr><td>Rosuvastatin</td><td>15.2</td><td>18.7</td><td>20.1</td><td>21.9</td><td>---</td></tr><tr><td>Atorvastatin</td><td>---</td><td>16.4</td><td>18.9</td><td>20.7</td><td>25</td></tr><tr><td>Simvastatin</td><td>---</td><td>9.3</td><td>12.7</td><td>13.3</td><td>14.1</td></tr></table>
% reductions in serum Apo-B with various doses:
<table><tr><th></th><th colspan="5">Daily dose (mg)</th></tr><tr><th>Statin</th><th>5</th><th>10</th><th>20</th><th>40</th><th>80</th></tr><tr><td>Rosuvastatin</td><td>30.2</td><td>34.5</td><td>39</td><td>42.9</td><td>---</td></tr><tr><td>Atorvastatin</td><td>---</td><td>27.6</td><td>33.3</td><td>36.7</td><td>40.8</td></tr><tr><td>Simvastatin</td><td>---</td><td>20.1</td><td>25.3</td><td>30</td><td>34.1</td></tr></table>
A greater percentage of patients achieved lipid goals with increasing doses of all agents</td><td>Doubling statin dose was associated with greater LDL reductions by 4-6%.

Greater lipid goal achievement with increasing doses supports use of high-dose statin therapy.</td><td>Potential bias due to pharmaceutical company involvement

No validity assessment performed of trials

Potential information bias as 65% of trials were open-label

No test for statistical heterogeneity between trials

No sensitivity analysis performed</td></tr>
</table>

<table>
<tr><th>Systematic Reviews and Meta-Analysis</th><th>Results</th><th>Authors' Conclusions</th><th>Limitations</th></tr>
<tr><td></td><td>No safety data reported</td><td></td><td></td></tr>
<tr><td>Edwards et al. (2003)[12]</td><td><table><tr><th></th><th colspan="2">Mean % reduction</th></tr><tr><th>Statin & mean dose</th><th>TC</th><th>LDL</th></tr><tr><td>Atorvastatin 10mg</td><td>27%</td><td>37%</td></tr><tr><td>Fluvastatin 40mg</td><td>17%</td><td>24%</td></tr><tr><td>Lovastatin 40mg</td><td>23%</td><td>30%</td></tr><tr><td>Pravastatin 40mg</td><td>21%</td><td>28%</td></tr><tr><td>Rosuvastatin 5mg</td><td>30%</td><td>44%</td></tr><tr><td>Rosuvastatin 10mg</td><td>33%</td><td>49%</td></tr><tr><td>Simvastatin 40mg</td><td>26%</td><td>34%</td></tr></table>
No safety data reported</td><td>Reductions in TC of ≥25% and LDL ≥30% were recorded for fixed doses of simvastatin 40mg, atorvastatin10 mg and rosuvastatin 5mg and 10mg.</td><td>Few trials for atorvastatin (5), fluvastatin (9) and rosuvastatin (4)

Most dose-specific analyses limited to fewer than 1000 patients

Dose titration studies lacked reporting of mean/median daily statin dose</td></tr>
</table>

ALT: alanine aminotranferease; Apo-B: apolipoprotein B**,** AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein cholesterol, TC: total cholesterol; TG: triglycerides, ULN: upper limit of normal.

Effects of Statins in Heart Failure

A systematic review conducted by Lipinski et al. (2009)[13] evaluated the impact of statins in heart failure (HF) patients. Two reviewers independently searched Cochrane CENTRAL, clinicaltrials.gov and PubMed for RCTs of statins versus placebo for the treatment of heart failure. Ten RCTs (n=10,192) were included in the review with studies randomizing patients to treatment with rosuvastatin (3 RCTs), simvastatin (1 RCT) and atorvastatin (6 RCTs). All studies were formally assessed for quality. Four had adequate sequence and allocation concealment and half were double blinded. The duration of the studies varied from a mean follow-up of 3 to 46.8 months. Most included trials recruited patients with a New York Heart Association (NYHA) classification of II or above and included patients had a mean left ventricular ejection fraction (LVEF) ranging from 25 to 39%. Overall trials with atorvastatin and simvastatin had smaller sample sizes and shorter mean follow-up periods compared with studies with rosuvastatin. Pooled analysis of all 10 trials found no significant decrease in the risk of all-cause mortality with statin therapy [Odds ratio (OR) 0.89, 95% confidence interval (CI) 0.72 to 1.10]. Data from seven trials found no significant decrease in the risk of cardiovascular death (OR 0.89, 95% CI 0.71 to 1.13) or sudden cardiac death (OR 0.94, 95% CI 0.68 to 1.29). From the ten studies a trend toward decreased hospitalization for cardiovascular causes was found (OR 0.92; 95% CI 0.85 to 1.00). There was a significant decrease in hospitalizations for worsening HF (OR 0.67, 95% CI 0.50 to 0.90). Data from six trials demonstrated a significant 4.2% increase in LVEF versus placebo (95% CI 1.3 to 7.1) A subgroup analysis found randomization to atorvastatin significantly decreased all-cause mortality (OR 0.39, 95% CI 0.21 to 0.73) and resulted in a large decrease in hospitalization for worsening HF (OR 0.30, 95% CI 0.18 to 0.49). Atorvastatin and simvastatin demonstrated significant 5.6% increases in LVEF

