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REVIEW

An Update on the Measurement and Management of Cholesterol with Specific Reference to Secondary Prevention of Cardiovascular Disease (CVD)

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Abstract

Cardiovascular disease remains the largest contributor to non-communicable adverse disease outcomes. Treatment and prevention of cardiovascular disease have evolved at a dramatic pace in the last 40 years. Serum-cholesterol has emerged as the dominant risk factor for coronary artery disease and events. The link between serum-cholesterol and arterial atherosclerosis is well documented. The attainment of cholesterol goals has historically concentrated on low-density lipoprotein cholesterol (LDL-C) levels. Current evidence and guidelines have shifted to the attainment of non-HDL-C target levels which represent a more thorough inclusion of small dense atherogenic particles. Methods to reduce serum-cholesterol mainly centre around the use of the HMG CoA-reductase inhibitors also known as the statins. High intensity statins like atorvastatin (80 mg) and rosuvastatin (40 mg) are now the preferred starting therapies to lower cholesterol by at least 40–50% in patients with established cardiovascular disease as secondary prevention. In the event of failure of these medications, evidence suggests that the addition of ezetimibe may enhance the total serum-lowering levels to 50–60%. New therapies aimed at inhibiting PCSK9 revealed exciting new targets for LDL-C lowering, but the high cost of these antibodies could preclude access to this therapeutic intervention. Aggressive pursuit of lower LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C) levels may reduce the incidence of secondary myocardial infarctions, strokes and death from cardiovascular disease.

Keywords: secondary prevention, LDL-C, Non-HDL-C, high intensity statins, PSCK9 inhibitors, ezetimibe

Introduction

Patients with established cardiovascular disease (CVD) are at a higher risk for future CVD events.[1] All CVD prevention guidelines describe that the patients with the most to gain from treatment are those at greatest risk of coronary heart disease (CHD).[1] Prevention in high risk patients or very high risk groups is referred to as secondary prevention.[1,2,3] These individuals who are at high risk include those patients with established atherosclerotic disease such as: previous myocardial infarctions (MIs), a current history of angina, recipients of coronary revascularisation, type 2 diabetes, type 1 diabetes with microalbuminuria, genetic dyslipidaemia, chronic kidney disease (GFR < 60 ml/min/1.73 m^2), a previous stroke, a history of transient ischaemic attacks (TIA) and patients with peripheral artery disease (PAD). These patients are automatically eligible for secondary prevention measures. In addition to meeting the requirements for secondary prevention, guidelines also provide specific targets for blood pressure control or total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (Non-HDL-C).[1,2,3]

Measurement of Cholesterol – To Fast or Not to Fast?

Past dyslipidaemia guidelines have generally emphasised the need for fasting lipograms before starting therapy to ensure the accuracy in results.[2] There is recent evidence which has questioned the fasting requirement for lipograms.[4,5] From population-based studies, TC, high density lipoprotein cholesterol (HDL-C) and non-LDL-C only varied by 2% with population based studies.[4] Robust evidence supports the use of non-fasting blood draws for routine clinical practice and the role of the fasting lipograms now has a much more limited use.[5] The limited role of the fasting lipograms should be utilised only in the setting of abnormally increased triglyceride (TG) levels and prior to starting treatment in patients with genetic forms of dyslipidaemia.[4,5] For the purposes of monitoring LDL-C, a fasting sample may still be required.[4] Both the South African Diabetes Guidelines and the current EDL, have moved away from the need for a fasting lipograms to initiate statin therapy as secondary prevention.[6,7] The authors of the diabetes guidelines, state at the first visit a patient with type 2 diabetes should have their total cholesterol and triglycerides measured. If either of these is elevated then only a ten-hour fast lipogram should be performed.[6]

