Can LDL cholesterol ever be lowered too much?

DAVID LAIGHT

Current guidelines recommend reducing LDL cholesterol by specified amounts; however, a new treatment ‘lower is better’ paradigm advocates more dramatic LDL cholesterol reduction beyond current targets to maximise global cardiovascular risk benefits. This article examines the benefits and drawbacks of this approach.

Low-density lipoprotein (LDL) cholesterol, like blood pressure, is a very well-established, important modifiable risk factor for the prevention of cardiovascular disease and naturally a leading target for a growing number of LDL cholesterol-lowering therapeutic options. There is a diverse range of pharmacological lipid-regulating therapies available, but the current most commonly used options are high-intensity statin regimens involving atorvastatin (20–80mg daily), rosuvastatin (10–40mg daily) or simvastatin (80mg daily). These regimens are expected to reduce LDL cholesterol by over 40% in primary prevention settings, while atorvastatin (80mg daily) is expected to reduce LDL cholesterol by over 50% in people with cardiovascular disease.

In terms of the need for primary prevention, risk is ascertained by using the cardiovascular disease risk prediction algorithm QRISK®. The latest iteration of this tool (QRISK® 3) was made available in 2017 (see Table 1 for a summary of included risk factors), but current NICE guidance refers to QRISK® 2. In addition to those otherwise healthy individuals or type 2 diabetes patients receiving a ≥10%, 10-year cardiovascular risk score, patients to be considered for statin therapy (without measuring risk score) include those with type 1 diabetes, chronic kidney disease or established cardiovascular disease.

Non-statin lipid-regulating agents, such as bile-acid sequestrants, the specific cholesterol absorption inhibitor ezetimibe, niacin (nicotinic acid) and fibrates have traditionally been far less effective in lowering LDL cholesterol and are not endorsed as first-line preventers of cardiovascular disease, where statins set the standard. But a new breed of LDL cholesterol-lowering agents, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (represented by alirocumab and evolocumab), has now disrupted this status quo by providing a non-statin therapeutic option that rivals LDL cholesterol lowering by statins.
THERAPY FOCUS | LDL cholesterol lowering

Over the years, cholesterol has picked up a clinical reputation as a pariah lipid, driving cardiovascular harms (the cholesterol hypothesis). However, it is also essential for a host of physiological functions such as the maintenance of cell membranes, the digestion of other dietary lipids (by providing bile salts) and the support of steroid hormone production, including the generation of vitamin D following sunlight exposure. Cholesterol may also safeguard against malignancy and neurodegenerative disease. Such is the importance of an adequate supply of cholesterol that, in addition to being able to import circulating cholesterol as LDL cholesterol via the surface expression of LDL receptors and the process of receptor-mediated endocytosis, most cells can also synthesise it.

Making cholesterol requires the enzyme HMG CoA reductase, which catalyses the rate-limiting step of mevalonic acid production from HMG CoA (see Figure 1). This is the stage targeted by statins, which are HMG CoA reductase inhibitors, most clinically significantly in the liver. The subsequently upregulated hepatic cell surface expression of LDL receptors leads to greater hepatic LDL cholesterol clearance from the circulation – one of the most effective ways of lowering LDL known. Starving the liver of cholesterol, by either preventing its enterohepatic recirculation as bile salts using bile-acid sequestrants or limiting its dietary absorption/biliary reabsorption with ezetimibe, acts in qualitatively the same fashion, but with a less dramatic impact on LDL cholesterol. Alirocumab and evolocumab activate this hepatic LDL-lowering pathway in a complementary way, by blocking the action of the enzyme PCSK9 from binding to and tagging LDL receptors for intracellular degradation following LDL receptor-mediated endocytosis. This results in more recycling of LDL receptors back to the cell surface (with the liver normally accounting for approximately 70% of tissue-expressed LDL receptors).

**Cholesterol transport**

Other than non-esterified or free fatty acids, which are carried by circulating albumin, mass lipid transport in the blood is only made feasible by lipoproteins, which essentially provide emulsification. These lipid droplets consist of a highly lipophilic fatty core (containing cholesteryl ester and triglycerides), encapsulated by an amphipathic monolayer envelope of phospholipids, in which is found cholesterol and proteins known as apolipoproteins or apoproteins. Most lipoproteins feature several of these apoproteins (apoA–E) and these carry out a number of important enzyme regulatory and cell docking functions. However, LDL mainly features apoB100 and this is essential for LDL receptor-mediated endocytosis and tissue LDL cholesterol uptake.