(95% CI 3.3 to 7.8). Rosuvastatin, however, was not associated with significant reductions in all cause-mortality or hospitalizations for worsening HF. The authors concluded that overall statins do not reduce all-cause or cardiovascular mortality but significantly decrease hospitalizations for worsening heart failure and increase LVEF versus placebo in patients with heart failure. Subgroup analysis found heterogeneity between the three statins with significant benefits seen with atorvastatin and simvastatin but not with rosuvastatin. It is important to note that two RCTs evaluating 10mg rosuvastatin contributed 95% of the patients in the review. These two multicenter studies were of good quality with large sample sizes, adequate sequence and allocation concealment and the longest durations of follow-up. Neither reported a significant difference versus placebo for any outcome measure. The significant results for atorvastatin were based on five percent or less of the included patients. Thus results of the subgroup analysis should be interpreted with caution.

Effects of Statins on Insulin Sensitivity and Incidence of Diabetes

The characteristics of the three meta-analyses evaluating the effects of statins on insulin sensitivity and incidence of diabetes are summarized in Table 3. One analysis examined the effects of statins on insulin sensitivity[16] and the remaining two evaluated the relationship between statins and the development of diabetes.[14,15]

Table 3: Characteristics of systematic reviews and meta-analyses evaluating the effects of statins on insulin sensitivity and incidence of diabetes

Meta-Analysis	Objectives	Search Strategy	Study Criteria	Studies Selected
Baker et al. (2010)[16]	To determine if individual statins have differing effects on insulin sensitivity in non-diabetics	A search of MEDLINE (1966 to Dec 2008), EMBASE (1974 to Dec 2008) and Cochrane CENTRAL (1966 to Dec 2008)	Studies in non-diabetics comparing pravastatin, atorvastatin, rosuvastatin or simvastatin to placebo/control in which insulin sensitivity (IS) data was reported	16 RCTs (n=1,146, median sample size 206, range 10 to 401) Ten parallel group trials and 6 crossover studies. Eleven trials were double-blinded Most patients had either metabolic syndrome or hypercholesterolemia Pravastatin (3 trials; n=164) Atorvastatin (5 trials; n=315) Rosuvastatin (5 trials; n=419) Simvastatin (5 trials; n=369) Median study duration: 14 weeks (range: 4 to 24)
Sattar et al. (2010)[14]	To determine whether a relationship exists between statin use and development of diabetes	Search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from 1994 to 2009 Authors also	English language RCTs of statins having ≥1000 patients, with identical follow-up in both groups and duration of ≥1 year	13 RCTs (n=91,140) Ten double-blinded trials and 3 open-label studies pravastatin (6 trials) atorvastatin (1 trial) rosuvastatin (3 trials) simvastatin (2 trials)

Meta-Analysis	Objectives	Search Strategy	Study Criteria	Studies Selected
		requested unpublished data	Excluded patients with diabetes, organ transplants or on hemodialysis	lovastatin (1 trial) Most patients at risk of, or had a history of cardiovascular disease Mean follow-up: 4 years
Rajpathak et al. (2009)[15]	To evaluate the effects of statin therapy on the development of diabetes	Search of MEDLINE and the Cochrane Library from inception to February 2009. Science Citation Index was used for cross-referencing	RCTs comparing placebo with any statin for prevention of cardiovascular disease which reported data on incidence of diabetes during follow-up	6 RCTs (n=57,593) All trials rated at ≥3/5 on the Jadad quality scale. 3 primary prevention trials and 3 secondary prevention trials pravastatin (2 trials; n=13,911) atorvastatin (1 trial; n=7773) rosuvastatin (2 trials; n=21,336) simvastatin (1 trials; n=14,573) Median follow-up ranged from 1.9 to 5 years (weighted mean of 3.9 years)

RCT: randomized controlled trial.

