Research Prioritization Topic Brief: Comparative Effectiveness of Non-Statins, Epecifically Ezetimibe and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors, for Patients with High Cholesterol Who Did Not Respond to Maximally-Tolerated Statins or Who Are Intolerant of statins

This report was prepared by Johns Hopkins University. Quality. All statements, findings and conclusions in this publication are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI) or its Board of Governors. This publication was developed through a contract to support PCORI's work and is being made available free of charge for the information of the scientific community and general public as part of PCORI's ongoing research programs. Questions or comments may be sent to PCORI at info@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

Assessment of Prevention, Diagnosis and Treatment Options

PCORI Scientific Program Area:
Comparative Effectiveness Research

Executive Summary

Overall Comparative Research Question: What is the comparative effectiveness of non-statins, specifically ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitors), for patients with high cholesterol who did not respond to maximally tolerated statins or who are intolerant of statins?

Brief Overview of the Topic: Despite the well-established efficacy and safety of statins, residual cardiovascular disease (CVD) risk remains among patients receiving intensive statin therapies and those who cannot tolerate statins.[1-5] Ezetimibe and PCSK9 inhibitors are promising new lipid-lowering agents that may benefit these patients.

Patient-Centeredness: Managing high cholesterol is an imperative to many patients and their doctors because high total cholesterol and low-density lipoprotein cholesterol (LDL-c) cause atherosclerosis, the key underlying process contributing to most clinical atherosclerotic CVD events.

Impact on Health and Populations: Nearly 73.5 million Americans age 20 years or older had high LDL-c (≥ 130 mg/dL) in 2012. About 40% of patients receiving statins are not able to reach target LDL-c levels. Muscle syndromes, the most common adverse events of statin occur in 10-15% of patients under a statin therapy. Long-term, high-dose statins are also associated with an increased incidence of diabetes.

Assessment of Current Options: US and international guidelines recommended addition of non-statin cholesterol-lowering drugs to maximum tolerated statins for patients who continue to have a less-than-anticipated therapeutic response, and for patients who are intolerant of statins. All these guidelines and systematic reviews on this topic predated IMPROVE-IT, the first randomized controlled trial that showed an incremental benefit of adding ezetimibe to a moderate intensity statin on clinical endpoints in a high-risk population. However, the comparative effectiveness and safety of statin-ezetimibe combination therapy in low/moderate risk groups is unknown. PCSK9 inhibitors are being tested in four large ongoing CVD outcome trials and in five trials involving statin intolerant patients (not powered for CVD events). The practical definitions for statin intolerance used in individual trials and in clinical practice are highly variable and may impede the interpretation of the results. There might be value for bringing back the LDL-c treatment goals and assess whether treating to a specific target confers

benefit. The treatment strategies for patients experiencing statin side effects should be tested in clinical trials.

Likelihood of Implementation of Research Results in Practice: Given the high disease burden, general interest in this topic, and the existence of practice guidelines, it is likely that reliable research evidence will be implemented in practice.

Durability of Information: This is a fast-evolving topic with new agents brought to the market as recently as 2015. New information from comparative effectiveness research focusing on CVD and patient-centered outcomes will take years to accumulate, but is likely to remain current for several years.

Topic 8: Comparative effectiveness of non-statins, specifically ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, for patients with high cholesterol who did not respond to maximally tolerated statins or who are intolerant of statins?

1. Contributors:

Tianjing Li, MD, MHS, PhD - Johns Hopkins Evidence-based Practice Center
Erin Michos, MD, MHS - Johns Hopkins School of Medicine
Catalina Suarez-Cuervo, MD - Johns Hopkins Evidence-based Practice Center
Eric B. Bass, MD, MPH - Johns Hopkins Evidence-based Practice Center

2. Introduction:

The 2013 guidelines from the American Heart Association and the American College of Cardiology (AHA/ACC) moved away from treating a cholesterol target to treating people at elevated risk.[6] The guidelines emphasized that people at increased risk for cardiovascular disease (CVD) benefit from statin therapy across a broad range of low-density lipoprotein cholesterol (LDL-c) values, and that statins should be considered as the first line treatment for hyperlipidemia.[6] Despite the comprehensive use of statins, cardiovascular risk remains among some patients who are on maximum tolerated intensity of statins, or those who cannot tolerate statins because of their side-effects.