Lowering LDL-C as a goal in Secondary Prevention of CVD

Another set of different clinical guidelines recommend lowering LDL-C as the goal of cholesterol management in secondary prevention of CVD.[2,8,9,10,11] Each of these organisations have different goals with regards to LDL-C reduction ranging from obtaining an LDL-C of less than 1.8 mmol/l to an LDL-C of less than 2.6 mmol/l.[2,8,9,10,11] Additionally, the South African guidelines suggest that for patients who cannot achieve an LDL-C goal of less than 1.8 mmol/l for secondary prevention, they must at least achieve a greater than 50% reduction in LDL-C from baseline. It is important to remember that there is no single study that has evaluated an LDL-C goal of < 1.8 mmol/l as a target for therapy.[12,13] All trials of LDL-C lowering have, however, demonstrated better outcomes in groups that received more aggressive LDL-C lowering therapy when compared to either the placebo or lower intensity statins.[12,13] In many trials, participants have achieved an LDL-C below 1.8 mmol/l.[12,13]

There is a lack of reliable data regarding the optimal method of monitoring the effects of lipid-lowering therapy.[14] The NCEP ATP-III guidelines suggest that LDL-C should be monitored approximately six weeks after the initiation or change of treatment whilst the South African guidelines suggest that testing should commence ±4 weeks after the initiation of pharmacotherapy.[2,14] Should the LDL-C be less than expected, the practitioner should consider issues such as possible non-tolerance or non-adherence.[12] Once the goal is achieved, the follow-up testing should be every 6 months.[2,14]

The question does remain, however, what are the benefits of lowering of LDL-C in secondary prevention of cardiovascular disease? Table 1 illustrates the benefits of lowering LDL-C.

Table 1: Benefits of lowering LDL-C[2]

For every mmol/l reduction in LDL-C there is a:
1. 10% reduction in mortality
2. 20% reduction in all-cause morbidity
3. 23% reduction in major cardiac events
4. 17% reduction in stroke.

Non-High-Density Lipoprotein-Cholesterol (Non-HDL-C) as a goal in Secondary prevention in CVD

It is generally accepted that high levels of LDL-C play the main role in the initiation and progression of atherosclerosis.[15] However, despite therapies being available to reduce LDL-C a large number of clinical events still occur in patients who have reached LDL-C goals.[16] This is where non-HDL-C comes into the picture. Non-HDL-C represents the cholesterol content in all the atherogenic lipoproteins and not just the LDL-C.[16] Virani therefore goes on to suggest that treatment of non-HDL-C is a more grounded and holistic approach to the management of dyslipidaemia than simply targeting a particular LDL-C level.[16] Non-HDL-C is calculated as follows: Non-HDL-C = Total Cholesterol - HDL-C.[3]

The advantage of using non-HDL-C is that it does not require a fasting sample and can be done at any time.[3] A meta-analysis of 68 studies show that non-HDL-C was a better predictor when compared to all other cholesterol measurements for both coronary artery disease (CAD) events and strokes.[17] Elevated levels of non-HDL-C, when found in combination with normal levels of LDL-C, can identify a subset of patients with elevated LDL particle numbers, elevated apoprotein B concentrations and LDL of small and dense morphology.[16] With increased incidence of the metabolic syndrome, there might be a decrease in the accuracy of LDL-C to predict CAD events, whereas non-HDL-C, total apoprotein B concentrations and LDL particle concentrations retain their predictability in this population.[16] Non-HDL-C is treatable using all the treatment modalities available for dyslipidaemia.[16]

Compared to other guidelines around the world, the National Institute of Health Care and Excellence (NICE) saw fit in 2014 to adopt non-HDL-C instead of LDL-C as the goal for dyslipidaemia management.[2,3,6-10,13] NICE suggests that if a patient has established cardiovascular disease, they should be started on a high-intensity statin, e.g. atorvastatin 80 mg.[3] After three months on this regimen, the authors suggest a lipid profile must be obtained. In this situation total cholesterol, HDL-C and non-HDL-C should be measured and the goal of therapy is to have reduced non-HDL-C by more than 40%.[3] If this is not obtained they suggest the practitioner should institute one of the measures stated in table 2.