The results, conclusions, and limitations of the three meta-analyses evaluating the effects of statins on insulin sensitivity and incidence of diabetes are summarized in Table 4. Baker et al.(2010)[16] concluded that overall statins did not have a significant impact on insulin sensitivity in non-diabetic patients. However, a subgroup analysis suggested differential effects on insulin sensitivity between agents with pravastatin improving sensitivity, atorvastatin and rosuvastatin demonstrating no impact and simvastatin worsening insulin sensitivity. Both studies evaluating the relationship between statins and the development of diabetes reported a small increase in the risk of diabetes with statins. Sattar et al. (2010)[14] found no difference in risk between individual statins or statin type (i.e. lipophillic versus hydrophilic statins).

Table 4: Results, conclusions and limitations of systematic reviews and meta-analyses evaluating the effects of statins on insulin sensitivity and incidence of diabetes

Meta-Analysis	Results	Authors' Conclusions	Limitations and Notes
Baker et al. (2010)[16]	Overall, statins had no significant impact on insulin sensitivity compared to placebo/control [SMD -0.084 (95%CI -0.210 to 0.042)] Subgroup analysis found: Pravastatin significantly improved insulin sensitivity [SMD 0.342 (95% CI 0.032 to 0.621)],	Overall statins do not have a significant impact on insulin sensitivity, however, differences between	Reviewers did not report obtaining unpublished data Two reviewers independently selected trials and used a standardized data extraction form to collect data No formal assessment of study

Meta-Analysis	Results	Authors' Conclusions	Limitations and Notes
	torvastatin [SMD -0.019 (95% CI -0.243 to 0.205] and rosuvastatin [SMD -0.037 (95% CI -0.223 to 0.148)] did not significantly impact insulin sensitivity Simvastatin significantly worsened insulin sensitivity [SMD -0.321 (95% CI -0.526 to -0.117)]	statins likely exists	quality was performed All trials were randomized and 11 were double blinded. However, the trials were small with a mean sample size of 72 patients.
Sattar et al. (2010)[14]	Statin use was associated with a 9% increased risk of diabetes (OR 1.09; 95% CI 1.02 to 1.17). This translates to one additional case of diabetes per 255 patients taking a statin for four years No difference was found between individual statins or group type (lipophillic versus hydrophilic statins) for the risk of developing diabetes	Statin therapy was associated with a slightly increased risk of diabetes The absolute risk is low and small compared with the reduction in coronary events.	Relevant studies may have been missed by restricting search to English language trials, however, authors did obtain unpublished data Error and bias was reduced by having two reviewers independently select and extract data from trials No formal quality assessment of trials was done, though most trials were large and double-blinded
Rajpathak et al. (2009)[15]	Analysis of 5 trials found statins were associated with increase in diabetes (RR 1.13, 95% CI 1.03 to 1.23), corresponding to a risk difference of 0.5% with no significant heterogeneity present. Analysis of all six trials found a non-significant increase in diabetes	There is evidence of a small but significant increased risk of diabetes with statins	Data extraction process reported to be robust, however, insufficient details on the processes of study selection Quality assessment performed but not reported in detail

CI: confidence interval; OR: odds ratio; RR: relative risk; SMD: standard mean difference.

Randomized controlled trials

The characteristics of the eight RCTs evaluating the lipid lowering effects of rosuvastatin compared with other statins are summarized in Table 5. Six of the RCTs were open-label,[17,18,20,22-24] and the remaining two were double-blinded.[19,21] Study duration ranged from 6 to 48 weeks. The patient populations varied and included both primary and secondary prevention patients. One study enrolled post-myocardial infarction patients [22] and one enrolled children and adults with homozygous familial hypercholesterolemia.[21] One study compared rosuvastatin to four times the dose of simvastatin.[22] The other seven trials compared rosuvastatin with atorvastatin.[17-21,23,24] Four compared rosuvastatin with the same dose of atorvastatin[18-21] and three compared rosuvastatin with twice the dose of atorvastatin.[17,23,24]

Table 5: Characteristics of RCTs evaluating the lipid lowering effects of rosuvastatin compared with other statins

