Lipids and cardiovascular disease 1

LDL cholesterol: controversies and future therapeutic directions

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Lifelong exposure to raised concentrations of LDL cholesterol increases cardiovascular event rates, and the use of statin therapy as an adjunct to diet, exercise, and smoking cessation has proven highly effective in reducing the population burden associated with hyperlipidaemia. Yet, despite consistent biological, genetic, and epidemiological data, and evidence from randomised trials, there is controversy among national guidelines and clinical practice with regard to LDL cholesterol, its measurement, the usefulness of population-based screening, the net benefit-to-risk ratio for different LDL-lowering drugs, the benefit of treatment targets, and whether aggressive lowering of LDL is safe. Several novel therapies have been introduced for the treatment of people with genetic defects that result in loss of function within the LDL receptor, a major determinant of inherited hyperlipidaemias. Moreover, the usefulness of monoclonal antibodies that extend the LDL-receptor lifecycle (and thus result in substantial lowering of LDL cholesterol below the levels achieved with statins alone) is being assessed in phase 3 trials that will enrol more than 60 000 at-risk patients worldwide. These trials represent an exceptionally rapid translation of genetic observations into clinical practice and will address core questions of how low LDL cholesterol can be safely reduced, whether the mechanism of LDL-cholesterol lowering matters, and whether ever more aggressive lipid-lowering provides a safe, long-term mechanism to prevent atherothrombotic complications.

Introduction

In mammals, the lipoprotein transport system serves many functions that are crucial for survival including the initial transport of dietary fats from the intestine to the liver, the secondary transport of processed cholesterol particles to peripheral tissues for steroid hormone production and membrane synthesis, and the processing of free fatty acids which ultimately serve as a source of fuel for immediate and future needs. The movement of cholesterol through plasma is mediated by lipoprotein particles that carry hydrophobic cholesteryl esters and triglycerides in a central core, enveloped within an external layer of hydrophilic phospholipids and free cholesterol. Each lipoprotein particle typically includes one of a set of highly conserved apolipoproteins that provide structural integrity for the complex, allow for its assembly and secretion, and provide a mechanism for receptor binding. Lipoproteins are traditionally classified according to their size and density, with chylomicrons, chylomicron remnants, and VLDL being relatively large and light, whereas LDL and HDL are sequentially smaller and heavier. In human beings, LDL particles are the major carrier of cholesterol to peripheral tissues where they are internalised through the LDL receptor, a crucial mediator of plasma LDL concentrations. Genetic defects that result in loss of function within the LDL receptor are a major determinant of inherited hyperlipidaemias, and novel monoclonal antibodies that can extend the lifecycle of the LDL receptor represent a major new direction in the treatment of these disorders. The size of LDL particles varies such that particles with more triglycerides and fewer cholesteryl esters result in smaller, denser LDL. For LDL cholesterol, the associated apolipoprotein molecule is apolipoprotein B. Figure 1 schematically shows the structural elements of lipoproteins and their relation to size (diameter) and density.

For clinicians, few circulating molecular structures have as much importance for daily practice as LDL cholesterol. Epidemiological evidence consistently shows that increased concentrations of LDL cholesterol are associated with an increased risk of myocardial infarction and vascular death. Findings from classic genetic studies suggest that early exposure to excessive LDL cholesterol, which is often the result of mutations of the LDL receptor, results in markedly early atherothrombosis. Compared with healthy individuals in whom atherosclerosis is typically expressed in their 5th and 6th decades, individuals who inherit one copy of a defective LDL receptor-related gene (heterozygous familial hypercholesterolaemia) often have clinical onset of symptoms in their 30s and 40s. By contrast, those who inherit two copies of a defective LDL receptor-related gene or who inherit combined genetic defects (homozygous familial hypercholesterolaemia) could have myocardial infarction and stroke in their teens and early 20s (figure 2). These data have led to the concept of so-called cholesterol years of exposure and suggest that reduction of LDL early in life might result in long-term gains. Results from mendelian randomisation studies infer that LDL cholesterol is likely to be a causal agent for plaque initiation and progression, data that are consistent with the known cellular processes promoted by LDL that

Search strategy and selection criteria

Data for this Review were identified through searches of PubMed, Google Scholar, and references from relevant articles published between 2000, and 2014, using the terms “low-density lipoprotein cholesterol”, “hyperlipidaemia”, “lipid lowering”, “cholesterol measurement”, and “familial hyperlipidaemia”.

