PURSUING THE NEXT STEP IN REDUCTION OF RESIDUAL CV RISK

Lipid Lowering: The Road to Current Treatment Guidelines

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The Development and Promise of PCSK9 Inhibitors

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LDL-C Remains the Single Best Target for CV Risk Reduction

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Guest Editor

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Lipid Lowering: The Road to Current Treatment Guidelines

On the basis of randomized trials over the past 2 decades, the treatment goals for low-density lipoprotein cholesterol (LDL-C) have been lowered repeatedly. In Canada, the current LDL-C goal for patients with high risk of cardiovascular (CV) events is ≤2.0 mmol/L or a ≥50% reduction from a pre-treatment level.[1] This represents a practical target for LDL-C reductions, even though the level of LDL-C with no additional CV risk reductions has yet to be defined. Whether or not newer, more effective therapies for control of LDL-C provide the evidence for another, yet still-lower LDL-C target, many Canadians with established CV disease or a risk equivalent are not at current goals. The reasons are varied, but such individuals represent a missed opportunity to avoid CV events and CV-associated mortality.

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Background

The evidence that LDL-C is a treatable risk factor for CV events predates the introduction of HMG-CoA reductase inhibitors (statins). In 1984, the Lipid Research Clinics - Coronary Primary Prevention Trial (LRC-CPPT) associated a 12.6% reduction in LDL-C with a 19% reduction in coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) over a median follow-up of 7.4 years.[2] In that placebo-controlled study, which enrolled more than 3800 men, the study agent was the bile acid sequestrant cholestyramine. The data from that study was employed to conclude that LDL-C might play a causal role in the pathogenesis for heart disease.

The lipid hypothesis has largely evolved into the lipid principle of CV risk management over many years of large trials with statins, a relatively well-tolerated and convenient therapy that facilitated treatment. The first of these large trials, the Scandinavian Simvastatin Survival Study (4S), associated a 35% reduction in LDL-C with a 42% reduction in coronary deaths and a 30% reduction in all-cause mortality after a median follow-up of 5.4 years.[3] In this secondary prevention study, simvastatin was compared to placebo in 4444 men and women with a previous MI or angina pectoris.

The landmark secondary and primary prevention trials that followed generated equally impressive reductions in CV risk. The earliest of these studies, such as the West of Scotland Coronary Prevention Study (WOSCOPS)[4] and the Heart Protection Study (HPS),[5] compared a statin to placebo. Subsequent studies, such as the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial and the Treating to New Targets (TNT) trial,[6,7] compared more aggressive to less aggressive lipid lowering. Each study supported the principle that lower is better in regard to LDL-C. Many of these trials were influential in defining new and lower LDL-C targets for a series of revised treatment guidelines developed in Canada and elsewhere.

On the basis of data consolidated from 26 controlled statin trials that randomized at least 1000 patients and had at least 2 years of follow-up, it was estimated that each 1.0 mmol/L reduction in LDL-C is associated with a 20% reduction in deaths due to coronary heart disease, an 11% reduction in deaths due to other cardiac causes, and a 10% reduction in all cause-mortality (Figure 1).[8] In this meta-analysis, performed by the Cholesterol Treatment Trialists' Collaboration (CTT), no significant

Each 1.0 mmol/L reduction in LDL-C is associated with a 20% reduction in deaths due to coronary heart disease.

association was made between relative reductions in LDL-C and increase risk of death from non-vascular causes, including cancer.

FIGURE 1 | Reduction in Death for each 1.0 mmol/L Reduction
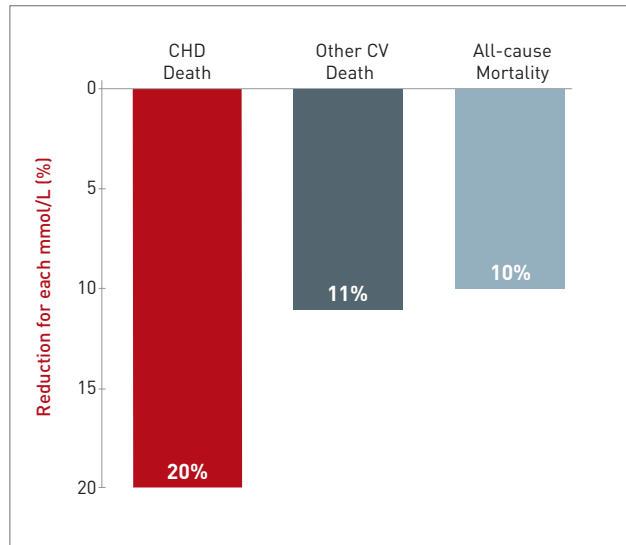
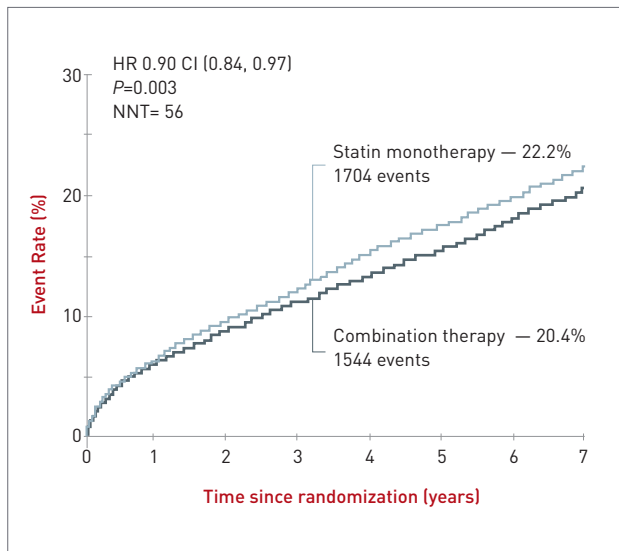Adapted from the Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet.* 2010;376:1670-1681.

Due to the preponderance of data in which CV risk reductions were achieved with LDL-C lowering on statins, Canadian and other treatment guidelines have emphasized the use of agents within this class. However, LDL-C reductions with non-statins, such as those seen with cholestyramine in the LRC-CPPT trial and diet in smaller studies, suggest that similar reductions are achieved with non-statins.[2,9] A recently published multinational trial also suggested that combining a non-statin with a statin provides additional reductions in both LDL-C and CV events relative to a statin alone.[10] In that study, called Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), an additional 0.4 mmol/L reduction in LDL-C achieved with ezetimibe relative to simvastatin alone was associated with a 6.64% reduction in a composite CV endpoint that included MI, hospitalization for angina, or revascularization. For the endpoint of CV death, non-fatal MI, or non-fatal stroke, the risk reduction was 10% with the addition of ezetimibe (Figure 2). The risk reduction, although modest, is consistent with the expected CV risk reduction that was established in the CTT meta-analysis (Figure 3).