Study *Country*	Trial Design	Patients	Intervention	Endpoints
Mazza et al. (2008)[17] *Italy*	RCT, open-label, parallel group Duration: 48 weeks	N=106 non-diabetic patients aged 18 to 65 with primary hypercholesterolemia (LDL >200mg/dL)	rosuvastatin 10mg vs. atorvastatin 20mg	% change in LDL, TC, TG, non-HDL and HDL levels
Adsule et al. (2009)[18] *India*	RCT, open-label, parallel group, Duration: 12 weeks	N=60 type 2 diabetic patients with dyslipidemia and good glycemic control	rosuvastatin 10mg vs. atorvastatin 10mg vs. simvastatin 10mg	% change in LDL, TC, TG, VLDL and HDL
Betteridge et al. (2007)[19] *UK*	MC, RCT, DB, phase III trial Duration: 16 weeks	N=509 patients age ≥18 with controlled type 2 diabetes and no history of cardiovascular disease	First 8 weeks: rosuvastatin 10mg vs. atorvastatin 10mg Both titrated to 20mg after 8 weeks	1^0 endpoint: % change in LDL 2^0 endpoints: % change in CRP
Jayaram et al. (2004)[20] *India*	RCT, open-label, parallel group, phase III trial Duration: 6 weeks after randomization	N=45 patients aged 18 to 80 with hypercholesterolaemia (LDL from 160 to < 250 mg/dL and TG < 400 mg/dL)	rosuvastatin 10mg vs. atorvastatin 10mg	1^0 endpoint: % change in LDL 2^0 endpoints: % change in TC, HDL, TG, Apo-B, Apo-A1 and TC:HDL
Marais et al. (2008)[21] *South Africa & USA*	Non-inferiority RCT, DB, cross-over study Duration: 6 weeks after cross-over randomization	N=38 patients aged 8 to 63 with homozygous familial hypercholesterolaemia (LDL >12.9mmol/L and TG <6.8mmol/L) 4 patients had portacaval shunts & 11 were receiving plasmapheresis	All patients initially received rosuvastatin titrated over 18 weeks to 80mg/day Patients were then randomized to rosuvastatin 80mg vs. atorvastatin 80mg	% change in LDL
Hall et al. (2009)[22] *UK*	MC, RCT, open-label, blinded-endpoint study Duration: 3 months	N=1263 patients hospitalized for acute myocardial infarction ≤2 weeks prior to study enrollment (mean baseline LDL of 3.27mmol/L)	rosuvastatin 10mg vs. simvastatin 40mg for 3 months	1^0 endpoint: % achieving 2003 European Society of Cardiology (ESC-03) LDL & TC targets

Study *Country*	Trial Design	Patients	Intervention	Endpoints
Kurabayashi et al. (2008)[23] *Japan*	MC, RCT, open-label, parallel group Duration: 8 weeks	N=446 patients age ≥20 with hypercholesterolemia who had received ≥4 weeks of atorvastatin 10mg	rosuvastatin 5mg vs. atorvastatin 10mg for 8 weeks	1^0 endpoint: % achieving 2002 Japan AtherosclerosisSociety LDL targets, % change in LDL, LDL:HDL ratio
Milionis et al. (2006)[24] *Greece*	RCT, open-label, parallel group Duration: 24 week	N=120 non-diabetic patients with primary hyperlipidemia and no history of cardiovascular disease (TC >6.2mmol/L and TG <4mmol/L prior to enrollment)	rosuvastatin 10mg vs. atorvastatin 20mg Dose titration after 6 weeks if needed to: rosuvastatin 20mg vs. atorvastatin 40mg for 18 weeks	Efficacy: % achieving LDL target, change in LDL, Apo-B, TG, ApoB:ApoA1 ratio, hs-CRP LDL target= 130mg/dL

Apo-A1: Apolipoprotein A-I; Apo-B: apolipoprotein B; CRP: C-reactive protein; DB: double-blind; HDL: high-density lipoprotein; hs-CRP: high sensitivity C-reactive protein; LDL: low-density lipoprotein; MC: multi-center; RCT: randomized controlled trial; TC: total cholesterol; TG: triglycerides; VLDL: very-low-density lipoprotein.

The results, conclusions, and limitations of the eight RCTs evaluating the lipid lowering effects of rosuvastatin compared with other statins are summarized in Table 6. Overall, the results of these RCTs are in keeping with the findings of the previous meta-analyses. In the study comparing rosuvastatin to four times the dose of simvastatin a similar proportion of patients in both groups achieved a target LDL <2.5mmol/L or TC <4.5mmol/L;however, lower TC and LDL values were achieved in the rosuvastatin group.[22] In three trials comparing rosuvastatin with the same dose of atorvastatin, rosuvastatin resulted in greater LDL reductions.[18-20] When compared to twice the dose of atorvastatin, one trial reported similar reductions in LDL[24] and two reported significantly greater reductions in LDL[17,23] with rosuvastatin. Rosuvastatin and atorvastatin produced similar reductions in C-reactive protein (CRP)[19,24] and similar increases in HDL.[19,20,24]

Table 6: Results, conclusions, and limitations of RCTs evaluating the lipid lowering effects of rosuvastatin compared with other statins

Study	Results	Authors' Conclusions	Limitations and Notes
Mazza et al. (2008)[17]	% lipid lowering at 48 weeks for rosuvastatin vs. atorvastatin TC: 35.8% vs. 21.6% LDL: 44.3% vs. 30% TG: 36.4% vs. 4.6% (Combined p<0.005) Neither agent significantly increased HDL	Rosuvastatin 10mg/day was more efficacious than atorvastatin 20mg/day in reducing LDL levels	Small sample size (n=106) Randomization methods and allocation concealment not described Open-label design may introduce information bias Type of data analysis not

