Statins And Coronary Artery Disease

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Abstract

Statins have been proven to be clinically effective in both the prevention and treatment of coronary artery disease. Coronary artery disease is a common and serious condition due to an underlying pathology of atherosclerosis, which is caused mainly by increased levels of low-density lipoprotein that accumulate in the walls of the coronary arteries.

The main treatment option for high cholesterol levels is a group of cholesterol-lowering drugs called statins. They act mainly on the liver enzymes responsible for cholesterol synthesis, reducing the production of cholesterol. This has been proven to be very effective in decreasing the morbidity and mortality associated with coronary artery disease, as evidenced in a number of clinical trials and studies using statins.

INTRODUCTION

Coronary artery disease is a disease of the coronary arteries, most commonly caused by atherosclerosis [1]. Atherosclerosis is the thickening or hardening of the artery walls, formed by a combination of damage to the endothelial lining, the deposition and accumulation of low-density lipoprotein (LDL) cholesterol, and the development of atherosclerotic plaques within the walls [2].

Over time, the formation of atherosclerosis will limit the amount of blood and oxygen that is able to reach the myocardium. The presence of coronary artery disease is often manifested by unstable angina, myocardial infarction due to thrombus formation within the narrowed arteries, heart failure and death [3].

Coronary artery disease is one of the most common diseases in the world today. Coronary artery disease causes 6.9 million deaths worldwide each year, and is the leading cause of premature death in developed countries. [3,4] In the year 2000 alone in Australia, it accounted for 21% of all deaths, equalling 26,521 people [3,4].

The most recent figures on the cost of coronary heart disease are from 1993 – 1994. In Australia during this time, $894 million was spent on coronary artery disease, and this is considered to be an average indication of the annual cost, even today [3]. This value equates to 2.8% of the total recurrent health expenditure, and includes the cost of hospital stays, specialist medical services, and pharmaceutical drugs [4].

The prevention and treatment of coronary artery disease has been greatly improved by the recent development of a new class of drug known as 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors, or statins. A number of clinical studies have been conducted to investigate the impact of statins on coronary artery disease, and these have proven that statins have a very significant and positive benefit associated with their use.

PATHOGENESIS OF CORONARY ARTERY DISEASE

Coronary artery disease results in an insufficient blood supply to the heart. Atherosclerosis is the most common cause of this disease, and develops over many years, eventually causing the complete obstruction of coronary blood flow, if left untreated [4,5,6]. It consists of a build-up of plaques on the inside of the artery walls, which advance in size gradually over time and narrow the vessel lumen [4,7].

The process of atherosclerosis begins with damage to the endothelial lining of the coronary artery. This damage is most often caused by a combination of the following four main factors: smoking, hypertension, high blood cholesterol and diabetes [6,7].

Because of this damage, LDL particles can penetrate through the inner layer of the arterial wall, the tunica interna, into the subendothelial space [7]. Unless the blood concentration of

LDL cholesterol is within the normal low limits, the rate of entry of these particles begins to exceed their rate of exit from the walls. Once within this space, the LDL particles become chemically modified, producing LDL cholesterol aggregations, and promoting the differentiation of monocytes into macrophages [9]. The macrophages produced by this process begin to express increased numbers of LDL receptors with higher activity levels, and these recognise and engulf the modified LDL cholesterol particles [6]. The accumulation and breakdown of cholesterol within the macrophages causes them to become foam cells, a classic hallmark of atherosclerosis [7,9].

These foam cells cause the first visible signs of coronary artery disease, as the deposition of 'fatty streaks' within the tunica interna. The fatty streaks consist of many foam cells and lymphocytes; the lymphocytes being part of the immune response due to arterial damage [6,7,9,10].

Macrophages and foam cells produce and express various growth factors and proteinases, which cause cell proliferation, matrix degradation, and therefore the progression of the atherosclerotic plaque development. At the same time as this, macrophages are also releasing cytokines which cause the endothelial cells of the artery to express adhesion molecules. This causes more monocytes to be taken up from the blood, and produces a continual cycle of macrophage production [9].