Dietary lipids, including both cholesterol and triglycerides, arrive in the blood via the lymphatics from the small intestine packaged as chylomicrons and this represents the ‘exogenous’ lipid pathway (see Figure 2). On the other hand, hepatically-produced lipids are exported into the circulation as very low-density lipoprotein (VLDL; representing the ‘endogenous’ pathway). Both these triglyceride-rich lipoproteins serve up fatty acids for uptake by extrahepatic tissues such as skeletal muscle and fat, following lipolysis by cell surface-expressed lipoprotein lipase. This route of cholesterol clearance in fact helps account for one of the major therapeutic lipid-lowering benefits of fibrates, through the increased expression of lipoprotein lipase.

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• Statins are relatively safe and generally well-tolerated lipid-lowering agents with principal roles in the treatment of primary hypercholesterolaemia and mixed dyslipidaemia
• The treatment target for LDL cholesterol lowering in this context, either alone or in combination with other lipid-lowering therapies, typically involves reaching a specified threshold, which can be dependent on the presence or absence of cardiovascular disease and degree of cardiovascular risk
• In addition, high-intensity statin regimens are recommended in the management of LDL cholesterol as a modifiable cardiovascular risk factor in the primary and secondary prevention of cardiovascular disease
• The treatment target in this context is >40% reduction in non-HDL cholesterol
• The decision to offer statins for prevention is prompted by either a 10-year risk of heart attack or stroke of ≥10%, measured using the prediction QRISK® algorithm, or the presence of cardiovascular disease or other high-risk conditions

Table 2. LDL cholesterol lowering with statins: prescribing summary

The triglyceride-depleted lipoprotein remnants are either entirely removed from the circulation by the liver in the case of chylomicron remnants; or partially cleared in the case of VLDL remnants (also known as intermediate-density lipoprotein [IDL]). Those remaining IDL not cleared by the liver are instead modified by hepatic lipase to become cholesterol-enriched LDL, which accounts for approximately 75% of cholesterol transport in the blood. Compared with other mammals, this in fact represents an unusually large fraction of circulating cholesterol to be carried by LDL, reflecting the significant level of conversion of IDL to LDL.

Cholesterol: the good, the bad and the ugly
Circulating cholesterol originally exported as VLDL (as a precursor of LDL) is ultimately destined for uptake by tissues expressing surface LDL receptors. In contrast to this highly controlled, saturatable LDL cholesterol uptake pathway, LDL cholesterol scavenging by macrophages in the arterial wall represents an unregulated, unlimited cholesterol uptake pathway, which leads to foam cell formation and drives atherogenic lipid deposition. This unsurprisingly is the major reason for regarding LDL cholesterol as ‘bad’ circulating cholesterol in terms of both marking and mediating cardiovascular risk. LDL’s poor reputation has been further tarnished by the discovery of a variant of LDL known as Lp(a), which features a modified form of apoB100 identified as apo(a) (produced by the liver) and which is considered to be especially atherogenic (the ‘ugly’). On the other hand, ‘good’ blood cholesterol in the context of reduced cardiovascular risk, is conventionally associated with what is being transported away from the periphery by high-density lipoprotein (HDL) in ‘reverse’, ie excess cholesterol returning to the liver to be cleared, out of harm’s way. In addition to lowering LDL cholesterol, statins also modestly raise HDL and furthermore reduce triglyceride levels.

This dichotomy of ‘good’ and ‘bad’ cholesterol in fact simply reflects the pathological importance of the compartmentalisation of cholesterol in the blood. This is further illustrated by now considering all non-HDL lipoproteins, not just LDL, as atherogenic. Indeed, non-HDL cholesterol is better associated with coronary atheroma progression than is LDL cholesterol. This places VLDL and IDL as well as Lp(a) and even chylomicrons and their remnants firmly in the ‘bad’ cholesterol camp. The current NICE recommendation is that non-HDL cholesterol (= total cholesterol minus HDL cholesterol) is reduced by more than 40% with high-intensity statin regimens for both primary and secondary prevention (see Table 2). Of course, given the unusually large contribution of LDL cholesterol to non-HDL cholesterol in man (see Table 3), lowering LDL cholesterol is likely to remain a principal clinical target for cardiovascular risk-modifying, lipid-regulating therapeutics.