Guidelines and Treatment Success

A substantial proportion of individuals in Canada at high risk of CV events, including those who have already had a CV event, are not at the current LDL-C treatment goal. In a cross-sectional study of 2436 outpatients 45 years of age or older who were taking a statin, 45% of those who met high-risk criteria were not at the treatment goal established by the Canadian Cardiovascular Society (CCS) in the 2006 guidelines (Figure 4).[11] In a multinational study

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FIGURE 2 | IMPROVE-IT Results: CV Death, Non-fatal MI, or Non-fatal Stroke

HR 0.90 CI (0.84, 0.97)
P=0.003
NNT= 56

Statin monotherapy — 22.2%
1704 events

Combination therapy — 20.4%
1544 events

7-year event rates. Statin monotherapy: simvastatin 40 mg. Combination therapy: ezetimibe/simvastatin 10 / 40 mg.
Adapted from Cannon CP et al. *N Engl J Med* 2015;372:2387-97.

of patients with diabetes mellitus that included more than 1000 Canadian participants, only 40% were at LDL-C goal despite statin treatment.[12] In both of these studies, statin doses were frequently low, but the list of reasons for failing to reach guideline targets in these studies was varied and included poor tolerance to statins, lack of adequate lipid lowering on maximally tolerated high intensity statins, failure of physicians to titrate statins to reach the guideline target, and lack of adherence.

FIGURE 3 | IMPROVE-IT vs. CTT: Even Lower is Even Better

IMPROVE-IT
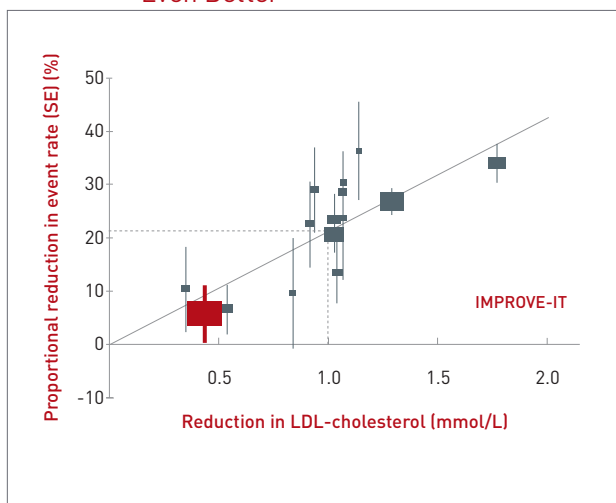
CTT: Cholesterol Treatment Trialists' (CTT) Collaboration
Adapted from Cannon CP et al. *N Engl J Med* 2015;372:2387-97.

The proportion of patients who should be at an evidence-based guideline goal but are not has been referred to as a care gap. Although such patients face an avoidable risk of life-threatening complications, care gaps are complex. Each of the reasons patients fail to reach goals is likely to be multifactorial and not necessarily easily derived

FIGURE 4 | High-risk Patients in Canada Not at LDL-C Treatment Goal of ≤2.0 mmol/L

45% of Canadian patients not at LDL-C target of ≤2.0 mmol/L
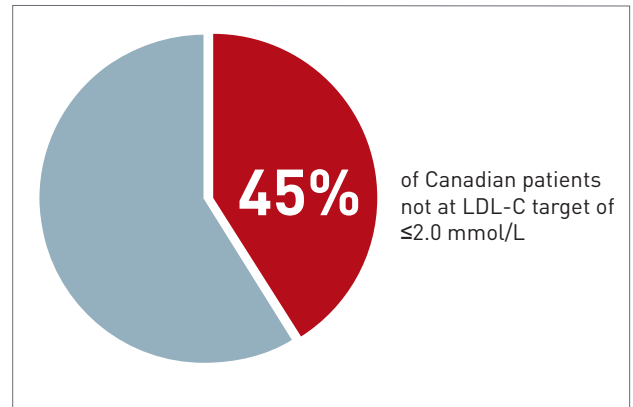
Adapted from Goodman SG et al. *Can J Cardiol*. 2010; 26(9):e330-e335.

from objective data. For example, there has been a large disparity between trial-defined and clinically reported intolerance to statins. In a meta-analysis of 44 atorvastatin trials, the overall incidence of myalgias was 1.9% (versus 0.8% for placebo),[13] but cohort studies from large databases suggest muscle-related adverse events in up to 20% of patients,[14] complicating efforts to understand the causes of discontinuation outside of clinical trials.

High intensity statins, such as atorvastatin and rosuvastatin, are capable of achieving LDL-C reductions from pre-treatment levels of approximately 50% when used at the upper level of the recommended dose range, but maximally tolerated dose is a subjective term in an empirical sense. Some degree of muscle symptoms on statins have been reported in up to 29% of patients, and many of these individuals discontinue therapy, switch therapy, reduce their dose of therapy, or use therapy inconsistently.[15] In addition, many high-risk patients are unable to reach the current relatively aggressive treatment goals on statin monotherapy. In one study that employed data from healthcare databases, only 25% had reached the treatment goal of <2.0 mmol/L even though nearly 75% of patients reached the target of <2.5 mmol/L (Figure 5).[16]

There is evidence that physicians who place high-risk patients on statins do not initiate therapy at sufficient doses or confirm that targets have been met. In a study that evaluated statin prescriptions in patients hospitalized for an acute coronary syndrome, almost all were treated with statin, but only 52% received a high intensity statin.[17] In the previously cited Canadian study of high-risk males in which only 45% were at goals,

There is evidence that physicians who place high-risk patients on statins do not initiate therapy at sufficient doses or confirm that targets have been met.

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FIGURE 5 | Proportion of High-risk Patients who Reach Target Goals on Statin Monotherapy
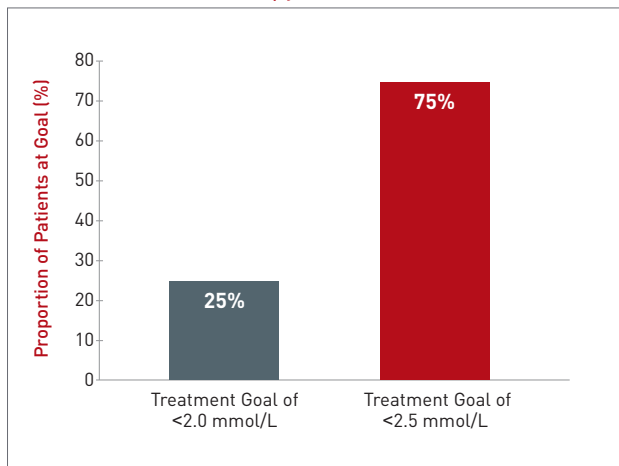
Adapted from Jones PH et al. *J Am Heart Assoc.* 2012;1:e001800.

nearly 90% had been prescribed atorvastatin or rosuvastatin, but doses were intermediate or low.[11] In a retrospective review of more than 9000 patients with coronary artery disease, only 37% on statin monotherapy were at the treatment goal, but 41% of those on statins were taking regimens with only moderate potency.[18]

