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The Need for Combination Drug Therapies in Patients with Complex Dyslipidemia

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Abstract Statins are first line therapy for the prevention of cardiovascular disease (CVD). Only 30 %–70 % of high risk patients will attain standard low-density lipoprotein cholesterol targets. Patients with familial hypercholesterolemia and genetic mixed hyperlipidemias do not meet goals with standard therapy. Patients with mixed hyperlipidemia secondary to the metabolic syndrome, diabetes, renal, or HIV infection are at high residual risk due to low HDL-cholesterol or high triglycerides. Newer therapies can be added to statins. The use of ezetimibe has CVD outcomes evidence in chronic renal disease. Adding omega-3 fatty acids, fibrates, or niacin to statins has failed to show any benefit except possibly with fibrates in patients with diabetes and low HDL-C/high triglycerides. Additional benefits on lipid profiles have been shown with pro-protein convertase subtilisin/kexin-9 (PCSK9), mipomersen, lomitapide, and cholesterol ester transfer protein inhibitors (CETPIs). Two CETPIs have failed to show benefit in hard outcomes trials but others remain under investigation. It remains unclear whether additional therapies add to statins for the prevention of CVD in most patients. They may have some added benefit in patients with complex dyslipidemias.

Keywords Triglyceride · HDL-cholesterol · Combination drug therapy · Cardiovascular disease · Dyslipidemia

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Introduction

Cardiovascular disease is one of the leading causes of mortality and morbidity in the world [1]. Epidemiological studies consistently show an association of cardiovascular disease (CVD) risk with total and LDL-cholesterol [2]. In InterHeart, a worldwide case-control study of 52 countries the lipid-related risk was related to the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio or their constituent apolipoproteins (apo B:apo A1) and a high proportion of the risk (55 %) in this cross-sectional study risk was attributed to lipids [3]. Given the epidemiological data, trials of lipid-lowering therapies initially concentrated on reducing initially total cholesterol in the 1970s but later switched to the reduction of low density lipoprotein cholesterol (LDL-C) in the 1990s.

Lipid Targets

Patients with dyslipidemia are major targets of global health prevention strategies with the primary emphasis on reducing LDL-C [4, 5••, 6, 7]. Multiple lipid-lowering therapies have been investigated in monotherapy over the last 50 years but since the discovery of statins, these agents have become universal first-line drugs for the management of CVD risk [8••]. They have been successful in monotherapy in almost all population groups except those with severe renal [9] or cardiac failure [10, 11]. LDL-C levels have been shown in large epidemiological studies to correlate with CVD and meta-analyses of statin therapy show that a 1 mmol/L reduction in LDL-C is associated with a 21 % reduction in relative risk of CVD events [8••]. Controversy exists about whether statins have actions beyond that can be explained by reduction of LDL-C eg, reduction in inflammation [12]. These actions are likely to be mediated through isoprenoid intermediates of cholesterol synthesis and possibly the rho kinase

pathway [13]. However, meta-analyses of studies where anti-inflammatory effects of statins have been documented failed to support the original hypothesis [14].

Guideline groups have derived targets for LDL-C based on extrapolation from epidemiological studies and from linear regression equations for surrogate outcomes such as intravascular ultrasound (IVUS) measured atheroma burden. Randomized controlled trials of lipid-lowering therapies are then interpreted with regard to the lipid levels attained rather than through their design, which usually compares fixed doses. Statins reduce CVD events by up to 50 % in extrapolations of data from high-dose vs placebo studies but 30 %–50 % of patients do not reach LDL-C targets [15]. The figures for the targets (eg, <1.8–2.0 mmol/l in secondary prevention [4, 5••]) are derived from epidemiological and surrogate marker studies as well as the mean LDL-C attained in endpoint trials of fixed doses. Thus there may be a role for additional LDL-C reduction beyond that possible as sub-groups from the studies suggest that further benefit may be derived at lower LDL-C levels [16, 17].

In addition epidemiological studies show that CVD risk is dependent on the ratio of total cholesterol: HDL-cholesterol (TC: HDL-C)(equivalent to apoB:apoA1 in terms of apolipoproteins) so some of the residual risk that remains after statin therapy may be attributed to triglyceride-rich lipoproteins [18, 19••]. No trials have investigated the utility of treating to a TC:HDL-C ratio but epidemiological studies and post-hoc analyses of trials have shown that non-HDL-C (the difference between total and HDL-C concentrations; equivalent to apo B) may be superior to LDL-C for prediction of future CVD events with the greatest difference being seen in patients with elevated triglycerides [20]. Some lipid-lowering drugs such as some fibrates that do no change LDL-C do have significant effects on non-HDL-C. Thus other approaches to changing lipid profiles may have benefit on CVD events. Some of these drugs eg, fibrates, niacin or omega-3 fatty acids have some evidence for benefit in monotherapy. Statins are now established first line therapy so the role of these or other new agents has to be assessed in the context of addition to statins. This review article assesses the need for combination drug therapies in patients with dyslipidemias. It is based on multi-keyword searches of the scientific literature. We focus on secondary causes of dyslipidemia including diabetes, HIV, and chronic kidney disease.

