Do PCSK9 Monoclonal Antibodies plus SOC Prevent Major Adverse Cardiovascular Events in Adults with Hypercholesterolemia Compared to Placebo Plus SOC?

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Do PCSK9 monoclonal antibodies plus SOC prevent major adverse cardiovascular events in adults with hypercholesterolemia compared to placebo plus SOC?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not PCSK9 monoclonal antibodies plus SOC prevent major adverse cardiovascular events in adults with hypercholesterolemia compared to placebo plus SOC.

Study Design: This review is using one double-blinded randomized controlled trial (RCT) and two open-label RCTs investigating alirocumab and evolocumab, published in 2014 and 2015.

Data sources: Articles were found on PubMed, and were published in peer-reviewed journals in English.

Outcome Measured: The outcome measured was major adverse cardiac events (MACE), which included death, MI, hospitalization for unstable angina, revascularization, or cerebrovascular event.

Results: Robinson, et al. showed a lower incidence of MACE in the alirocumab group compared to the placebo group ($p=0.02$, CI 0.31-0.90) with a number needed to treat (NNT) of -62. Sabatine, et al. showed a lower incidence of MACE in the evolocumab group compared to SOC group ($p=0.003$, CI 0.28-0.78) with NNT of -93. Koren, et al. showed lower incidence of MACE in the evolocumab group compared to SOC with NNT of -105.

Conclusions: The results of the three studies indicate that PCSK9 monoclonal antibodies (alirocumab or evolocumab) prevented MACE when compared to placebo or SOC. More studies could investigate which of the two drugs has better efficacy to prevent MACE and safety. Further studies could be done to compare specific characteristics like those who are statin-intolerant or those with familial hypercholesterolemia to patients already on a statin.

Key Words: hypercholesterolemia, alirocumab and cardiovascular events, evolocumab and cardiovascular events
INTRODUCTION

Hypercholesterolemia is multifactorial, with causes originating from genetic defects, secondary to other disease, increasing age, diet, and lack of exercise. Hypercholesterolemia is associated with an increased risk for cardiovascular disease, which is the most common cause of death worldwide.\(^1\) Atherosclerosis due to hypercholesterolemia over time can lead to plaque rupture and can cause myocardial infarction, cerebrovascular accident, angina pectoris, mesenteric ischemia, and renal artery stenosis.\(^1\) This paper evaluates three randomized controlled trials (RCTs) comparing the efficacy of proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies for the prevention of major adverse cardiac events (MACE).

There are approximately 26.5 million adults with known cardiovascular disease in the U.S., with about 59% of these patients having dyslipidemia.\(^2\) About 73.5 million American adults have an elevated low-density lipoprotein (LDL) level; and in 2009, there were 96 million healthcare visits which included ordering a lipid panel.\(^3\) Therefore, most healthcare providers, including physician assistants, will be involved in the care of patients with hypercholesterolemia and its effects. The estimated cost of cardiovascular disease in the U.S. in 2010 was $273 billion, and a MACE costs an average of $16,582.\(^2\) Despite the increase in medical technology and cardiovascular medications over the past century, cardiovascular disease accounted for 40% of deaths in high-income countries in 2010.\(^1\) This is likely due to the change in lifestyle and increased age in high-income countries over this time period, and is expected to increase.\(^4\)

PCSK9 monoclonal antibodies have been shown to reduce LDL cholesterol in patients also treated with statins.\(^5\) Patients with elevated LDL cholesterol have twice the risk for cardiovascular disease than patients without elevated LDL\(^3\), and this cardiovascular disease can lead to a MACE due to atherosclerosis. Lipid-lowering therapy can improve endothelial
dysfunction in the arterial lumen, correct abnormal vascular reactivity, and increase plaque stability.⁴

Lifestyle changes are implemented in the recommended treatment and prevention of hypercholesterolemia and MACE. These include a low-cholesterol diet, exercise, and weight reduction. HMG-CoA reductase inhibitors (statins) have become the mainstay for treatment of hypercholesterolemia.¹ Some other treatments that have controversial outcome studies include: bile acid sequestrants, nicotinic acid, fibric acid derivatives, and omega-3 fatty acids.¹ While statins have been shown to reduce MACE, there are still many patients on statins who have cardiac events or whose risk remains high for cardiac events, and there are patients who are statin-intolerant due to side effects.¹ When PCSK9 interacts with the LDL receptor, LDL levels increase. PCSK9 monoclonal antibodies act as an inhibitor of this interaction.¹ PCSK9 monoclonal antibodies (alirocumab and evolocumab) have been shown to significantly reduce LDL levels⁵,⁶,⁷, and reduction of LDL has been shown to lower cardiovascular risk. However, it is not clear whether PCSK9 monoclonal antibodies prevent MACE.