In high-risk patients who have not yet had a CV event or for those who do not fully appreciate the relationship between elevated LDL-C and risk of a recurrent event, adherence may be another obstacle to treatment goals. Approximately 50% of patients prescribed a statin discontinue therapy in the first year.[19] Although these data include both low- and high-risk patients, a claims database study found adherence was slightly lower on high- relative to low-intensity statins.[20] In a study

Approximately 50% of patients prescribed a statin discontinue therapy in the first year.

of Medicare beneficiaries, 80% of patients who were on a high intensity statin prior to hospitalization for CHD filled a prescription for a high intensity statin after discharge, but only 23.1% filled a high intensity prescription if they had not been on a statin previously. Inadequate adherence to evidence-based therapy is a well-recognized barrier to optimal risk reduction for many types of CV therapies, such as blood pressure lowering medications,[21] but the large CV risk reductions anticipated from statins predict the toll in morbidity

and mortality from non-adherence to these agents to be particularly high.[22]

How to Improve
The care gap, which defines the distance between the current rate of CV events and the substantially lower rate of events if all high-risk patients were at LDL-C goals, is not likely to be fully closed, but it could be reduced. Several strategies are required. Most important, current treatment options should be applied for optimal effect. This not only includes encouraging physicians to employ high intensity statins at maximally tolerated doses, but to educate patients about the goals of therapy and to encourage adherence even in the event of bothersome but benign adverse events. It also includes greater willingness among both patients and physicians to employ non-statin therapies adjunctively when goals are not reached on statins alone. Ezetimibe, which is well tolerated, has been rendered an evidence-based option on the basis of the IMPROVE-IT trial.

Reductions in all-cause mortality observed in some clinical trials as well as the CTT meta-analysis provides the ultimate test and proof of the critical role played by LDL-C lowering in CV risk management. The development of new therapies that provide greater reduction of LDL-C either as an alternative to statins or when combined with statins will certainly extend the large risk reductions to those who are not now achieving treatment goals on available therapies. The phase 3 trials with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors suggest drugs within this class may fulfill this role. These and other agents may also allow new, even lower targets of LDL-C to be evaluated for their ability to prevent CV events.

Summary
In high-risk individuals, evidence-based guidelines define treatment goals for LDL-C associated with major reductions in both CV events and overall mortality. The evidence that a substantial proportion of such individuals are not at goals suggests a need to revisit and revise strategies that will reduce untreated risk. New treatment options that can be used adjunctively or in place of statins would be expected to reduce this care gap, but there is also likely to be a substantial opportunity for an improvement in outcomes from better use of existing treatments.●

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Guest Editor

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The Development and Promise of PCSK9 Inhibitors

Low-density lipoprotein cholesterol (LDL-C) concentrations in the blood are to a large degree controlled by the activity of LDL-C cell surface receptors (LDLr). When bound and removed from the circulation by these receptors, LDL-C is no longer available as a substrate for atherosclerosis. Increasing the activity of LDLr is the principle of the lipid-lowering proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. PCSK9 is a protein that enhances LDLr degradation. By inhibiting PCSK9, LDLr activity is preserved, increasing the amount of LDL-C removed from the circulation. Monoclonal antibodies to PCSK9 in clinical trials have produced sustained reductions in LDL-C exceeding those typically achieved with HMG-CoA reductase inhibitors (statins). The trajectory of PCSK9 discovery and clinical development of targeted inhibitors has been an exceptional demonstration of the ability of molecular biology to rapidly develop novel therapies for human pathology.

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Background and History

The first characterization of the ninth member of the proprotein convertase family, proprotein convertase subtilisin/kexin type 9 (PCSK9), was published in 2003.[1] PCSK9, which was initially labeled neural apoptosis-regulated convertase 1 (NARC-1), was isolated before its biological function was understood, but a rapid series of genetic discoveries of PCSK9 mutants established that this enzyme played an important role in cholesterol metabolism.[2,3] Subsequent studies more specifically demonstrated that PCSK9 binds to and then degrades the LDL-C receptor.[4,5] Less than 10 years after its initial characterization, a phase 1 clinical trial with a monoclonal antibody to PCSK9 showed significant LDL-C lowering activity in human subjects.[6]

PCSK9 is expressed by a limited number of cells that include hepatocytes, kidney mesenchymal, and colon epithelia.[1] Its role in LDL-C metabolism was pursued after PCSK9 gene mutations were identified in two families with hypercholesterolemia.[2] These gain-of-function (GOF) mutations suggested that greater PCSK9 activity results in an increase in circulating LDL-C levels. Loss-of-f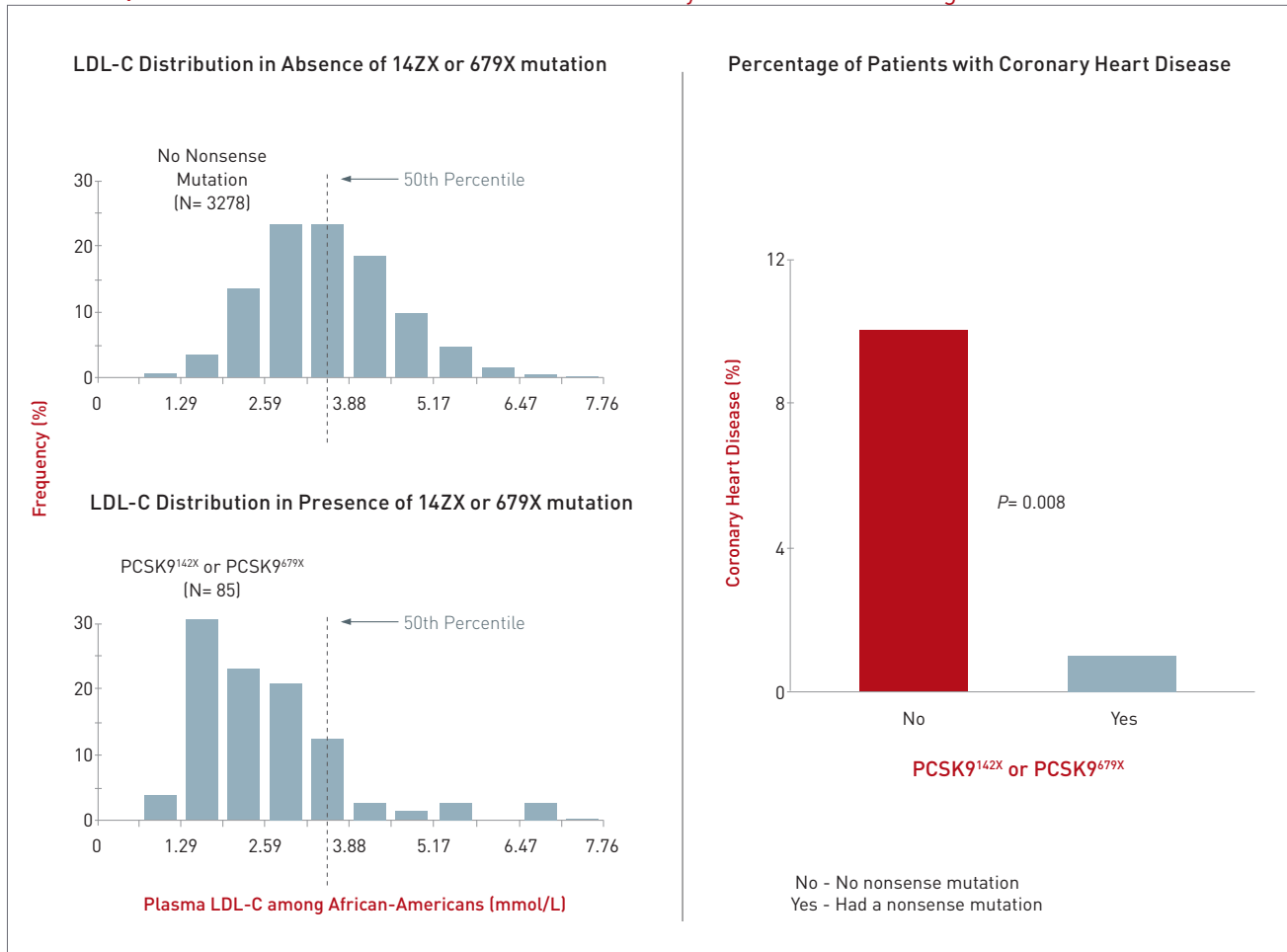unction (LOF) PCSK9 mutations were later associated with the opposite effect, joining an accumulating body of evidence that this enzyme is an important mediator of circulating LDL-C.[3] The potential clinical relevance of these findings was further emphasized when the presence GOF or LOF PCSK9 mutations were associated with higher and lower rates, respectively, of CV events relative to those without these mutations.[3,7] In one study, for example, the presence of a LOF PCSK9 nonsense mutation found in approximately 3% of Caucasians was associated with a 15% reduction in LDL-C and a 47% reduction in coronary heart disease (CHD).[3] Although somewhat less common in African-Americans, the same mutation was associated with even greater protection from CHD in this population (Figure 1).