A related interesting question is whether LDL attributes such as size and density, and in particular particle quantity, for which LDL cholesterol level might simply be a proxy (ie high LDL cholesterol concentration tracks risk by reflecting high particle number), are the really significant targets in lipid-regulating therapy. Small, dense (so-called ‘pattern B’) LDL are thought to represent an aggressively atherogenic phenotype, irrespective of LDL cholesterol level, while high particle number is likely to facilitate arterial wall lipid deposition and dyslipidaemia-driven atherogenesis. This suggests therapeutic efforts to improve LDL particle quality and reduce particle number, independently of reducing LDL cholesterol, may provide another legitimate treatment goal.

How low should LDL cholesterol go?
Chasing down global cardiovascular risk by reducing LDL cholesterol to potentially extremely low levels (which is especially...
of relevance to patients at highest risk), naturally raises important concerns about the health consequences of iatrogenic hypocholesterolaemia. This, of course, is with regard to cholesterol’s multiple and essential physiological intracellular roles. However, there are indications that the clinical prospect of profoundly reducing circulating LDL cholesterol may not be quite so alarming.

This is in view of observations in populations with very low LDL cholesterol levels, for example neonates, traditional hunter-gatherer populations and individuals with hypobetalipoproteinaemia (where LDL production is limited) or PCSK9 loss of function mutations (with a naturally high expression of hepatic LDL receptors), which suggest that very low levels are tolerable and for long periods.21 Furthermore, investigations, including a meta-analysis looking at the safety and efficacy of more intensive LDL cholesterol reduction, have indicated that cardiovascular benefits are safely achievable.12,22 Such observations serve to eschew conventional fixed notions of LDL cholesterol treatment thresholds or desirable levels (see Table 3 for desirable lipid levels in adults suggested by NHS and Heart UK).23 Moreover, misgivings about potential harms arising from extremely low LDL cholesterol might need to be weighed against the anticipated cardiovascular benefit in individuals at high risk, such as in a secondary prevention setting. Indeed, reducing LDL cholesterol to the ‘lower normal’ boundary of 0.52mmol/L based on epidemiological findings (ie some six-times lower than the declared desirable limit in healthy adults – see Table 3), might be suggested as justifiable in patients at highest cardiovascular risk with extensive atherosclerosis.21 This all reinforces the impression that LDL cholesterol reduction, at least with statins, is a cardiovascular ‘gift that keeps on giving’ and furthermore that lower LDL cholesterol really is better. In this clinical picture, only the incidence of statin side-effects might be expected to impose a major limitation on LDL cholesterol lowering in highest risk patients. However, the lowest safe or tolerated LDL cholesterol level has yet to be determined.

Role of statins in lowering LDL cholesterol beyond current targets
Notwithstanding the clinical supremacy of intensive statin therapy, there may still be a question of exactly how best to pursue dramatic reductions in LDL cholesterol. Despite offering clear lipid-lowering and other pleiotropic cardiovascular benefits,13,24 the use of intensive statins runs into potential problems with the (admittedly rare but serious) risks presented by myopathy, myositis, rhabdomyolysis and hepatotoxicity, as well as the more common phenomenon of statin intolerance. The nature of this intolerance is in fact an ongoing area of contention, as it has been suggested that statin-associated muscle symptoms (SAMS) may not necessarily be related to pharmacological statin effects.25 Nevertheless,
non-adherence to statins in the face of considerable levels of intolerance, coupled with large variability in patient LDL cholesterol-lowering responses, are already thought to contribute to a state of suboptimal LDL cholesterol control and cardiovascular risk management. Furthermore, lipid-lowering with statins has been linked with haemorrhagic stroke, dementia, cancer and diabetes and even an increased risk of death from violent causes.

A recent literature survey incorporating data from randomised controlled trials and genetic studies, while confirming a modest risk of new-onset diabetes with statins, came to the overall conclusion that long-term statin therapy is indeed safe with a low risk of clinically relevant adverse events. Moreover, this risk is thought to be far outweighed by established cardiovascular benefits. This pronouncement may still not be enough to allay the controversy surrounding the decision by NICE to recommend treatment with a high-intensity statin regimen at the lower, primary prevention threshold of ≥10% cardiovascular 10-year risk with respect to expanding the statin-medicated population. It is also important to note here that there remains some dissent from the mainstream view that statins are a largely unqualified therapeutic good and even some disillusionment with the whole conventional cholesterol hypothesis.

