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Review article

Management of residual risk after statin therapy

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. Observational data indicate that low-density lipoprotein cholesterol (LDL-C) levels are strongly positively associated with the risk of coronary heart disease (CHD) whilst the level of high-density lipoprotein cholesterol (HDL-C) is strongly inversely associated, with additional associations being observed for other lipid parameters such as triglycerides, apolipoproteins and lipoprotein(a) (Lp(a)). This has led to an interest in the development of a range of lipid intervention therapies. The most widely used of these interventions are statins, but even with intensive statin therapy some groups of patients remain at significant residual cardiovascular (CV) risk. In addition, some people are intolerant of statin therapy. In these circumstances, additional therapeutic agents may be needed. This review considers the evidence behind and the pros and cons of such additional agents.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of adult mortality and morbidity worldwide. Preventive measures such as reductions in smoking, blood pressure and atherogenic lipids, and advances in treatments and healthcare have led to large reductions in age-standardised death rates for CVD, particularly in high income regions [1,2]. However its prevalence is rising in developing countries [1,2] and it remains a substantial public health issue.

The aetiological relationship between long-term average blood cholesterol concentrations and risk of cardiovascular (CV) morbidity and mortality has been established reliably by the more than 60 years' of evidence from observational, randomized and genetic studies. Many of the older prospective observational studies which established these relationships were incorporated into comprehensive meta-analyses of the lipid risk factors for CVD undertaken by the Emerging Risk Factors Collaboration (ERFC) [3]. This confirms the log-linear positive association between non-high-density lipoprotein cholesterol [non-HDL-C] (or, approximately analogously, low-density lipoprotein cholesterol [LDL-C]) and the risk of coronary heart disease (CHD) with no apparent threshold level below which a lower non-HDL-C level does not confer a lower risk (Fig. 1). The pooled data from the ERFC observational studies of about 10 years follow-up shows a hazard ratio of 1.5 (1.39–1.61) per 1 standard deviation (43 mg/dL or 1.1 mmol/L) higher non-HDL-cholesterol; whereas more recent Mendelian Randomisation [MR] studies show that life-long differences in LDL-cholesterol, based on genetics, are associated with CHD risk even more strongly with about a 2-fold increase in risk per mmol/L higher LDL-C. This indicates about a 3-fold greater reduction in the risk of CHD associated with a unit lower LDL-C than that observed during treatment with a statin started later in life [4]. This implies that residual risk following standard LDL-lowering treatment may be partly explained by treating late in the course of the disease, and that earlier treatment would increase benefit.

The association between non-HDL-C and risk of ischaemic stroke, although also positive, is much less strong although LDL-C lowering clearly reduces ischaemic stroke in the randomized trials [3,5]. MR data has not to date been published to help clarify this. By contrast, observational data indicate that HDL-C levels are strongly inversely associated with CHD and also, although less clearly so, with ischaemic stroke [3]. However, the MR studies do not imply that HDL-C is causally related to CHD risk and to date the randomized trials support this (discussed below) [6]. The positive associations between triglyceride levels and risk of vascular disease typically disappear on adjustment for the other lipid factors [3], although recently it has become clear that remnant cholesterol, the cholesterol content of triglyceride-rich lipoproteins, is independently associated with CHD even after adjustment for HDL-C [7,8] and MR studies also support the importance of triglyceride

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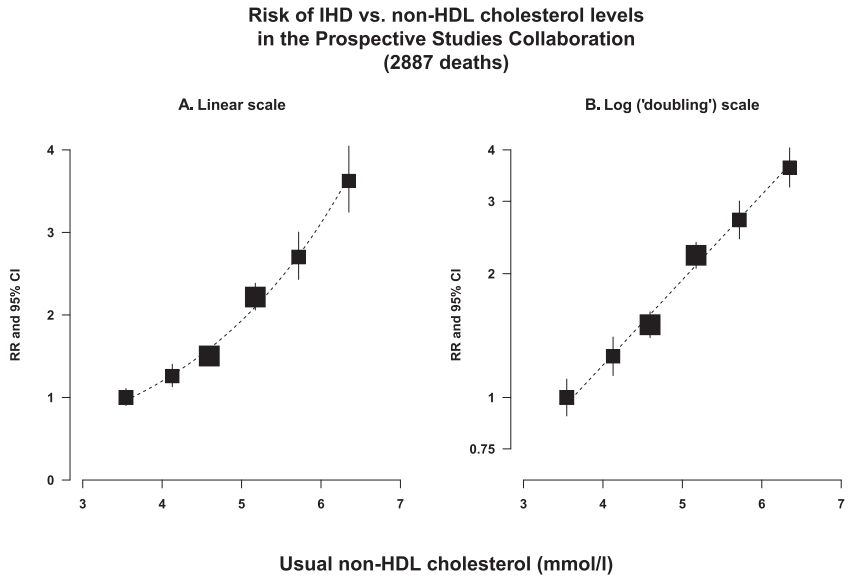

Fig. 1. Adapted from Prospective Studies Collaboration (S Lewington, personal communication): Ischaemic Heart Disease mortality (2887 deaths) versus usual non-HDL cholesterol on linear scale; and log-linear scale.

pathways in CHD risk [9].