**OBJECTIVE**

The objective of this selective systematic review is to determine whether or not PCSK9 monoclonal antibodies plus standard of care (SOC) prevent major adverse cardiovascular events in adults with hypercholesterolemia compared to placebo plus SOC.

**METHODS**

One double-blinded randomized controlled trial (RCT) and two open-label RCTs were used in this study. The population includes patients at least 18 years old with an LDL>70 mg/dl and at least one of the following: coronary artery disease, coronary heart disease risk equivalent, or familial hypercholesterolemia. The interventions were the PCSK9 monoclonal antibodies
alirocumab or evolocumab, and the comparison was standard of care hypercholesterolemia treatment which most commonly included a statin. The Robinson, et al. double blinded RCT compared alirocumab to placebo for 78 weeks while both groups were being treated with a maximum-tolerated dose of statins with or without other lipid-lowering therapy. The change in LDL was calculated from baseline to week 24. A post-hoc analysis was done to assess MACE between the two groups up to 78 weeks after baseline. The Sabatine, et al. open-label RCT compared evolocumab plus SOC to SOC for 11.1 months. There was no placebo treatment. The Koren, et al. open-label RCT compared evolocumab plus SOC to SOC for 12 months. Outcomes measured for all 3 trials were MACE: death, MI, hospitalization for unstable angina, revascularization, or cerebrovascular event. (See Table 1 for more details)

Keywords used in the research of this paper included: alirocumab and cardiovascular events, evolocumab and cardiovascular events, and hypercholesterolemia. The articles were found on PubMed, and were published in English in peer-reviewed journals. The three articles were selected based on relevance to the objective, patient-oriented outcomes, and type of trial. Inclusion criteria included: randomized controlled trial including adults with hypercholesterolemia published after 2000, not researched by a previous PCOM student, and no published Cochrane meta-analyses or systematic reviews on this topic. Exclusion criteria included disease-oriented outcomes only. (See Table 1 for detailed inclusion/exclusion criteria per study.) Robinson, et al. and Sabatine, et al. reported the following statistics: hazard ratio, p-value, relative risk reduction (RRR), absolute risk reduction (ARR), and number need to treat (NNT). Koren, et al. reported: RRR, ARR, and NNT.
### Table 1 – Demographics & characteristics of included studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TYPE</th>
<th># PTS</th>
<th>AGE</th>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
<th>W/D</th>
<th>INTERVENTION</th>
</tr>
</thead>
</table>
| Robinson, 2015⁵      | Double blinded RCT | 2341  | 60.4 ± 10.4 years old | ≥18 yrs old w/ familial hypercholesterolemia, CAD, or CHD risk equivalent | • Use of meds that affect lipids  
• Plasmapharesis w/in 4 weeks  
• MACE, CABG, uncontrolled arrhythmia, PCI, carotid surgery, PVD intervention w/in 3 months  
• NYHA Class III or IV  
• SBP>180 or DBP>110  
• Hx of stroke (hemorrhagic)  
• Active optic nerve disease  
• Systemic steroid use  
• HRT  
• HIV +  
• Cancer w/in 5 years | 470 | Alirocumab 150 mg as a 1 mL SC injection q2weeks |
| Sabatine, 2015⁶      | Open Label RCT | 4465  | ≥18 years old  
Mean age = 58 years old | ≥18 years old with hypercholesterolemia  
Participation in 1 of the following trials: Mendel 1 & 2, Laplace TIMI 57, Laplace 2, Gauss 1 & 2, Rutherford 1 & 2, Yukawa 1, Descartes, Thomas 1 & 2 | • Adverse events in parent trial  
• Unstable medical condition  
• Need of unblinded lipid measurements for 1st 12 weeks | 204 | Evolocumab 140mg SC q2weeks or 420mg SC q4weeks |
OUTCOMES MEASURED

The outcomes measured in this paper are major adverse cardiovascular events, which include the following: death, myocardial infarction, hospitalization for unstable angina, revascularization, or cerebrovascular event. Any adverse event was reported using patient-reported symptoms or events/hospitalizations, laboratory tests, vital signs, and EKG. These events were reported either in person at office visits or via telephone.\(^5,6,7\)

RESULTS

This review included one study comparing alirocumab plus a statin to placebo plus a statin, and two studies comparing evolocumab to standard of care hypercholesterolemia treatments. All the trials included adult patients with hypercholesterolemia. Two of the trials included patients from one of many parent trials. Efficacy and safety were investigated in the trials and were presented as dichotomous data, with the outcome of having a MACE or not.