LDLr binds to the LDL-C particle and, through endocytosis, eliminates the particle from the circulation.[8] Typically, PCSK9 binds to LDLr and is internalized along with the LDL-C particle (Figure 2).[9,10] In the cell, PCSK9 induces a change in LDLr conformation that subjects the receptor

Less than 10 years after its initial characterization, a phase 1 clinical trial with a monoclonal antibody to PCSK9 showed significant LDL-C lowering activity in human subjects.

FIGURE 1 | Distribution of LDL-C and Incidence of Coronary Heart Disease among African-Americans

Adapted from Cohen JC et al. *N Engl J Med* 2006; 354:1264-72.

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to lysosomal degradation, which eliminates its physiological function. In the absence of PCSK9, LDLr is returned to the cell surface where it can again bind to LDL-C, sustaining its activity. The direct inverse correlation between the activity of this escort protein and circulating levels of LDL-C makes it an attractive target for cholesterol-lowering treatment strategies.

FIGURE 2 | Synthesis, Secretion of PCSK9 and Effect on LDLr
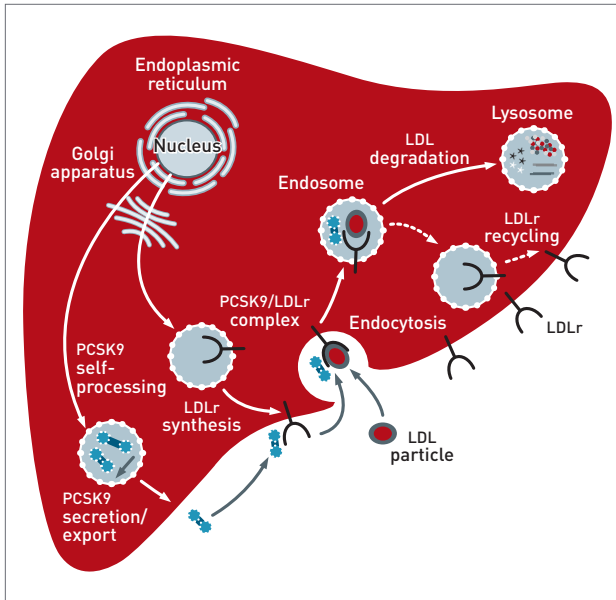
Adapted from Farnier M. *Arch Cardiovasc Dis*. 2014;107(1):58-66.

PCSK9 is primarily synthesized in the liver, but it may have biological functions other than regulation of LDL-C. In experimental studies, for example, PCSK9 activity has been implicated in triglyceride metabolism and regulation of cholesterol balance in adipocytes and enterocytes.[11,12] So far, there is

no clear signal in human studies that loss of PCSK9 function imposes detrimental effects on cholesterol metabolism or other biological activities. Although such detrimental effects cannot yet be ruled out, otherwise healthy individuals with no detectable PCSK9 due to multiple LOF PCSK9 mutations have been identified in two reports.[13,14] In both, complete absence of PCSK9 was associated with a LDL-C level of approximately 0.4 mmol/L.[13]

Clinical Trials Programs

Multiple clinical trials programs with monoclonal antibodies (mAbs) to PCSK9 have validated PCSK9 as a target for achieving reductions in LDL-C. Although other strategies for inhibiting the activity of PCSK9 have been or are being pursued, including antisense oligonucleotides, small interfering RNA (siRNA), small peptide inhibitors, and adnectins,[10,15,16] these remain in early phase or preclinical studies. The large trial programs with mAbs, including phase 3 clinical trials, have confirmed large and sustained reductions in LDL-C with PCSK9 inhibition.