Patients who are intolerant to statins usually present with muscle discomfort, soreness, tenderness, pain, or weakness (myalgias). In most instances, the symptoms are mild and are rarely associated with muscle inflammation (myositis), markers of muscle injury (creatine kinase elevation), or death of muscle fibers (rhabdomyolysis).

Recent research has found that novel lipid-lowering agents, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may provide additional cardiovascular benefit when used in combination with statins. They also may be an alternative for statin intolerant patients.

Ezetimibe lowers plasma cholesterol by decreasing cholesterol absorption in the small intestine and the amount of cholesterol normally available to liver cells. The mechanism of how ezetimibe works appears to be independent and additive to that of a statin.[7] Ezetimibe was approved by the U.S. Food and Drug Administration (FDA) in 2002 for lowering cholesterol levels in patients with primary hyperlipidemia. In a high-risk patient population with acute coronary syndromes, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that, when added to a moderate intensity statin therapy (simvastatin 40mg), ezetimibe resulted in an incremental lowering of LDL-c and a modest reduction in rates of major cardiovascular events with no increase in cancer risk.[8,9] Furthermore, post-hoc analyses of IMPROVE-IT showed that those that achieved even lower LDL-c (< 70 mg/ml) had

lower cardiovascular events, supporting the "LDL" hypothesis (i.e., the lower LDL-c the better in high risk patients using proven therapies).[10-12] The incremental benefit of simvastatin-ezetimibe combination therapy in low or moderate risk patients remains unknown, as does the comparative effectiveness of the combination therapy relative to a high intensity statin.

PCSK9 inhibitors are monoclonal antibodies that inactivate PCSK9. They lower cholesterol levels by decreasing LDL receptor degradation and increasing recirculation of the receptor to the surface of hepatocytes.[13-15] Alirocumab and evolocumab, both given by subcutaneous injection, were approved by the FDA in 2015 for use in addition to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or patients with clinical atherosclerotic CVD who require additional lowering of LDL-c.[16,17] These agents have shown marked LDL-c lowering effect (by 60% or more) and promising short-term efficacy data with reduction in myocardial infarctions and all-cause mortality without increased risk of serious adverse events.[18] However, their long-term effectiveness on CVD endpoints and safety are currently unknown.[14-16] Several ongoing, large randomized clinical trials (RCTs) powered for CVD endpoints should answer this question in the next few years (see under "6. Ongoing Research"). It is worth noting that PCSK9 inhibitors are not approved for use in statin intolerant patients.

Other non-statin lipid lowering therapies include niacin, fibrates, omega 3 fatty acids, and cholesterylester transfer protein inhibitors, which may improve atherogenic dyslipidemia and have benefit as monotherapy. However, none of these agents have demonstrated additional CVD benefits when added to a statin therapy in clinical trials.

3. Patient-Centeredness:

Because of the role of high total cholesterol and LDL-c in the underlying process contributing to most clinical atherosclerotic CVD events, managing high cholesterol levels is an imperative to many patients and their doctors. Atherosclerosis is a systemic process and can present as coronary, cerebrovascular, or peripheral vascular diseases. In 25% of individuals, sudden cardiac death is the first manifestation of CVD. Coronary heart disease is the cause of about 75% of sudden cardiac deaths in the western world.[19] Cholesterol-lowering medications have to demonstrate their effect on reducing clinical endpoints and improving patient-centered outcomes, including CVD events, survival, side effects, and quality of life. Furthermore, the 2013 AHA-ACC cholesterol guidelines, while endorsing statins as the first line therapy, also emphasized the importance of a shared decision making process between patients and their providers.[20] Patient engagement requires careful benefit-risk assessment for patients with different absolute risk for CVD as well as consideration of patient preferences for treatment strategies, which may in turn help to promote medication adherence.

