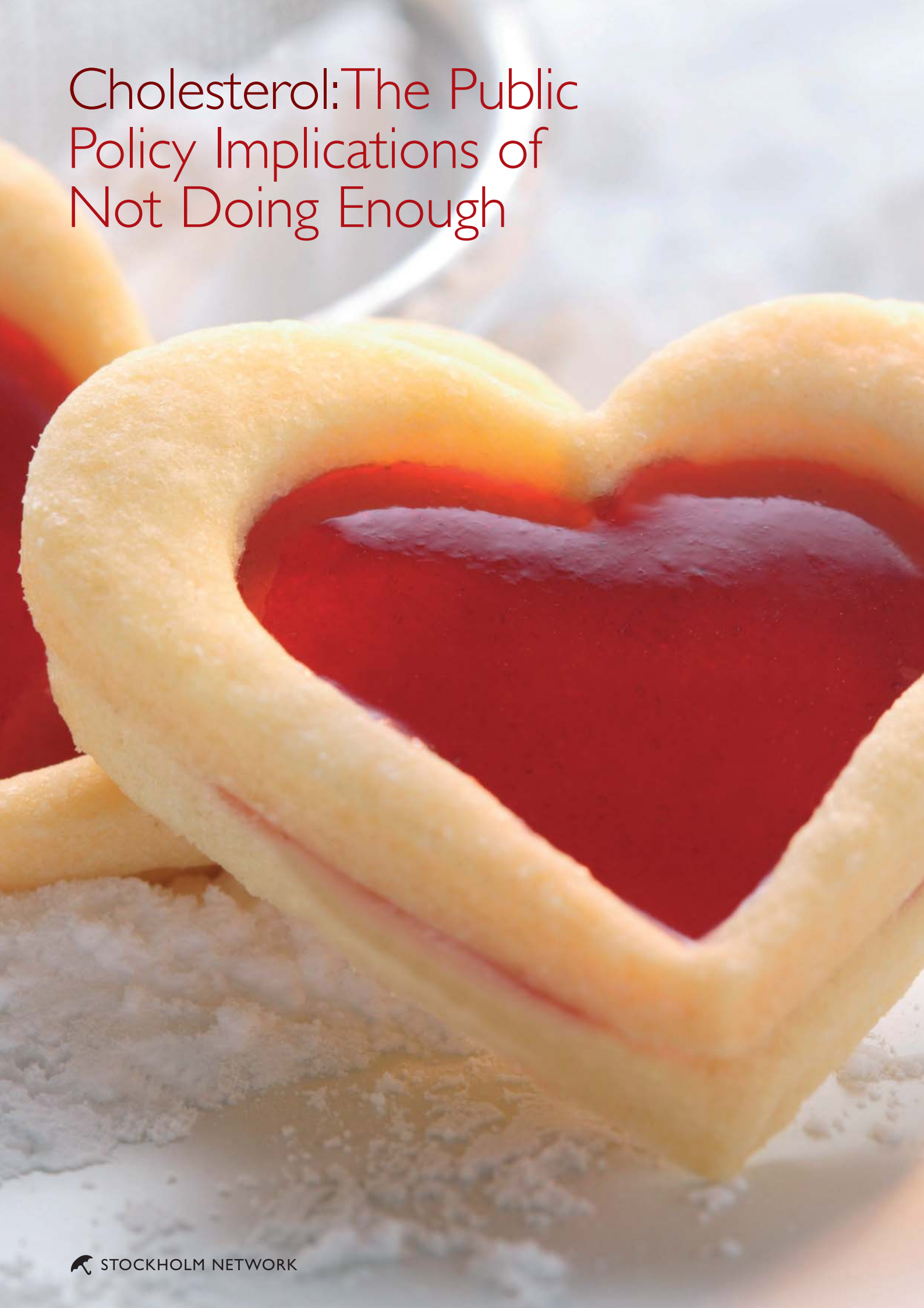
Cholesterol: The Public Policy Implications of Not Doing Enough



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Cholesterol: The Public Policy Implications of Not Doing Enough

Stephen Pollard

Abstract

The purpose of this paper is to consider the implications for public policy within Europe of a continued lack of attention to the impact of high and rising levels of cholesterol between now and 2020. Rather than dealing with the purely medical impact, it will concentrate on an area of public policy of universal concern, namely, the impact on Europe's welfare systems and the knock-on effect on national budgets and economic growth. After examining the likely state of play in future years, it will show how cholesterol levels will make the situation far worse and threaten to undermine proposed policy solutions. Finally, it offers non-medical policy solutions which might be adopted as a means of averting such problems.

An Ageing Population

The single biggest cause of death in the UK today is coronary heart disease. Throughout the 25 countries of the European Union, heart disease causes 1.9 million deaths a year.[1] At the age of 40, there is now – in the West generally – a 50% lifetime risk for men of developing coronary heart disease and a 33% risk for women.[2]

Total costs of treating heart disease in the EU amount to €169 billion per year, of which €105 billion is for direct treatment and €64 billion is due to lost productivity and the cost of informal care.

The reasons for this are many and varied, such as high blood pressure, cigarette smoking and too high a body weight. But right at the top of the list sits the ever rising level of cholesterol amongst EU citizens.

At a time when governments and health care providers are rightly focused on reducing the other main risk factors of heart disease and early death – smoking and obesity – there is a gaping hole in the policy agenda: tackling cholesterol. Just as it is important to reduce levels of smoking and obesity, it is equally – if not more – important to counter cholesterol,

Rising cholesterol levels are, to adopt a phrase from another field, a clear and present danger.

This paper seeks to explain why we should all be concerned by cholesterol levels, why they impact on society in general, and what we might do about this.

Before any appreciation of the implications of high and rising levels of cholesterol can be reached, it is necessary to look at the demographics.

During at least the first few decades of the present century, the central issue of social policy within the member states of the European Union – and perhaps for all other developed countries – will be an ageing population. This is the effect, since the end of the Second World War, of falling birth-rates combined with longer life expectancy.

Taking Germany as an illustration – Germany being the largest and the richest of the member states – the mode age of the male population has risen from 25-29 in 1991 to 35-39 in 2000. This mode age is expected to rise still further by 2020, to 55-59, with great increases in the upper age cohorts and reductions in the lower.

These changes in demographic profile can be seen graphically in the population pyramids constructed by the United States Census Bureau.[3]

The median age in most member states of the European Union is even now over thirty years, the highest being 41.6 years in Italy. By 2020, 20 per cent of the population in the European Union member states will be over the age of sixty, compared with around 15 per cent in 2005. More than 5 per cent will be over the age of eighty.[4]

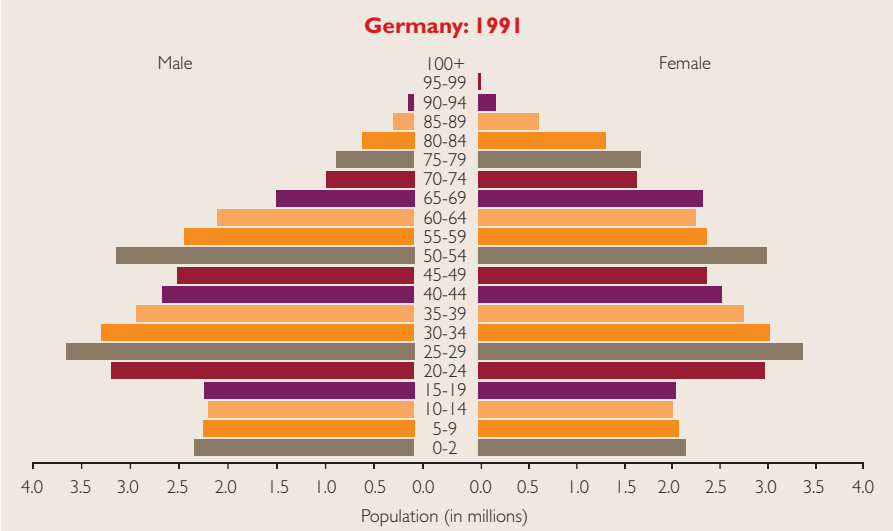
So far as individuals are concerned, these trends are entirely benign. Fewer children mean higher disposable personal incomes during the most active years of life. Longer life expectancy can be taken as a good in itself. A problem arises, however, when the trends are considered as a collective fact. Older people are a financial burden on the community, requiring greater medical attention and imposing greater costs on national governments.

Pensions Policy

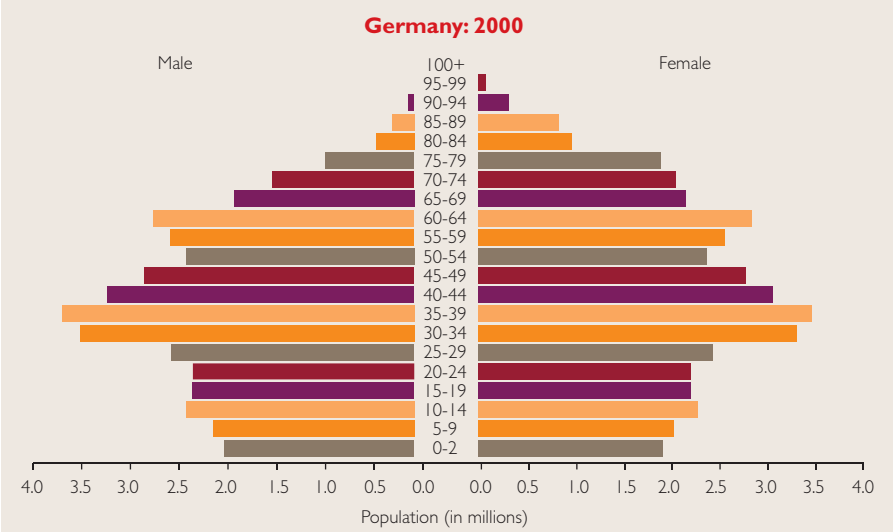
This need not be the case. If we had pension and other social security arrangements based on voluntary cooperation, the old need never be a burden. A typical person would sell his labour power between the ages of about twenty and sixty. During this time, he would regularly save a fraction of his earnings. The weight of repeated contributions to the principal, plus the interest earned on these, would accumulate to an adequate capital sum at the time of retirement to buy an annuity, or even a perpetual income, that would cover all the pension and other costs of old age – including the costs of ill-health and chronic conditions, such as heart disease and cancer. This being so, an average person would pass his entire adult life as a provider of factor services – first labour and then capital – that would never, after the years of childhood, make him a financial burden on others. This would be both personally and collectively beneficial.