Complex Dyslipidemias and Combination Therapy

Primary Dyslipidemias

Those with family history of premature coronary heart disease should be investigated for familial lipid disorder. These include familial hypercholesterolemia (FH), polygenic hypercholesterolemia, and familial combined hypercholesterolemia.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH), an autosomal dominant condition, affects 1 in 500 individuals and is associated with premature CVD. The primary defect is in expression of the LDL receptor and plasma LDL-C levels are in the range 4–6 mmol/L. The National Institute of Health and Clinical Excellence (NICE) [21] and National Lipid Association [22] guidance on FH recommends a greater than 50 % reduction in LDL-C based on evidence from the Atorvastatin and Simvastatin Atherosclerosis Prevention (ASAP) study [23]. Though a 50 % reduction can be achieved in about 50 % of patients few reach the standard targets used in general CVD prevention (eg, <2 mmol/L; see above). Thus additional LDL-C lowering therapies are required to enable these patients to reach standard targets. The most commonly used in ezetimibe though bile acid sequestrants eg, colesevelam are also needed in some cases.

Familial Combined Hyperlipidemia

The other common genetic disorder is familial combined hyperlipidemia (FCH). This condition whose underlying genetic etiology is still unknown is distinguished by overproduction of apoB containing lipoproteins and increased risk of premature CVD due to triglyceride-rich lipoproteins [24].

Type IV and Type V Hyperlipidemias

These disorders of triglyceride-rich lipoproteins are usually associated with heterozygous mutations in genes associated with the function of lipoprotein lipase. These conditions are associated with increased rates of atherosclerosis and as triglyceride levels increase further increased risks of diabetes and pancreatitis [19••, 25•].

Diabetes and Metabolic Syndrome

The metabolic syndrome is defined by central obesity, low HDL-C, high triglycerides, dysglycemia, and elevated blood pressure. It is associated with insulin resistance and type 2 diabetes. In patients with long-established diabetes risk of CVD equal those of normoglycemic patients with prior CVD. Risks of CVD increase due to the secondary effects of modulation of LDL particles by other enzymes (eg, lipoprotein lipase), and transfer factors (eg, cholesterol ester transfer protein). The changes occur secondary to insulin resistance through modulation of apolipoprotein C-III and enzyme production. These changes result in the formation of small dense particles of LDL, which are more atherogenic

than standard size LDL [26]. Small dense HDL are either dysfunctional or non-functional and are cleared more rapidly in the kidney. In meta-analyses the difference between total and HDL-C levels – non-HDL-C or apolipoprotein B levels are better correlates of CVD risk in this group than LDL-C levels [27••].

Other Conditions Associated with Dyslipidemia

Significant insulin resistance and dyslipidemia are features of other conditions. Patients with chronic renal disease have CVD risk that can be equivalent to those with type 2 diabetes or CVD [28]. Similarly the insulin resistance and lipodystrophy associated with HIV infection and its treatment lead to increased CVD risk [29]. Some drugs lead to increase in adipose tissue or primary dyslipidemia. Systemic glucocorticoids, bexarotene and some anti-psychotics increase triglycerides, while ciclosporin raises LDL-C. Long-term use of any of these agents may be associated with increased CVD risk.

Treatment Options

Statins are excellent drugs for the treatment of CVD risk and have evidence in all groups of patients in monotherapy except in severe chronic renal failure (Chronic kidney Disease stage 3–5) [9] and chronic cardiac failure (New York Heart Association class 2–3) [10, 11] where the atherosclerotic disease process may be too advanced to be easily reversible. It is also possible that many events classified as atherothrombotic in these conditions are actually arrhythmic in origin and thus not susceptible to improvement with statins. However, in early stage renal impairment they do seem to be effective in reducing progression of renal function deterioration as well as reducing CVD events [30]. Similarly in sub-group analyses of trials that included cohorts with mild cardiac failure suggest they may be beneficial [31]. Statin therapy reduces CVD events by 21 % per 1 mmol/L LDL-C reduction [8••]. Statins can deliver up to a 2.5 mmol/L reduction in LDL-C in patients with average LDL-C levels. In between 2 % and 10 % of patients cannot tolerate statins due to either muscle or gastro-intestinal side-effects [32]. In these individuals other lipid-lowering agents with evidence in prevention of CVD are used. These include niacin, fibrates, and bile acid sequestrants.

