Abstract

Evidence from epidemiological and clinical studies continues to improve our understanding of the pathogenesis of coronary heart disease (CHD). However, despite major advances in the development of diagnostic methods and effective treatment, CHD remains the leading cause of mortality in the Western world. That cholesterol lowering is of major importance in lowering the risk of developing coronary artery disease (CAD) is now an accepted principle in medicine. Most patients with CAD will require drug therapy to achieve target lipid levels. Subgroup analyses of data from the landmark statin trials show that this benefit is seen in all patient groups: male and female, older and younger patients, diabetics and non-diabetics, and patients with and without myocardial revascularization. Recent evidence suggests that the extent to which cholesterol is lowered is also important and that the attainment of reduced low-density lipoprotein cholesterol levels is associated with greater reductions in the risk of cardiovascular events. Unfortunately, data from studies to date do not provide a definitive answer to the question of whether there is a benefit in lowering cholesterol to very low levels.

Keywords: Pathogenesis; Coronary heart disease; Western world

1. Introduction

The World Health Organization (WHO) data for 1997 showed cardiovascular disease to be responsible for approximately 30% of all mortality worldwide amounting to approximately 15 million deaths [1]. Cardiovascular disease is the principle cause of mortality in all developed countries, responsible for 50% of all deaths, and is also emerging as a prominent public health problem in developing countries, with approximately 16% of all deaths. The WHO data show that most cardiovascular deaths are a result of coronary heart disease (7.2 million), followed by cerebrovascular disease (4.6 million) and other heart diseases (3 million) [1]. By 2025, the WHO predicts that infectious diseases will still dominate as the leading cause of death in developing countries, but as the economies of these countries grow, non-communicable diseases will become more prevalent. This will be largely due to the adoption of ‘Western’ lifestyles and their accompanying risk factors — smoking, high fat diet, obesity and lack of exercise.

In the USA, coronary heart disease (CHD) was first recognized as the leading cause of death in the late 1940s. Hypertension, hypercholesterolemia, cigarette smoking and diabetes mellitus were identified by the early 1960s as principal risk factors [2,3]. More recently, clinical trials of antihypertensive, lipid-lowering and hypoglycemic drugs, along with investigations of smoking cessation, have documented the benefits of treating these risk factors and established beyond any doubt their causal roles in promoting CHD [4,5]. Despite important advances in treatment and prevention, cardiovascular disease still surpasses all other major causes of death combined in the USA (Fig. 1) [6], with direct and indirect costs relating to the disease expected to reach US$274 billion for 1998 [7].

The underlying disorder in the vast majority of cases of cardiovascular disease is atherosclerosis, for
which low-density lipoprotein (LDL) cholesterol is recognized as the major and conditional risk factor. Dietary therapy and lipid-lowering drugs are central to the management of hyperlipidemia. In patients with pre-existing coronary artery disease (CAD) the cardiac event rate is extremely high (Fig. 1) and the aim is to prevent atherosclerotic plaque progression, or even induce regression, and to decrease the risk of acute coronary events. In patients at high risk of CAD, but without evidence of clinical vascular disease, treatment is designed to stabilize atherosclerotic plaques and prevent the premature development of CAD.

Data from epidemiological studies have suggested that lower cholesterol levels are associated with a lower overall risk of morbidity and mortality due to CAD [8,9]. Populations with relatively low cholesterol levels, such as China [10] and Japan [11], have been shown to have a reduced CAD mortality.

Numerous clinical trials support these epidemiological data and have provided evidence that cholesterol-lowering therapies lead to a significant reduction in the morbidity and mortality associated with CAD [12,13]. Of these, studies with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have shown the greatest lipid-lowering effects and benefits on morbidity and mortality [14–17].

In the statin trials, the difference between the placebo and the intervention group for risk of CHD is seen in some trials by 1 year [14,17], and in most trials after 2 years [15]. This effect becomes more evident with each year of treatment. The benefit of statin treatment not only extends to the prevention of cardiovascular disease but also to quality of life.

The benefits of statins for the management of hyperlipidemia are clear, but three important questions remain. First, most of the trials above have been conducted in middle-aged men, but what are the effects of statin treatment on other patient groups? Second, what are the potential uses of statins beyond their current indications? Third, is there a limit to the benefits that can be achieved with cholesterol-lowering therapy with statins?