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result in cholesterol-laden activated macrophages, a hallmark of atherosclerotic plaques. Lastly, reduction of LDL cholesterol is strongly associated with reduced vascular event rates, particularly when that reduction is achieved with statin agents that block the rate-limiting step of cholesterol synthesis.8,9 If public health policies that are currently under debate are fully implemented, more than a third of all middle-aged or older adults in the USA and the UK will be recommended for statin therapy.10 Yet, despite LDL cholesterol being the most important and extensively studied risk factor for cardiovascular disease, substantial controversy remains in clinical practice with regard to its measurement and the net benefit-to-risk ratio for different LDL-lowering drugs. Furthermore, many new targets for LDL reduction which are being assessed have the potential to provide benefits beyond statin therapy.11

In this Review we outline several controversies that are relevant for the daily practice of medicine and highlight areas in which ongoing research is likely to be informative.

**When and how should lipid fractions be measured?**

For general screening purposes for which the goal is to identify individuals with high concentrations of LDL, indirect calculation of LDL-cholesterol with the Friedewald equation is an adequate technique. However, because the Friedewald equation uses a fixed factor to estimate VLDL from triglyceride concentrations, calculated LDL concentrations will underestimate true concentrations when triglycerides are high. This underestimation is increased when untreated LDL concentrations are very low or when LDL is aggressively lowered by potent statins and other lipid-lowering interventions.12 Similar underestimation of true concentrations of LDL can also occur when HDL concentrations are very high, an issue that has been reported in some studies of inhibitors of cholesteryl ester transfer protein (CETP).13

Thus, in settings where increased accuracy of measurement at low LDL concentrations is desired, alternative methods for LDL assessment should be considered. One alternative is to use an adjustable rather than a fixed factor for the triglyceride-to-VLDL ratio. A second option is to measure LDL-cholesterol directly. In screening populations, direct measurements of LDL-cholesterol and Friedewald-estimated LDL-cholesterol concentrations are often highly correlated with each other ($r>0.9$ in a study of...
In some situations, there is discordance between risk based on LDL cholesterol and risk based on apolipoprotein B, non-HDL cholesterol, or LDL particle number (LDL-P). In an assessment of lipid fractions in the prospective Women’s Health Study, one in four women were discordant between LDL-cholesterol and the number of LDL particles (discordance was defined as having one measure more than, and one measure less than the median LDL cholesterol). In situations where LDL cholesterol was lower than the median, apolipoprotein B, non-HDL cholesterol, or LDL particle number (LDL-P) were higher than the median.

Figure 4: Differential predictive usefulness of the atherogenic lipoproteins LDL-C and apolipoprotein B
Assessed in individuals where there was concordance and discordance between LDL-C and apolipoprotein B. Adapted from Mora and colleagues. LDL-C=LDL cholesterol. ApoB=apolipoprotein B.
than, the study median for these two lipid markers). One in five were discordant between LDL-cholesterol and apolipoprotein B, and one in ten were discordant between LDL-cholesterol and non-HDL-cholesterol. For these discordant individuals, vascular risk differed substantially when calculated on the basis of either non-HDL-cholesterol, apolipoprotein B, or the number of LDL particles instead of LDL-cholesterol concentrations (figure 4).²⁷

Many of the limitations associated with measurement of LDL can be avoided with use of non-HDL-cholesterol concentrations for screening purposes and for on-treatment assessment.³⁵ Non-HDL-cholesterol does not depend on VLDL estimation, consists of a simple measure of all cholesterol carried by the atherogenic apolipoprotein B-containing lipoproteins, and reduces the discordance difficulty discussed earlier. Moreover, because non-HDL-cholesterol can be directly calculated from measures of total and HDL-cholesterol, this approach is cost effective and avoids the need for advanced lipid testing. Movement towards non-HDL-cholesterol and away from LDL cholesterol will take substantial educational efforts but is likely to improve overall patient care.¹⁴

How effective is LDL-cholesterol for identification of those who will benefit from statin therapy?