Study	Results	Authors' Conclusions	Limitations and Notes
			indicated (i.e. ITT or PP) No description of dropouts or patients lost to follow-up
Adsule et al. (2009)[18]	TC, TG, LDL and VLDL were reduced and HDL increased significantly in all groups % reduction in LDL: Rosuvastatin 44.3% vs. atorvastatin 35.6% (p>0.05) vs. simvastatin 25.2% (0<0.05) No adverse events were observed in any group	Rosuvastatin 10mg/day was comparable to atorvastatin 10mg/day and more effective than simvastatin 10mg in reducing LDL levels	Small sample size (n=60) Allocation concealment not described Short duration (12 weeks) Data analysis type not indicated (i.e. ITT or PP) No description of dropouts or patients lost to follow-up
Betteridge et al. (2007)[19]	Rosuvastatin had significantly greater % reduction in LDL vs. atorvastatin at 8 weeks (51% vs. 39%; p<0.001) and 16 weeks (57% vs. 46%; p<0.001) No significant difference between agents for % change in CRP or HDL at 8 or 16 weeks	Both rosuvastatin and atorvastatin effectively reduce CRP Rosuvastatin decreases LDL significantly more than atorvastatin	Moderate sample size (n=509) Unclear allocation concealment Short duration (16 weeks) 1:1 dose comparison ITT analysis performed including all patients receiving ≥1 dose of study medication with baseline and ≥1 post-baseline assessment data
Jayaram et al. (2004)[20]	% LDL lowering at 6 weeks: rosuvastatin 40.1% vs. atorvastatin 29.8% (p<0.05) Rosuvastatin had significantly greater % reductions compared to atorvastatin in TC (31% vs. 24%), ratio of TC:HDL (39.8% vs. 28.9%) and apo-B (38.1% vs. 30.6%) No significant difference between agents for % change in HDL or TG	Rosuvastatin 10mg has significantly better efficacy than atorvastatin 10mg in reducing LDL and results in greater improvement in other lipid parameters	Small sample size (n=45) Randomization methods and allocation concealment not described Open-label design may introduce information bias Short duration (6 weeks) 1:1 dose comparison Data analysis type not indicated (i.e. ITT or PP)
Marais et al.	Mean % LDL reduction from	Similar mean LDL	Unique population

Study	Results	Authors' Conclusions	Limitations and Notes
(2008)[21]	baseline to end of cross-over treatment: rosuvastatin 19% vs. atorvastatin 18% (p=0.67)	reductions from baseline to end of crossover treatment were similar with rosuvastatin 80mg and atorvastatin 80mg	(including children) Small sample size, only 22 patients (58%) included in cross-over efficacy analysis Interpretation limited by lead in period with rosuvastatin 80mg and short duration of crossover
Hall et al. (2009)[22]	% achieving ESC-03 target LDL <2.5mmol/L or TC <4.5mmol/L: rosuvastatin 79.9% vs. simvastatin 77.6% (p=0.286) Secondary endpoint: TC and LDL values were significantly lower with rosuvastatin than simvastatin	A similar proportion of patients achieved ESC-03 targets with rosuvastatin 10mg and simvastatin 40mg Rosuvastatin 10mg lowered mean cholesterol more than simvastatin 40mg	Failed to meet a priori sample size of 1554 patients Appropriate randomization and allocation concealment procedure described Open-label design may introduce information bias ITT analysis performed PP analysis found similar results as ITT analysis
Kurabayashi et al. (2008)[23]	% achieving Japan Atherosclerosis Society target LDL : Rosuvastatin 80.3% vs. Atovastatin 67.3% (p<0.01) % reduction from baseline in LDL (6±17% vs. 1.2 ±14.7%) was significantly greater with rosuvastatin	Rosuvastatin 5mg/day is a useful treatment option for high-risk patients with hypercholesterolemia	Randomization methods and allocation concealment not described Short duration (8 weeks) Open-label design may introduce information bias Large variability in data with wide confidence intervals
Milionis et al. (2006)[24]	% of patients achieving target LDL (130mg/dL) at 6 weeks (rosuvastatin 75% vs. atorvastatin 71.7%; pNS) and at completion (rosuvastatin 93.3% vs. atorvastatin 91.7%; pNS) Both agents resulted in similar reductions in LDL, TC, TG, and CRP	Rosuvastatin and atorvastatin were equally effective in achieving LDL targets	Small sample size (n=120) Randomization methods and allocation concealment not described Open-label design may introduce information bias Data analysis type not indicated (i.e. ITT or PP)

Apo-B: apolipoprotein B; CRP: C-reactive protein; hs-CRP: high sensitivity C-reactive protein; HDL: high-density lipoprotein; ITT: intention-to-treat; LDL: low-density lipoprotein cholesterol; PP: per protocol; TC: total cholesterol; TG: triglycerides; VLDL: very-low-density lipoprotein.