In light of these associations, interventions to modify lipids have been a key component of CVD treatment and prevention. People whose diet is relatively high in saturated fat can achieve some reduction in blood cholesterol and LDL-C through dietary intervention, but this effect is modest [10,11]. Statins are the cornerstone of lipid modification but, despite intensive statin therapy, many high patients remain at significant risk. This article reviews drug options for the management of this residual risk through further lipid modification. Nevertheless, it should be remembered that effective CVD reduction strategies need to adopt a multi-faceted approach to address other major CVD risk factors, such as blood pressure and diabetes, and ensure smoking cessation and avoidance of obesity. Equally, any intervention is only as effective as its associated compliance, highlighting the importance of patient understanding of any treatment and its acceptability in practice Box 1.

1.1. Statin therapy: current mainstay of treatment

Statins are inhibitors of 3-hydroxy 3-methylglutaryl Co A (HMG Co A) reductase, a key enzyme in cholesterol biosynthesis whose inhibition leads to reduced intracellular cholesterol synthesis and up-regulation of LDL receptors [12]. This up-regulation leads to reductions in circulating levels of LDL-C by 20–60%, depending on the type of and dose of statin [13,14]. Statins also modestly increase HDL-C and reduce triglyceride concentrations but these effects are not thought to contribute significantly to their clinical impact. Their impact on lipoprotein(a) (Lp(a)) remains uncertain, but is likely to be small [15,16]. Statins were first approved in 1987, and after several pivotal trials in both primary and secondary prevention of CVD, their use in routine clinical practice has become widespread. However, early in their development there were lingering concerns that lowering cholesterol might increase the risk of particular cancers and/or non-vascular mortality [17,18]. Such issues would not have been addressed by the early statin trials since no single trial would have sufficient statistical power to reliably assess effects on mortality. The Cholesterol Treatment Trialists' (CTT) Collaboration was established in 1994 to bring together individual participant data from all the large, long-term randomized trials of statins in order to assess more reliably the effects of cholesterol-lowering with statins on non-vascular mortality and cancer in addition to quantifying the benefits on CVD [19].

The CTT Collaboration meta-analyses [20–23] have shown clearly that statin therapy proportionally reduces the risk of major vascular events (i.e. myocardial infarction (MI), coronary death, stroke or coronary revascularisation) by about one fifth per mmol/L absolute reduction in LDL-C, largely irrespective of baseline cholesterol concentration (even when LDL-C is already less than 2 mmol/L) or other presenting characteristics. The absolute benefit relates chiefly to an individual's absolute risk of such events and to the absolute reduction in LDL-C achieved [20] with further reductions in LDL-C with more intensive statin regimens having been demonstrated to yield further reductions in risk [21] (Fig. 2). Typically, newer statin regimens will reduce LDL-C by 2 mmol/L or more, leading to reductions in risk of about 40%.

Statins are well-tolerated with no significant excess of symptomatic side-effects in the blinded randomized trials or their associated meta-analyses [24] but do rarely cause myopathy (typically defined as muscle symptoms with creatine kinase [CK] >10 times the upper limit of normal [ULN]) [25,26]. Although statins are highly effective, even those who have achieved significant LDL-C reductions with intensive statin therapy may still experience CV events, referred to as 'residual risk'. This risk is particularly high in certain patients such as those with diabetes and atherosclerosis affecting multiple vascular beds (eg, cerebrovascular, peripheral vascular as well as coronary). Some of this risk may be addressed by earlier initiation of statin treatment and better blood pressure and diabetes management, but additional lipid-modifying therapies may be appropriate.

1.2. Options for additional LDL-lowering/lipid modification

Cholesterol absorption inhibitors

Ezetimibe selectively inhibits the absorption of cholesterol in the small intestine by binding to the transporter Niemann-Pick C1 Like1 (NPC1L1), which is responsible for the uptake of cholesterol and phytosterols (plant sterols) from the intestinal lumen. Only