In one of the first series of clinical experiences published, reductions in LDL-C ranged in a dose-dependent manner from 28.1% to 65.4% after a single intravenous dose of the PCSK9 inhibitor alirocumab.[6] In this series, data was summarized from three phase 1 clinical trials conducted in both healthy volunteers and individuals with familial hypercholesterolemia already on atorvastatin. In
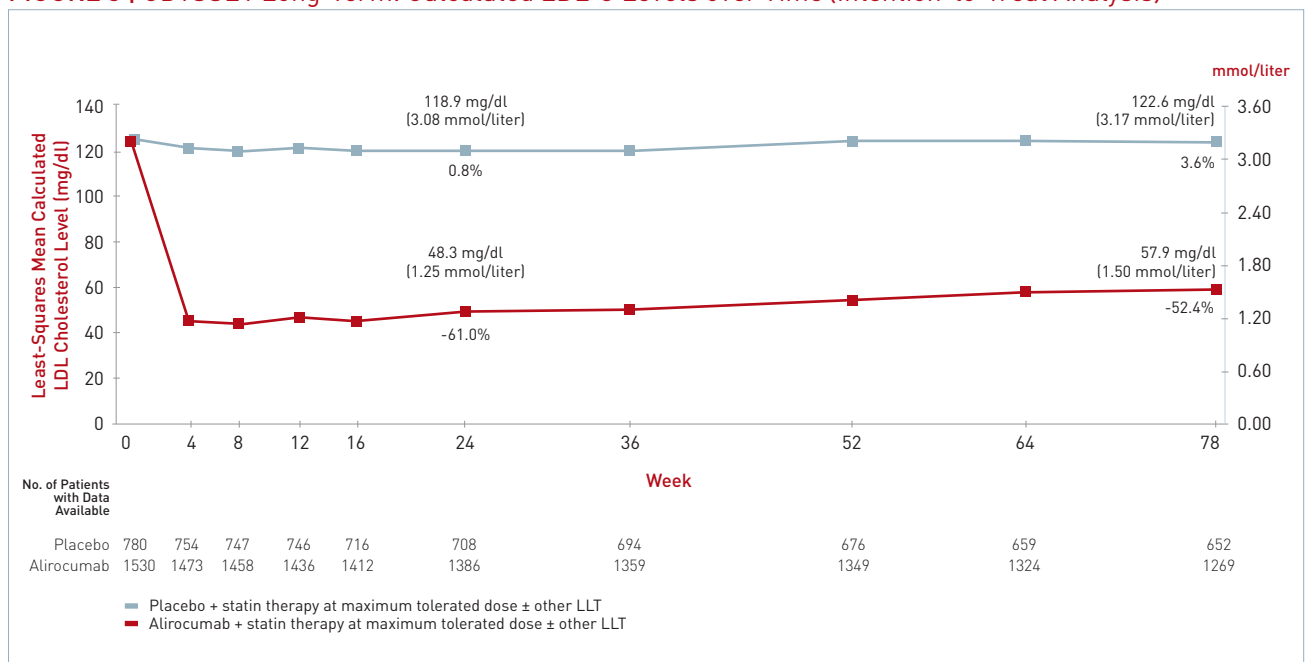
The large trial programs with mAbs, including phase 3 clinical trials, have confirmed large and sustained reductions in LDL-C with PCSK9 inhibition.

FIGURE 3 | ODYSSEY Long-Term: Calculated LDL-C Levels over Time (Intention-to-Treat Analysis)

Adapted from Robinson JG et al. *N Engl J Med.* 2015;372:1489-99.

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one study of multiple doses, sustained reductions in LDL-C were observed over the study period when alirocumab was administered on days 1, 29, and 43. In familial hypercholesterolemia patients taking atorvastatin, the effects of the PCSK9 inhibitor were largely additive.

On the basis of this and other clinical studies, a phase 3 development program called ODYSSEY was initiated. One of the largest studies completed to date, ODYSSEY Long-Term, randomized 2,341 patients at 320 participating sites in 27 countries.[17] Relative to placebo, 150 mg of alirocumab administered every 2 weeks was associated with a 62.1% reduction in LDL-C. The treatment effect was consistent over the course of the 78-week trial (Figure 3). The most common adverse events more frequently observed on alirocumab than placebo were injection-site reactions (5.9% vs. 4.2%) and myalgia (5.4% vs. 2.9%). Other adverse events were infrequent, although both neurocognitive (1.2% vs. 0.5%) and ophthalmologic events (2.9% vs. 1.9%) were numerically higher on alirocumab. A post-hoc analysis associated alirocumab with a reduction of major adverse CV events (1.7% vs. 3.3%; *P*=0.02) consistent with its lipid-lowering activity (Figure 4).

Other already completed phase 3 trials from the ODYSSEY program include ODYSSEY COMBO I,[18] ODYSSEY COMBO II,[18] and ODYSSEY OPTIONS 1.[19] All placebo-controlled studies conducted in patients at high risk for CV events, the COMBO studies associated alirocumab with large reductions in LDL-C among patients taking maximally-tolerated statins and the OPTIONS study associated alirocumab with greater reductions in LDL-C than other lipid-lowering strategies when each was added to a high-intensity statin (atorvastatin or rosuvastatin). In the ODYSSEY ALTERNATIVE trial, which has so far only been presented in abstract form,[20] alirocumab was associated with large and sustained reductions in LDL-C among patients intolerant to statins (Figure 5).

The ODYSSEY OUTCOMES trial, which is designed specifically to evaluate the ability of alirocumab to prevent CV events, is ongoing. In that multinational trial, approximately 18,000 high-risk patients who have had an acute coronary syndrome within the previous 52 weeks have been randomized to alirocumab or placebo on top of standard therapies for dyslipidemia. The primary composite endpoint includes CHD death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, and hospitalization for unstable angina. Results are expected in early 2018.

Randomized studies have also now been conducted with the mAbs evolocumab and bococizumab. Of these, the largest body of evidence is available for evolocumab, for which combined data were published from open-label extensions of phase 2 (OSLER-1) and phase 3 (OSLER-2) studies.[21] In the combined data from these extension studies with 4,465 patients, evolocumab in doses of 140 mg

FIGURE 5 | ODYSSEY ALTERNATIVE: Significantly More Statin-Intolerant Patients Achieved Target LDL-C with Treatment

*P<0.0001 versus ezetimibe for difference in LS mean LDL-C % reduction.

Adapted from Moriarty PM et al. As presented during AHA 2014, LBCT.02.

FIGURE 4 | Cardiovascular Events: Exploratory Analyses

Adapted from Robinson JG et al. *N Engl J Med* 2015;372: 1489-99

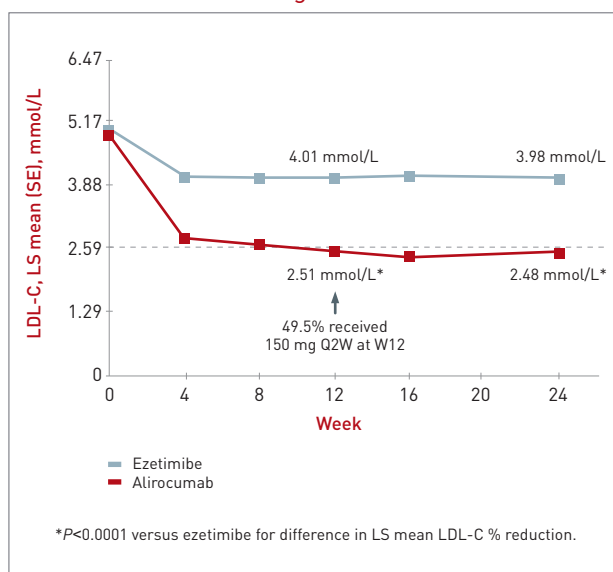Adapted from Sabatine MS et al. *N Engl J Med* 2015;372: 1500-9

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every two weeks or 420 mg once per month were associated with large and sustained reductions in LDL-C with a low rate of adverse events. Although the extension studies were not randomized, numerically higher rates of arthralgia (4.6% vs. 3.2%), headache (3.6% vs. 2.1%) and fatigue (2.8% vs. 1.0%) were observed on evolocumab relative to standard therapy. Rates of serious adverse events were low for both, but neurocognitive events were again numerically higher among individuals taking evolocumab (0.9% vs. 0.3%). As in ODYSSEY LONG-TERM, a non-randomized evaluation of CV events in the OSLER extension studies suggested an advantage for the PCSK9 inhibitor over usual therapy (Figure 4).

