



LDL - The Lower the Better?

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Introduction

Based on the evidence from laboratory basic researches, epidemiologic studies and clinical trials, hypercholesterolaemia is a well-established risk factor for atherosclerotic cardiovascular disease. More importantly, with the development of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, the level of cholesterol could be safely lowered which was proven to be associated with lowered risk of myocardial infarction, coronary heart disease (CHD) related deaths and overall death rates.

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) launched the National Cholesterol Education Program (NCEP) in November 1985. The goal of the NCEP is to contribute to reducing illness and death from CHD by reducing the percentage of people with high blood cholesterol. The Executive Summary of the Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) was published in December 2002. It provided evidence-based recommendation on the management of high blood cholesterol and related disorders. The publication of five major clinical trials with statin therapy and clinical end points had prompted the revision and updates of the ATP III guidelines. These updated guidelines suggested that a lower low-density lipoprotein (LDL) cholesterol of <1.8mmol/l as a treatment option for moderate to high risk patients. In order to avoid over-generalisation of this recommendation, we review in this article the updated ATP III guidelines and the latest statin clinical trials, and their implication in daily clinical practices.

ATP III updated guidelines

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL is a major cause of CHD. LDL-lowering therapy has been robustly proven to reduce the CHD risks. The ATP I, II and III guidelines all have identified LDL as the primary target of cholesterol lowering therapy. Compared with previous guidelines, ATP III¹ emphasised on not only the importance of intensive treatment of patients with documented CHD or CHD risk equivalents (**Table 1**) but also primary prevention in patients with multiple risk factors (**Table 2**). Beyond counting the number of risk

Table 1. CHD risk equivalents comprise

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- Diabetes
- Multiple risk factors that confer a 10-year risk for CHD >20%

Table 2. Major risk factors (exclusive of LDL) that modify LDL goals

- Cigarette smoking
- Hypertension (blood pressure \geq 140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (<1.0mmol/l)*
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men \geq 45 years; women \geq 55 years)

*HDL cholesterol \geq 1.6mmol/l counts as a "negative" risk factor
LDL indicates low-density lipoprotein; HDL indicates high-density lipoprotein; CHD indicates coronary heart disease

factors, ATP III also recommended the use of the Framingham Risk Score (FRS)² to further triage patients with two or more risk factors. In brief, the FRS developed by the Framingham Heart Study allowed prediction of 10-year CHD risk. Risk factors used in FRS include age, total cholesterol, HDL cholesterol, blood pressure and cigarette smoking. FRS will then divide persons with multiple risk factors into those with 10-year risk for CHD of >20%, 10-20%, and <10%.

Based on the recent publication of a number of statin trials (to be elaborated in later part of this review), an updated NCEP ATP III guideline was published in 2004.³ According to this updated guidelines, in high-risk persons (i.e. CHD or CHD equivalents), the recommended LDL goal is still 2.6mmol/l. But, a LDL goal of 1.8mmol/l is a therapeutic option, especially for patients at very high risk. If LDL \geq 2.6mmol/l, a LDL-lowering drug is indicated simultaneously with lifestyle changes. If baseline LDL is <2.6mmol/l, institution of a LDL-lowering drug to achieve a LDL <1.8mmol/l is a therapeutic option.

For moderately high-risk persons (2+ risk factors and 10-year risk 10 to 20%), the recommended LDL goal is also kept at <3.4mmol/l. But a LDL goal of <2.6mmol/l is a



therapeutic option. When the LDL level is between 2.6 to 3.4mmol/l, at baseline or on lifestyle therapy, initiation of an LDL lowering drug to achieve a LDL level of <2.6mmol/l is also considered as a therapeutic option.

LDL goal - what is the best goal?

Clinical trials robustly showed that LDL lowering was associated with lower cardiovascular event rates. Moreover, the more LDL lowering achieved, the lower would be the event rate attained. However, by the time of the publication of ATP III guidelines, there were no data to answer whether the reduced LDL and reduced CHD risk demonstrated in prior secondary prevention trials of statins hold true even at very low levels of LDL.