The Robinson, et al. trial was a double-blinded RCT initially investigating the efficacy and safety of long-term alirocumab treatment, and then investigating MACE associated with the treatment group versus placebo group. There were 2431 patients enrolled and randomized in the study over 320 sites worldwide. The participating patients were required to be on a maximum-tolerated dose of statin and still have LDL >70 mg/dl at the time of screening. All patients were
instructed to follow a cholesterol-lowering diet, exercise, and quit tobacco products. However, tobacco use did not exclude patients from this study. Patients were excluded from participation if they were using any product that affects lipid levels except statins or fenofibrate to ensure the results were truly due to the study drug. Patients could not have received plasmapheresis within two months prior to screening or plan to receive it during the study, so that LDL and other bloodwork could be accurately obtained. Although patients in this trial must be at significant cardiovascular risk, patients were excluded if they had a MACE, cardiac surgery, or hospitalization within three months prior to screening. Patients were excluded if they were NYHA Class III or IV heart failure within 12 months of screening or had systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg at time of screening. Other conditions that excluded patients included: hemorrhagic stroke, active optic nerve disease, homozygous familial hypercholesterolemia, known loss of function of PCSK9, cancer within five years, HIV positivity, pregnancy/breastfeeding, or hepatitis B or C. Patients using systemic corticosteroids or hormone replacement therapy were excluded, as well as those patients with any of the following lab values: triglyceride levels >400 mg/dl as it becomes difficult to measure LDL, eGFR <30 ml/min, HbA1c>10%, ALT or AST >3x upper normal limit, or CPK >3x upper normal limit. This study used a mixed effects model to account for those patients lost to follow up during the study – 20.9% of the alirocumab group and 18.5% of the placebo group were lost to follow up. There was a lower incidence of MACE in the alirocumab group (1.7% of patients) than in the placebo group (3.3% of patients) with a 95% confidence interval (0.31 to 0.90) and \( p=0.02 \). The hazard ratio was 0.52, indicating that if a patient on a statin adds alirocumab to his/her regimen, he/she will be about half as likely to have a MACE compared to the placebo group on a statin. The NNT for this study was -62, indicating that for every 62 patients taking
alirocumab in addition to a statin for the prevention of MACE, there was 1 fewer incidence of MACE when compared to patients taking placebo plus a statin. Myalgia was the most significant adverse event associated with the alirocumab group, with 5.4% of the treatment group and 2.9% of the placebo group reporting myalgia; \( p = 0.006 \). The number need to harm (NNH) for myalgia was 40, indicating that for every 40 patients treated with alirocumab plus statin, 1 more incidence of myalgia occurs compared to those taking placebo plus a statin. A higher percentage of patients also reported neurocognitive disorders (amnesia, memory impairment, or confusional state) in the alirocumab group when compared to the placebo group, 1.2% to 0.5%, respectively. However, this result was not found to be significant, \( p = 0.17 \).

The Sabatine, et al. trial was an open-label RCT conducted at 305 sites and was first investigating the longer-term efficacy and safety of evolocumab, and then investigated MACE in treatment versus SOC groups. There were 4465 patients randomized, with 3128 of those on a statin. Inclusion criteria for this trial was completion of one of the parent studies without any adverse events that caused discontinuation. The parent trials had slightly different inclusion criteria but all had LDL of at least 75 mg/dl. Patients in the MENDEL parent trials were not on any other lipid therapy. Patients in the LAPLACE, YUKAWA, DESCARTES, and THOMAS parent trials were on statins. Patients in the GAUSS parent trials were statin-intolerant. Patients in the RUTHERFORD parent trials had heterozygous familial hypercholesterolemia and were taking a statin. Exclusion criteria for this trial were: any unstable medical condition, need for unblinding of LDL results within first 12 weeks of the trial, or need for adjustment of background lipid therapy within first 12 weeks of the trial. There were 4.88% of patients in the treatment group and 3.96% in the SOC group that were lost to follow up. There was a lower incidence of MACE in the evolocumab group (0.95% of patients) than in the SOC group (2.11%
of patients) with a 95% confidence interval (0.28 to 0.78) and \( p = 0.003 \). The hazard ratio was 0.47, indicating that if a patient adds evolocumab to his/her regimen, he/she will be about half as likely to have a MACE compared to the SOC group. The NNT for this study was -93, indicating that for every 93 patients taking evolocumab for the prevention of MACE, there was 1 fewer incidence of MACE when compared to patients taking SOC hypercholesterolemia treatment. The NNH for myalgia was 250, indicating that for every 250 patients treated with evolocumab, 1 more incidence of myalgia occurs compared to those taking SOC medications. There were 0.9% of patients in the treatment group that reported neurocognitive events, compared to the 0.3% in the SOC group.

