Impact of Dyslipidaemia
Lessons from Clinical Trials

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Abstract

Coronary heart disease (CHD) is a major cause of morbidity and mortality in Western countries, and is associated with significant healthcare costs. Epidemiological studies have shown that elevated cholesterol levels, particularly elevated low density lipoprotein (LDL) cholesterol, are a major established risk factor for the development of CHD. There is a large amount of clinical data available to indicate that lowering total or LDL-cholesterol levels reduces the risk of cardiovascular events and mortality. The most recent cholesterol treatment guidelines from the US and Europe recommend intensive treatment (usually pharmacological) for patients at highest risk for CHD. Results from a number of landmark primary and secondary prevention studies are in support of these guidelines and also suggest that the lower the level of LDL-cholesterol achieved with treatment, the better clinical benefit attained. Thus, these findings indicate that even more aggressive lipid lowering than that recommended by available treatment guidelines may be warranted.

Finding and treating all individuals at risk for CHD would be expected to increase the overall treatment costs of hypercholesterolaemia because many patients may not otherwise be treated; however, targeting high risk patients, rather than treating all patients or treating inappropriately, would be expected to reduce other healthcare costs and the indirect costs of lost productivity due to cardiovascular morbidity and mortality. Studies with the HMG-CoA reductase inhibitors, which show that these drugs substantially lower LDL-cholesterol, are the most convincing since they have consistently shown reductions in cardiovascular morbidity and mortality. As a result, statins are now well-established agents for the treatment of dyslipidaemia.

Cardiovascular disease is the leading cause of death for both men and women in the Western world, accounting for nearly a million deaths annually in the US alone.[1] For the years 1990 to 1992, annual mortality rates from cardiovascular disease per 100 000 men and women, respectively, in European countries ranged from 330 and 122 for France to 1490 and 830 for the Ukraine.[2] Over 200 risk factors for cardiovascular disease have now been identified, the most well established of which are abnormal lipoprotein levels, high blood pressure, diabetes and cigarette smoking.[2] Other factors such as haemostatic factors (e.g. fibrinogen, factor VII, plasminogen activator inhibitors, homocysteine), menopausal status, inactivity and obesity are known to increase the clinical risk of cardiovascular disease.[2-4]

Coronary heart disease (CHD) alone accounts for 50% of deaths from cardiovascular disease in the US[1] and Europe.[2] The causal link between elevated low density lipoprotein (LDL) cholesterol and CHD is well established. Recent analysis of
data from the Prospective Cardiovascular Münster (PROCAM) study revealed that elevated triglycerides are also an independent risk factor for CHD.\[5\] The occurrence of elevated blood triglycerides with low levels of high density lipoprotein (HDL) is a powerful risk factor for CHD morbidity and mortality.\[5,6\] In addition, elevated lipoprotein (a) and higher levels of small dense LDL may contribute to CHD risk.

The most recent guidelines from the US\[7\] and Europe\[8\] recommend aggressive cholesterol-lowering treatment in individuals with multiple risk factors. This article will briefly assess the impact of dyslipidaemia from an epidemiological perspective, and will review important clinical trials of LDL reduction as well as discuss the potential impact of treatment guidelines.

1. Incidence of Cardiovascular Disease

It is estimated that about 58 million people (1 in 5) in the US have one or more types of cardiovascular disease.\[1\] In 1995, 42% (1 of every 2.4 deaths) of all deaths in the US were attributed to cardiovascular disease. Indeed, more than 2600 Americans die each day of cardiovascular disease, an average of one death every 33 seconds. Moreover, cardiovascular disease claims more lives each year than the next 7 leading causes of death combined.\[1\] Similarly, approximately 431,000 deaths (=50% of all deaths) in Germany in 1994 were attributed to cardiovascular disease.\[9\]

Although cardiovascular disease is often thought of as a ‘male disease’, it claims the lives of nearly half a million females annually in the US – more deaths than from the next 16 causes combined.\[1\] In terms of total deaths, cardiovascular disease has caused more deaths in females than males in every year since 1984.\[1\]

Approximately one-half of all deaths from cardiovascular disease are attributable to CHD, leading to 481,287 deaths (1 of every 4.8 deaths) in the US in 1995.\[11\] It is estimated that this year over a million people in the US will have a new or recurrent coronary attack and about one-third of these will die.\[1\] About 80% of CHD-related mortality in individuals aged <65 years occurs during the first attack. Moreover, there had been no previous diagnosis of CHD in 48% of men and 63% of women who died suddenly from this disease.\[1\]

The impact of cardiovascular disease on the healthcare system and society is considerable. About one-third of individuals in the US aged ≥65 years receiving home care have a primary diagnosis of cardiovascular disease. Cardiovascular disease accounted for more hospital discharges than any other disease category in the US in 1995; it was a first-listed diagnosis in about 5.8 million inpatients (3 million males and 2.8 million females). CHD alone accounts for about 2 million hospital discharges in the US.\[11\] Moreover, there were approximately 52 million physician office visits, 4.4 million hospital outpatient visits and 4.2 million emergency room visits with a principal diagnosis of cardiovascular disease in 1995.\[1\]

The American Heart Association estimates the overall costs of cardiovascular disease and stroke in 1998 at US$274.2 billion.\[1\] This figure includes direct costs such as those for hospitalisation/nursing home care, physician and drug costs, and the indirect costs of lost productivity associated with cardiovascular disease-related morbidity and mortality. CHD, stroke, hypertensive disease and congestive heart failure account for US$95.6, US$43.3, US$31.7 and US$20.2 billion, respectively, of this figure.\[1\]

2. Dyslipidaemia and CHD Risk

It is estimated that about 38 million individuals in the US have high blood cholesterol levels ≥6.2 mmol/L (240 mg/dl). Importantly, about 37% of those aged 19 years or less (about 28 million individuals) have a blood cholesterol level of 4.4 mmol/L (170 mg/dl) or higher, which is comparable to a borderline high level of 5.2 mmol/L (200 mg/dl) in adults.\[1\]

There is a large body of epidemiological evidence to support a direct relationship between the level of LDL-cholesterol (or total cholesterol levels) and the CHD risk.\[10-13\] There is also strong epidemiological evidence of an inverse association