However, while the advocacy of statin use in primary prevention remains contentious, especially in low-risk groups, their use in secondary prevention settings is generally considered favourable from the perspective of an increasingly advantageous risk/benefit ratio. This naturally aligns with the observation that subjects at highest absolute cardiovascular risk, and with the most severe disturbance in LDL cholesterol, have much to gain from LDL cholesterol-lowering intervention with statins. Furthermore, such gains may not be limited to primary and secondary prevention, as apparently healthy individuals without known cardiovascular risk factors still appear to derive a cardiovascular benefit associated with LDL cholesterol lowering below normal values with statins in the setting of primary prevention. This may possibly also reflect the actions of statins to, for example, stabilise atherosclerotic plaques, improve vascular endothelial function and reduce inflammation and thrombosis. Such pleiotropic effects might therefore help to chip away at unaccounted for or residual cardiovascular risk, as well as ameliorating predictable risk by LDL cholesterol lowering.

### Optimising lipid-lowering therapy

Of course, the optimal choice of prescribed LDL cholesterol-lowering intervention(s) should be personalised, based on factors such as drug efficacy, tolerability, polypharmacy, co-morbidities and patient safety profile, and informed patient preference. In addition to whatever may be achieved by lifestyle change and statins, any future adherence to a ‘lower is better’ clinical approach to LDL cholesterol control (especially in those patients at highest cardiovascular risk) will likely require a much greater role for add-on or alternative therapies that can further upregulate hepatic LDL receptors. Interestingly in this regard, a recent change to the marketing authorisation for the PCSK9 inhibitor evolocumab means that it is now also licensed in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk (as add-on therapy to a maximum tolerated dose of a statin). However, NICE is yet to appraise its use for this indication.

Here, the PCSK9 inhibitors might be expected to do an even better job at targeting non-HDL cholesterol by virtue of reducing Lp(a). Furthermore, importantly, cardiovascular benefits related to LDL cholesterol reduction via the hepatic upregulation of LDL receptors are reported to be equivalent to those offered by statins. While the inherently higher acquisition costs of monoclonal antibody therapies may cause concern about any potential future wider use of current PCSK9 inhibitors in aggressively pursuing even lower LDL cholesterol than that managed by high-intensity statins alone, this probably needs to be considered in the context of the broader economic benefits expected to arise from the anticipated additional prevention of cardiovascular outcomes.

### So does LDL cholesterol lowering have its limits?

LDL cholesterol-lowering, primarily achieved with the generally well tolerated and relatively safe statins, clearly has an ongoing fundamental part to play in helping reduce the incidence of heart attack or stroke in a range of individuals at increased cardiovascular risk. The central importance to primary and secondary prevention accorded to LDL cholesterol lowering likely reflects the importance of improvements in the cholesterol:HDL ratio, which of course represents one of the most clinically significant modifiable risk factors included in the QRISK® prediction algorithm (see Table 1).

However, it is interesting to consider that this single QRISK® lipid risk factor continues to be diluted by the addition of new, non-lipid risk factors (see Table 1). Furthermore, there is a plethora of emerging novel, non-traditional cardiovascular risk factors that are no doubt yet to be considered for inclusion in risk prediction algorithms. This may therefore

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**Table 3.** NHS/Heart UK desirable lipid values in adults

<table>
<thead>
<tr>
<th>Lipid fraction</th>
<th>Level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>≤5 (&lt;4 if high risk)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>≤3 (&lt;2 if high risk)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>≤4</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&gt;1 (men)</td>
</tr>
<tr>
<td></td>
<td>&gt;1.2 (women)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;1.7 (fasting) &lt;2.3 (non-fasting)</td>
</tr>
<tr>
<td>Total cholesterol:</td>
<td>&lt;4</td>
</tr>
<tr>
<td>HDL cholesterol ratio</td>
<td></td>
</tr>
</tbody>
</table>

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suggested at least a theoretical limit to what LDL cholesterol (or non-HDL cholesterol) reduction alone can achieve – however profound, however achieved and however well tolerated – in terms of reducing either predictable or residual cardiovascular risk.

References
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