Non-randomized studies

The three non-randomized studies evaluating the safety of statins include two cohort studies[25,26] and one case-control study.[27] Additional articles of interest are found in the appendix.

Hippisley-Cox and Coupland (2010)[25] conducted a cohort study of primary care patients using QResearch, a general practice research database. The authors aimed to quantify the unintended effects of statins according to type, dose and duration of use. The study included patients aged 30 to 84 registered with 368 general practices in England and Wales between January 1, 2002 and June 30, 2008. A total of 2,004,692 patients were included in the study of whom 225,922 (10.7%) were new users of statins and the remaining non-users. Of the new users of statins 70.7% were prescribed simvastatin, 22.3% atorvastatin, 3.6% pravastatin, 1.9% rosuvastatin and 1.4% fluvastatin. The authors found that individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fractures or cancers including gastric, colon, lung, renal, breast, prostate or melanoma. Statins were, however, significantly associated with a reduced risk of esophageal cancer Number Needed to Treat (NNT)=1266 but an increased risk of acute renal failure, cataract, moderate to serious liver dysfunction (alanine aminotranferease >120IU/L) and moderate to serious myopathy (rhabdomyolysis, myopathy, or creatine kinase $\geq$4 times the upper limit of normal). Adverse effects were similar across the statin types for each outcome except liver dysfunction where fluvastatin was associated with the highest risks. Overall, in new statin users, the Number Needed to Harm (NNH) for one additional case of acute renal failure over five years was approximately 434 (range: 284 to 784), of cataract was 33 (range: 28 to 38) and of moderate to severe liver dysfunction was 136 (range: 109 to 175). The NNH for moderate to severe myopathy was 259 (range: 186 to 375) in women and 91 (range: 74 to 112) in men. The authors concluded that claims of unintended benefits of statins, except for esophageal cancer, remain unsubstantiated. They state that adverse effects were similar across the statin types for each outcome except liver dysfunction where fluvastatin was associated with the highest risk. These results suggest a similar risk of adverse events with rosuvastatin as with the other statins studied, however, there were relatively few patients prescribed rosuvastatin and thus differences may be difficult to detect. Other limitations include no description of confounding variables which were adjusted for and no reporting of unadjusted hazard ratios.

Taguchi et al.(2008)[26] conducted a prospective observational cohort study to examine the risk of fetal toxicity in women taking statins during the first trimester of pregnancy. The study included 64 women with hypercholesterolemia who were pregnant or planning a pregnancy and taking a statin antenatally from 1998 to 2005. Patients were recruited upon contacting the teratogen information service at the Hospital for Sick Children, Toronto, Canada, for safety concerns. An unexposed comparison group, consisting of 64 women who had contacted the Motherisk program with ordinary therapeutic uses of non-teratogens, was matched with cases. Women were matched for maternal age, gravidity, parity, previous spontaneous abortions, smoking habits, alcohol consumption and gestational age at the initial time of contact. Baseline characteristics were similar between the groups. In the exposed group atorvastatin was the most commonly used statin (n=46), followed by simvastatin (n=9), pravastatin (n=6) and rosuvastatin (n=3). The study found no statistically significant difference in the rate of major birth defects between the two groups, with a rate of 2.2% in the statin exposed group versus 1.9% in the unexposed group (p=0.93). Statin exposed infants did have significantly lower birth weights and shorter gestation period. The authors concluded that the absolute risk of

teratogenicity of statins, if any, appears relatively small. The study is limited by the small sample size. The different statins were analyzed as a group and thus the study does not provide information about possible differential risks among agents.