The problem is that this is almost nowhere the case at present. In most European Union member states, welfare policies may be expressed in the language of insurance. In fact, they are 'pay as you go' schemes. The contributions of those now in work are used to cover the pension and other needs of the retired. The future pension and other needs of those now in work will be covered by the contributions of those who will be in work when such needs arise.

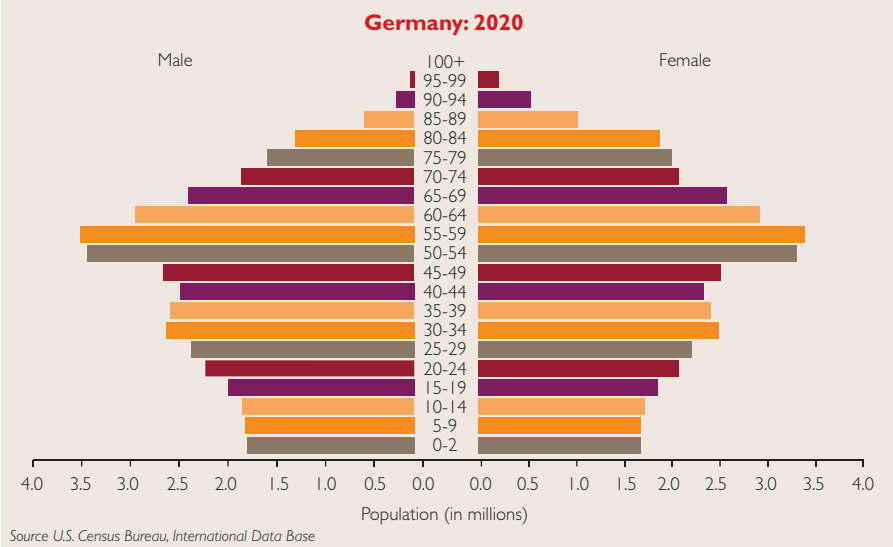
The costs may be enormous. According to the Institute for Public Policy Research, the percentage of gross national product spent on long term care can be expected to rise from 1.8 per cent in 1995 to five per cent in 2031.[5]



Source U.S. Census Bureau, International Data Base



Source U.S. Census Bureau, International Data Base



Source U.S. Census Bureau, International Data Base

To put this in context, six per cent of gross national product is now spent on the whole National Health Service in the UK. Assuming that the bill for long term care is to be paid mostly – as at present – by taxpayers, we may be facing the prospect of an increasingly heavy tax burden on every new generation of workers.

Economic Growth as the Solution?

It can be argued that there is not really a problem here. One of the benefits of economic growth is that it enables a higher tax burden as a percentage of gross domestic product. Today, most developed countries support a burden of around 40 per cent without what most regard as a critical strain. Perhaps the funds will be available by 2020 to support a tax burden higher still.

However, considerations of public policy should be based at least in part on considerations of the worst case scenario. What reason is there to suppose that European economic growth will be sufficient to close the expected funding gap created by longer-lived populations, whose ill-health late in life is costly?

The answer is very little reason. At its meeting in Lisbon in March 2000, the European Council launched a strategic goal – to make the European Union by 2010 "the most competitive and dynamic knowledge-based economy in the world, capable of sustainable growth with more and better jobs and greater social cohesion". Yet, numerous reforms and investments, which are the responsibility of the member states, have yet to be achieved.

Indeed, in certain domains there are significant problems which hold back the entire strategy and which hinder the return of strong growth. What is more, the most important delays have been identified in three strategic domains which are crucial for growth: knowledge and networks, industrial and service sector competitiveness, and active ageing.

There is substantially lower economic growth in the European Union than in the two other main world economies, and much higher unemployment. Indeed, the raw unemployment figures do not tell the whole story. If we look at the figures for long term unemployment, we can see that the European figure is three times that of the United States. In America, unemployment is a largely cyclical phenomenon. In mainland Europe, it is chronic. And these figures are biased by the fact that they include the United Kingdom,

which has a more American approach to economic policy, and correspondingly, a better performance.

It may be that the Lisbon objectives are realised, and that European economic growth will enable a growth of spending on the old and on diseases such as heart disease and cancer, which are more common in affluent, longer-living societies. But the evidence so far available does not suggest this will happen. Short of a revolution in macro and micro economic management that will transform the economy of the European Union, the prospects are of low growth for the foreseeable future.

Raising the Retirement Age

This is currently the preferred option for easing the burden of welfare state costs. The UK government recently proposed gradually raising the retirement age to 68 for those now in work. This will be hotly debated, and may not be accepted in so stark a form. But there is little doubt that the retirement age across Europe as a whole is more likely to rise in the coming years than to stay where it is, let alone to fall.

This would do much to close the gap in funding. It is, however, based on the assumption that sufficient numbers of people can be expected to continue working and paying sufficient amounts of tax into their late sixties. There is some reason to suppose this to be a correct assumption. The ageing of European populations, as said, has been due not just to a fall in the birth rate, but also to increased life expectancy. This has largely been accompanied by increased vigour. In 1950, the average person of sixty was old and of greatly reduced economic efficiency. The average person of sixty by the year 2000 was not old, but could look forward to many years of continued health and at least personal activity. Should this extension of activity be continued at the same rate over the next fifteen to fifty years, it would be a simple matter of justice for the young that those who are able should continue to provide labour factor services rather than rely on transfer payments from the young.

However, considerations of public policy should not be wholly based on existing trends, but should also take account of other possible, even likely, developments. It is possible – again, even likely, as we will see – that large numbers of people will not able to continue working into their late sixties due to the growing prevalence of obesity, heart disease, cancer and other chronic conditions.

What then? How much will raising the retirement age to 68 or even 75 contribute to stabilising the problem of funding for the old?

The Problem of Heart Disease

There is indeed reason to fear that large numbers of people will not be able to continue working into their late sixties. For all the improvements in health for the elderly over the past few decades, heart disease has continued to be a problem.

According to a recent study published in *Heart Online*,

> Coronary heart disease…, is the leading single cause of death in the UK and one of the most important causes of years of life lost before the age of 65... At the age of 40, lifetime risk for developing coronary heart disease in the West is 50% in men and 33% in women.[7]

The study attempts to quantify the total economic cost of fatal heart disease. This is taken as the direct health care cost, the cost in terms of lost output, and the cost of informal care – for example, forgone output by partners and friends as a result of providing various kinds of care. The annual total is given as £7,055.29m.[8]

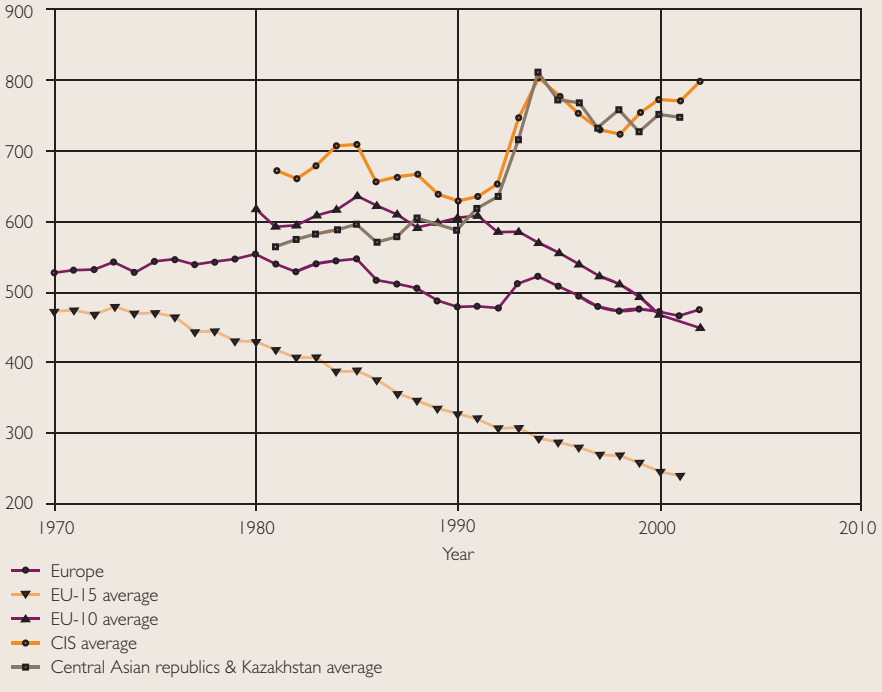
These figures are based on the assumption that people stop working after the age of 65. If they are expected to continue working to the age of 68, at the very least the cost of foregone output will rise – thereby eating into any anticipated tax revenues from raising the retirement age.

Throughout the 25 countries of the European Union, heart disease causes 1.9 million deaths a year at present.[9] Historically, clinical care in the treatment of heart disease has been expensive and prolonged and is a major economic burden in Europe.[10] The lifetime costs of cardiovascular disease to Germany alone are estimated at $25 billion in direct health costs, and indirect costs in productivity at $48 billion.[11]

Total costs of treating heart disease in the EU amount to €169 billion per year, of which €105 billion is for direct treatment and €64 billion is due to lost productivity and the cost of informal care. This gives us an approximate present total cost per person of €90,000 per year. This accounts for around 12 per cent of total health care spending in the European Union. The majority of the health care costs – 57 per cent – are for hospital care. Outpatient care is estimated at five per cent, primary care at nine per cent and medications at 27 per cent of the total.[12]

Granted, there has been a significant decrease in heart disease during recent decades.[13]

Trends in CVD mortality (all age groups) in the European Region since 1970



Source: *Noncommunicable diseases in the WHO European Region: the challenge*, Fact sheet EURO/06/04 Copenhagen, 6 September 2004

In 1970, around 480 people per hundred thousand died in the 15 western member states of the European Union died from heart disease. By 2000, this figure had fallen to around 240 per hundred thousand. We see this graphically illustrated on page 5.