The smooth muscle cells contained in the middle layer of the artery, the tunica media, also migrate to the tunica interna, as part of the atherosclerotic process. Once there, they begin to proliferate and form layers with the fatty streaks, producing the more advanced fibrotic plaques of atherosclerosis [6,7].

Through this pathogenic process, the atherosclerotic plaques will continue to grow and advance, unless the plasma levels of LDL cholesterol decrease, and remove the stimulus for further growth [9].

CHOLESTEROL AND CORONARY ARTERY DISEASE

The link between coronary artery disease and cholesterol has been clearly proven in many population studies, including the Framingham Study. This was a study commenced shortly after World War II, in the year 1948. It included 5,209 patients aged from 28 – 62 years, and monitored their incidence of coronary events and mortality over a period of 50 years [9]. It was one of the first studies to show a direct link between high blood cholesterol levels and the development of coronary heart disease. It also showed a link between many other risk factors, such as hypertension, cigarette smoking (modifiable), male gender, family history, and age, with coronary heart disease development [9,10]. Australian data has also demonstrated that the combination of high blood cholesterol, high blood pressure, and cigarette smoking are responsible for 75% of the cases of coronary artery disease that occurs [4].

High density lipoprotein (HDL) cholesterol is considered'good' cholesterol, because it is not taken into the walls of arteries, due to the fact that these structures have no HDL receptors. It therefore does not contribute to atherosclerosis, and it has been proven that the higher the level of HDL in the body, the lower the risk of forming coronary artery disease [6].

The Framingham study mentioned earlier is one such study that has provided clear evidence in the benefit of high HDL cholesterol levels as shown in Figure 3 below. This is a graph illustrating the decreased morbidity risk of coronary disease associated with increased levels of HDL cholesterol.

OTHER RISK FACTORS FOR CORONARY ARTERY DISEASE

Other risk factors that may be modifiable for coronary artery disease include smoking, high blood pressure (hypertension), diabetes, obesity, lack of exercise or physical inactivity, excessive alcohol consumption, and stress [4,5,7].

Non-modifiable risk factors include gender, age, and family history [4,5,7]. The risk for men is much greater than that of women until they reach menopause; at this time the risk becomes equal between men and women. The reason for this change is not entirely understood, however it is thought to have something to do with a protective mechanism provided by the hormones produced by a woman throughout her life, which cease to be produced when she reaches menopause [7]. At this time, their risk increases to equal that of equivalently aged men [5,7,10].

The risks for coronary artery disease are associated with age, they increases as a person gets older. This is thought to be indicative of the total accumulated time of exposure to all other risk factors [7].

The family history of a person is a well-known risk factor in atherosclerosis, and therefore, coronary artery disease development; a family history of familial hypercholesteremia especially increases the risk. Familial

hypercholesteremia is an inherited genetic disorder, which causes a series of mutations in LDL receptors so that they no longer function, causing an excessive amount of LDL cholesterol to be present in the circulation and unable to remove them [5,10].

Obviously there are many risk factors contributing to coronary artery disease, and many of the modifiable risk factors can be reduced through lifestyle changes, behavioural changes, and/or pharmacological treatments. Of particular importance, especially for this review, is the risk posed by elevated blood cholesterol levels, which can be reduced with the cholesterol lowering drugs called statins [3,4].

ROLE OF STATINS IN THE PREVENTION AND MANAGEMENT OF CORONARY ARTERY DISEASE

The presence of coronary artery disease will result in an increased risk of unstable angina and the development of myocardial infarction due to thrombus formation within the narrowed arteries [3]. It can also cause cardiac failure, cardiac arrhythmia, and sudden death [5].

Dietary modification would reduce the levels of blood cholesterol by 10 – 20%, but to reduce it any further; cholesterol lowering drugs are usually required.

The most recent drugs developed for this purpose are the statins. They lowers cholesterol levels by 20 – 30%, and even more at higher doses, and this has been clinically proven to produce an equivalent decrease in the risk of myocardial infarction and death [5].