In a placebo-controlled, dose-ranging study of bococizumab, reductions in LDL-C appeared to be on the same order of magnitude as that observed previously with alirocumab and evolocumab.[22] Adverse events in this 24-week study were observed in low frequency and at rates that were generally comparable to placebo. Based on the study, phase 3 bococizumab clinical trials are planned with every 2-week subcutaneous dosing.

Findings similar to those from the individual studies were produced by a meta-analysis combining data from 12,200 patients participating in 25 randomized controlled trials with alirocumab or evolocumab.[23] Reductions in LDL-C have ranged from approximately 50% to 60%. Although it is essential to reserve judgment about long-term safety until large sets of clinical data are accumulated over several years, no significant safety concerns were identified. Overall, the evidence to date creates a strong likelihood that PCSK9 inhibitors will provide the next major step forward in reducing CV events through lipid lowering, particularly in high-risk individuals.

Patients Who Will Benefit Most From PCSK9 Inhibitors

Statins, which are effective and well tolerated, permitted the landmark trials that have made reductions in LDL-C an essential step in CV risk reduction, but many individuals, particularly those at highest risk of CV events, cannot reach the guideline-based targets established by those trials. In Canada, one survey found 40% of high-risk patients, most of whom on statin therapy, were below their guideline-recommended goal.[24] These data suggest a substantial unmet need for additional effective and well-tolerated lipid-lowering therapies.

The data accumulated so far suggest that PCSK9 inhibitors may provide a major contribution to CV risk reduction simply by increasing the proportion of patients able to reach current treatment goals. The reasons for failing to reach goals on statins include absolute and relative intolerance, particularly at the highest doses of statins, and insufficient potency when baseline levels of LDL-C are particularly elevated. PCSK9 inhibitors also have potential to improve LDL-C control in some forms of familial hypercholesterolemia. There are already supportive data for all of these clinical applications. For those not adequately compliant to once-daily statin therapy taken orally, a subcutaneous injection of a PCSK9 inhibitor every 2 to 4 weeks may be a viable alternative.

PCSK9 inhibitors also offer an opportunity to explore the value of reducing LDL-C below the levels routinely attainable in high-risk patients on statins alone. In a recent trial evaluating the non-statin ezetimibe on top of statin, patients in the experimental arm achieved a median LDL-C of 1.4 mmol/L, which was associated with an incremental reduction in CV events relative to a LDL-C of 1.8 mmol/L achieved in the arm receiving high-intensity statins alone.[25] Due to the limitations of currently available lipid-lowering therapies, the optimal level of LDL-C has yet to be established. PCSK9 inhibitors may play a role in redefining the maximum CV risk reductions achievable through LDL-C control.

Summary

PCSK9 inhibitors have the potential to address an important need in the prevention of CV events. Relative to statins in randomized trials, PCSK9 inhibitors have produced greater reductions in LDL-C and have been at least as well tolerated. Whether used as alternatives to statins or in combination with statins, PCSK9 inhibitors appear likely to substantially increase the proportion of patients at risk of CV events who achieve maximum protection through LDL-C control. The potential for these agents to redefine optimal LDL-C levels in patients at high risk of CV disease is likely to be a focus in future clinical trials.●

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Guest Editor

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LDL-C Remains the Single Best Target for CV Risk Reduction

When data from large lipid-lowering trials are aggregated, the relationship between reduction in low-density lipoprotein cholesterol (LDL-C) and risk of cardiovascular (CV) events has been described as log linear.[1] With some variability, there is about a 1% reduction in CV risk for each 1% reduction in LDL-C (Figure 1). Reductions of this magnitude have been reported with statins, non-statins, surgery and diet.[2] Although there is a need for more potent lipid-lowering therapies to increase the proportion of high-risk patients who reach guideline-defined targets for LDL-C, the point at which reduction in LDL-C provides no additional reduction in CV risk has yet to be defined. It is reasonable to determine whether treating LDL-C beyond current guideline targets provides additional protection against CV events, particularly in high-risk individuals.

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Background

According to the lipid hypothesis, elevated blood levels of LDL-C are a treatable and fundamental mediator of atherosclerosis. A large body of evidence has been accumulated to support this hypothesis. Much of this data has been derived from multicenter statin trials, which have repeatedly associated large LDL-C reductions with major reductions in CV events. In the 14-trial meta-analysis performed by the Cholesterol Treatment Trialists' (CTT) Collaboration, which included data from approximately 90,000 randomized patients, each 1 mmol/L reduction in LDL-C was associated with a 23% reduction in CV risk.[3]

FIGURE 1 | Relationship between LDL-C Levels and Relative Risk for CHD
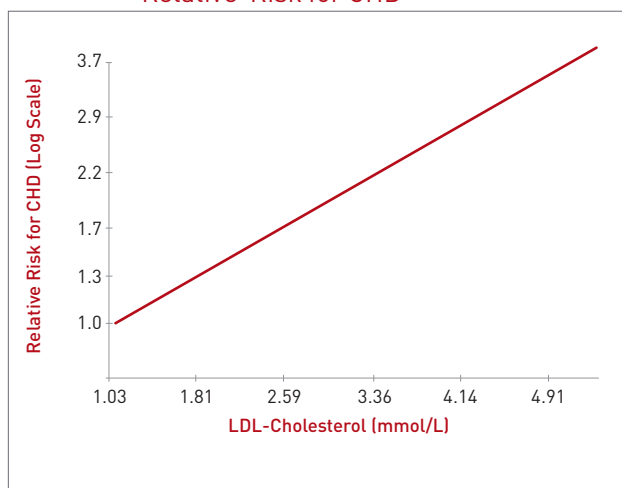
Adapted from Grundy SM et al. *J Am Coll Cardiol*. 2004;44:720-32.

Clinical Trial Programs

Due to the fact that the preponderance of evidence supporting the benefits of LDL-C lowering was derived from statin trials, drugs within this class have been identified as the first-line option in Canadian guidelines.[4] This is appropriate on the basis of both the efficacy and the favourable

A meta-analysis that included 5 trials of diet, 3 trials of bile acid sequestrants, 1 trial of surgery and 10 statin trials found the reduction in CV risk relative to LDL-C reduction was consistently proportional across methodologies to achieve these reductions.

tolerability profile of statins, but assertions that benefits are unique to these agents are refuted by several studies. For example, a meta-analysis that included 5 trials of diet, 3 trials of bile acid sequestrants, 1 trial of surgery (partial ileal bypass) and 10 statin trials found that the reduction in CV risk relative to LDL-C reduction was consistently proportional across the methodologies to achieve these reductions.[2] The lower is better adage for LDL-C in relation to CV risk reduction is based on

a history of clinical trials that have each shown a lower LDL-C level to be advantageous relative to a higher level. In the initial trials, pre-treatment LDL-C levels were relatively high, particularly by current standards. In the Scandinavian Simvastatin Survival Study (4S), for example, the average LDL-C at entry was nearly 5.0 mmol/L.[5] While this study associated a nearly 40% reduction in LDL-C relative to placebo with a 34% reduction in CV events, subsequent studies, such as PROVE-IT and Treating to New Targets (TNT),[6,7] enrolled patients with much lower LDL-C levels at entry and still demonstrated large CV risk reductions commensurate with relative reductions in LDL-C on treatment.