4. Impact/Burden of the Condition:

Nearly 73.5 million Americans age 20 years or older (32% of this age group) had LDL-c greater than or equal to 130 mg/dL in 2012.[21,22] About 28% of the population older than 40 years old was using a cholesterol-lowering medication. From those, 93% were receiving a statin.[23] Statin use increases with age, but did not differ by sex or ethnicity.[21] Among those patients treated with high intensity statin therapy, more than 40% did not reach a LDL-c of less than 70 mg/dL.[24,25] The majority of Medicare beneficiaries do not fill prescriptions for high-intensity statins after hospitalization for coronary heart disease events, showing underutilization of statins in the high risk population.[26] One study estimated that adherence with statin therapy in the elderly patients is only 40% for those with recent acute coronary syndrome, 36% for chronic coronary artery disease, and 25% for primary prevention at 2 years following stain initiation.[27]

Muscle syndromes are observed in 10-15% of patients after statin therapy, but very few develop serious adverse events such as myopathy (3-5% of patients), myositis (0.1-0.2% of patients) or rhabdomyolysis (0.01% of patients).[25,28,29] An elevated hepatic enzyme (aminotransferase) occurs in 0.5 to 2% of patients.[30] Long-term, high-dose statin therapy has been reported to increase the incidence of diabetes.[31-33] Many patients who experience muscle syndromes can take a statin after switching to a different statin or an alternative statin regimen, dose, or type. Up to 5% of patients discontinue statins due to drug-related adverse events.[32,33]

Many definitions for statin intolerance exist. The 2015 position paper from the International Lipid Expert Panel provided a "unified definition" as follows:[25]

1. *the inability to tolerate at least 2 different statins – one statin at the lowest starting average daily dose and the other statin at any dose*;
2. *intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities;*
3. *symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation*;
4. *symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of statin intolerance*.

5. Evidence Gaps:

Guidelines issued by the AHA/ACC[6], European Society of Cardiology/European Atherosclerosis Society, [30] the Japan Atherosclerosis Society,[34] the National Institute for Health and Clinical Excellence,[35 45] and the International Atherosclerosis Society[36] recommended addition of non-statin cholesterol-lowering drugs to maximum tolerated intensity of statin for patients who continue to have a less-than-anticipated therapeutic response; and the use of non-statins for patients who are intolerant of statins.

Evidence gaps at the time of the guideline

The guideline panels acknowledged that these recommendations were based on expert opinion rather than evidence from clinical trials at the time of the guideline development (which pre-dated IMPROVE-IT). Specifically, the 2013 AHA/ACC Expert Panel found no data supporting the routine use of non-statin drugs combined with statin therapy to further reduce CVD events. In addition, they found no RCTs that assessed CVD outcomes in statin intolerant patients.

Ezetimibe

IMPROVE-IT[8] is the first RCT that showed an incremental benefit of adding a non-statin lipid-lowering agent to a moderate intensity statin therapy on clinical endpoints in high-risk patients who recently experienced an acute coronary syndrome. This study found that simvastatin-ezetimibe combination therapy resulted in a lower LDL-c (53.7 mg/dL) than simvastatin monotherapy (69.5 mg/dL). The event rate for the primary end point, a composite of cardiovascular death, major coronary event, or nonfatal stroke, at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (hazard ratio, 0.94; 95% confidence interval, 0.89 to 0.99; P=0.016). While the relative risk reduction seems modest (6%), given the high absolute risk of recurrent events among this high risk population, the number needed to treat of 50 is very acceptable. The two groups had similar rates of muscle, gallbladder, and hepatic adverse effects, and cancer.