Table 2: Suggested measures primary care practitioners should take if a patient has not achieved a 40% reduction from baseline non-HDL-C

1. Discuss adherence and timing of dose with the patient.
2. Optimise adherence to diet and lifestyle measures.
3. Consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

It remains unclear whether the goal of lipid-lowering therapy in secondary prevention of CVD should be centred on LDL-C or non-HDL-C. It is clear, however, that non-HDL-C may be an alternative goal to LDL-C.

Pharmacological therapy

For secondary prevention patients, high-intensity statin therapy is recommended, which is consistent with the NICE guidelines, ATP-III guidelines, South African guidelines and European guidelines.[2,3,8,9,14] High-intensity statin therapy is expected to lower LDL-C by 50–60%. Combination therapy (a statin plus ezetimibe) is recommended in cases where the LDL goal is not met with statin therapy alone.[2,3] If a compliant patient's LDL goal is still not met with combination therapy of a statin with ezetimibe, referral to a cardiologist specialist in lipid disorders is necessary for the possible addition of PCSK9 antibody therapy.[3]

Statin therapy

The principle therapeutic benefits of statins derive from their ability to reduce cholesterol low-density lipoprotein (LDL)

by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG COA) reductase enzymes. This results in lower intrahepatic cholesterol and an up-regulation of cell surface LDL receptors, resulting in enhanced receptor-mediated uptake of LDL and other apoB-containing lipoproteins from circulation.[18] The benefit of statin therapy in reducing cardiovascular events in patients with known atherosclerotic cardiovascular disease has been well-established.[19,20,21] In addition, more intensive statin regimens have been found to have a greater efficacy compared to less-intensive regimens. According to the NICE guidelines, secondary prevention is started with a high intensity statin (atorvastatin 80 mg) unless the patient experiences high incidence of adverse effects, are on interaction drugs or patient preference.[3] If a patient presents with statin intolerance, it is best to treat with the maximum tolerable dose or change over to a different statin. A meta-analysis involving approximately 170 000 patients on statin therapy, found that there was an 18% risk reduction for fatal myocardial infarction and 26 % reduction in non-fatal myocardial infarction.[22] The CTT meta-analysis demonstrated that 1 mmol/l reduction in LDL-C resulted in a 10% relative reduction in all-cause mortality and 21% reduction in MVE for statins versus placebo.[23] Table 3 classifies the potency of different statins.

Table 3: The classification of statin potency[3]

High intensity	Medium Intensity	Low Intensity
Atorvastatin 20–80 mg	Fluvastatin 80 mg	Fluvastatin 20–40 mg
Simvastatin 80 mg	Simvastatin 20–40 mg	Pravastatin 10–40 mg
Rosuvastatin 10–40 mg	Atorvastatin 10 mg	Simvastatin 10 mg
	Rosuvastatin 5 mg	

While the benefits of statins are undisputed, they have also been evaluated for potential long-term adverse effects. Adverse event data reported excess risk of myopathy of 0.5 per 1000 in statin therapy trials and was associated with 80 mg rather than 20 mg simvastatin use.[24] It has been proposed that higher potency statins at standard doses could help patients attain their treatment goals without increasing the risk of myopathy.[25] Statins are associated with an increased risk of new-onset diabetes, with adverse event data in more moderate intensity statin trials reported 5 per 1000 diabetogenic potential.[26] Statins have also been associated with increasing the risk of hepatic injury which occurs rarely in 1 % of patients and is reversible with dose reduction or discontinuation.[27,28] Higher doses of statins confer significant CVD benefits, but a higher risk of adverse events. Table 4 illustrates the trials related the combination of statins and PCSK9 inhibitors, statins and ezetimibe as well as comparator statin intensity trials all in the secondary prevention of CVD.