Heart Protection Study (HPS)

In this 5-year clinical trial, 20536 patients with CHD, other occlusive arterial disease, or diabetes were recruited and randomised to simvastatin 40mg daily or placebo.⁴ Hence, all patients belonged to the high risk category in the ATP III guideline. All-cause mortality was significantly reduced by 13% in the simvastatin arm due to a significant 18% reduction in the coronary death rate (5.7% vs 6.9%, $p=0.0005$), a marginally significant reduction in other vascular deaths (1.9% vs 2.2%, $p=0.07$) and a non-significant reduction in non-vascular deaths (5.3% vs 5.6%, $p=0.4$). Major vascular events were reduced by 24%, nonfatal myocardial infarction and coronary death rate by 27%, nonfatal or fatal stroke by 25% and cardiovascular revascularisation by 24%. Most importantly, the proportional reduction in the event rate was similar and significant in each subcategory of participants studied, including: those without diagnosed CHD who had cerebrovascular disease, or had peripheral artery disease, or had diabetes; men and women; those aged either under or over 70 years at entry. Most importantly, subgroup analysis suggested that simvastatin therapy produced similar reduction in relative risk regardless of the baseline levels of LDL, including subgroups with baseline LDL ≥ 3.5 mmol/l, ≥ 3.0 to < 3.5 mmol/l, or < 3.0 mmol/l. Hence, the benefit of statin therapy depends much on a patient's overall cardiovascular risk rather than on the lipid level alone. Meanwhile, HPS suggested that reduction of LDL below the ATP III goal may further reduce the cardiovascular risk in these high risk patients.

Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22 (PROVE IT - TIMI 22)

In this study, 4162 patients with recent acute coronary syndrome were enrolled and randomised to pravastatin 40mg daily or atorvastatin 80mg daily.⁵ The study was designed to determine whether intensive LDL lowering would reduce major coronary events more than standard LDL lowering with statin therapy in high risk patients. The LDL level attained on pravastatin 40mg was 2.5mmol/l, whereas the level attained on atorvastatin 80mg was 1.6mmol/l. The composite cardiovascular end point (death, myocardial infarction, unstable angina requiring

rehospitalisation, revascularisation and stroke) was reduced by 16% with atorvastatin compared with pravastatin ($p<0.005$). Non-significant trends were observed on atorvastatin therapy for total mortality ($p<0.07$) and for death or myocardial infarction ($p<0.06$). The results of PROVE IT suggested a more intensive LDL lowering therapy reduces major cardiovascular events in patients with acute coronary syndrome compared with less intensive therapy over a period of 2 years. In line with HPS, PROVE IT supported a lower LDL goal compared to the ATP III guideline.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Trial (ALLHAT-LLT)

The primary objective of ALLHAT trial⁶ was to determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of CHD or other cardiovascular disease events vs treatment with a diuretic. The lipid-lowering component,⁷ which was a subset of this study, was designed to determine whether pravastatin therapy compared with usual care reduces all-cause mortality in older, moderately hypercholesterolaemic, hypertensive participants with at least one additional CHD risk factor. Hence, most participants would belong to the moderately high risk category (i.e. 10 to 20% 10 year risk) in the ATP III guidelines. The lipid-lowering component of ALLHAT randomised 10355 persons to pravastatin or usual care. After a mean follow-up of 4.8 years, all-cause mortality and CHD event rates were similar for the 2 groups. The high cross over rate and the modest lipid lowering effect of pravastatin might be the reasons for these unexpected negative results.

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA)

Of 19342 hypertensive patients (aged 40-79 years with at least three other cardiovascular risk factors) randomised to one of two antihypertensive regimens in the ASCOT,⁸ 10305 with non-fasting total cholesterol concentrations of 6.5 mmol/L or less were randomly assigned to atorvastatin 10 mg or placebo. In the atorvastatin group, fatal and nonfatal stroke was reduced by 27% ($p=0.024$), total cardiovascular events by 21% ($p=0.0005$), and total coronary events by 29% ($p=0.0005$). There was a non-significant trend toward a reduction in total mortality in the atorvastatin group. The positive results were in contrary to the ALLHAT-LLT. This might be explained that patients in the ASCOT-LLA had higher risk profile, the statins used and hence the degree of LDL lowering achieved in these two studies was different.

Treating to New Targets Trial

The recently published five-year Treating to New Targets Trial (TNT) further supported a lower LDL goal.⁹ In this trial, 10001 patients with clinically evident CHD and LDL level less than 3.4mmol/l were randomly assigned to double-blind therapy and received either 10mg or 80mg





atorvastatin per day. The mean LDL levels were 2.0mmol/l and 2.6mmol/l for the 80mg and 10mg atorvastatin groups respectively. The 80mg atorvastatin group was associated with a significantly lower (22% relative risk reduction) composite end point (death from CHD, nonfatal non-procedural related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke) compared with the 10mg atorvastatin group. Hence, the authors concluded that the TNT results confirmed and extended the growing body of evidence indicating that lowering LDL level well below the recommended level could have clinical benefits.

Hence, both the HPS, PROVE-IT and TNT results showed concordantly that the lower LDL level that could be achieved, the lower cardiovascular event would be (Figure 1) in those high risk patients with documented coronary artery disease.