None of the systematic reviews on ezetimibe included the results from IMPROVE-IT. In the absence of clinical endpoints such as CVD events, these systematic reviews found that:

- For patients in whom a statin is considered inappropriate or is not tolerated, ezetimibe is effective in reducing LDL-c when administered as monotherapy (mean difference: -18.56%; 95% confidence interval: -19.68% to -17.44%).[37] When used as a monotherapy, the ability of ezetimibe to lower LDL-c is less effective than that of statins.
- For patients whose condition is not adequately controlled with a statin monotherapy, adding ezetimibe to a statin therapy is significantly more effective in reducing LDL-c than statin alone (fixed-dose studies; mean difference: -13.94%; 95% confidence interval -14.90% to -12.98%)[37] or doubling statin dose alone (titration studies; mean difference: -14.1%; 95% confidence interval: -16.1% to -12.1%).[38]

PCSK9 inhibitors

The most recent systematic review on PCSK9 inhibitors included 24 RCTs comprising 10,159 patients.[18] Twelve trials compared a PCSK9 inhibitor with placebo alone; and the remaining twelve trials compared a PCSK9 inhibitor with ezetimibe and/or placebo. Twelve trials were of patients with familial hypercholesterolemia, nine were of nonfamilial or unspecified hypercholesterolemia, two were of statin-intolerant hypercholesterolemia, and one was of mixed familial and nonfamilial hypercholesterolemia. Except for four trials, all other trials used a background statin therapy. This systematic review showed a benefit in mortality with PCSK9

inhibitors. The review found that, compared with no PCSK9 inhibitors, treatment with PCSK9 inhibitors

- Reduced all-cause mortality: odds ratio 0.45; 95% confidence interval (0.23 to 0.86);
- Did not result in a statistically significant reduction in CVD mortality: odds ratio 0.50; 95% confidence interval (0.23 to 1.10);
- Reduced myocardial infarction: odds ratio 0.49; 95% confidence interval (0.26 to 0.93);
- Reduced LDL-c: mean difference -47.49%; 95% confidence interval (−69.64% to −25.35%);
- Reduced the incidence of an increase in serum creatine kinase levels: odds ratio 0.72; 95% confidence interval (0.54 to 0.96);
- Did not increase serious adverse events: odds ratio 1.01; 95% confidence interval (0.87 to 1.18).

Three trials recruited statin intolerant patients (ODYSSEY ALTERNATIVE, GAUSS, and GAUSS-2). ODYSSEY ALTERNATIVE found that, compared with ezetimibe, alirocumab lowered LDL-c 30% more, but the trial was not powered to examine clinical endpoints. In GUASS and GUASS-2, treatment with evolocumab resulted in a 41% to 51% reduction in the LDL-c level; and there was no statistically significant effect on clinical endpoints compared with placebo. The overall effect is robust based on sensitivity analyses by type and dose of PCSK9 inhibitors, and subgroup analyses stratified by placebo or ezetimibe as the control arm and by background statin therapy.

6. Ongoing Research:

We found 262 records by searching “ezetimibe” and 92 records by searching “PCSK9 inhibitors OR alirocumab OR evolocumab” on ClinicalTrials.gov (search date January 16, 2016). All of these records registered lipids level as an outcome and only a few registered CVD endpoints.

For ezetimibe, we did not find any ongoing CVD outcomes trials.

For PCSK9 inhibitors, we identified four large ongoing CVD outcomes trials, all in a high-risk population (expected completion by 2018).

- FOURIER (NCT01764633) compares evolocumab added to an effective statin therapy (defined as ≥ atorvastatin 20 mg or an equivalent statin) with an effective statin therapy alone in patients with established CVD. The trial is expected to enroll 27,564 patients.
- ODYSSEY Outcomes trial (NCT01663402) compares alirocumab with placebo on major adverse CVD events in patients who recently experienced an acute coronary syndrome. The trial is expected to enroll 18,600 patients.
- SPIRE-1 (NCT01975376) and SPIRE-2 (NCT01975389), the two phase 3 pivotal trials for bococizumab, compare bococizumab with placebo in more than 22,000 patients who are receiving background lipid lowering therapy. SPIRE-1 also will assess whether lowering LDL-c to levels well below current guideline-recommended targets will lead to further reduction in CVD events.

For statin intolerant patients, we identified five ongoing studies, GAUSS-3 (NCT01984424), GAUSS-4 (NCT02634580), CHOLESS (NCT01807078), ECLIPSE (NCT01490229), and NCT00972829. Two of these trials included a comparison between ezetimibe and a PCSK9 inhibitor. None of these five studies registered CVD endpoints. In addition, the definition for statin intolerance varies from study to study. For example, some studies included "patients not on a statin or on a low dose statin with stable dose for at least 4 weeks; and a history of statin intolerance to at least 2 statins." Other studies simply described "patients with a history of statin intolerance."