Statin therapy is highly effective at reducing vascular event rates. In results from a comprehensive meta-analysis from the Cholesterol Treatment Trialists' Collaboration of 27 randomised trials,²⁸ statins reduced the risk of major coronary events by 24% for each 1 mmol/L reduction in LDL cholesterol (95% CI 0.73–0.79), stroke by 15% (0.80–0.89), and coronary revascularisation by 24% (0.73–0.79).³⁹ The magnitude of these benefits is similar between women and men, smokers and non-smokers, in elderly and young people, and across all levels of obesity, blood pressure, and glucose. Moreover, the benefits of statin therapy accrue with no evidence of an increased risk of incident cancer (hazard ratio 1.00, 95% CI 0.96–1.04) or cancer mortality (0.99, 0.93–1.06). Although individual randomised trials³⁰ and meta-analyses have shown a small increase in the risk of developing diabetes with statin therapy,³¹ the benefits of treatment in terms of vascular event reduction outweigh this adverse effect in patients both at low and high risk for diabetes. Indeed, statin therapy is the treatment of choice to prevent macrovascular events in those with diabetes.³² Potent statins, now widely recommended in US and European guidelines, result in regression of coronary atherosclerosis in some patients.³³

Although not often discussed, the relative risk reductions observed in statin meta-analyses might be greater in patients with lower absolute risk than in those with higher absolute risk (figure 5).²⁹ This is consistent with the biological view that inhibition of LDL cholesterol synthesis earlier in the disease process is likely to confer more protection than delayed treatment. Indeed, the only statin trials that have not shown clear event reduction were those initiated in the settings of heart failure and end-stage renal failure for which absolute risk is very high. Moreover, despite the overwhelming evidence of efficacy associated with LDL cholesterol reduction after statin therapy, baseline LDL cholesterol concentrations are not a particularly effective marker to determine which patients might benefit from treatment. In all major trials, the relative risk reductions from statin therapy are unrelated to baseline LDL cholesterol concentrations (figure 5).³⁰ This is an important issue in understanding the discrepancy between LDL cholesterol as a biologically essential mediator of atherosclerosis on the one hand, and LDL cholesterol as a relatively modest biomarker of absolute risk on the other.

Although a trial-based approach to statin allocation would ensure prescription for patients in whom evidence is certain,³³ global risk-prediction models that are based on calculations of absolute risk remain the mainstay for both US and European guidelines for the use of statin therapy. This approach is based on the concept that higher absolute risk usually (but not always) results in higher absolute risk reductions. Thus, at least for patients without heart failure
or renal failure, the number of vascular events avoided that were associated with reductions in LDL cholesterol with statin therapy will be greater in those at sequentially greater levels of absolute risk (figure 6).9

Unfortunately, no global risk score has been used as an entry criterion in any statin trial. Furthermore, allocation approaches that are based on epidemiological modelling invariably lead to recommendations to treat many when trial data do not exist or when absolute risk is driven almost entirely by older age, even in the absence of other vascular risk factors.31,32 Investigators of the largest, contemporary, primary prevention trial addressing statin therapy allocated treatment to patients with raised concentrations of high-sensitivity C-reactive protein (hsCRP), not elevated LDL cholesterol concentrations.33 For these reasons, several alternative approaches to statin allocation are being investigated, including the use of individualised prediction of treatment effects. Among such emerging methods is the individualised number needed-to-treat (iNNT) that seeks to balance the known benefits of therapy with potential weighted risks for individuals rather than populations.34 At the other end of the range is the approach of treating all individuals who are older than a fixed age threshold, such as those older than 55 years.35 Thoughtful outcomes research is needed to address these approaches because they lead to markedly different numbers of individuals recommended for therapy.

Are the LDL-cholesterol targets achieved after statin therapy relevant for clinical practice?

Until quite recently, physicians in the USA were strongly recommended to treat-to-targets with regard to LDL cholesterol reduction, an approach that remains the mainstay for most other nations. This recommendation was made on the basis of post-hoc analyses suggesting greater event reductions in those with LDL cholesterol concentrations below specific targets such as less than 1.8 mmol/L. However, the main focus on LDL cholesterol from a biological perspective does not necessarily provide a rationale for use of LDL cholesterol targets in clinical practice because head-to-head statin trials compared different agents at different doses, not comparisons of different concentrations of on-treatment LDL cholesterol.36 LDL cholesterol concentrations contribute only modestly to overall risk prediction, and no trial has shown that baseline or on-treatment LDL cholesterol concentrations alter the beneficial effects of statin therapy.