The Cholesterol Threat

The risk factors associated with heart disease include blood pressure, blood cholesterol, cigarette smoking and body weight. It has been estimated that 80 per cent of major heart problems in middle aged men can be attributed to the three principal risk factors of blood pressure, cholesterol and smoking.[14]

Since the identification of the principle risk factors for CVD in the 1960s, a substantial reduction in CVD mortality has been seen in the Western world. This reduction can be attributed, in part, to changing lifestyle and a decrease in the incidence of smoking. Lifestyle modifications can play a key role in the management of CVD and more should be done to encourage at risk populations to make life saving lifestyle changes. It is however important to note that although lifestyle modifications can play a significant role in managing CV health, such changes can only have a certain impact, after which the addition of long term medical intervention should take place. Improvements in primary and secondary prevention and better clinical management of high blood pressure and high cholesterol through medicinal intervention have also played an important part in reducing CV mortality since the 1960s.

There has been a significant decrease in smoking over recent decades, and this may have contributed much to the reduction in heart disease. But there has been no corresponding fall in levels of cholesterol. Bearing this in mind, it may be that the fall in heart disease is reaching a natural limit. Smoking to the extent where it causes significant damage to health may be reaching a practically irreducible minimum. Therefore, any continued fall in the rate of heart disease will have to be based increasingly on the treatment or avoidance of high levels of cholesterol.

Yet there is little evidence of policies on cholesterol reduction comparable to those implemented since the 1960s on the discouragement of smoking. There are rising levels of obesity. This is associated with rising levels of diabetes, which are in turn associated with rising levels of cholesterol and heart disease.[15]

By 2020, it is predicted that the diabetic population in the 29 present and likely entrant countries of the European Union will have risen from 23 million in 2000 to more than 34 million.[16]

What does this mean for European social policy as a whole?

Obtaining clear international measures of the threat from cholesterol is extremely difficult, and attributing cardiovascular incidents and deaths to individual risk factors remains controversial. But let us assume what is predicted – that the diabetic population in the 29 current and prospective countries of the European Union[17] will rise by 2020 from 23 million people in 2000 to more than 30 million. Let us further assume that there is no wonderful breakthrough in heart disease treatment between now and then. This gives us an average rate of 10 per cent by that year of serious or fatal stroke or heart attack. Large as these figures might seem, they exclude the avoidance of subsequent coronary events through secondary use of lipid lowering treatments, and exclude the remaining groups at high risk from elevated cholesterol levels above those established by international guidelines.[18]

This gives us three million deaths as a result of diabetes, which is related to high cholesterol. More than two million of these events are concentrated in just six countries, as shown in the table.[19]

Country	Diabetics	
	2020	Vascular Events
Turkey	5.3m	525,000
Italy	5.0m	500,000
Spain	3.4m	340,000
Germany	3.4m	339,000
UK	2.4m	237,000
France	2.3m	233,000

What this means in monetary terms depends on further assumptions. Let us assume that all of the seven million extra diabetics are under the age of 65 – a reasonable assumption, as most diabetics develop their condition in middle to later middle age. We arrive at 700,000 additional extra deaths per year, or serious heart attack or strokes. Taking the figure given above of €90,000 per patient, this gives us increased total health care and related costs of €63,000 million per year.

We cannot assume that all these 700,000 diabetics will have suffered their misfortune because of high cholesterol. On the other hand, high cholesterol leads in many other cases to fatal heart disease without proceeding through diabetes. And it is not unreasonable to insist on increased total health care and related costs of €63,000 million per year throughout an extended European Union.

The obvious result of this analysis is that even raising the retirement age may do little to avert the crisis of funding for the old.

Beneficial Effects of Heart Disease?

Of course, a reduced life expectancy for the old may, at the collective level, be a benefit – at least so far as state-run healthcare systems are currently constituted. Let us assume that a British man dies of a heart attack at the age of 65 – the present age of retirement. As of 2005, the average life expectancy of a British male was 76.[20] A fatal heart attack or stroke will cost the state very little in terms of the National Health Service – perhaps a few days of intensive care and an insignificant sum to cover the administration of the death. There will at most be one dependant, and this will almost certainly be a dependant in any case, being also of pensionable age. There will on average be no loss of tax, because the dead person will already have approached or be approaching retirement age. But this death will, at present levels of old age pension, save the state a minimum of £49.15 per week over the 11 years between the actual age of death and the average age of death. This is calculated by measuring the drop from £131.20 per week for a couple to the single person's pension of £82.05. Assuming the dead person to have been single, the saving will be £82.05 per week. Even the minimum figure works out to a saving over the eleven years of lost retirement of £46,932.60. It will also save the state hard to quantify but certainly substantial sums in treatment and long term care that can be expected to be required after the age of seventy.

There is also the release of personal assets to children and grandchildren at an earlier time than would otherwise be the case. It is a fading custom – at least among the white British population – for children to assume the costs of looking after their aged parents. Instead, they look increasingly on their parents as a source of relative enrichment. Any surviving partner can be expected to move into a smaller property, and will require a

considerably smaller income than would be the case for a healthy older couple. This would enable a transfer of wealth to children at a time when their own children were starting out in life. They would be better able to pay for continued education or for deposits on property purchases that would enable their own children to become settled at earlier ages. This might even contribute to a slightly higher birth-rate – which would in time moderate the problem of funding for the old.

Whatever the personal misfortune, such a death will be a financial benefit for the state, and is, in cold actuarial terms, to be welcomed. This assumes, however, that the death would be sudden and not preceded by any significant period of reduced economic efficiency. But improvements in palliative care, both actual and expected, mean that, increasingly, death from heart disease is neither sudden nor cheap.

As said, the present total cost in Britain of heart disease is £7,055.29m per year. At the moment, so far as heart disease commonly strikes in the earlier years of retirement, this can be offset against the costs of treatment and long term care that would arise in the later years of retirement. And there is the saving of pension costs. But if people are expected to continue working during the ages when debilitating heart disease is currently most common, the offset is itself offset by the loss of tax revenues. If those tax revenues are needed to stabilise the problem of funding for the old, there may be little or no such stabilisation.

Towards a Solution

There will be a health and welfare crisis in Europe. The facts, and the laggardly response of politicians to those facts, make that unavoidable – unless action is taken. This cannot be solved by greatly increasing taxation on those still in work. It cannot be solved by importing more tax payers. It can only be stabilised in the long term by reforming European welfare systems. This may mean lower levels of health care provided by the State, greater encouragement of savings and personal investment in healthcare, and a raised retirement age.

The costs of imposing this solution – both moral and financial – will increase with the projected increases in heart disease that will occur at least largely because of the increases in levels of cholesterol. It is therefore sensible to suggest that the coming problem should be moderated – though never entirely avoided – by a range of policies targeted at the issue.

The demographic changes which are happening within the European Union will have dramatic consequences on health and welfare systems. As things stand even today, they cannot continue to be financed by a pay-as-you-go-scheme where the employed pay for the health and nursing care of the elderly. By about 2030, as we have seen, there will be about one pensioner for every worker, meaning that payroll taxes would have, on average, to equal the average pension. The question is thus not *whether* but *how* reform will be introduced. The existing systems are simply unsustainable. Almost all the same factors apply everywhere: ever greater consumer demand, pivotal demographic shifts, the up front costs of ever better medical technology, political resistance. The list goes on. Add to that the more obvious immediate problem – increased rationing everywhere to control budgets – and it is clear that something has to give.

What it is that gives is, of course, a key and politically charged question. But while such proposals are outside the scope of this paper, there is at least one contribution to the crisis which leaps out: reducing the harm posed by high levels of cholesterol. After all, a healthier population – especially when older – is a less expensive (medically and in terms of welfare provision) population.

One means of such reduction is offered by a wider use of statins, a class of medication that lowers cholesterol. They have been shown to be highly effective in decreasing heart disease and preventing death. In terms of providing health benefits to a broad segment of the population, they are perhaps the most important drugs yet to emerge. They include:

- atorvastatin (Lipitor)
- fluvastatin (Lescol)
- lovastatin (Mevacor, Altocor)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastatin (Zocor)

These drugs lower cholesterol levels in the body by between 20 and 60 per cent, by slowing the production of cholesterol and by increasing the liver's ability to remove the 'bad' cholesterol (low-density lipoprotein or LDL) already in the blood. Statins lower LDL cholesterol levels more effectively than other types of drugs. They also modestly increase 'good' cholesterol (high-density lipoprotein or HDL) and decrease total cholesterol and triglycerides. Results are usually seen after four to six weeks of taking statins.

Statins have been studied extensively and overall have been proven to decrease the risk of heart attack, stroke, and other coronary artery diseases that are related to high cholesterol levels.

There is evidence of a rapid and increasing rise in the use of statins and similar drugs, from the middle to late 1990s across European countries. However, the overall use in recent years has not reflected the envisaged potential of the drugs to prevent and manage cardiovascular diseases. In current clinical practice there is still not optimal prescribing of the drugs, based on a comprehensive assessment of risk factors[21] and there is now extensive documentation of a pervasive under-use of statins.

A study of statin prescribing in men with established heart disease in the United Kingdom between 1998 and 2000 concluded that "among patients with established CHD, the prevalence of lipid lowering drug use remains low and statin regimens suboptimal. Major improvements in secondary prevention are essential if the benefits of stains are to be realised."[22] The overall proportion of patients with increased blood cholesterol concentrations controlled by lipid lowering drugs was very similar to the estimate of 16 per cent in the Health Survey for England.