Second-line therapy: Ezetimibe

Ezetimibe inhibits the function of the NPC1L1 protein which is responsible for the transportation of dietary cholesterol from the gut lumen to intestinal enterocytes, thus reducing the absorption of intestinal enterocytes.[36,37] Combination therapy of ezetimibe with statin therapy compared to statin therapy by itself modestly decreases the risk of cardiovascular disease events, but not mortality in high-risk patients with an acute coronary syndrome. Findings from the IMPROVE-IT trial suggest that the ezetimibe-induced cardiovascular risk reduction by LDL-C reduction is similar to statins.[38] Ezetimibe is the first LDL-C lowering drug to show a reduction in CV outcomes in patients well-treated with statins.[18]

Third-line therapy: PCSK9 inhibitors

In certain patients, satisfactory control of dyslipidaemia is not achieved even with combination lipid lowering therapy and recent attention has focused on a new class of agents, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[3] These agents provide great promise for patients who require additional LDL lowering or are unable to take statins (statin-intolerant and familial hypercholesterolemia).[3] The PCSK9 protein plays a crucial role in the regulation of LDL receptors by reducing the number of LDL-C receptors.[39] Targeted monoclonal antibodies have the ability to bind to PCSK9, thereby inhibiting its interaction with LDL cholesterol receptors.[39] Outcomes with regard to their efficacy indicate a reduction in LDL cholesterol of greater than 50% and an elevation in HDL cholesterol levels, especially when administered with statin therapy.[40] In clinical trials the two PCSK9 inhibitors that have shown significant promise are evolocumab and alirocumab.[41]

It is clear that high intensity statins provide benefit irrespective of the baseline LDL-C levels in the secondary prevention of cardiovascular events.[2,9-11,14] Statins by their nature increase PSCK9 levels(Table 5).[42-45] It is evident that PCSK9 inhibitors modulate the effects of statins leading to an increased reduction in LDL-C levels demonstrated by clinical trials such as ODYSSEY LONG TERM.[30]

Table 5: The impact of statin therapy on PCSK9[42-45]

Statin	PCSK change
Atorvastatin 80 mg	+47%
Atorvastatin 40 mg	+37%
Rosuvastatin 20 mg	+28% (men) +35% (women)
Controls	
Statin therapy	+45%
Statin Ezetimibe therapy	+77%
Titration of atorvastatin 5 to 80 mg/day	+30%
Titration of atorvastatin 5 to 40 mg/day	+37%

The recent ODYSSEY LONG TERM study (a post-hoc analysis of the ODYSSEY trial) demonstrated that alirocumab resulted in a 62% LDL-C reduction from baseline and the incidence of major cardiovascular events reduced by 48%.[30] The OSLER studies evaluated demonstrated that evolocumab plus high intensity statin therapy reduced LDL-C by 61% and the incidence of major cardiovascular events by 53%.[32] PCSK9 inhibition was well-tolerated without excess of new-onset diabetes or neurocognitive effects with the exception of a 2% incidence of injection site reactions, despite dramatic LDL reduction. In the OSLER and ODYSSEY LONG TERM studies, the rate of any adverse events was similar in patients receiving PCSK9 inhibitors compared to placebo.[30,32] The recently announced Odyssey Outcome Trial, demonstrated that in 18000 patients with recent

Table 4: Evidence relating to pharmacotherapy used to lower LDL-C levels in secondary prevention of CVD.[19,20,21,29,30–35]