Beyond LDL lowering

Statin was shown to have a greater clinical benefit when levels of inflammatory biomarker C-reactive protein are elevated. Meanwhile, statins lower CRP levels in a manner independent of LDL levels. Hence, statin is now recognised not only as a lipid lowering agent but also as an anti-inflammatory agent. In a substudy of the PROVE IT - TIMI 22,¹⁰ the relationship between the LDL and CRP levels and the risk of clinical outcomes were studied. It was found that patients who had low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, an effect present at all levels of LDL achieved. Patients who received 80mg of atorvastatin daily were significantly more likely than those received 40mg pravastatin daily to have a decrease in the levels of both LDL and CRP to target values. However, once target levels were met, there was no differential outcome according to the specific statin given. This suggested that achieving target levels of LDL and CRP was more important than the specific choice of agents.

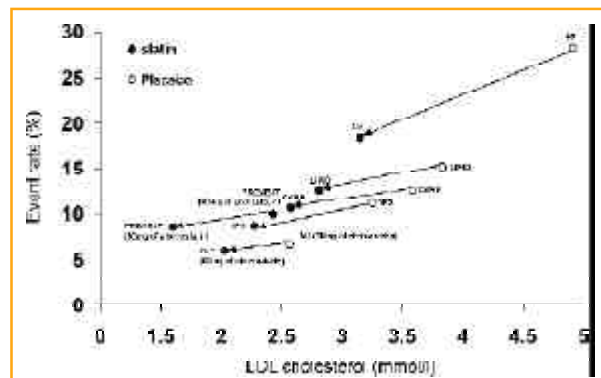
In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial,¹¹ intensive therapy with 80mg of atorvastatin per day slowed the progression of atherosclerosis more than did moderate treatment with 40mg of pravastatin per day. A post-hoc analysis showed that decrease in CRP levels was independently and significantly correlated with the rate of plaque progression.¹² Patients with reductions in both LDL and CRP that were greater than the median had significantly slower rates of progression than patients with reductions in both biomarkers that were less than the median.

Hence, these two substudies suggested that statin therapy has an anti-inflammatory effect which is associated with slower plaque progression and less clinical event. They both preferred a more intensive and aggressive lipid lowering therapy to a moderate therapy.

In epidemiological studies, low HDL cholesterol level is associated with an increase risk of CHD. Indeed, it is one of the risk factors used in the calculation of the FRS. Whether raising the HDL level should be a therapeutic target beyond reaching LDL goal is still controversial.

Figure 1 Relationship between the decreases in LDL achieved and the decreases in cardiovascular event rate in secondary prevention studies.

HPS denotes Heart Protection Study,⁴ CARE Cholesterol and Recurrent Events Trial,¹⁸ LIPID Long-term Intervention with Pravastatin in Ischaemic Disease,¹⁹ 4S Scandinavian Simvastatin Survival²⁰ and PROVE-IT Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 study.⁵



Brown et al reported that a combination of simvastatin and niacin in patients with coronary artery disease was associated with a significant increase in HDL, a regression of angiographic determined coronary stenosis and reduction in cardiovascular event.¹³ However, a recent meta-analysis showed that there was a linear but non-significant trend between raising HDL level and lowering of CHD mortality rate.¹⁴

Limitation of current data

Both the PROVE IT and the TNT data supported to achieve LDL level well below the current recommended level. However, only patients with recent acute coronary syndrome were enrolled into the PROVE IT and patients with stable coronary artery disease were recruited into the TNT. Whether these positive results would be applicable to other high risk group of patients (e.g. diabetes, 2+ risk factors and 10-year risk >20%, stroke) remain to be proven.

Meanwhile, previous clinical trial showed that, even with high-dose statins¹⁵ or LDL-lowering drug combinations,^{16,17} LDL reduction >50% often could not be achieved. Hence, it may be difficult and impractical to achieve a LDL of <1.8mmol/l in daily practice. The use of higher dose of statin may be associated with more side effects (e.g. myositis and elevated liver enzymes), although both PROVE IT and TNT confirmed the safety of high dose atorvastatin. On the other hand, whether the use of second medication (e.g. ezetimibe) to lower the LDL level is associated with the same clinical benefit as a high dose statin is unknown.

Last but not the least, it has to be stressed again that these results should not be extrapolated to lower risk persons (e.g. primary prevention).



Conclusion

There is a growing body of evidence to support the use of intensive lipid lowering therapy to reach a very low level of LDL in persons at high risk of cardiovascular events. However, current data supported a LDL goal <1.8mmol/l only in those with established CHD and not in those just with multiple risk factors. In moderately high risk patients, the threshold to initiate drug therapy is lowered. The use of CRP, in addition to lipid level, may be helpful in monitoring lipid lowering therapy. Finally, alternative non-LDL targets such as HDL should be considered in high risk subsets.

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