Under-treatment has been extensive across the whole of Europe, emphasised in many studies of clinical practice. People with heart disease or diabetes remained under-treated with statins, women to a greater degree than men. Of those with a heart attack, angina, stroke or diabetes, 45 per cent of men and 35 per cent of women were taking a statin; and of those with heart disease or diabetes taking statins, only around half – 61 per cent of men and 40 per cent of women – achieved total serum cholesterol levels of below 5mmol/l.[23] These findings in Norway are corroborated elsewhere, where both a lack of primary prevention and appropriate secondary prevention of those diagnosed with heart disease are evident. Another key finding has been the lower level of dose found in clinical practice when compared with evidence-based doses used in large-scale studies, which may help explain the persistence of treatment failure.[24]

We therefore have available a clear contribution towards reducing the coming problem – but this solution has not been as effectively implemented as it could and should be.

In 2004, the British Government ruled that statins should be made available from pharmacies without the need for a prescription.[25] Competition between manufacturers of rival brands has reduced the

price of statins. Therefore, neither price nor availability is a problem. The problem seems to be one of information. There are millions of people throughout the European Union who would benefit in themselves, and would greatly assist in moderating the coming health and welfare crisis, if they were made more fully aware of an increasingly cheap and openly accessible means of reducing their cholesterol levels, and thus their tendency towards heart attack or stroke.

Equally, doctors should consider newer therapies in concert with, or exclusive of, statin treatment. While statin use is likely to increase over the next fifteen years – they have been one of the fastest growing categories of prescribed drugs – so is the incidence of cardiovascular heart disease. Crucially for future cholesterol treatment, newer treatments such as cholesterol absorption inhibitors will allow doctors to help patients lower the absorption of dietary and biliary cholesterol, as well as merely inhibit its production through the use of statins. This combination approach has been shown to greatly facilitate patients achieving their lipid-management goals – a Pan-European study examined patients in Germany, Norway and Spain, and discovered that between 40 - 76% of diabetic patients who had previously been prescribed only statins reached their lipid goals once doctors co-prescribed the cholesterol absorption inhibitor ezetimibe. Equally, a study in the United States found that the co-administration of small ezetimibe and statin doses produced an average reduction in cholesterol equivalent to levels seen only during a clinical trial wherein patients were given an eight-fold increase in their statin dose. Certainly, further research is needed in this area, but, particularly in the case of high risk groups such as those with diabetes or metabolic syndrome, co-administrative approaches to cholesterol management are already showing considerable signs of promise.

More appropriate use of statins – in other words, increased use of statins – is far from being a 'golden bullet' which will avert the gathering storm. In the bigger picture it represents, of course, just a few pixels. But those pixels, if fixed, will make a clear and lasting improvement on the overall quality of the picture.

Unlike the broader systemic changes which are required, the increased use of statins and newer cholesterol management therapies will have an immediate and demonstrable impact for the better, and should not be in the least bit politically contentious. Better take-up would merely represent the appliance of science to sensible ends, and the use of emerging new medicines would ensure a greater benefit to all.

A Comprehensive Review of the existing literature on Cholesterol Management

By Mike Sedgley and Tony Hockley

Abstract

This paper aims to summarise the practice of cholesterol management across European countries through a review of the published literature in academic journals and other publications and literature, including a large number of observational studies of cholesterol management in clinical practice. A variety of studies have been used including single-centre and single-country studies as well as comparative studies across clinical settings and across European countries. The paper outlines the development of tools for risk factor assessment and comprehensive guidelines for cholesterol management, and focuses on their implementation in clinical practice. A wide gap has been found between the guidelines and their implementation across European countries. In many cases raised cholesterol, as well as other risk factors, are not addressed by GPs and recommendations on blood cholesterol management are not met. Moreover, statin prescribing to prevent coronary heart disease remains low and does not conform to guidelines that have been developed, and there remains enormous variation in use of statins between countries in the use of statins to control cholesterol. Many of the reasons identified as underpinning these discrepancies could be ameliorated through the growing use of newer cholesterol therapies. The economic and social salience of cholesterol management is likely to grow substantially as Europe's population ages over the coming decade and more.

Cardiovascular diseases (CVD) are the principal cause of mortality in the Western world and the EU. Coronary heart disease (CHD), or ischaemic heart disease (IHD), accounts for the largest proportion of CVD and is itself the single greatest cause of mortality in the EU. The prevention and treatment of CVD and CHD have progressed steadily over the past three decades. The major risk factors have been identified and treatments for both the management and acute treatment of cardiovascular diseases and events have been transformed.

Risk factors

The identification of major coronary risk factors owes much to the early Framingham study in the United States between 1948 and 1951. The study introduced the concept of risk factors for coronary heart disease and identified the three major risk factors as elevated blood pressure, elevated cholesterol and smoking. These have been confirmed consistently through further studies in the decades since. The study, and others that followed, have formed the basis of preventative cardiology. The identification of the major risk factors underpinned the development of the SCORE (Systemic Coronary Risk Evaluation) risk assessment tool for estimating 10-year risk of developing coronary heart disease on the basis of combined blood pressure, cholesterol and smoking status, weighted for age and gender.[1]

The WHO MONICA project, the largest community-based study on heart disease ever undertaken, was established in the early 1980s in 32 centres around the world to monitor trends in cardiovascular diseases, and to relate these to risk factor changes in the population over a ten year period. Results from the project showed that heart disease rates are related to changes in major coronary risk factors and to the introduction of new medical treatments. The risk factors studied by MONICA included blood pressure, blood cholesterol, cigarette smoking and body weight. It has been estimated that 80% of major CHD events in middle aged men can be attributed to the three principal risk factors of blood pressure, cholesterol and smoking. Population-wide control of them is essential for effective CVD prevention.[2]

Cholesterol levels have been shown to correlate well with cardiovascular mortality across countries.[3] As well as CHD, raised blood cholesterol is a significant factor in stroke and has been shown to correlate with overall incidence. One study states that:

"increases in age-adjusted rates of both non-hemorrhagic CVD and verified ischemic stroke were identified with increasing cholesterol and low-density lipoprotein cholesterol levels, decreasing high-density lipoprotein cholesterol levels, and decreasing percentage of total serum cholesterol contained in the HDL moiety."

A complicating factor in the prevention of cardiovascular disease is the interaction of the various risk factors. Here, blood pressure, cholesterol and smoking remain central; diabetes also represents a major CVD risk factor and in itself can be a cause of raised cholesterol. Eliminating the combination of the three principal risk factors reduced overall risk by two thirds in the Multiple Risk Factor Intervention Trial (MRFIT) in 35-57 year old men in the mid-1980s.[4] Understanding the cumulative effect of high blood pressure and cholesterol in total risk is important for targeting patients in primary care; and the effects of one risk factor on the success of the treatment of another is an additional complicating factor. The negative effects of smoking on treated hypertension have been demonstrated, in which there may be patient compliance and/or pharmacological factors at work.[5]

The identification of the principal risk factors for cardiovascular diseases has underpinned a substantial reduction in CVD mortality across Europe and the Western world since the late 1960s.[6] In most industrialised countries cardiovascular disease mortality has shown decreasing trends since around 1970, following stagnation or increases observed during the 1950s and 1960s.[7] Studies have broadly demonstrated consistent decreases in mortality, heart attacks, and strokes, as well as a significant decrease in the need for angioplasties and heart bypass surgeries. Alongside the identification of risk factors, treatments for coronary heart disease have improved markedly during the same period, contributing both to improved mortality and an improvement in case fatality.

All risk factors have been important in this improvement, as lifestyles have improved and better treatments for the management of blood pressure and cholesterol have been developed. Major changes in smoking incidence have played a significant part in the longer term reduction in CHD throughout the Western world. In Scotland, a country with historically extremely poor cardiovascular health, the fall in smoking had a significant influence on the reduction in coronary deaths in the 1980s and 1990s; a similar picture is also true for England. Management of high blood pressure and cholesterol have also

made major contributions to this improvement.[8] Studies have shown that both primary and secondary prevention have played an important part in advances made in European countries.[9]

Developments in cholesterol treatments have changed the nature of cholesterol management and played a central role in the reduction in CVD deaths. Prior to the introduction of statins in 1987, cholesterol treatments had included nicotinic acids and resins, from the 1950s and1960s, followed by the introduction of fibrates in the 1970s, which became the principal cholesterol treatment until statins were introduced in 1987.

Statins

The introduction of statins

Since statins were introduced in 1987, great strides have been made in the management of cholesterol among CHD patients and those with elevated cholesterol. In the five years following their introduction, the prescription of statins grew by over 30% a year.[10] Statins enabled a shift in focus from treatment in secondary care to prevention and treatment in primary care, with implications for the organisation of health systems and the costs of coronary care, as well as for the patient's treatment experience. Moreover, the identification of individual risk assessments together with drug therapies has emphasised this shift of focus to the individual, creating new opportunities for prevention on the basis of individual risk profiles.

In early studies the effectiveness of statins in reducing CHD risk were extremely positive, underpinning a rise in their use through the 1990s. The Scandinavian Simvastatin Survival Study (4S) evaluated the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease. Results showed that simvastatin produced mean changes in total cholesterol, low-density-lipoprotein cholesterol (LDL-C), and high-density-lipoprotein cholesterol (HDL-C) of -25%, -35%, and +8%, respectively, with few adverse effects.[11]

Early on, the effects of patient compliance with drug regimens were demonstrated in the West of Scotland Coronary Prevention Study (WOSCOPS), which examined primary prevention over five years in the early 1990s. It found that those who took 75% or more of their prescribed lipid-lowering medication reduced their risk of death from any cause by one third compared with those who took less than 75% of their medication, and there was a significantly reduced need for revascularisation procedures.[12]

Cholesterol management in the 1990s

The use of statins increased rapidly through the 1990s across Europe. The publication of clinical trials, as well as many observational studies, showing the effectiveness of statins in patients with CVD in the mid-1990s, appears to have had a significant effect on prescribing in subsequent years.