2. Benefits of statins extend to other patient groups

2.1. Women

That lowering elevated cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to CAD has been demonstrated most conclusively in middle-aged men with elevated blood cholesterol levels, but much evidence supports the conclusion that a similar protection will be afforded in other patient groups. The Scandinavian Simvastatin Survival Study (4S) included 827 women out of a total study population of 4444 [18]. Simvastatin reduced the risk of major coronary events in women to approximately the same extent as it did in men [14]. The Cholesterol and Recurrent Events (CARE) study included 576 women out of a total population of 4159 patients [16]. Compared with patients receiving placebo, both men and women treated with pravastatin had significantly lower rates of major coronary events. In this trial the effect of pravastatin was greater among women than men. Female patients taking pravastatin reduced their risk of having a secondary coronary event by 46% ($P = 0.005$) compared with 20% for men ($P = 0.005$).

More recently, AFCAPS/TexCAPS, the only primary prevention trial to include women (997 women out of a total study population of 5608), demonstrated that although at lower risk for heart attack than men, the female participants in this trial gained the same benefits as men from taking lovastatin [17].

2.2. Type 2 diabetes patients

In patients with non-insulin-dependent diabetes or type 2 diabetes, the incidence of atherosclerotic vascular disease is greatly increased. Although the most frequent lipoprotein abnormalities in this type of diabetes are an increase in triglyceride-rich lipoproteins and a decrease in high-density lipoproteins, hypercholesterolemia is still as powerful a predictor of CHD risk in diabetic patients as in non-diabetic subjects. In spite of this knowledge, there is to date no
solid evidence to indicate whether correction of dyslipoproteinemia in order to reduce CHD risk in patients with type 2 diabetes is more, equally, or less beneficial than it is in non-diabetic subjects [19]. The only currently available data are from post-hoc subgroup analyses of the Helsinki Heart Study [20] and the 4S trial [21], although prospective intervention trials are now in progress. These analyses suggest that diabetic patients benefit to the same extent, if not more, from statin therapy.

2.3. Revascularization patients

Catheter-based revascularization procedures such as percutaneous transluminal coronary angioplasty (PTCA) are intended to provide rapid symptom relief to patients with CAD. As hypercholesterolemia is one of the most important risk factors for CAD, a recent study [Aggressive Lipid Lowering with Atorvastatin Versus Revascularization Treatment (AVERT)] has investigated whether aggressive lipid lowering with atorvastatin may significantly delay or prevent the occurrence of a cardiovascular ischemic event (cardiac death, cardiac arrest, non-fatal myocardial infarction, coronary artery bypass graft surgery, angioplasty, worsening angina verified by objective evidence resulting in hospitalization in these patients [22]. Atorvastatin is a highly effective HMG-CoA reductase inhibitor that has been shown to provide significantly greater reductions in LDL-cholesterol than other drugs in the same class at milligram equivalent doses over the 10–40 mg dose range [23]. After 18 months, 22 (13%) atorvastatin patients vs. 37 (21%) angioplasty patients had experienced ≥ 1 ischemic event, a 36% reduction in favour of atorvastatin (P = 0.048 vs an adjusted significance level of P = 0.045). Furthermore, the time to the first ischemic event was significantly longer (P = 0.027) for the atorvastatin than the PTCA group. Atorvastatin not only resulted in a reduction in ischemic events but also a significant delay in the time to first event and was generally well tolerated. AVERT supports the benefits of aggressive cholesterol lowering with atorvastatin in stable CAD patients.

2.4. Unstable angina pectoris / acute myocardial infarction patients

Several trials have demonstrated that cholesterol lowering with statins reduces cardiovascular morbidity and mortality in patients at high risk for CHD, as well as in patients with established, but stable, CHD. However, there are no data on whether lipid-lowering drugs should be administered as soon as possible after an acute coronary event, in doses that cause rapid and extensive lipid lowering, in an attempt to stabilize coronary plaques and reduce early, recurrent ischemic events. Unstable angina pectoris or non-Q-wave acute myocardial infarction are usually managed by invasive procedures, i.e. routine coronary angiography followed by myocardial revascularization. However, a recent study has demonstrated that most patients with non-Q-wave myocardial infarction do not benefit from routine, early invasive management [24]. An ongoing trial, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), is investigating whether plaque rupture can be influenced by the fast institution of a lipid-lowering drug (atorvastatin) to reduce early recurrent ischemic events in such patients without the need for surgical interventions [25].