For these reasons, the most recent US guidelines no longer advocate treatment to specific LDL cholesterol targets, and instead advocate the use of higher-intensity statin agents in those with higher absolute risk. This change in policy away from LDL cholesterol targets should reduce the promotion and prescription of non-statin LDL-lowering drugs that have not shown evidence of reductions in clinical events. Despite this recommendation, many physicians will probably continue to measure on-treatment LDL cholesterol, if only as a measure of drug compliance.

Current European and Canadian guidelines have chosen to maintain LDL targets. A discussion of differences between regional guidelines has recently been presented.37

Are the anti-inflammatory effects of lipid-lowering relevant for clinical practice?

Inflammation has a fundamental role in all stages of the atherothrombotic process. Statins, in addition to reducing LDL cholesterol, also have anti-inflammatory properties.38 The ability of statins to reduce hsCRP concentrations represents the clinical expression of these anti-inflammatory effects. In most39 but not all40 statin trials in which hsCRP concentrations were systematically assessed before and after therapy, participants with the largest reductions had the lowest residual risks for recurrent vascular events. In two statin trials that measured atheroma progression by serial intravascular ultrasound,41,42 progression was reduced in those with both lowered hsCRP and LDL cholesterol. The primary prevention JUPITER trial showed that statin therapy reduced myocardial infarction, stroke, and all-cause mortality in patients with elevated hsCRP concentrations who would not otherwise qualify for treatment because of their already-low concentrations of LDL cholesterol.43 As in the secondary prevention trials, primary prevention participants in JUPITER who achieved lower on-treatment hsCRP concentrations had better clinical outcomes than those who did not reduce hsCRP. Imaging studies further show that intensive statin therapy reduces atherosclerotic inflammation.44 By contrast, not all statin trials have shown that on-treatment hsCRP strongly

![Figure 6: Estimated numbers of major vascular events avoided according to estimated 5-year level of risk and the magnitude of LDL reduction achieved with statin therapy](From Mihaylova and colleagues.9)
predicts residual risk and CRP itself is a biomarker of systemic inflammation, not a causal agent. Furthermore, although raised remnant cholesterol concentrations seem to be related to both low-grade inflammation and vascular events, marked increases in LDL cholesterol seem to be associated with vascular events without the need for overt inflammation.45,46

Although current US and Canadian guidelines endorse the use of hsCRP screening in situations in which risk assessment is uncertain, the clinical usefulness of inflammation assessment after initiation of statin therapy remains controversial. So far, the only evidence-based response to persistently elevated hsCRP despite statin therapy would be to increase the dose of the current statin, or to select a more potent one.

**Should non-statin approaches continue to be used for LDL reduction?**

In view of the robust trial evidence showing safety and event reduction, statin therapy is appropriately emphasised in current US and European guidelines as the main treatment to reduce LDL cholesterol. Statins, however, should be an adjunct rather than a substitute for strong dietary and lifestyle interventions, which on their own can substantially reduce cholesterol in compliant individuals. Nonetheless, not all patients can tolerate statins, and statins are contraindicated in pregnancy. Physicians might also wish to add a second, non-statin, lipid-lowering agent to further reduce LDL when treating patients with familial hyperlipidaemias.

In the pre-statin era, surgical approaches to hyperlipidaemia such as partial ileal bypass were shown to lower LDL cholesterol. More recently, gastric bypass surgery has proven effective at reducing vascular event rates in obese patients, although this benefit is more closely linked to improved glucose control than lipid changes.47–49

Approved non-statin agents for LDL reduction include bile acid-binding resins (colestipol, cholestyramine, and colesevelam), which have the advantage of not being absorbed systemically and thus can be used in pregnancy; fibrates (fenofibrate, bezafibrate, and gemfibrozil) which mainly decrease triglycerides and increase HDL cholesterol; niacin which slightly decreases LDL cholesterol and triglycerides while increasing HDL cholesterol; the cholesterol-absorption inhibitor ezetimibe; and omega-3 fatty acid supplements. Although these agents can clearly improve lipid profiles in many patients, contemporary event reduction trials have shown little evidence to support their use either as monotherapy or as an adjunct to statins in the general population. As prominent examples, neither the AIM-HIGH50 nor HPS-2-THRIVE51 trials showed efficacy for niacin in reduction of vascular event rates, yet both trials showed hazards for gastrointestinal events and infection. Similarly, in the FIELD52 and ACCORD53 trials fenofibrate did not show efficacy, although subgroup analyses suggest efficacy in those with elevated triglycerides and reduced HDL-cholesterol—a hypothesis that requires direct testing. The VA-HIT54 study of gemfibrozil did show a reduction in vascular events but this effect was not clearly related to LDL reduction. Furthermore, gemfibrozil increases the risk of side-effects with statin therapy, and is generally not recommended in combination with statins. With regards to omega-3 fatty acid supplements, contemporary trial data are highly conflicting.55–57