There is evidence of a rapid and increasing rise in the use of lipid lowering drugs (LLDs), principally statins, from the mid to late 1990s across European countries. In England during the period 1994 to 2001, prevalence of treated IHD rose from 6.4% to 7.7% in one study, reflecting both population aging and an increase in treatment. The increase in prescribing of LLDs (nearly all accounted for by statins) was far greater; by 2001 56.3% of men and 41.1% of women with IHD were receiving a prescription for LLDs. The consumption of lipid-lowering drugs increased dramatically in Spain in the 1990s, and there have been indications of a greater rationality in their use since 1995, when statins overtook fibrates as the most common lipid lowering drug. The increase in LLDs increased almost eight-fold between 1986 and 1998.[13] The PREVENSE studies in Spain demonstrated a significant improvement in the practice of preventative cardiology. Between 1994 and 1998, there were significant changes in the use of drug therapies at the time of hospital discharge: an increase in the use of beta blockers from 33% to 45%; in ACE inhibitors from 33% to 47% and a six fold increase in the use of statins from 5% to 29%.

Other countries have shown a consistent rise in the use of LLDs through the 1990s as well, though there remained differences between countries. Statin use for patients following acute myocardial infarction in Denmark increased from 13% in 1995 to 61% in 2002, and 81% for patients aged 30-64 years. The rise for patients aged 75-84 rose from 1.3% to 43%.[14] Statins were prescribed to 52% of IHD patients (and 40% of patients with diabetes) by December 2002 in Ireland. Increased frequency of prescribing to IHD patients as well as increased doses, were found in an Irish study between 1998 and 2000. Increased dose was due mainly to increases in pravastatin doses while atorvastatin showed the greatest increase rate over time.[15]

The variations in use that have been documented between countries are indicative of disparities in drug utilisation that suggest major deviations from evidence-based medicine.[16] Some of the differences but not all may be explained by variations in morbidity: *"We must consider other explanations, and these may lie in factors unique to each country: for example, differences between Norway and Denmark may reflect the involvement of Norwegian doctors in seminal trials, while in Denmark these drugs were only reimbursed from 1998 onwards and their use has lagged behind other countries. Low use in Italy may reflect low coronary morbidity or poor adherence of Italian patients to statins, worse than elsewhere in Europe. Other differences may lie in national guidance and policies. These national figures also hide wide variations within countries."*[17]

Following a rapid increase in use in the 1990s, however the overall use in recent years has not reflected the potential of the drugs to prevent and manage cardiovascular diseases. In current clinical practice there is still not optimal prescribing of the drugs, based on a comprehensive assessment of risk factors[18] and there is now extensive documentation of a pervasive under-use of statins. Critical to the management of cholesterol in clinical practice has been the development of guidelines at European and national levels.

Guidelines & Treatment gap

A comprehensive understanding of risk factors and of individual risk, as well as an understanding of its management with appropriate treatments, has generated comprehensive best practice guidelines that now form the framework for the clinical management of cholesterol. Yet studies consistently show a significant treatment gap between such best practice guidelines and real-life cholesterol management.

The most comprehensive examination of cardiac care in clinical practice across Europe has been undertaken by the EUROASPIRE studies. The first EUROASPIRE study was undertaken by the European Society of Cardiology (ESC) in nine European countries in 1995-6. It revealed wide variations in modifiable risk factors and in medical practice between countries and a real potential to reduce CHD morbidity and mortality. The second Joint European Societies Task Force in 1998 reinforced the recommendations of the EUROASPIRE study to identify those at high risk of CHD.

The EUROASPIRE II study was undertaken in fifteen European countries in 1999-2000:[19] Belgium, the Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Slovenia, Sweden, Spain

and the UK, to provide systematic information on patient management in Europe and to verify the applicability of European guidelines on the investigation, treatment and prevention of CVD in order to facilitate their implementation. Specifically it aimed to:

Determine whether European Society guidelines on secondary prevention of CHD were being followed in patients with CHD.

Determine whether the practice of preventative cardiology in patients with established CHD has improved in those centres that took part in EUROASPIRE I.

Determine whether risk factors had occurred in the first degree blood relatives of patients with premature CHD and if so to describe their management by lifestyle and drug therapies.

The study used hospital records and follow up interviews with CHD patients in one or more centres in each of the fifteen countries. It represented the first real acknowledgement in a large scale European study of the personal risks associated with CVD and underlined the importance of not only population-level actions but also a personalised approach to CVD prevention.

The EUROASPIRE II study revealed that the overall proportion of CHD patients taking a statin was 55.3%, ranging from 0.7% to 75.1%. The highest proportion of statin use was found in the Netherlands (75.1%), Sweden (73.5%) and the UK (67.6%). The lowest use was found in Greece (30.7%), Poland (34.7%) and the Czech Republic (38.8%).

Guidelines

The guidelines drawn up under the auspices of the European Society of Cardiology were the most comprehensive clinical guidelines produced at the European level, by the Joint Task Force of European and other Societies, bringing together national societies of cardiology and other organisations. The guidelines of the Third Joint Task Force of European and other Societies are broad ranging and draw attention to psychosocial issues such as unrewarding work, stressful family environments and so forth, which physicians should make an effort to address. Attention is also drawn to diet, physical exercise and obesity. To assess individual risk of CVD, the guidelines use the SCORE system of risk analysis combining blood pressure, cholesterol level and smoking.[20]

On cholesterol, the recommendation is that total plasma cholesterol should be below 5mmol/l and LDL-C below 3mmol/l. For those with established CVD or diabetes, the treatment goals should be lower: 4.5mmol/l total cholesterol and 2.5mmol/l LDL-C. No specific treatment goals for HDL cholesterol and triglycerides are defined but concentration levels can serve as markers for increased risk: HDL-C under 1.0mmol/l for men and under 1.2mmol/l for women; fasting triglycerides above 1.7mmol/l. Those at high multifactorial risk of CVD would benefit from the lower total and LDL cholesterol levels of 4.5mmol/l and 2.5mmol/l respectively.

Blood pressure is considered in the guidelines to represent a high risk where systolic blood pressure (SBP) is 140mmHg or above and diastolic blood pressure (DBP) is 90mmHg or above. Immediate drug therapy should be initiated where individuals have sustained SBP at 180mmHG or above, or DBP of 110mmHg or above. The guidelines recommend advice to stop smoking and agree on a smoking cessation strategy tailored to the patient.

The guidelines specify that if total CVD risk remains above or equal to 5% (using the SCORE analysis), following lifestyle and dietary advice, lipid lowering drug therapy should be considered to lower total cholesterol to

Table 1: Reported medications for hospital patients with established CHD, around 1995

	Lipid-lowering	Anti-platelets	Beta-blockers	ACE inhibitors	Calcium antagonists	Diuretics	Digitalis glycosides	Anti-diabetics	Anti-coagulants	Nitrates
France-Lille	41.7	82.1	56.3	33.6	33.3	18.7	6.1	12.1	5.6	72.0
Finland-Kuopio	39.0	82.2	77.8	17.4	24.1	12.1	5.1	7.2	7.5	37.8
Netherlands-Rotterdam	36.0	77.7	46.9	27.2	22.0	13.7	5.4	8.3	9.1	12.2
Germany-Munster	35.2	82.9	43.6	31.4	36.0	14.5	12.2	8.9	6.1	45.4
Spain-Barcelona & province	30.3	84.1	34.7	17.7	47.3	15.7	5.7	16.5	6.9	41.4
Slovenia	30.3	79.6	51.9	31.3	35.4	14.3	5.1	7.3	5.8	38.8
Czech Rep-Pilsen & Prague	28.7	85.2	65.3	28.1	25.1	15.7	7.9	10.6	3.9	65.7
Italy-Udine, Friuli, Treviso & Verona	25.2	86.1	49.2	31.8	43.5	17.7	7.5	10.6	3.1	61.9
Hungary-Budapest	22.3	72.0	57.7	46.3	57.0	15.9	5.7	12.6	13.5	69.1

Source: EUROASPIRE, European Society of Cardiology.

Table 2: Use and choice of statins 1997-2002

	Simvastatin		Lovastatin		Pravastatin		Fluvastatin		Atorstatin		Cerivastatin		All Statins	
Country	Total	Rate‡	Total*	Rate‡	Total*	Rate‡	Total*	Rate‡	Total*	Rate‡	Total*	Rate‡	Total use*	Rate use‡
Aus	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	64.96	21.94
Bel	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	NK	146.9	39.32
Den	14.83	7.60	1.37	0.70	3.32	1.70	0.98	0.50	8.97	4.60	0.78	0.40	30.25	15.50
Fin	23.05	12.12	6.45	3.39	3.97	2.09	6.55	3.44	18.12	9.53	0.52	0.27	58.65	30.85
Fra	206.81	13.57	0.00	0.00	145.17	9.58	29.79	1.97	357.52	23.56	107.60	7.09	846.88	55.82
Ger	144.10	5.54	31.20	1.20	55.90	2.15	41.30	1.59	299.70	11.52	116.20	4.47	688.40	26.47
Ire	1.27	3.02	0.00	0.00	4.63	11.05	0.50	1.19	4.24	10.12	4.16	1.00	14.80	26.38
Ita	132.51	6.29	0.00	0.00	41.18	1.96	5.15	0.24	93.84	4.46	37.04	1.79	309.72	14.74
Neth	115.30	22.13	0.00	0.00	32.58	6.25	7.94	1.53	96.87	16.72	3.60	0.69	256.29	47.28
Por	14.13	5.29	7.38	2.76	8.69	3.25	8.68	3.25	9.21	3.44	2.85	1.07	50.93	19.06
Spa	101.83	6.89	37.88	2.56	57.36	3.88	9.00	0.61	111.81	7.56	42.59	2.88	360.30	24.13
Swe	59.46	18.60	0.00	0.00	11.49	3.59	2.13	0.66	34.46	10.78	2.11	0.66	109.65	34.29
UK	178.03	9.72	0.00	0.00	48.52	2.65	12.02	0.66	172.01	9.39	26.47	1.44	437.03	23.86

*NK=Not known. *Total use in million defined daily doses. †Rate use in defined daily doses/1000 of population covered/day.*
‡ Data available only for the following periods: Austria, Norway, Spain 1997-2001; Finland, Sweden 1998-2002; Italy 2002; Germany, Netherlands, UK 1997-2002
Source: BMJ. 2004 February 14; 328 (7436): 385–386

4.5mmol/l or below. They emphasise the importance of risk assessment of the individual and of the need for both primary and secondary prevention.