Trial name	Population and sample size	Agent(s) investigated	Comparator	% LDL-C reduction relative to the comparator	Primary Outcome	Comments
Secondary Prevention Trials for PSCK9 Inhibitors and Statins						
FOURIER[29]	27 564 patients with atherosclerotic cardiovascular disease (ASCVD)	Evolocumab and high intensity statin if tolerable	High intensity statin and placebo	39–62	Primary composite endpoint consisting of cardiovascular death, MI, stroke, revascularisation or unstable angina	• EEvolocumab plus high-intensity statin reduced the risk of the primary composite endpoint at a median of 2.2 years vs placebo and high-intensity statin (9.8% vs 11.3%; Hazard Ratio (HR) 0.85, 95% CI 0.79–0.92). • Reduced risk of nonfatal MI (relative risk (RR) 0.73, 95% CI 0.65–0.82) with evolocumab + high intensity statin vs placebo + high intensity statin. • Reduced risk of nonfatal stroke (RR 0.79, 95% CI 0.66–0.95) with evolocumab + high intensity statin vs placebo + high intensity statin. • No decrease in CVD mortality (RR 1.05, 95% CI 0.88–1.25) or all-cause mortality (RR 1.04, 95% CI 0.91–1.19) between either group.
ODYSSEY LONG TERM[30,31]	2341 patients with heterozygous familial hyperlipidemia or high CV risk	Alirocumab and statin therapy	Placebo and statin therapy	61	Primary endpoint consisting of reduction in LDL-C levels	• Alirocumab plus statin therapy resulted in a maintained reduction in LDL-C compared to placebo(61% vs 0.8%; p < 0.0001). • Death from coronary heart disease, MI, stroke, or unstable angina: 1.7% vs 3.3% (p=0.02),respectively for alirocumab vs placebo. • This study was a post-hoc analysis of the ODYSSEY trial.
OSLER[32]	4465 patients with ASCVD and familial hypercholesterolaemia	Evolocumab and statin therapy	Placebo and statin	61	Primary endpoint was the incidence of adverse events. Secondary outcome was the reduction of LDL-C, and pre-specified exploratory outcome was the incidence of cardiovascular events	• Evolocumab resulted in sustained reduction in LDL-C by 61% compared to 26% in the standard therapy group (95% CI, 59 to 63, p < 0.001). • Evolocumab raised s HDL cholesterol levels by 7% compared to 4% in placebo group, (p < 0.001). • Rates of overall adverse effects were similar in both groups (69.2% vs 64.8%).
Secondary Prevention Trials for Ezetimibe with a Statin						
IMPROVE IT[33]	18 144 patients with ACS	Ezetimibe 10mg daily and Simvastatin 40mg daily	Simvastatin 40mg and placebo	23.9	Primary composite endpoint consisting of CVD, nonfatal MI, unstable angina requiring hospitalisation, coronary revascularisation more than 29 days after randomisation, nonfatal stroke.	• Median time weighted average achieved LDL-C was lower in the ezetimibe/ simvastatin group (1.4 mmol/l vs 1.8 mmol/l). • After a median 6 year follow-up, there was a reduction in the primary composite outcome in the treatment arm vs the control with a significant HR (0.94, 95% CI 0.89–0.99). • The absolute reduction in the primary end point at seven year was 32.7 vs 34.7% in the placebo. • No reduction in all-cause mortality (HR 0.99, 95% CI 0.91–1.07). • No reduction in cardiovascular mortality (HR 1.00, 95% CI 0.8–1.13). • There was a significant reduction in the development of MIs (HR 0.87, 95% CI 0.80–0.95).

Statin Trials						
ALLIANCE[21]	2442 patients with coronary heart disease (CHD) & hyperlipidaemia	Atorvastatin 80mg daily	Atorvastatin 10mg daily	34	Primary composite end point of cardiovascular events	• Aggressive treatment with atorvastatin was associated with significantly lower LDL cholesterol levels (3.8 mmol/l to 2.5 mmol/l vs usual care (3.8 mmol/l to 2.9 mmol/l). • Improved outcomes in the composite primary end point of cardiovascular events (-17% with atorvastatin vs. usual care; p=0.02). • Improved outcomes in nonfatal myocardial infarction (-47% with atorvastatin vs. usual care; p= 0.0002).
4S[19]	4444 patients with CHD	Simvastatin 20 mg daily	Placebo	38	Primary composite endpoint was mortality and major coronary events	• There were 189 coronary deaths in the placebo group and 111 in the simvastatin group (relative risk 0.58, 95% CI, 0.46–0.73). • Major coronary events were seen in 622(28%) patients in the placebo group and 431(19%) patients in the simvastatin group (relative risk 0.66, 95% CI, 0.59–0.75 p < 0.00001). • Other benefits of treatment included a 37% reduction (p < 0.00001) in the risk of undergoing myocardial revascularisation procedures.
LIPID[34]	9014 patients with recent history of MI or hospitalisation for unstable angina	Pravastatin 40	Placebo	25	Primary study outcome was mortality from coronary heart disease	• Death from coronary heart disease occurred in 8.3% of patients from placebo group and 6.4% in pravastatin group (relative risk reduction 24%, 95%CI, 12–35%, p < 0.001). • The incidence of cardiovascular events was overall lower in pravastatin groups: MI (RR reduction 29%, p < 0.001), stroke (RR reduction 19%, p < 0.048), coronary revascularisation (RR reduction 20%, p < 0.001).
IDEAL[20]	8888 patients with a history of MI	Atorvastatin 80 mg daily	Simvastatin 20 mg daily	35	Primary study outcome was the occurrence of a major coronary event	• A major coronary event occurred in 463 (10.4%) simvastatin patients and 411 (9.3%) atorvastatin patients (HR 0.89, 95% CI, 0.78–1.01, p=0.7). • Patients in atorvastatin group had higher rates of drug discontinuation due to non-serious adverse events; transaminase elevation resulted in 43 vs 5 withdrawals (p < 0.001).
TNT[35]	10 001 patients with stable CHD	Atorvastatin 80 mg daily	Atorvastatin 10 mg daily	35	Primary study outcomes was the occurrence of major cardiovascular events	• The mean LDL-C levels 2.0 mmol/L during treatment with 80 mg atorvastatin and 2.6 mmol/L during treatment with 10 mg. • A primary event occurred in 434 (8.7%) patients receiving 80 mg compared to 548 (10.9%) patients receiving 10 mg atorvastatin representing an absolute reduction rate of major cardiovascular events 2.2% and a 22% relative risk reduction (HR 0.78, 95% CI, 0.69–0.89, p < 0.001).