Statins are the most effective and powerful cholesterol lowering drugs available. [12]They have moved to the forefront of coronary artery disease prevention and treatment, and most patients with elevated LDL cholesterol levels will be prescribed statins as a first line treatment [4,5].

There are several different statins available, including atorvastatin, fluvastatin, pravastatin, and simvastatin. Of these, simvastatin is the most commonly prescribed, followed by atorvastatin [4,5]. All statins come in tablet form, except fluvastatin, which is a capsule, and are administered orally; usually just before going to bed at night. They are well absorbed, and easily extracted by the liver where they perform their actions [13].

PHARMACOLOGICAL ACTIONS OF STATINS

The major action of statins is the lowering of blood cholesterol levels, and this is the main reason for their clinical uses as discussed above [12,13,14]. However, statins also have some other actions, known as pleiotropic effects. Based on the evidence provided by recent clinical studies, the benefits provided by statins cannot be fully explained by their cholesterol lowering effects alone, and that other factors must be involved [14]. The pleiotropic effects of statins include antithrombotic actions, an increase in fibrinolysis, antiinflammatory effects, and a decrease in smooth muscle cell proliferation and migration [15].

The antithrombotic effect of statins is provided by their ability to decrease platelet aggregation, which assists in the prevention of thrombus formation. Statins also increase the occurrence and effectiveness of fibrinolysis and this may provide them with an effective mechanism against thrombus that have already formed, allowing them to be broken down.

The development of atherosclerosis is similar to the inflammatory response, also exhibiting the properties of recruitment and the accumulation of leukocytes, which are stimulated by various cytokines and most particularly, interleukins. The antiinflammatory effect of statins is their ability to decrease the concentration of these molecules, and therefore decrease, and in some patients, prevent the formation of atherosclerosis. Statins also have this function of decreasing the proliferation of smooth muscle cells, and inhibiting their migration to the tunica interna [15].

Pharmacologically, statins act on the liver to decrease its ability to synthesise cholesterol, most particularly low-density lipoprotein (LDL) cholesterol [11]. They do this by inhibiting the enzyme HMG-CoA reductase, which catalyses the rate-limiting step in the synthesis of cholesterol. The decreased level of intracellular cholesterol produced by this action, stimulates the production of more LDL receptors, and increases the activity of those LDL receptors already present. This larger number of active LDL receptors allows the liver to remove more LDL cholesterol from the blood, and reduces the risk of atherosclerosis formation, and in turn, coronary artery disease [6,9].

Statins are considered to be a safe and well-tolerated group of drugs, which have a very low incidence of adverse effects. Generally, if no adverse effects occur within the first few weeks of treatment, they are very unlikely to occur at all. The serious side effects of statins are very rare. They include rhabdomyolysis and angio-oedema [5,13]. In the event of serious adverse effects, stopping the administration immediately will usually reverse their effects [5,13].

PRIMARY PREVENTION STUDIES

WEST OF SCOTLAND CORONARY PREVENTION STUDY (WOSCOPS)

This study included 6,595 male patients, aged between 45 and 64 years. All of these patients had an initial average cholesterol level of 7.0mmol/L and had no evidence of any previous myocardial infarction. Each patient was randomly assigned to receive either, pravastatin at a dose of 40mg/day, or the equivalent of placebo; and all patients received dietary advice throughout the study duration, which was an average of 4.9 years [13,17].

At the end of the study, the use of pravastatin had reduced the LDL cholesterol levels by 26%. The overall mortality was decreased by 22%, and the risk of non-fatal myocardial infarction or death from coronary disease was decreased by 31% [7,13,17].

This study clearly proves that statins have a beneficial effect in lowering cholesterol levels, and by doing so, reducing the incidence of coronary artery disease-associated mortality.

HEART PROTECTION STUDY (HPS)

This study included 20,536 patients with coronary disease, other occlusive arterial disease, diabetes, or no coronary history at all. Every patient was randomly assigned to receive either simvastatin at a dose of 40mg/day, or the equivalent of placebo. The initial total plasma cholesterol levels were ?135mmol/L, and all patients were considered to be at a 5-year risk of death from coronary disease [18].