The treatment of CVD in European countries shows significant variation. Comprehensive and in-depth studies are lacking across health care systems but a very large number of valuable studies have been undertaken across European countries. Data on the use of statins across the health care system shows a wide variation in their overall use among EU and European countries, as well as in the choice of statin, as highlighted by the EUROASPIRE and other studies. (Tables 1 and 2).

Failure to treat patients to goal

Following the production of substantial treatment guidelines for both the primary and secondary prevention of CVD the principal focus of attention has recently been on the extent to which implementation at the clinical level is occurring to an appropriate and satisfactory degree. Despite the increase in the use of statins, there is widespread documented evidence of low uptake, and a persistent treatment gap that manifests itself in both a lack of treatment of those at risk of cardiovascular disease and an undertreatment of those being prescribed LLDs. The advances made over several decades in the ability of physicians to identify those at risk are not being translated into adequate coronary care and where treatment is undertaken, large numbers of patients – in most studies, the majority – are not reaching their cholesterol goal. Such a lack of treatment and undertreatment has been highlighted by the development of comprehensive guidelines in Europe, since the mid-1990s, for the management of cholesterol and CVD risk in general.

The EUROASPIRE II study found that only 51% of patients on lipid lowering therapy were achieving goal, ranging from 70% in Finland down to 31% in the Czech Republic (see Chart 1).

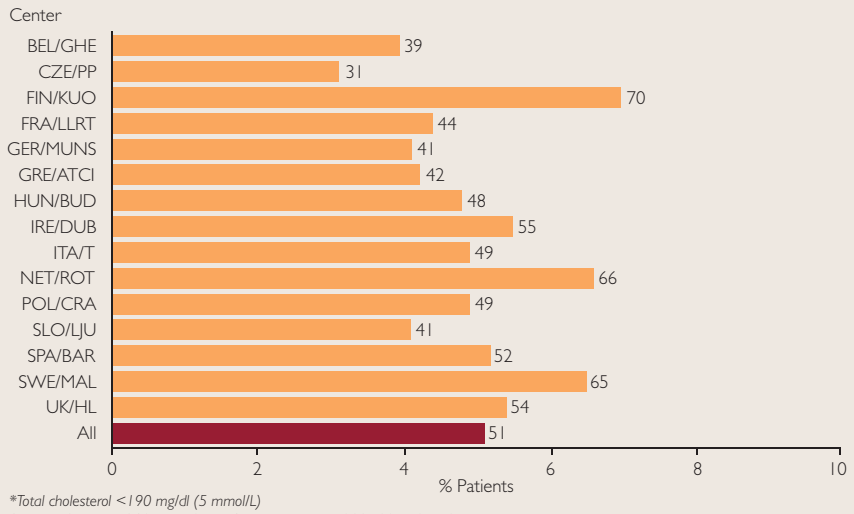
This evidence has been corroborated across many studies, both pan-European and in individual countries. The REALITY study, which was a series of observational studies in nine European countries, with 59,000 patients, noted a similar failure of goal achievement in large numbers of patients (see Chart 2).

Similar lack of adherence to goals has been found in the United States.[21]

In the UK in 1996, through 288 general practices in England and Wales, only 13.3% of men and 8.2% of women with a diagnosis of ischaemic heart disease received a prescription for a statin, in a study undertaken by Dr Chris Isles, of Dumfries and Galloway Royal Infirmary.[22] Similarly, a study of statin prescribing in men with established CHD in the UK between 1998 and 2000 concluded that "among patients with established CHD, the prevalence of lipid lowering drug use remains low and statin regimens suboptimal. Major improvements in secondary prevention are essential if the benefits of stains are to be realised."[23] The overall proportion of patients with increased blood cholesterol concentrations controlled by lipid lowering drugs was very similar to the estimate of 16% in the Health Survey for England.

Under-treatment has been extensive across Europe, emphasised in many studies of clinical practice. People with CVD or diabetes remained under-treated with statins, women to a greater degree than men, in the Oslo health study, 2000-2001. Of those subjects with a heart attack, angina, stroke or diabetes, 45% of men and 35% of women were taking a statin; and of subjects with CVD or diabetes taking statins, only around half – 61% of men

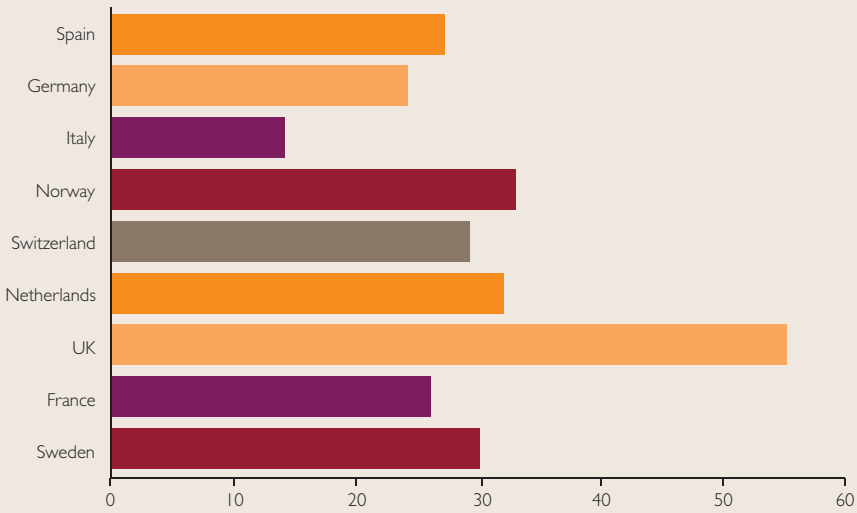
Chart 1



**Total cholesterol <190 mg/dl (5 mmol/L)*
Adapted from EUROASPIRE II Study Group Eur Heart J 2001;22:554–572.

Source: *Noncommunicable diseases in the WHO European Region: the challenge*, Fact sheet EURO/06/04 Copenhagen, 6 September 2004

Chart 2



Source: *Noncommunicable diseases in the WHO European Region: the challenge*, Fact sheet EURO/06/04 Copenhagen, 6 September 2004

and 40% of women – achieved total serum cholesterol levels of below 5mmol/l.[24] These findings in Norway are corroborated elsewhere, where both a lack of primary prevention and appropriate secondary prevention of those diagnosed with CVD are evident. Another key finding has been the lower level of dose found in clinical practice when compared with evidence-based doses used in large-scale studies, which may help explain the persistence of treatment failure.[25]

A failure to achieve cholesterol goal by coronary patients has been a continuing feature of cholesterol management across European countries. Lack of appropriate management of patients in primary care was found in the Spanish REALITY study, which examined prescribing patterns of lipid-lowering drugs used in the management of patients at risk of coronary heart disease in clinical practice. It assessed low-density lipoprotein cholesterol goal attainment and found that only 12.9% of patients attained their LDL cholesterol goal on their initial lipid-lowering drugs, and an additional 13.4% achieved goal after a change in their lipid-lowering therapy, resulting in 73.7% of patients not attaining goal after at least three years of follow-up after the initiation of lipid-lowering therapy. Patients who would gain the most from aggressive lipid lowering (CHD patients and patients with high baseline LDL cholesterol) were least likely to achieve goal. The study demonstrated clearly that patients are not being managed effectively and statin use is not being carried out in an optimal way.[26] The treatment goal was not reached in 74% of patients in a Danish study into the management of dyslipidaemia by GPs. It found that one-third of patients monitored for dyslipidaemia had IHD, and that 54% were treated with lipid lowering medications. Again, statin doses used were generally lower than those used in clinical trials.[27] No substantial improvement in secondary prevention was found in a study in Munster, Germany between 1996 and 2000, although there had been a general increase in the frequency of statin use.[28]

Failure to implement guidelines

The EUROASPIRE II study showed that therapeutic goals set by the Joint European Societies Recommendations on the prevention of coronary heart disease were not being met in a majority of patients.[29] The failure of patients to attain cholesterol goal and the further failure to implement adequate primary prevention shows a clear gap between guidelines and clinical practice.

Specifically, there has been a widespread failure to achieve lipid levels recommended by relevant guidelines. Not all patients who would benefit from lipid lowering drugs are being managed properly. This treatment gap varies across different clinical settings but to some degree or other it is present across Europe.[30] Aside from the ESC guidelines, the German-based International Task Force for Prevention of Coronary Heart Disease recommended in its 2004 Treatment Guidelines for dyslipidemia that patients with atherosclerotic disease require low LDL cholesterol target values (2.5 mmol/l) and that patients at high risk of coronary events should receive the same treatment as patients with symptomatic CHD.[31]

Yet international, European and national guidelines are not being implemented, as documented in studies in Germany, France, the UK, Italy, Finland, the Netherlands, Belgium, Ireland and other countries. In Germany, the discontinuation of lipid lowering treatment caused cholesterol levels to rise within an outpatient CHD population, where only a 7.4% reduction in LDL cholesterol level was achieved under real life treatment conditions. A wide gap was reported between treatment guidelines and real life treatment patterns and awareness among both physicians and patients of the risk of high cholesterol levels was found wanting.[32] Statins as secondary prevention were given at discharge in only 60% of suitable patients, declining to about 50% in ambulatory visits, in another German study of a group of patients over 65 years of age with at least two cardiovascular diagnoses requiring chronic medication.[33]

A third of men and half of women patients with coronary heart disease had never had a cholesterol measurement in a study in the NHS in England.[34] For those whose cholesterol had been measured, 75% had total cholesterol above 5mmol/l yet only 16% were receiving statin treatment. This is despite the target for statin use, that 80-90% of CHD patients should be taking statins in the UK National Service Framework (NSF) on CHD,[35] which specifies treatment guidelines for physicians, and despite the fact that NSFs are one of the chief factors influencing GP decision making.