Our search of the NIH reporter and PCORI's website did not identify any currently funded clinical trials that focus specifically on this topic.

7. Likelihood of Implementation of Research Results in Practice:

Given the high disease burden, the high residual risk for atherosclerotic CVD events among statin treated patients,[1-5] general interest in this topic, and the existent of practice guidelines, it is likely that the research results will be implemented in practice. The current guideline recommendations will need to be updated to include the latest evidence (i.e., IMPROVE-IT). However, some clinicians and patients may still feel uncomfortable with aggressive cholesterol-lowering therapies.

8. Durability of Information:

This is a fast-evolving topic with new agents brought to the market as recently as 2015. New information from comparative effectiveness research focusing on patient-centered outcomes (not purely surrogate outcome of LDL-c level) will take years to accumulate, but is likely to remain current for several years.

9. Potential Research Questions:

There is no universally accepted definition for statin intolerance; and the practical definitions used in individual studies and in clinical practice are highly variable. The "unified" definition provided by the International Lipid Expert Panel in 2015 is an attempt to harmonize the definitions out there. The European Atherosclerosis Society, on the other hand, suggested focusing on statin associated muscle symptoms and avoiding use of the term "statin intolerance."[39,40] A clear definition of this phenomenon and a wide acceptance by the community are crucial to understand the "true" prevalence of statin intolerance, effectively recruit eligible patients into clinical trials, and ultimately guide clinicians in deciding whether to continue statins or use non-statin lipid lowering drugs.

- What is the comparative effectiveness of statin-ezetimibe combination therapy in different risk groups compared to statin monotherapy?
  IMPROVE-IT showed benefit of simvastatin-ezetimibe combination therapy in a very high-risk population. Would adding ezetimibe to a statin also benefit (1) lower-risk patients as secondary prevention and (2) high-risk patients as primary prevention?

- What are the longer-term clinical benefits and safety of PCSK9 inhibitors, especially in patients with high absolute risk for CVD but intolerant to statins?
  PCSK9 inhibitors have not been proven to prevent CVD in patients intolerant of statin therapy (primary prevention). None of the ongoing trials on PCSK9 inhibitors are being conducted in patients with low or moderate risk of CVD. The long-term side effects of PCSK9 are also unknown.

- What is the comparative effectiveness of different treatment strategies for patients experiencing statin side-effects?
  The care process for patients who experience side-effects from a stain typically involves: 1) ruling out reversible causes such as medication interaction; 2) with mild symptoms, try reducing the dose of statin; 3) with intolerable symptoms, stop the statin; 4) when symptoms resolve, attempt re-challenge with a low dose of the same statin, intermittent dosing of the same statin, or an alternative statin; and 5) if symptoms return, use a non-statin based cholesterol lowering medication.[41] The exact process varies, as it is not clear what strategy works best to lower cardiovascular risk without causing serious side-effects. The benefits of statins are large and potentially lifesaving. Thus, patients and their physicians must weigh the risk of drug discontinuation versus the benefits before making permanent decisions.

- What is the comparative effectiveness of lipid-lowering treatment with versus without using a specific LDL-c treatment goal?
  The 2013 AHA/ACC guidelines moved away from LDL-c treatment goals because the lack of RCTs explicitly designed to test treatment goals. The National Lipid Association Expert Consensus's view[42] is that treatment goals are still useful because they facilitate communication between patients and clinicians, providing an easily interpretable means to support long-term adherence to the treatment plan. There is also concern that prescribing moderate- to high-intensity statins without treatment targets may result in under-treatment. In addition, the data from IMPROVE-IT gave credence to the "LDL-c hypothesis" rather than the "statin hypothesis:"[43] reducing LDL-c levels, regardless of the means, should produce a corresponding reduction in CVD events in patients at high absolute risk, and that further lowering of LDL-c confers additional benefit. However, this concept should only be extended to drugs with proven benefit and not to all lipid-modifying drugs. Previous trials on combination therapy of niacin,[44,45] fibrates,[46] and dalcetrapib (a cholesterylester transfer protein inhibitor)[47] with statins did not show incremental cardiovascular benefits.