Although fewer trials have been conducted with non-statins, the lower is better principle has been relatively consistent with only rare exceptions, such as the HPS2-THRIVE study, which did not associate niacin with CV risk reduction.[8] The largest non-statin trial ever conducted, IMPROVE-IT, was recently completed.[9] In this trial, ezetimibe was compared to placebo in 18,144 very high-risk patients (enrolled within 10 days of hospitalization for an acute coronary syndrome) taking simvastatin. Relative to simvastatin alone, the addition of ezetimibe produced a 22% further reduction in LDL-C, which was associated with a 6.4% reduction (P=0.016) in risk of a composite endpoint of CV death, non-fatal myocardial infarction (MI), unstable angina requiring hospitalization, revascularization, and non-fatal stroke after a median of 6 years of follow-up.

The IMPROVE-IT data expanded evidence that LDL-C lowering with non-statin therapies achieves statistically significant CV risk reductions. Although the reduction in risk was somewhat less than that predicted by the reduction in LDL-C relative to previous trials, end-of-study LDL-C levels were the lowest ever achieved in the comparator arm of a large multicenter trial. In the group receiving simvastatin plus ezetimibe, the median time-weighted average LDL-C at end of study was 1.4 mmol/L. In the comparator arm, the average LDL-C was 1.8 mmol/L. Both meet or exceed the Canadian guideline target of ≤2.0 mmol/L for high-risk patients.[4]

These data draw attention to the potential for LDL-C reduction below current guideline-defined targets to provide even greater CV risk protection, particularly in the very high-risk patients enrolled in IMPROVE-IT. The evidence-based Canadian guidelines define targets that are near the maximum LDL-C reductions currently achieved with available lipid-lowering therapies. However, the potential for even lower LDL-C levels to provide additional CV risk reductions has yet to

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be evaluated. While IMPROVE-IT demonstrates a relative risk protection for 1.4 mmol/L relative to higher levels of LDL-C, exploratory analyses conducted with data from several studies suggest benefit from even lower levels.

For example, 45% of the approximately 2,000 patients randomized to the experimental arm of PROVE-IT, which was the first trial to demonstrate an advantage for a high-intensity relative to more moderate statin therapy,[6] achieved LDL-C levels <1.55 mmol/L. When patients in the experimental arm were stratified into quartiles, a stepwise further reduction in CV events was observed for each 0.5 mmol/L increment reduction in LDL-C below 2.0 mmol/L in a published post-hoc analysis (Figure 2).[10] There was no safety signal observed for very low LDL-C across several types of adverse events, such as those involving liver or muscle function.

FIGURE 2 | PROVE-IT: Hazard Ratio of the Primary End Point compared with Achieved LDL-C
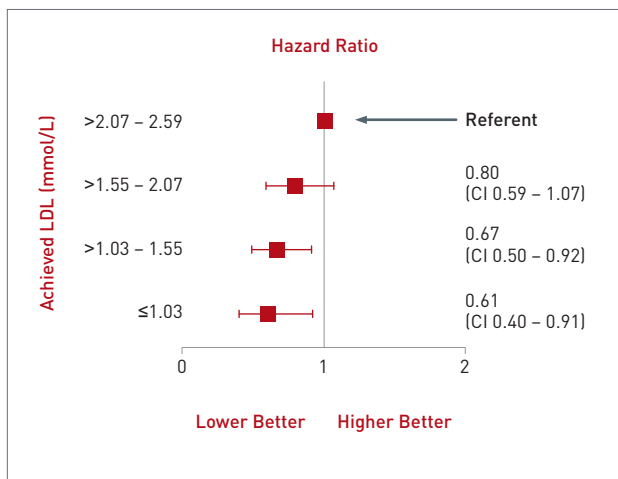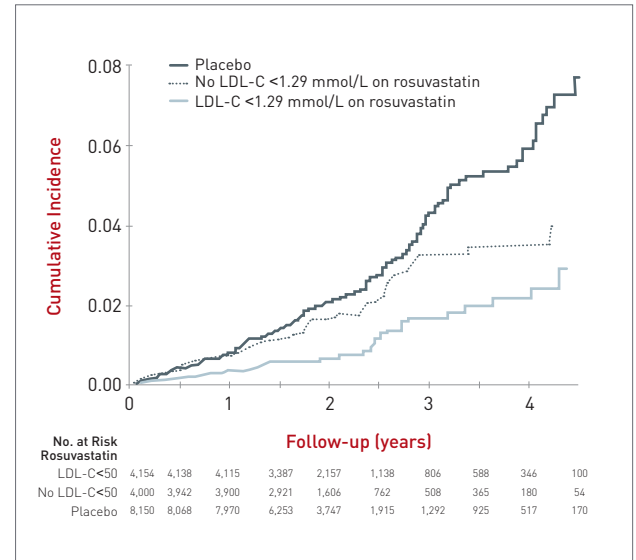

Adapted from Wiviott SD et al. *J Am Coll Cardiol*. 2005;46:1411-6.

Similarly, the TNT trial, which associated an average LDL-C of 2.0 mmol/L with a major reduction in CV risk relative to an average LDL-C of 2.6 mmol/L in the comparator arm,[7] provided data on 6,107 patients who achieved LDL-C levels below 1.5 mmol/L. When these were stratified, a post-hoc analysis again showed a trend for a mortality benefit for those with an LDL-C of <1.0 mmol/L versus those with LDL-C >1.0 mmol/L but <2.0 mmol/L.[11]

In the JUPITER trial, which randomized 17,802 apparently healthy individuals to a high-intensity statin or placebo,[12] a post-hoc study compared the risk reduction in the 4,000 patients on a high-intensity statin that achieved LDL-C <1.3 mmol/L to the 4,154 on a high-intensity statin with end-of-treatment LDL-C >1.3 mmol/L.[13] Both levels of LDL-C provided a significant risk reduction relative to placebo even though this was a population

with moderate CV risk, but the lower LDL-C was associated with an incremental additional risk reduction relative the higher LDL-C (Figure 3). In an analysis of adverse events, the authors reported no differences in rates of muscle-related side effects, cancer, diabetes, or neuropsychiatric conditions.

FIGURE 3 | JUPITER: Time to Occurrence of Major CV Events

Adapted from Hsia J et al. *J Am Coll Cardiol*. 2011;57(16):1666-75.