3. Is there a limit to the benefits that can be achieved with statins?

The importance of treating patients to lower cholesterol levels to lessen the risk of developing atherosclerosis is well accepted. However, whether there is a threshold below which cholesterol reduction does not translate into any additional clinical benefit is the subject of some debate.

Clinical trials of cholesterol lowering have produced conflicting results. In a subanalysis of the CARE study, researchers found that the incidence of cardiovascular events fell progressively as LDL-cholesterol levels were reduced from 175 to 125 mg/dl (4.5–3.2 mmol/l) [26]. However, further reductions to as low as 71 mg/dl (1.8 mmol/l) had little impact on risk, suggesting a threshold effect at an LDL-cholesterol level of 125 mg/dl (3.2 mmol/l) [26].

A subanalysis of the 4S study showed that on average drug therapy with simvastatin lowered LDL-cholesterol levels by 35% and reduced the incidence of heart attacks by 34% [18]. The goal was to reduce total cholesterol to below approximately 200 mg/dl (5.2 mmol/l). However, many patients achieved greater reductions, which produced continuing but progressively smaller reductions in heart attack risk. The subgroup analysis of the 4S trial estimated that each additional 1% reduction in LDL-cholesterol reduced the risk of major coronary events by 1.7% [18].

The Post Coronary Artery Bypass Graft (Post-CABG) trial was the first randomized study prospectively designed to answer the question of whether an aggressive approach to cholesterol lowering is more effective than a moderate approach [27]. As the Post-CABG trial was designed as an angiographic trial, it did not have the statistical power to detect differences in clinical events between the aggressive and moderate treatment arms. However, strong trends were seen and there was a significant reduction in the need for revascularization. The Post-CABG trial has demonstrated that an aggressive approach to lipid lowering is beneficial. However, important questions remain.
For instance, can findings from saphenous vein grafts be extended to the coronary arteries? Would aggressive lipid lowering benefit patients with low baseline levels of LDL-cholesterol? A new statin trial, the Treating to New Targets TNT study, may provide the data to validate the lower is better hypothesis (Fig. 2), although results are not expected for another 5 years.

The TNT study will enroll approximately 8600 patients at high risk of recurrent CAD due to previous evidence of clinical CHD. To be considered for admission into the study, patients must have LDL-cholesterol levels between 130 and 230 mg/dl (3.4–5.9 mmol/l) and triglycerides ≤ 600 mg/dl (6.8 mmol/l). Patients are first included in an 8-week run-in with diet and treatment with atorvastatin 10 mg/day. Patients who achieve LDL-cholesterol < 130 mg/dl (3.4 mmol/l) will be randomized to double-blind therapy with either atorvastatin 10 mg/day [target LDL-cholesterol 100 mg/dl (2.6 mmol/l)] or atorvastatin 80 mg/day [target LDL-cholesterol 75 mg/dl (1.9 mmol/l)]. The TNT study is designed to run for 5 years. The primary endpoints are major coronary events including coronary death or non-fatal myocardial infarction. Cost-effectiveness will also be evaluated.

Statin trials strongly support guidelines that advocate adjusting the intensity of cholesterol reduction to absolute risk. The TNT trial will test directly whether LDL-cholesterol reductions below 100 mg/dl (2.6 mmol/l) do indeed confer additional benefit in CHD patients.

As a relatively new addition to the statin class, there is still a lack of documentation of the effects of atorvastatin on clinical outcome, including mortality and long-term safety. In the recently completed AVERT trial, atorvastatin not only resulted in a reduction in ischemic events but also a significant delay in the time to first event [22]. Trials that are currently underway include MIRACL and TNT. Atorvastatin provides significantly greater reductions in LDL-cholesterol than milligram equivalent doses of simvastatin, pravastatin, lovastatin or fluvastatin over the 10–40 mg dose range [23]. Moreover, atorvastatin has been compared individually with lovastatin, pravastatin and simvastatin in three multicenter trials involving more than 1500 patients with primary hypercholesterolemia. In addition to being more effective in terms of lowering LDL-cholesterol, atorvastatin 10 mg/day provided significantly greater reductions in total cholesterol, apolipoprotein B and triglyceride levels than once-daily doses of simvastatin 10 mg, pravastatin 20 mg and lovastatin 20 mg [28–30].

References