Finally, the ENHANCE trial of ezetimibe did not show a reduction in the surrogate endpoint of carotid intimal medial thickness despite a reduction in LDL cholesterol,19 and there is little evidence so far to suggest that this agent improves outcomes compared with statins alone. The ongoing IMPROVE-IT58 trial is nearing completion and will provide important data in this regard. In the SHARP59 trial of individuals with chronic renal failure, the combination of statin and ezetimibe reduced event rates, but ezetimibe alone was not investigated. Thus, use of these non-statin agents in most general practice settings should be restricted.

**What pharmacological strategies for LDL reduction beyond statins are emerging?**

Although statins are highly effective for reducing vascular events, not all LDL-lowering agents beneficially reduce rates of myocardial infarction, stroke, and vascular death. Examples of agents that reduce LDL cholesterol but in clinical trials did not reduce vascular event rates include post-menopausal hormone-replacement therapy (HRT) and the CETP inhibitors torcetrapib and dalceptrapib.60,61 Whether the success of statins and the failure of HRT and the two CETP inhibitors in reduction of vascular events is because statins have additional anti-inflammatory properties, but the other agents do not, is hypothetical. Different agents within the same class might have differential clinical benefits; with regard to CETP inhibition, two other agents, anacetrapib and evacetrapib (which both lower LDL cholesterol and raise HDL-cholesterol) are in phase 3 assessment and other CETP inhibitors are in earlier stages of development.61 The mechanism by which LDL cholesterol is lowered could matter for event reduction, therefore each new LDL-cholesterol lowering agent should be assessed in outcome trials.

Several new approaches to LDL reduction are under aggressive clinical investigation, and two new agents were approved in 2013 as orphan drugs by the US Food and Drug Administration to treat patients with homozygous familial hypercholesterolaemia, a rare autosomal dominant condition that typically results from an inheritance from both parents of mutations in the LDL receptor. These new drugs are important clinical advances because individuals with homozygous familial hypercholesterolaemia (estimated prevalence rate one case per 500,000 people to one case per 1 million) will...
often have LDL cholesterol concentrations of more than 13 mmol/L and very early onset of atherothrombotic complications (figure 2). Individuals who are either LDL-receptor defective or LDL-receptor negative are typically resistant to statin therapy and must rely on LDL apheresis to reduce the circulating cholesterol. Unfortunately, LDL apheresis is expensive, inconvenient, and largely unavailable outside tertiary referral centres.

Mipomersen
Mipomersen, the first newly approved agent for homozygous hypercholesterolaemia, is a short, single-stranded, antisense oligonucleotide that binds to a specific 20-base sequence on messenger RNA coding for apolipoprotein B-100. By doing so, translation of this specific mRNA is inhibited, cellular synthesis of apolipoprotein B is reduced, and there is decreased secretion of VLDL into the systemic circulation. So far, three phase 3 trials of mipomersen have been completed in patients with familial hyperlipidaemias, each showing a 25–35% mean reduction in LDL cholesterol and concomitant reductions in triglycerides and lipoprotein(a). Common adverse effects with mipomersen include injection-site reactions and transient influenza-like symptoms. Because of concurrent increases in alanine aminotransferase concentrations and an increase in hepatic fat in some patients, hepatic function must be carefully monitored and mipomersen is contraindicated in those with existing hepatic disease.

Lomitapide
Lomitapide, the second newly approved agent for homozygous familial hypercholesterolaemia, is an inhibitor of microsomal triglyceride transport protein (MTP) and also reduces circulating LDL cholesterol by targeting hepatic VLDL production. MTP is associated with the transfer of triglycerides to apolipoprotein B within hepatocytes and in the assembly and secretion of VLDL. The conceptual basis for inhibition of MTP with lomitapide partly derives from the observation in human beings of a rare recessive genetic disorder known as abetalipoproteinaemia, in which functional MTP is absent, VLDL cannot be secreted from hepatocytes, and there is no apolipoprotein B-containing lipoproteins in the systemic circulation. Approval of lomitapide was granted largely on the basis of data from two open-label studies of 35 individuals with homozygous familial hypercholesterolaemia who were already taking statins; in this setting, lomitapide reduced LDL-cholesterol by 40–50% in a dose-dependent manner. As with mipomersen, reductions in lipoprotein(a) have been reported after lomitapide treatment. Common adverse effects include diarrhoea, nausea, and abdominal pain. Hepatic fat accumulation occurred in 8% and elevations of liver enzymes in 30% of those studied; thus, physicians choosing to prescribe lomitapide must pay substantial attention to hepatic function.