Molokhia et al.(2008)[27] conducted a case-crossover study of UK primary care patients to compare the risk of statin associated myopathy with each type of statin and fibrate. The study was conducted between 1991 and 2006. Data was collected using The Health Improvement Network (THIN) and MediPlus primary care databases. Patients were included following the first ever myopathy event code after registration. Patients were excluded if they had never received a statin prescription, had received steroids within two weeks of the myopathy event, were receiving anti-retrovirals or had been diagnosed with any rheumatic disease. Patients were considered to be exposed if the myopathy event code occurred within 12 weeks of starting a new statin or change of statin, including an increase in statin dose. Patients were considered unexposed if they were not on a statin at the time of the myopathy event. The investigators calculated the relative risk of a myopathy event when exposed versus when unexposed. There were 27,689 patients with a myopathy or myalgia event identified from the THIN database of which 4258 patients had recently used statins. The relative risk (RR) for all myopathy events after 12 weeks of statin exposure was 8.2 (95% CI 4.1 to 16.3) based on the MediPlus data and 10.6 (95% CI 9.8 to 11.4) based on THIN data. At 26 weeks exposure, fluvastatin had the highest RR for myopathy at 33.3 (95% CI 16.8 to 66) followed by pravastatin (RR 25.8; 95% CI 17.8 to 37.4), simvastatin (RR 19.5; 95% CI 15.9 to 23.9) and atorvastatin (RR 15.2; 95% CI 12.2 to 19). Rosuvastatin had the lowest RR at 9.9 (95% CI 5 to 19.4), however it should be noted that rosuvastatin also had the lowest number of total prescriptions during the study period. The authors concluded that the data suggests an annual incidence of statin induced myopathy or myalgia of 689 per million per year.

Limitations

The literature search did not identify any relevant health technology assessments. No studies were identified comparing the effects of rosuvastatin with other statins in reducing cardiovascular events or mortality. Of the five meta-analyses evaluating the effects of statin on lipid parameters, two were industry funded with more than half of the included trials being open-label.[9,11] Three of the analyses either did not assess or report study validity.[9-11] The findings of the meta-analyses could potentially be affected by the limitations of the included studies. Also, these meta-analyses were limited to RCTs, which are often too small and of short duration to adequately assess adverse events and safety concerns. The results of the meta-analysis evaluating the impact of statins in heart failure patients were primarily driven by two large rosuvastatin trials which accounted for 95% of participants.[13] Of the three meta-analyses evaluating the effects of statins on insulin sensitivity and incidence of diabetes, two did not formally assess study quality[14,16] and the remaining analysis assessed quality but did not report the findings in detail.[15]

The RCTs reviewed had significant methodologic limitations as outlined in Table 6. Most had small sample sizes and limited durations of follow-up. The majority did not adequately describe the randomization or allocation concealment methods and most were open-label which may introduce information bias.

All three non-randomized studies evaluating the safety of statins used pharmacoepidemiologic methods. A number of biases and confounding variables can threaten the validity of the results.

Of the cohort studies, one did not adequately describe potential confounders and thus may not have adequately adjusted for all relevant factors.[25] All three did not adequately describe how missing data was dealt with.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Comparative Efficacy of Rosuvastatin

No studies were identified comparing the efficacy of rosuvastatin versus other statins for reducing cardiovascular events and mortality. Based on the included studies, rosuvastatin provides the most potent per milligram LDL lowering; however, other statins given in therapeutically equivalent doses can achieve similar LDL lowering. The data suggest that rosuvastatin provides similar increases in HDL and reductions in TG and CRP compared with other statins. In heart failure, patients the evidence suggests statins may decrease hospitalizations for worsening heart failure and increase LVEF; however, these benefits were not seen in the larger, higher quality trials of rosuvastatin.

Comparative Safety of Rosuvastatin

Based on the meta-analyses evaluating the effects of statins on the incidence of diabetes, statins are associated with a small increase in the risk of diabetes with an estimated NNH of 255 patients over four years. The evidence suggests no difference in risk among agents.

Data from three non-randomized studies suggest similar rates of adverse events with rosuvastatin compared to other statins including acute renal failure, cataract, liver dysfunction, and myopathy. Observational cohort data suggest statin exposure in the first trimester is not associated with an increase in major birth defects; however there are insufficient data to determine differential risk between agents.

According to the current evidence, the clinical effectiveness of rosuvastatin is similar when compared with therapeutically equivalent doses of other statins. The safety profile of rosuvastatin is comparable to that of other statins.

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REFERENCES:

1. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2011. Cardiovascular disorders: dyslipidemias 2010 [cited 2011 Feb 7]. Available from: https://www.e-therapeutics.ca/ Subscription required.

2. Vrecer M, Turk S, Drinovec J, Mrhar A. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. Int J Clin Pharmacol Ther. 2003 Dec;41(12):567-77.

3. Yusuf S, Lonn E, Bosch J. Lipid lowering for primary prevention. Lancet. 2009 Apr 4;373(9670):1152-5.

4. Canadian Institute for Health Information (CIHI) [Internet]. Drug use among seniors on public drug programs in Canada, 2002-2008. Ottawa: CIHI; 2010. [cited 2011 Feb 7]. Available from: https://secure.cihi.ca/estore/productSeries.htm?pc=PCC520

5. Apotex overcomes Lipitor drug patents saving healthcare system billions of dollars [Internet]. Toronto: Apotex Worldwide; 2010. [cited 2011 Feb 7]. Available from: http://www.apotex.com/ca/en/about/press/20100519.asp

6. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2011. Crestor®: rosuvastatin calcium 2010 [cited 2011 Feb 7]. Available from: https://www.e-therapeutics.ca/ Subscription required.