All of these data suggest that lower is better with no point identified at which further relative reductions do not appear to provide further relative protection. Based on experimental evidence and epidemiologic studies conducted in populations consuming low-fat diets, such as hunter-gatherers, it has been speculated that the appropriate physiological level of LDL-C in humans is in the range of 1.3 to 1.8 mmol/L.[14] However, physiologic levels may not be the appropriate target in patients with existing atherosclerosis. This is suggested by the continuum of benefit at very low levels suggested by the previously cited post-hoc trial analyses. Although published studies have made an association between very low LDL-C and an increased risk of a broad array of adverse events, including cancer,[15] suicide,[16] and intracranial hemorrhage,[17] these risks are not consistent across sets of data, including the safety analyses from PROVE-IT, TNT, and JUPITER.

All of these data suggest that lower is better with no point identified at which further relative reductions do not appear to provide further relative protection.

More recent data with the PCSK9 inhibitors provide additional evidence that very low LDL-C levels are safe and efficacious in regard to CV risk protection. In the ODYSSEY Long-Term trial, which randomized 2,341 high-risk patients to the PCSK9 inhibitor alirocumab or placebo on top of

maximally-tolerated statins, alirocumab provided a 62% additional reduction in LDL-C at the end of 24 weeks relative to maximally-tolerated statins alone (Figure 4).[18] Longer follow-up is needed to evaluate relative protection against CV events, but a favourable trend at 78 weeks consistent with this reduction in LDL-C was reported.

The large reductions in LDL-C that can be achieved on PCSK9 inhibitors provide an opportunity to further explore the limits of the lower-is-better hypothesis. In ODYSSEY Long-Term, the average LDL-C was 1.1 mmol/L after 24 weeks on treatment. Of the 1,550 patients receiving this therapy, 38% achieved LDL-C <0.65 mmol/L of which nearly half achieved LDL-C levels <0.4 mmol/L. In a detailed safety analysis presented at the 2015 annual meeting of the American College of Cardiology (ACC), this was characterized as one of the largest evaluations of patients with pharmacologically-induced LDL-C levels this low.[19] In this analysis, no meaningful imbalances were observed in musculoskeletal, neurologic, or gastrointestinal disorders, and the author concluded that no specific signals of safety risks were detected. However, the longer-term safety of achieving such low LDL-C levels remains to be confirmed.

In the open-label OSLER 1 and 2 trials with the PCSK9 inhibitor evolocumab, LDL-C was reduced 61% from baseline to a median on-treatment LDL-C of 1.25 mmol/L.[20] Again, a favourable trend toward reduced risk of major CV events commensurate with the reductions in LDL-C was observed on the PCSK9 inhibitor relative to placebo, while safety data remained reassuring. In this study, 37.1% of
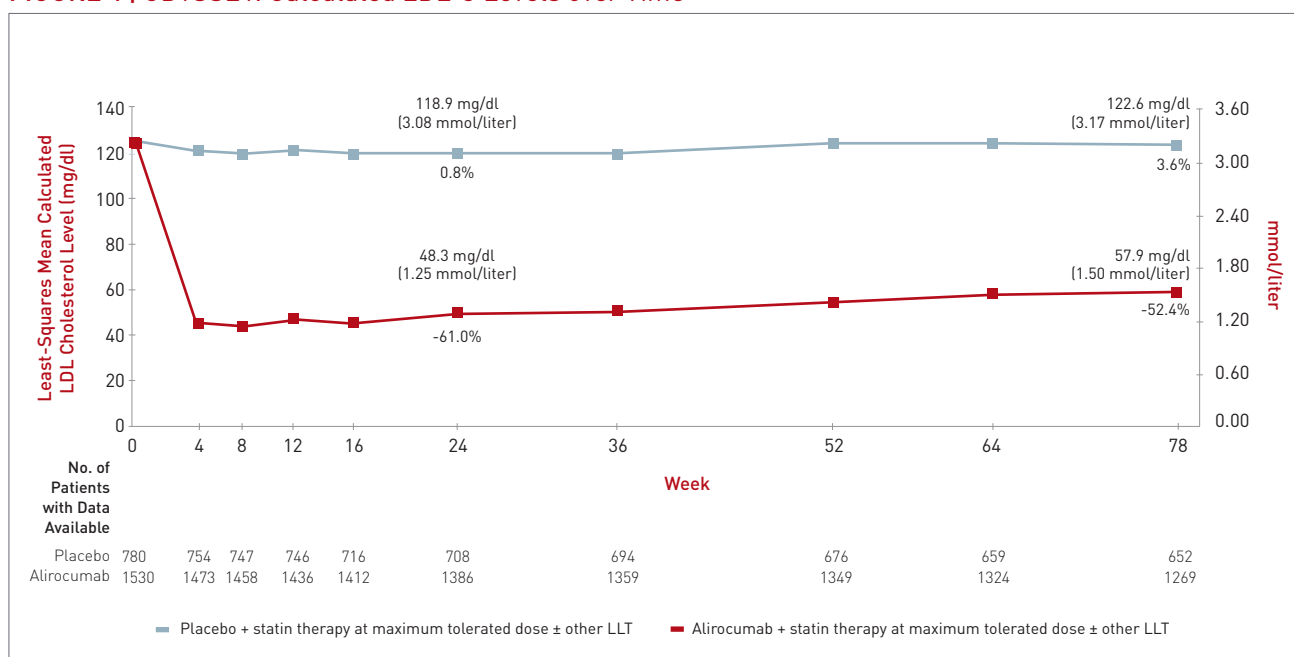
patients achieved a LDL-C <0.65 mmol/L. The rate of adverse events and types of adverse events were comparable in this subgroup relative to those with higher LDL-C levels.

These studies are sufficiently large to permit further exploratory analyses regarding the premise that lower is better when long-term follow-up is completed and CV events are adjudicated. Like data from the post-hoc analyses conducted with data from PROVE-IT, TNT, and JUPITER, lower event rates corresponding with lower LDL-C stratifications, if observed, will not prove lower is better. Rather, it will be another step in the journey toward defining optimal LDL-C targets in high-risk patients. Trials will be needed both to confirm an incremental advantage for the extremely low LDL-C levels possible on PCSK9 inhibitors as well as evaluate relative safety. Such large outcome trials are underway with several PCSK9 inhibitors in high-risk patients.

Summary

Incremental reductions in LDL-C in clinical trials have been nearly uniformly associated with incremental reductions in risk of CV events in high-risk patients. Current guidelines based on these trials have identified targets but do not define the optimal level of LDL-C to achieve maximum reduction in CV risk. Despite high-intensity statin therapy, very low levels of LDL-C have not been a realistic goal in most high-risk individuals, but a new generation of therapies with greater LDL-C lowering efficacy may provide the opportunity to finally identify the level at which protection from CV risk is safely optimized.●

FIGURE 4 | ODYSSEY: Calculated LDL-C Levels over Time

Adapted from Robinson JG et al. *N Engl J Med*. 2015;372:1489-99.

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