ACS, alirocumab and high intensity statin therapy significantly reduced measures of acute and/or adverse cardiovascular outcomes (MACE) compared to the placebo.[46] The goal of the trial was to reduce patient's serum LDL-C to between 0.65mmol/l and 1.30mmol/l which was much lower than the current goals in patients with established coronary artery disease. The trial met its primary endpoint of a 15% hazard reduction (HR 0.85, 95%CI 0.78-0.93, p=0.0003) in the composite outcome of CHD death, nonfatal MI, fatal or nonfatal ischaemic stroke and unstable angina and thus the trial was considered a success. Therapy with alirocumab and high intensity statins resulted in significant hazard reductions in nonfatal MI (HR 0.86, 95%CI 0.77-0.96, p = 0.006), ischaemic stroke (HR 0.73, 95%CI 0.57-0.93, p=0.01) and unstable angina (HR 0.61, 95%CI 0.41-0.92, p=0.02) at 4 years. However, patients in the treatment group experienced no significant hazard reduction in CHD death when compared to the placebo. In the case of both MACE and all-cause mortality a difference in the Kaplan–Meier was only seen after one year. Subgroup analysis of this study indicates that patients with serum LDL-C level consistently greater than 2.59mmol/l benefited most from this therapy 4 years after randomiation.[46]

PCSK9 inhibitors show promising features alone or in combination in patients with unmet LDL-C goals, statin intolerance or heterozygous familial hyperlipidaemia.[3] However, being a monoclonal antibody, it has higher cost implications in comparison to current therapies and the fact that it is a subcutaneously administered agent may lead to patient dosing inconsistencies.

Conclusion

Treatment of cholesterol in cardiovascular disease is mainly confined to the use of the statins. Research has indicated that a preferred target for therapy maybe non-HDL-C which might be a better predictor of cardiovascular events compared to LDL-C. The statins ranging from low intensity fluvastatin to high intensity rosuvastatin have demonstrated the relationship between cholesterol reductions linked to a decrease or a reduction in fatal and non-fatal cardiovascular events. Guidelines have suggested that if cholesterol targets are not reached, the addition of a GIT-cholesterol blocker like ezetimibe should be considered. Since statins increase PCSK9 levels, their effect is modulated in this manner. Thus, the addition of PSCK9-inhibitors to statins can dramatically reduce serum LDL levels to as low as 0.4 mmol/l, however the cost of this new technology means that a majority of patients will not have access to this class of drugs. As a result, statins remain the first and most affordable class of drugs to reduce cardiovascular mortality and morbidity.

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