Bile Acid Sequestrants

Bile acid sequestrants (BAS) bind to bile acids preventing the uptake of lipid-rich particles in the intestine. Typically they reduce LDL-C by 15 %–20 % but may raise triglycerides [33]. As BAS are not absorbed they have no systemic side effects, but they commonly cause abdominal distension, nausea, and diarrhea. Newer agents such as colesevelam have fewer side-effects than older drugs such as cholestyramine or Colestid. There is outcome evidence from the Lipid Research Clinics trial for cholestyramine where it reduced CVD events by 18 % and a few smaller studies [34]. The combination of BAS with statin is effective in further reducing LDL-C. BAS were added to statins to deliver additional LDL-C reduction in 8 % of patients in the Cholesterol And Recurrent Events (CARE) study but this group was not reported separately [35]. There are no surrogate outcome or endpoint trials of BAS added to statins.

Ezetimibe

Ezetimibe reduces LDL-C by reducing cholesterol absorption in duodenal enterocytes through the Niemann-Pick C-1-Like 1 (NPC1L1) sterol transporter. It delivers a 23 % reduction in LDL-C with little effect on triglycerides or HDL-C in monotherapy or when added to a statin [36, 37]. However, its use has proved controversial as ezetimibe failed to add to high dose statins in a surrogate outcome study in familial hypercholesterolemia (ENHANCE) [38]. In combination therapy with statins it failed to reduce a combination of heart valve and CVD endpoints in the underpowered Simvastatin-Ezetimibe and Aortic Stenosis (SEAS) study in 1873 patients [39]. In SEAS ezetimibe did reduce CVD events nonsignificantly by 21 % and in line with predictions [40]. More definitive evidence on CVD outcomes with ezetimibe came from the Simvastatin And Renal Protection (SHARP) study in 9270 patients [41•]. Previous statin studies had failed to reduce CVD events in this group despite 40 %–45 % reductions in LDL-C. In SHARP the combination reduced LDL-C by 55 % and CVD events by 17 % with minimal side-effects. Thus ezetimibe has evidence in combination therapy but not in monotherapy as yet through the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study in acute coronary syndromes is underway [37].

Niacin

Niacin is the oldest lipid-lowering drug. Niacin raises HDL-C but also reduces triglycerides, LDL-C, and lipoprotein (a) [42]. It main side-effects are flushing and itching and increasing dysglycemia. It has monotherapy evidence from the Coronary Drug Project in 1975[43] and in surrogate outcome studies combining it with fibrates and bile acid sequestrants. Surrogate outcome studies also suggested that it added to statins in the Familial Atherosclerosis Trial Study (FATS) and HDL-C and Atherosclerosis Treatment Study (HATS) [42]. Recently 2 trials have been conducted on CVD events of adding niacin to statins. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study had a complex design [44]. It aimed to add niacin to LDL-C

lowering therapies and then optimized LDL-C after randomization of high-dose or minimal dose niacin. Despite a 4 % net increase in HDL-C, a reduction in the triglyceride level and lower LDL-C, the trial did not reach its endpoint of CVD events and was terminated for futility [44]. The results of the far larger Heart Protection Study-2/ Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2/THRIVE) trial in 27,000 patients have been announced [45]. It used a combination of niacin and laropiprant to reduce flushing by blockade of prostaglandin D2 type 1 receptors. It too did not reach its end point of reducing CVD events and there was a significant increase in non-fatal side effects. Niacin is the only therapy that reduces lipoprotein (a) by 25 % but no outcome studies have investigated the benefits of niacin in patients with elevated lipoprotein (a) (>0.5 g/L) but the FATs trial did suggest that reducing LDL-C was enough to negate any additional risk [5••, 46, 47].

A meta-analysis of 83 trials of HDL-raising drugs including both fibrates and niacin suggested that these agents may be beneficial with fibrates reducing risk by 25 % and niacin by 27 % [48]. A more recent meta-analysis that included AIM-HIGH and 10 other clinical trials, showed a significant reduction (34 %, P=0.007) in the composite endpoints of any CVD event [49]. Addition of the HPS2/THRIVE results given the large numbers of patients enrolled will likely change the overall outcome to negative in combination therapy.