7. Atorvastatin (e-formulary) [Internet]. Drugs funded by Ontario drug benefit (ODB) program [Internet]. Toronto: Ministry of Health and Long-Term Care; 2010 [cited 2011 Feb 7]. Available from: http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html.

8. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010 Apr;35(2):139-51.

9. Wlodarczyk J, Sullivan D, Smith M. Comparison of benefits and risks of rosuvastatin versus atorvastatin from a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008 Dec 15;102(12):1654-62.

10. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003 Jun 28;326(7404):1423. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC162260/pdf/el-ppr1423.pdf

11. Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ. Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol. 2010 Jan 1;105(1):69-76.

12. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. BMC Fam Pract. 2003 Dec 1;4:18.

Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC317299/pdf/1471-2296-4-18.pdf

13. Lipinski MJ, Cauthen CA, Biondi-Zoccai GG, Abbate A, Vrtovec B, Khan BV, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. Am J Cardiol. 2009 Dec 15;104(12):1708-16.

14. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen J. Database of Abstracts of Reviews of Effects (DARE). Oxford (UK): York University; 2010 [cited 2011 Feb 3]. CRD Summary available from: http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12010001084

15. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care. 2009 Oct;32(10):1924-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752935/pdf/zdc1924.pdf

16. Baker WL, Talati R, White CM, Coleman CI. Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2010 Jan;87(1):98-107.

17. Mazza F, Stefanutti C, Di GS, Vivenzio A, Fraone N, Mazzarella B, et al. Effects of low-dose atorvastatin and rosuvastatin on plasma lipid profiles: a long-term, randomized, open-label study in patients with primary hypercholesterolemia. Am J Cardiovasc Drugs. 2008;8(4):265-70.

18. Adsule SM, Baig MS, Gade PR, Khandelwal PN. A comparative evaluation of safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia. Int J Diabetes Dev Ctries. 2009 Apr;29(2):74-9.

19. Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin versus atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (< 70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). Am J Cardiol. 2007 Oct 15;100(8):1245-8.

20. Jayaram S, Jain MM, Naikawadi AA, Gawde A, Desai A. Comparative evaluation of the efficacy, safety, and tolerability of rosuvastatin 10 mg with atorvastatin 10 mg in adult patients with hypercholesterolaemia: the first Indian study. J Indian Med Assoc. 2004 Jan;102(1):48-50, 52.

21. Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Palmer M, et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008 Mar;197(1):400-6.

22. Hall AS, Jackson BM, Farrin AJ, Efthymiou M, Barth JH, Copeland J, et al. A randomized, controlled trial of simvastatin versus rosuvastatin in patients with acute myocardial infarction: the Secondary Prevention of Acute Coronary Events--Reduction of Cholesterol to Key European Targets Trial. Eur J Cardiovasc Prev Rehabil. 2009 Dec;16(6):712-21.

23. Kurabayashi M, Yamazaki T, SUBARU Study Group. Superior benefit of aggressive lipid-lowering therapy for high- risk patients using statins: the SUBARU study--more hypercholesterolemic patients achieve Japan Atherosclerosis Society LDL-C goals with rosuvastatin therapy than with atorvastatin therapy. J Atheroscler Thromb. 2008 Dec;15(6):314-23.

24. Milionis HJ, Rizos E, Kostapanos M, Filippatos TD, Gazi IF, Ganotakis ES, et al. Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin. 2006 Jun;22(6):1123-31.

25. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874131/pdf/bmj.c2197.pdf

26. Taguchi N, Rubin ET, Hosokawa A, Choi J, Ying AY, Moretti ME, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. Reprod Toxicol. 2008 Oct;26(2):175-7.

27. Molokhia M, McKeigue P, Curcin V, Majeed A. Statin induced myopathy and myalgia: time trend analysis and comparison of risk associated with statin class from 1991-2006. PLoS ONE. 2008;3(6):e2522. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2432025/pdf/pone.0002522.pdf

APPENDICES:

Review articles

28. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005 Jun 14;111(23):3051-7.

29. Marie I, Delafenetre H, Massy N, Thuillez C, Noblet C, Network of the French Pharmacovigilance Centers. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990-2005 and review of the literature. Arthritis Rheum. 2008 Mar 15;59(3):367-72.

30. Shepherd J, Vidt DG, Miller E, Harris S, Blasetto J. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology. 2007;107(4):433-43.