10. Conclusion:

Ezetimibe and PCSK9 inhibitors are promising new lipid-lowering agents that are likely to benefit patients who continue to have a less-than-anticipated therapeutic response on maximally tolerated statins and patients who are intolerant of statins. The comparative effectiveness and safety of statin-ezetimibe combination therapy in low/moderate risk patients is unknown, and should be studied. PCSK9 inhibitors should be evaluated in well-defined statin intolerant patients with clinical endpoints and patient-centered outcomes measured. New studies could help to determine the value of using LDL-c treatment goals for patients taking ezetimibe and PCSK9 inhibitors.

APPENDIX

Methods

Literature search:

From December 2015 to February 2016, we conducted a literature search to identify reports around the effectiveness of non-statins, specifically ezetimibe and PCSK9 inhibitors, for patients with high cholesterol who did not respond to maximally tolerated statins or who are intolerant of statins. We searched the Cochrane Database of Systematic Reviews, the Agency for Healthcare Research and Quality's website, and PubMed for recent systematic reviews. We searched the websites of government agencies (such as the Centers for Disease Control and Prevention, and the NIH), and relevant professional associations (i.e., The American Heart Association, The American College of Cardiology, the European Heart Association, the International Atherosclerosis Society and other international societies) for practice guidelines and reports that contain data on the disease burden and impact of the condition on the population.

Ongoing studies:

We searched clinicaltrials.gov on January 16, 2016 for studies relevant to the topic. We used the broad search terms "ezetimibe" and "PCSK9". The results are described in the report. We searched NIH reporter (https://projectreporter.nih.gov/reporter.cfm) on February 10, 2016 for studies relevant to the topic. We used "text search" box and searched on "ezetimibe" and "PCSK9" separately. We searched PCORI's funded research database (http://www.pcori.org/research-results) on February 10, 2016 using terms "ezetimibe" and "PCSK9" separately. We did not find any awards that match the search.

References for topic Comparative effectiveness of non-statins, specifically ezetimibe and PCSK9 inhibitors, for patients with high cholesterol who did not respond to maximally tolerated statins or who are intolerant of statins?

1. Wong ND, Chuang J, Zhao Y, Rosenblit PD. Residual dyslipidemia according to low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B among statin-treated US adults: National Health and Nutrition Examination Survey 2009-2010. *J Clin Lipidol.* Jul-Aug 2015;9(4):525-532.
2. Fruchart JC, Sacks F, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol.* Nov 17 2008;102(10 Suppl):1k-34k.
3. Campbell CY, Rivera JJ, Blumenthal RS. Residual risk in statin-treated patients: future therapeutic options. *Curr Cardiol Rep.* Nov 2007;9(6):499-505.
4. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. *Circulation.* Apr 24 2012;125(16):1979-1987.
5. Sampson UK, Fazio S, Linton MF. Residual Cardiovascular Risk Despite Optimal LDL-Cholesterol Reduction with Statins: The Evidence, Etiology, and Therapeutic Challenges. *Curr Atheroscler Rep.* 2012;14(1):1-10.
6. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Jul 1 2014;63(25 Pt B):2889-2934.
7. Smith BA, Wright C, Davidson M. Role of Ezetimibe in Lipid-Lowering and Cardiovascular Disease Prevention. *Curr Atheroscler Rep.* Dec 2015;17(12):72.
8. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New Engl J Med.* Jun 18 2015;372(25):2387-2397.
9. Murphy SA, Cannon CP, Blazing MA, et al. Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. *J Am Coll Cardiol.* Feb 2 2016;67(4):353-361.
10. Michos ED, Martin SS, Blumenthal RS. Bringing back targets to "IMPROVE" atherosclerotic cardiovascular disease outcomes: the duel for dual goals; are two targets better than one? *Circulation.* Sep 29 2015;132(13):1218-1220.
11. Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation.* Sep 29 2015;132(13):1224-1233.
12. Wright RS, Murphy J. PROVE-IT to IMPROVE-IT: Why LDL-C Goals Still Matter in Post-ACS Patients. *J Am Coll Cardiol.* Feb 2 2016;67(4):362-364.
13. Joseph L, Robinson JG. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibition and the Future of Lipid Lowering Therapy. *Progr Cardiovasc Dis.* Jul-Aug 2015;58(1):19-31.
14. Turner T, Stein EA. Non-statin Treatments for Managing LDL Cholesterol and Their Outcomes. *Clin Ther.* Dec 1 2015;37(12):2751-2769.