PCSK9 inhibitors
The most promising novel target for additional LDL-cholesterol reduction is proprotein convertase subtilisin kexin type 9 (PCSK9), a protein secreted by hepatocytes that binds to the LDL receptor, leading to its cellular internalisation and subsequent lysosomal degradation. Individuals with loss-of-function mutations in the PCSK9 gene have less lysosomal degradation of the LDL receptor, greater surface expression of the LDL receptor, reduced plasma LDL-cholesterol concentrations, and reduced vascular risk during their lifetimes. Conversely, human gain-of-function mutations in PCSK9 are associated with autosomal dominant forms of hypercholesterolaemia.

Many phase 2 trials have shown that monoclonal antibodies targeting PCSK9 result in large reductions in plasma LDL cholesterol when they are given as monotherapy or to those already on statins—an important observation because statin treatment indirectly results in increased plasma PCSK9 concentrations. Inhibition of PCSK9 also reduces lipoprotein(a). Monoclonal antibodies targeting PCSK9 might have use as LDL-lowering agents, not only in those with heterozygous familial hyperlipidaemia (for whom there is reduced LDL-receptor activity), but also in patients with homozygous familial hypercholesterolaemia who are LDL-receptor defective. Antibodies to PCSK9 are effective for lowering of LDL in patients who are intolerant to statins.

Although they are likely to be approved for use in patients with severe inherited hyperlipidaemias, broader clinical use of PCSK9 inhibitors should ultimately be based on large-scale outcome trials that carefully address safety as well as efficacy for vascular event reduction, either as monotherapy for those who have specific statin intolerances or as adjunctive therapy for patients on statins for whom additional LDL cholesterol reduction is sought. Such outcome trials have now been launched globally for three monoclonal antibodies targeting PCSK9: alirocumab (Sanofi/Regeneron Paris, France, and Tarrytown, NY, USA; NCT01663402), bococizumab (Pfizer New York, NY, USA; NCT01975376), and evolocumab (Amgen Thousand Oaks, CA, USA; NCT01764633). Between these three development programmes, more than 60 000 patients worldwide will be exposed to PCSK9 antibodies for a minimum of 2–4 years. So far, human studies of PCSK9 inhibition have not suggested major side-effects, a finding consistent with the observation that rare individuals born with severe loss of function mutations in PCSK9 seem to have normal lifespans and reproductive capacity. Furthermore, almost all human cells retain the ability to make endogenous cholesterol, and the HDL transport system can deliver cholesterol from the liver to systemic organs. However, there have been concerns related to cognitive function in patients with very low levels of circulating LDL-cholesterol. Furthermore, many animal species...
As shown, several loci associate with many lipid traits. From Willer and colleagues.94 HDL-cholesterol, triglycerides, and total cholesterol

Figure 7: Venn diagram illustrating the overlap of genetic loci associated with LDL-cholesterol, HDL-cholesterol, triglycerides, and total cholesterol

As shown, several loci associate with many lipid traits. From Willer and colleagues.94

have no circulating LDL cholesterol yet maintain fully functional processes of lipid transport. However mouse knock-out models of PCSK9 inhibition have raised issues of hepatic dysfunction and glucose intolerance.22,23

Toxicity issues related to PCSK9 inhibition form part of the ongoing concerns among clinicians about the lowest safe concentration for LDL cholesterol. With statin therapy, on-treatment LDL cholesterol concentrations less than 1·3 mmol/L for up to 5 years do not seem to be associated with any specific increase in harm, although somewhat higher risks of diabetes have been observed.24 Although LDL reduction with statins does not increase the rate of coronary events (causal effects), whereas loci associated only with triglycerides. Many of the lipid-associated loci further significantly to LDL cholesterol, HDL cholesterol, and apoA1—contribute statistically

In addition to PCSK9 inhibition, other LDL-lowering pathways are under investigation. One example, is a novel agent that targets hepatic adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase (AMPK) that in two phase 2 studies reduced LDL-cholesterol by 27% in patients with hypercholesterolaemia90 and 43% in those with diabetes.91

What might the genetics of LDL-cholesterol teach us?