This study showed that after 5 years, irrespective of the initial cholesterol level, there was an average reduction in LDL cholesterol of 0.9mmol/L across all levels with the use of simvastatin. The coronary mortality rate was decreased by 18% and the incidence of a first non-fatal myocardial infarction was decreased by 38%; providing an overall combined benefit of 27% with the use of statin treatment [18].

This study proves that statin use is beneficial in all patients with hypercholesteraemia, regardless of the severity, and will result in a clear reduction in LDL levels.

SECONDARY PREVENTION STUDIES

SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY (4S)

This study included 4,444 patients, aged between 35 and 70 years. All of these patients had hypercholesteremia and pre-existing coronary disease. Each patient was randomly assigned to receive either simvastatin at a dose of 20mg/day or the equivalent of placebo. In 37% of patients however, this dose of simvastatin had to be titrated up to 40 mg/day in order to achieve adequate symptom control. The follow-up period of this study was 5.4 years [9,15].

The primary endpoint of the 4S study was all-cause mortality. In the simvastatin group, there was an overall decrease in all-cause mortality of 30%. There was also a significant difference in the rate of both the coronary events and the coronary deaths, with both being lower in the group receiving simvastatin. The major coronary event rate was decreased by 34%, and the coronary death rate was decreased by 42% in the statin group [9,15].

This study provides clear evidence of the benefit of statin use in the reduction of mortality caused by coronary artery disease.

CHOLESTEROL AND RECURRENT EVENTS (CARE) TRIAL

This study included 4,159 patients with elevated total cholesterol levels of <240mg/dL, elevated LDL cholesterol levels of 115-174mg/dL, and a history of myocardial infarction or recurrent coronary events. Each patient was randomly assigned to receive either pravastatin at a dose of 40mg/day, or the equivalent of placebo, for an average period of 5 years [19].

The use of pravastatin produced a decrease in LDL cholesterol levels of 32%, and when the LDL levels had been decreased even further to 125mg/dL, a 24% decrease in the incidence of major coronary events was produced [19]. This proved that not only could statins decrease the cholesterol levels to an acceptable level, but that by decreasing them even further, an even greater benefit could be produced.

The primary endpoint for this study was coronary death or nonfatal myocardial infarction, and this was reduced by 24% in the group receiving pravastatin. There was also a reduced risk in the occurrence of recurrent coronary events in patients with a history of previous myocardial infarction [9,15,19].

LONG-TERM INTERVENTION WITH PRAVASTATIN IN ISCHAEMIC DISEASE (LIPID) STUDY

This study included 9,014 patients, randomly assigned to receive either pravastatin at a dose of 40mg/day, or the equivalent of placebo, for a period of 6 years. The initial total plasma cholesterol levels of all patients were

155-271mg/dL, and throughout the study, both groups received dietary advice on consuming a reduced-cholesterol diet [20].

The end of the LIPID study saw the total cholesterol level reduced by 21% through the use of pravastatin. And, even despite the initial broad cholesterol range, the risk of death from coronary heart disease was reduced by 24%, and the overall mortality decreased by 22%; evidence that the use of statins is beneficial with any initial cholesterol level, and will significantly reduce coronary mortality [20].

CONCLUSIONS

The use of statins as a first line therapy to lower elevated blood cholesterol levels, particularly LDL levels, has a significant health benefit for all patients with coronary artery disease. As evidenced by recent clinical studies, statin use has been associated with a decreased risk of coronary artery disease development, and a reduction in the incidence of further coronary events, and even more importantly, a significant decrease in the mortality rates associated with coronary artery disease.

The indications for the use of statins are continually increasing, and it is expected that clinical studies being conducted now and in the future will continue to show a clear benefit associated with their use. Such evidence added to what already exists indicates that statins will continue to deliver a most important and positive benefit in both the prevention, and treatment, of coronary artery disease.

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