Fibrates

Fibrates are a complex group of drugs, which reduce triglycerides, raise HDL-C by 0 %–6 % and some may reduce LDL-C [50]. In monotherapy trials fibrates have delivered a 10 %–35 % reduction in CVD events in secondary prevention (Helsinki Heart Study [51], Fenofibrate Intervention In Endpoint Reduction in Diabetes (FIELD) [52]). In the Veterans Administration HDL-C Intervention Trial (VA-HIT), a secondary prevention trial in patients with low HDL-C, gemfibrozil reduced CVD events by 25 % despite having no effect on LDL-C [53]. Meta-analyses of fibrate trials show a 10 % (95 % CI 0–18) relative risk reduction for major CVD events (P=0.05) with most benefit on non-fatal myocardial infarction [54, 55•]. However, fibrates have no benefit on CVD mortality. The only direct comparison of fibrates with niacin in the CDP showed that niacin was superior to clofibrate [43]. One combination therapy study has been conducted of fibrate added to basal statin therapy. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) randomized in 5518 patients with diabetes showed a non-significant 8 % decrease in CVD event [56•]. Pre-specified analysis, however, did show, as in other fibrate studies, some positive findings with hypertriglyceridemia and low HDL-C levels [57]. The Food and Drug Administration has suggested that based on this finding, sub-group analyses and the improvements in LDL particle size a trial is required in high triglyceride low HDL-C patients with a fibrate.

Omega-3 Fatty Acids

Omega-3 fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). At low doses both DHA and EPA reduce CVD events in trials such as GISSI-Prevenzione in 11,324 secondary prevention patients [58] and the Japan EPA Lipid Intervention Study (JELIS) in 18,645 patients [59]. Both these trials had either low rates of statin usage (GISSI-P) or limited reduction in LDL-C (JELIS) [60]. Meta-analyses of 20 omega-3 fatty acid trials from both dietary and pharmaceutical sources have suggested a 14 % reduction in CVD death and a similar but non-significant benefit on coronary events but only 4 % on total CVD events [61]. At higher doses fatty acids DHA and EPA reduce triglycerides and VLDL-C, whilst increasing HDL-C in a dose-proportional manner [62]. No trial until recently investigated Omega-3 Fatty acids in combination with optimal statin therapy. The Outcome Reduction with Initial Glargine InterventioN (ORIGIN) trial investigated the effect of DHA omega-3 fatty acids in 10,000 patients with type 2 diabetes or metabolic syndrome. In the ORIGIN trial triglyceride levels were reduced, but there was no reduction in CVD risk [63]. The Alpha-Omega trial randomized 4837 elderly men with optimal risk factor control to either 400 mg DHA/EPA or 2 g daily of alpha-linolenic acid (ALA) but again no effect on triglycerides or benefits on the CVD event-rate were seen [64].

New Drugs

Many new lipid-lowering agents are in development [65••]. The highest profile ones are additional drugs to reduce LDL-C including antisense oligonucleotides to apoB (mipomersen) [65••] and antibodies to proprotein convertase subtilisin/kexin -9 (PCSK9) (REGN-727 or AMG-145) [66]. These reduce LDL-C by 20 %–65 % in addition to statins. The microsomal transfer protein inhibitor lomitapide reduces LDL-C and triglycerides [67]. Cholesterol ester transfer protein inhibitors (CETPIs) raise HDL-C and most reduce LDL-C by 30 %–40 % [65••] but torcetrapib increased CVD events in combination with statin therapy in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) study [68] and dalcetrapib did not reduce CVD events in acute coronary syndromes in the DalOutcomes study [69].

Conclusions

Meta-analyses show that statins are the best treatment for dyslipidemia. They reduce LDL-C, triglycerides, and can

raise HDL-C. The incidence of dyslipidemia is increasing in parallel with the increase in obesity and the metabolic syndrome. Approximately 25 % of patients in secondary prevention have reduced HDL-C and increased residual CVD risk not complete corrected by statin therapy. Recent trials involving the combination of anti-lipid drugs with statins have demonstrated mixed results [70]. The combination of ezetimibe and statins in the SHARP trial in patients with chronic renal failure produced a 17 % reduction in CVD events where statin monotherapy had previously been ineffective. Disappointing results were observed with niacin-statin combination therapy in AIM-HIGH and HPS2/THRIVE and with fibrates in the ACCORD trial. However, these studies have recruited too few patients with high triglycerides and low HDL-C, where these drugs are likely to be most effective, to definitively answer the question of residual lipid-related risk. Also optimization of LDL-C to <2 mmol/L may result in too low an event rate for their effects to be clearly discerned or if a curvilinear rather than a linear relationship exists for LDL-C reduction. Improvements may be required in trial design and specific high-risk dyslipidemic populations may need to be recruited for the efficacy of combination therapy to be proven.

Compliance with Ethics Guidelines

Conflict of Interest James Barnett declares that he has no conflict of interest.

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Anthony S. Wierzbicki is chairman of the Lipid Modification and Cardiovascular Disease Risk assessment guideline development group at the National Institute for Health and Clinical Excellence (NICE). The views expressed in this article are his own and do not reflect the view of the guideline group.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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