15. Everett BM, Smith RJ, Hiatt WR. Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs. *N Eng J Med.* 2015;373(17):1588-1591.
16. Food and Drug Administration. FDA approves Praluent to treat certain patients with high cholesterol. FDA News Release2015.
17. Food and Drug Administration. FDA approves Repatha to treat certain patients with high cholesterol2015.
18. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Int Med.* Jul 7 2015;163(1):40-51.
19. Deo R, Albert CM. Epidemiology and Genetics of Sudden Cardiac Death. *Circulation.* January 31, 2012 2012;125(4):620-637.
20. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol.* Apr 7 2015;65(13):1361-1368.
21. Centers for Disease Control and Prevention. High Cholesterol Facts. 2015; High Cholesterol in the United States. Available at: http://www.cdc.gov/cholesterol/facts.htm. Accessed December 10, 2015.
22. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association. *Circulation.* December 16, 2015 2015.
23. Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. *NCHS data brief.* Dec 2014(177):1-8.
24. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol.* Aug 5 2014;64(5):485-494.
25. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sc.* Mar 16 2015;11(1):1-23.
26. Rosenson RS, Kent ST, Brown TM, et al. Underutilization of High-Intensity Statin Therapy After Hospitalization for Coronary Heart Disease. *J Am Coll Cardiol.* 2015;65(3):270-277.
27. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA.* Jul 24-31 2002;288(4):462-467.
28. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Int Med.* Jun 16 2009;150(12):858-868.
29. Grundy SM. Can statins cause chronic low-grade myopathy? *Ann Int Med.* Oct 1 2002;137(7):617-618.
30. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J.* Jul 2011;32(14):1769-1818.
31. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. *BMJ.* 2014;349:g3743.
32. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet.* Feb 27 2010;375(9716):735-742.
33. 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.* Oct 2009;32(10):1924-1929.

34. Teramoto T, Sasaki J, Ishibashi S, et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. *J Atheroscler Thromb.* 2013;20(6):517-523.

35. NICE. National Institute for Health and Clinical Excellence: Guidance. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease*. London: National Institute for Health and Care Excellence (UK) Copyright (c) National Clinical Guideline Centre, 2014.

36. International Atherosclerosis Society. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. *J Clin Lipidol.* Jan-Feb 2014;8(1):29-60.

37. Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* May 2008;12(21):iii, xi-xiii, 1-212.

38. Mikhailidis DP, Lawson RW, McCormick AL, et al. Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis. *Curr Medical Res Opin.* Jun 2011;27(6):1191-1210.

39. Kavousi M, Leening MG, Nanchen D, et al. Comparison of application of the acc/aha guidelines, adult treatment panel iii guidelines, and european society of cardiology guidelines for cardiovascular disease prevention in a european cohort. *JAMA.* 2014;311(14):1416-1423.

40. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* May 1 2015;36(17):1012-1022.

41. Fitchett DH, Hegele RA, Verma S. Statin Intolerance. *Circulation.* March 31, 2015 2015;131(13):e389-e391.

42. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol.* Mar-Apr 2015;9(2):129-169.

43. Jarcho JA, Keaney JF. Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT. *N Engl J Med.* 2015;372(25):2448-2450.

44. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *New Engl J Med.* Dec 15 2011;365(24):2255-2267.

45. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *New Engl J Med.* Jul 17 2014;371(3):203-212.

46. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *New Engl J Med.* Apr 29 2010;362(17):1563-1574.

47. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *New Engl J Med.* Nov 29 2012;367(22):2089-2099.