In an assessment of the CVD risk of the Irish population it has been calculated that 25% of the overall adult population would be potential candidates for statin therapy if the Joint European Guidelines, which have been adopted in Ireland, were implemented. Using similar thresholds for intervention, the UK equivalent figure would be 16-25% of the adult population. And while only 44% of the overall at-risk group were being prescribed statins by the end of the Irish study, they have estimated that at least 80% of such at-risk populations would be able to receive an 'evidence-based' statin.[36]

The trend in daily dose increased markedly during the period 1994 to 2001, and it has been towards the higher doses likely to achieve the 25% reduction in total cholesterol specified in the UK's NSF on CHD.[37] Taking a 20mg dose of simvastatin as the amount required to affect a 25% reduction in total cholesterol, in 1994 only 22.6% of men and 21.9% of women on LLDs received this dose; this rose to 67.6% of men and 67.4% of women by 2001.

The French National Agency for the Development of Medical Evaluation (ANDEM), set out guidelines as early as 1996 for the treatment of patients at cardiovascular risk. Yet these have been shown to have been implemented poorly in clinical practice.[38] Local guidelines in France (AFSSAPS) have defined therapeutic objectives for LDL-C. These objectives vary with the number of cardiovascular risk factors in addition to dyslipidaemia. A recent study showed that only 26% of patients who were at high cardiovascular risk and not at their therapeutic objective received high doses of lipid-lowering agents in monotherapy. Applying ANDEM guidelines, 74% of secondary prevention patients had not achieved their treatment goal. The study showed that physician compliance with guidelines varied inversely with the level of cardiovascular risk and that the use of lipid-lowering agents was inadequate, depriving many patients of an effective protection against cardiovascular diseases.[39] A similar French study in a primary care setting among patients with multiple cardiovascular risk factors showed that recommended therapeutic objectives for LDL cholesterol were achieved, over a three year period, in only a quarter of patients at high risk of CVD.[40]

A wide variability in the delivery of secondary prevention for diabetes patients and a significant gap between therapeutic guidelines and actual treatment was found in a study of secondary prevention in high risk diabetes patients in Italy. Only 25% of coronary patients in secondary prevention were receiving lipid lowering drugs and 20% beta blockers.[41]

A Finnish study which specifically examined the relationship between guidelines and clinical management in acute coronary syndrome has found that more traditional medication with aspirin and beta-blocker was widely used, whereas statins, GPIIb/IIIa receptor antagonists and invasive therapy were all under-used. Well known risk factors were poor predictors of receiving in-hospital angiography. The study

showed that additional education and resources were needed if the ESC guidelines were to be reflected in clinical practice.[42]

Studies of the management of multiple risk factors have presented some anomalies. A Dutch study showed that where patients were eligible for both blood pressure and cholesterol screening, blood pressure screening was high (>86%) whereas cholesterol screening was much lower (<56%). Moreover, among patients newly identified with hypertension or hypercholesterolaemia who were eligible for pharmacotherapy, 29% and 43% respectively were not treated within one year of diagnosis, although under-treatment was much lower for those patients with both conditions (24% and 37% for antihypertensive and lipid-lowering treatment, respectively, and 28% were not treated for either).[43]

Guidelines and targets have been shown to have a clear influence over GPs in Belgium, even where implementation is patchy. Lipid-lowering drugs are reimbursed in primary and secondary prevention in Belgium when, after a cholesterol-lowering diet of at least three months, total cholesterol remains higher than 250 mg/dl (6.4 mmol/l) or triglycerides remain higher than 200 mg/dl (2.25 mmol/l).[44] Low-density lipoprotein cholesterol is only taken into account for the reimbursement of fibrates when it remains higher than 160 mg/dl (4.1 mmol/l) in secondary prevention. The majority of patients in Belgium, it has been claimed, at higher risk of coronary event do not benefit from lipid-lowering drugs, particularly the statins. Regulation based on blood cholesterol level encourages the overlooking of other risk factors relevant for selecting patients who would have the greatest chance of benefiting from statin treatment.[45] A study of patients in Belgium showed that CVD risk factors as a whole were not taken into account by physicians. The only two factors that correlated with a prescription for statins were high total cholesterol and an improvement of triglycerides during the diet.[46]

Lack of adequate guidelines remains an issue in some countries. For example, in Austria attention has been drawn to an absence of adequate national guidelines for statin use in secondary care.[47]

A particular area of concern, both in the formulation of guidelines and in their implementation, has been the prescribing of LLDs to older patients. A significant degree of inequality has been found in this area, with the over-70s and over-75s conspicuous for their relative lack of treatment. There are clear implications here for effective cholesterol management over the coming decade as Europe's population ages.

Because the initial studies of the benefits of statins were not focused on the older age groups, prescribing to the over 75s seems generally to have lagged behind, though studies suggest there has been a rapid increase in use by this age group in some countries. Statin use for patients following acute myocardial infarction was much lower for the over 75s in a Danish study between 1995 and 2000, although use had risen extremely quickly during the period.[48] Those aged 45-64 years were more likely to be prescribed statins than the over 65s in a study in England in 1998-2000,[49] corroborated in another study that shows a wide disparity according to age, with far lower numbers of those with IHD aged over 75 receiving LLDs. In 1998, 10.4% of those 75-84 years and only 1.2% of those 85 and over receiving LLDs, compared to 44.9% of patients aged 35-64 years.[50] Here guidelines themselves may have played a significant part in underlining a treatment bias, as the National Service Framework (NSF) in England does not specifically mention the need for statin treatment in the over-75s.[51]

Other inequalities in prescribing have been found in a variety of settings, indicating a lack of consistency in the application of best practice.

Age and gender differences have been revealed between countries, such as in a major European-Australian study, where variations with respect to both age and gender were found between Italy and Sweden.[52] In Scotland, one study between 1997 and 2002 found that women received a lower level of treatment than men, which increased over time; the most affluent patients were significantly less likely to receive a statin; and the oldest group were significantly less likely than the youngest group to receive a statin.[53] A study in Aberdeen showed a gender bias in the prescription of important secondary preventative therapies in primary care that may lead to increased mortality from ischaemic heart disease in these groups.[54] Gender seems to have strongly influenced prescribing in IHD patients in England in a 1998 study, with 31% of men and 21% of women being prescribed such drugs.[55]

Inequalities in secondary prevention, including the use of statins, by age, sex and region have been noted in Ireland. The wide variability may be due to uncertainty in prescribing secondary preventative therapies or variability in clinical need between regions.[56] A socioeconomic bias was also found among elderly patients in Ireland, with more affluent patients less likely to receive a prescription for medical treatments.[57]

Causes of the treatment gap

A variety of factors might underpin the failure to implement guidelines and the failure of patients to achieve their cholesterol goals.

The recording of medical notes and the interplay and communication between hospital cardiologists and GPs was emphasised by the EUROASPIRE II study. Medical notes were often incomplete and lifestyle information elicited from the patient was recorded incompletely. Cardiologists were seen to view their role primarily as to treat an acute event, yet inadequate advice and treatment before leaving hospital has often been continued into primary care. Primary care physicians are strongly influenced by hospital recommendations and they may perceive a lack of hospital treatment as an indication that the cardiologist does not endorse risk-lowering strategies. They are more likely to continue therapy prescribed by cardiologists than to initiate treatment themselves. Cardiologists need therefore to play a leadership role. Clearly, the management of CVD prevention has shown widespread inadequacy. An American study has suggested that there is compelling evidence that high-dose statins should be initiated prior to hospital discharge for all patients with acute coronary syndrome and an LDL target of 70 mg/dL (1.78 mmo/l/) or lower.[58]

The broader relationship between hospital care and primary care may be a key factor in appropriate prescribing of statins. A Polish study found that appropriate lipid management during hospitalisation is the most important factor related to lipid management in the post-discharge period. Patients undergoing percutaneous coronary interventions, treated in hospital outpatient clinics, obese patients as well as those better educated were more likely to be treated appropriately than the other groups. The study found that there is significant potential for further reductions in coronary risk among patients not undergoing coronary interventions in community hospitals and those who are under the care of general practitioners.[59] There is evidence from a British study that commencing LLD use in hospital at the time of an acute coronary event improves patient compliance, as well as offers more appropriate treatment for patients. Dr Chris Isles of Dumfries and Galloway Royal Infirmary cites several studies which show that treatment rates improved dramatically for patients prescribed statins from hospital at the

outset of their condition.[60] The follow-up period upon discharge may be critical in ensuring patient compliance with their treatment regimen, and a Scottish study found that those who attended outpatient clinics were far more likely to achieve their cholesterol goals than those who defaulted.[61]

The communication of guidelines to GPs is also an important area of concern. "Data on optimal use of statins (in terms of target populations), as reported in the pivotal studies, may not have been fully understood by prescribers in primary care, resulting in under-prescribing of statins," according to Teeling et al.[62] The results of statin use demonstrated in pivotal studies may not therefore be benefiting patients at primary care level.

There are also problems of up-titration in managing patients' cholesterol profiles and the need to move to higher doses of statins, in up to four successive stages, especially in the more severe cases, is a burden on both physician and patient. This has often been the principal hurdle in achieving successful cholesterol management over the longer term.[63]

Factors affecting treatment and patient compliance may also be quite complex, including the burden of treatment on the patient. Daily treatment burden was found to be a significant factor in determining goal attainment in Italy, where geographic location and out-of-pocket cost of medication were not found to have been of significant influence. The attitudes and activities of individual physicians have also been highlighted among the causes of inappropriate or inadequate use of statins.[64]

In the Oslo health study, determinants of statin use included use of other preventative drugs, family history and recent contact with a GP, emphasising the need for the active management of patients if appropriate treatment is to be maintained.[65]

Notwithstanding the increase in the use of LLDs and the development of guidelines at European and in some cases national levels, statin prescribing to prevent coronary heart disease remains low and does not conform to the guidelines that have been developed. Given both the documented potential of cholesterol management in general and statin use in particular to prevent cardiovascular disease and cardiac events, as well as the gravity of the CVD situation across Europe, it is remarkable that over a sustained period of time a notable failure of implementation in primary care has persisted. There may be a wide variety of explanations for the behaviour of doctors in this respect and barriers to statin prescribing may include concerns about cost, increased workload, adherence to treatment, variation in treatment targets for lowering cholesterol and communication between hospital and primary care, as well as concerns about medicalisation, lifestyle, and health behaviour.[66] Nevertheless, there is a clear 'Treatment Gap' between both what is possible and guidelines that have been produced, on the one hand, and the delivery of treatment to patients across Europe, on the other.