The Koren, et al. trial was an open-label RCT conducted at 156 sites, also first investigating efficacy and safety of evolocumab versus SOC, then investigating MACE. There were 1104 patients randomized in this trial, inclusion criteria was participation in one of four phase 2 parent trials without discontinuation due to adverse event. The parent trials included MENDEL, LAPLACE, GAUSS, and RUTHERFORD. Exclusion criteria for this trial included: any unstable medical condition, need for unblinding of LDL results within first 12 weeks of the trial, or need for adjustment of background lipid therapy within first 12 weeks of the trial. There were 7.47% in the treatment group and 10.6% in the SOC group that were lost to follow up during the study. There was a lower incidence of MACE in the evolocumab group (1.2% of patients) than in the SOC group (2.2% of patients). The NNT for this study was -105, indicating that for every 105 patients taking evolocumab for the prevention of MACE, there was 1 fewer incidence of MACE when compared to patients taking SOC hypercholesterolemia treatment. The NNH for myalgia was -166, indicating that for every 166 patients treated with evolocumab, 1 fewer incidence of myalgia occurs compared to those taking SOC medications. This differs from
the previous two studies in that more patients in the control group had myalgia than in the
treatment group. There were 1.09% of patients in the treatment group that reported amnesia or
memory impairment, compared to 0% in the SOC group.

**Table 2 – Treatment effects**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><em>p</em>-value</td>
<td>0.02</td>
<td>0.003</td>
<td>N/A</td>
</tr>
<tr>
<td>Confidence Interval</td>
<td>95% (0.31-0.90)</td>
<td>95% (0.28-0.78)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.52</td>
<td>0.47</td>
<td>N/A</td>
</tr>
<tr>
<td>RRR</td>
<td>-0.485</td>
<td>-0.5323</td>
<td>-0.4378</td>
</tr>
<tr>
<td>ARR</td>
<td>-0.016</td>
<td>-0.0107</td>
<td>-0.0095</td>
</tr>
<tr>
<td>NNT</td>
<td>-62</td>
<td>-93</td>
<td>-105</td>
</tr>
</tbody>
</table>

**Table 3 – Safety and adverse effects - Myalgia**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>p</em>-value</td>
<td>0.006</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>RRR</td>
<td>0.862</td>
<td>0.067</td>
<td>-0.061</td>
</tr>
<tr>
<td>ARR</td>
<td>0.025</td>
<td>0.004</td>
<td>-0.006</td>
</tr>
<tr>
<td>NNH</td>
<td>40</td>
<td>250</td>
<td>-166</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Alirocumab and evolocumab are monoclonal antibodies used to lower LDL cholesterol
levels that were approved by the FDA in 2015.⁸,⁹ Adverse effects reported for alirocumab
include: diarrhea, influenza, injection site reaction, myalgia, and cough.⁸ Adverse effects
reported for evolocumab include: nasopharyngitis, URI, dizziness, gastroenteritis, UTI,
influenza, local site reaction, and myalgia.⁹ Both reported contraindications with another
monoclonal antibody, belimumab. Two studies showed an increase in the number of patients who experienced myalgia who were on the experimental drug, while Koren, et al. showed more patients in the control group reported myalgia. It is unknown if this myalgia is due to the experimental drugs or due to the statins that most patients were on concurrently.

While all of these studies had a goal of evaluating LDL levels first, they also evaluated the outcomes of using PCSK9 monoclonal antibodies. It was not previously known if these agents prevented MACE, but all three trials showed a decrease in MACE when using the PCSK9 inhibiting drug compared to placebo or SOC over about one year. The Koren, et al. trial did not provide p-values, confidence intervals, or hazard ratios, while the other two trials did include these important statistical values. In addition, the Koren, et al. trial and the Sabatine, et al. trial included patients from some of the same parent trials, so it is unknown if the same patients were being accounted for twice in this review. While the monoclonal antibodies have the same mechanism of action, the actual drug was different in the Robinson, et al. trial – alirocumab was used instead of evolocumab. When looking at the NNT to prevent a MACE, it appears that alirocumab is more effective. It also appears that the NNH for myalgia is lower in the alirocumab study. However, more studies would have to be done to compare the two drugs. Finally, the Robinson, et al. trial was double-blinded and was more controlled than the other two trials. Therefore, the Sabatine, et al. and Koren, et al. trials may not be as valid.

CONCLUSIONS

This review showed that PCSK9 inhibitors prevented major adverse cardiac events when compared to standard of care treatment in adults with hypercholesterolemia over about one year. Longer-term studies could be done to see if safety and efficacy is maintained. Since there were two different drugs being investigated, future double-blinded RCTs could be done to
see which drug prevents more MACEs and which drug has more adverse events. There were also
different factors among the three studies that affected each patient’s individual risk for MACE,
like whether patients were also taking a statin during the study or whether patients had familial
hypercholesterolemia. If patients were already on statins, it is possible their risk would be lower
at the start of the study than a statin-intolerant patient. Overall, more studies would have to be
done to create a more-detailed picture of which specific populations would benefit greatly from
PCSK9 monoclonal antibodies.
REFERENCES