Genetic defects in the LDL receptor that lead to extremely high circulating LDL cholesterol have been instructive to understanding of lipid metabolism and its role in early atherothrombosis.2,3 The exploitation of such extreme phenotypes as an approach to identify and develop new lipid targets was also instrumental in the development of lomitapide, mipomersen, and the PCSK9 inhibitors. However, less profound genetic effects also account for slight, but highly statistically significant effects on circulating lipid concentrations.

A consortia study of nearly 190 000 individuals has described 157 genetic loci that associate with one or more circulating lipid fractions (figure 7).25 All but one of these loci seems to be protein-coding, and four loci—CETP, TRIB-1, FADS-1-2-3, and ApoA1—contribute statistically significantly to LDL cholesterol, HDL cholesterol, and triglycerides. Many of the lipid-associated loci further associate with metabolic traits such as obesity, insulin resistance, and hypertension. Loci associated with LDL cholesterol and triglycerides are in turn associated with coronary disease events (evidence supporting potential causal effects), whereas loci associated only with HDL-cholesterol do not clearly show this relationship (evidence challenging potential causal effects).

These emerging data outline the substantial challenge that researchers will face as they attempt to design the functional studies needed to prioritise new drug targets. Pathways analysis, protein–protein interactions, regulation of gene expression, fine mapping, and quantitative methods to assess the loci that do not reach genome-wide levels of significance will all be important to the translational discovery process.26 These limitations aside, translational research that exploits genetic concepts has already led to major new initiatives with the potential to reduce vascular event rates, which go beyond direct reduction of LDL cholesterol. For example, the genetic loci that are associated with statin-induced reductions in LDL cholesterol are distinct from the genetic loci that are
associated with statin-induced reductions in inflammation. Furthermore, the shift of soluble cholesterol to crystalline cholesterol that usually occurs within atherosclerotic plaques has been associated with activation of the NLRP3 inflammasome and consequent local secretion of interleukin-1, a major pro-inflammatory cytokine. These data could be of considerable importance because they provide a link between the deposition of crystalline cholesterol within arteries and activation of the innate immune system, a crucial step in the progression and initiation of atherothrombosis. Inhibition of interleukin 1 also results in decreased downstream interleukin-6 signalling. This is an important concept for atheroprotection that is supported by two studies suggesting that genetic alterations of interleukin-6 signalling not only reduce lifelong concentrations of inflammatory biomarkers but also associate with lifelong reduced vascular event rates.

Partly on the basis of these concepts, large-scale outcome trials are underway of agents that directly reduce inflammation such as canakinumab (a monoclonal antibody that targets interleukin-1β; NCT01327846) and low-dose methotrexate (a systemic anti-inflammatory that has long been first-line therapy for rheumatoid arthritis; NCT01594333). These two agents ultimately target the tumour necrosis factor-α–interleukin-6 signalling pathway, a characteristic that crucially differentiates them from failed anti-inflammatory agents such as darapladib, varespladib, and succinobucinol, which do not have this effect. As in trials of PCSK9 inhibition, trials of inflammation reduction will need to carefully focus on safety as well as efficacy.

Conclusion

In summary, there is extensive evidence that LDL cholesterol is a fundamental determinant of vascular risk and a causal agent in the atherothrombotic process. Data from many randomised, placebo-controlled trials consistently show that LDL cholesterol reduction with statin therapy is a safe and highly effective method to reduce the risk of myocardial infarction, stroke, and vascular death in both secondary and primary prevention. Nonetheless, controversy remains about the best methods to measure LDL functionality, the need to assess LDL cholesterol concentrations before or after initiation of treatment, how low can LDL cholesterol concentrations be safely reduced to, and whether all agents that lower LDL cholesterol will lower vascular risk.

Efficacy and safety data from hard endpoint trials will be available soon for several novel therapeutic approaches that reduce LDL cholesterol well below the concentrations that are currently achievable with statins alone. From a biological perspective, lifelong, early reduction in LDL cholesterol is likely to result in the largest absolute risk reductions. Thus, public health programmes emphasising diet and lifestyle changes in youth and young adulthood must also be aggressively implemented.

Declaration of interests

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