Communication and a common understanding between patient and prescriber is also an important factor in patient compliance. Studying the treatment gap present in the NHS in the UK, Minhas comments: *"The challenge for primary care is to ensure the delivery of CHD care in addition to treatment so that concordance, satisfactory compliance and persistence are achieved. Unless these issues are also addressed, the current goals and targets may seem elusive and the mortality reductions seen in clinical trials will remain theoretical."*[67]

Demographic and health trends and consequences of undertreatment for European health systems

Incidence of CVD in the EU

Diseases of the heart and circulatory system account for almost half of all deaths in Europe and the EU. CVD, including stroke, is also responsible for many premature deaths and is the leading preventable cause of death in Europe today. It is the leading cause of death among those under 75 years of age. Within cardiovascular diseases, coronary heart disease (CHD), or ischaemic heart disease (IHD), is a major cause of death. Indeed, CHD on its own is the largest single cause of death in the EU. CVD causes over 4 million deaths each year in Europe, and over 1.9 million in the EU.[68]

Incidence rates and death rates show some correlation yet the causes of case fatality are complex. Case fatality has been shown to be higher in Belgium, Denmark, France and Germany and lower in Finland (and Iceland), although it was falling quickly in France and rising slightly in Denmark and Finland. Statistics show a wide variation in the incidence of death caused by CVD (see Chart 3).[69]

The severity of elevated cholesterol in the EU, and elsewhere, has been demonstrated by the WHO MONICA project, which showed that across 25 regional studies between 18% and over 53% of men had blood cholesterol levels above 6.5mmol/l during the 1990s. The figures show not only wide variations between countries but also between regions within the same country (see Chart 4).

Regional disparities: the East-West divide

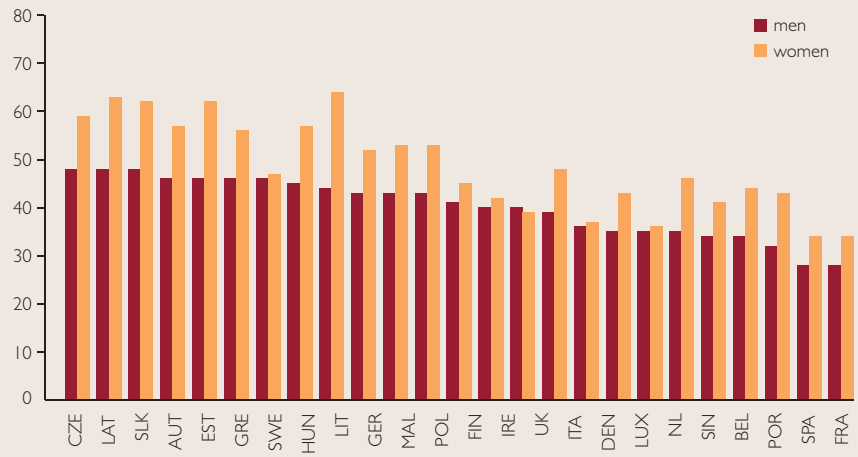
Importantly for EU policy makers and health care systems, there is a yawning disparity in cardiovascular health between the EU15 and the new member states. The division between east and west is not without its exceptions, and there are within-country variations as well, as demonstrated by the MONICA evidence, but there remains an extremely challenging disparity between the EU's new member states and the old in cardiovascular health.

Although historically there has been some discrepancy between the north and south of Europe, the gap has begun to close markedly. A recent report resulting from the WHO's MONICA project[70] shows that while incidence of coronary events is much higher in northern Europe than in the south, CVD is also falling more rapidly in the north than in the south. The great disparity now is between east and west. The Czech Republic, Slovakia, Hungary, Poland and the Baltic States have among the worst CVD mortality in the EU and are all in the worst half of the table (see Chart 3).

While CHD mortality rates have halved in many Western countries since the mid 1960s,[71] Eastern European countries have not experienced the same improvement and indeed mortality rates increased for most Eastern European countries up to the mid-1990s, after which an improvement in rates was seen in Poland and the Czech Republic, probably owing in some part to the improvement in diet, specifically in food availability. Other areas of Eastern Europe have not fared so well, seeing continued increases in CVD and CHD through to the late 1990s.[72]

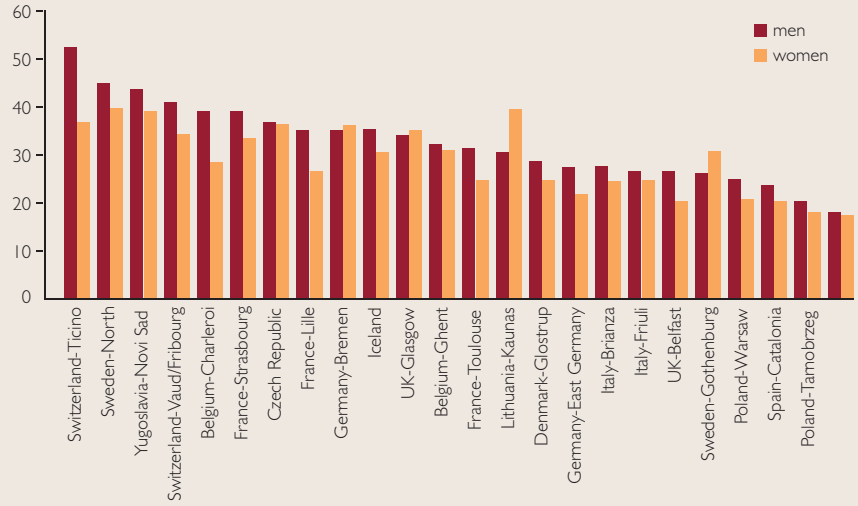
There is a lack of comprehensive studies on clinical practice between Eastern and Western EU countries but some studies have been undertaken. The preventative practices between East and West were directly compared by the WHO-CINDI programme, which compared Russia, Poland and Hungary in Eastern Europe and Germany, Finland and Spain in Western Europe. Preventative practices analysed were blood pressure reporting, cholesterol measurement and anti-smoking counselling. Major differences in reported preventative practices were found, although in both groups the focus was on secondary rather than primary prevention.

Chart 3: CVD Deaths as percentage of all deaths, men and women, EU countries (MEN AND WOMEN).



Source: European Cardiovascular Disease Statistics, 2005 edition, British Heart Foundation & European Heart Network.

Chart 4. Percentage of adults (men and women) aged 35-64 with blood cholesterol levels of 6.5mmol/l and above, MONICA project populations.



Source: European Cardiovascular Disease Statistics, 2005 edition, British Heart Foundation & European Heart Network.

Blood pressure measurement and anti-smoking counselling are more frequently reported to be carried out by primary health care physicians in the Eastern European areas while blood cholesterol measurement is more frequently reported in Western European countries.[73]

Implications for the future

The breadth of cardiovascular ill health in Europe is particularly poignant at a time when Europe's population is ageing rapidly. Primary prevention is especially relevant to CVD given that diseases of the heart and circulatory system result from decades of unattended risk factors. Such unattended risk factors have a greater salience in the context of an ageing society, in which action at the earliest possible opportunity is likely to yield the most effective results. As a major cause of avoidable mortality, the prevention of CVD has the potential to contribute most to reducing years of life lost to diseases amenable to effective treatment. Despite significant progress in the past two decades on reducing CVD mortality, some of the underlying causes of the principal CVD risk factors are set, if left unchallenged, to worsen, in particular growing rates of diabetes and obesity. Over half of diabetics suffer either elevated cholesterol or elevated blood pressure or both.[74] The financial implications of acute care in the context of a worsening dependency ratio are severe.

As CVD, and CHD in particular, remain by far the greatest cause of death and years of life lost in Europe, the clinical, personal and economic impact of cardiovascular disease is likely only to grow as the population ages, and as the underlying causes of some risk factors become more prevalent.

Demographic trends

Population ageing is well advanced in most European countries, with the proportion of the population over 65 years of age reaching 15 per cent in many countries (twice the world level). In most countries of Europe the median age is well over 30 years, the highest being 41.6 years, in Italy.[75]

Europe faces a historic challenge in the ageing of its population. With lengthening life expectancy and a falling birth rate, it is of truly historic significance, and the economic and social assumptions that have been underpinned by an ever rising population are now becoming obsolete. European countries face fairly similar rates of ageing over the coming 15 years, marked in particular by a worsening dependency ration of working age to retired people. In 1960 there were around 4.5 workers for every retired person in European countries; by 2020 there will be just two workers to each retiree and about 20% of Europe's population will be over 65, compared with 15 to 16% today, while more than one in twenty will be over 80 years of age.[76]

The economic and social implications of an ageing society are huge, most obviously in pension provision, long term care, social services and health care. There are political implications too: with additional burdens to bear, the working tax-payer population will have less political representation, as the 'grey vote' begins to have the power to swing elections. Maintaining inter-generational solidarity in European welfare systems may become a significant political challenge and may have implications for both the tax system and the structure of welfare and health funding. Governments may have to raise funding through additional contributions or expand private financing and funding of health care and welfare services, and perhaps consider extended patient co-payments, which have been strengthened in some countries in recent years.[77]

In health care, how the degenerative diseases of old age are dealt with will be critical to the extent of the burden that they present, both in people's quality of life and in financial terms.

Worrying trends in both obesity and diabetes, if unchecked, could present the unwelcome scenario of a larger older generation that is in a worse state of health than its recent predecessors.

The EU's finance committee, ECOFIN, has calculated that the increase in costs of pension provision will represent between 3% and 6% of GDP and for health and long term care 2% to 4% of GDP by 2050; half of this would occur by 2025.[78]

The treatment of conditions of avoidable mortality will be critical to the ability of European countries to manage the burden of an ageing population, and to reduce the high costs associated with hospital care. A study in Scotland suggests that *"Unless rapid and major changes occur in the incidence of heart failure, the burden of this disorder will continue to increase in both primary and secondary care over the next two decades."*[79] Projected rises in heart failure in Scotland by 2020 are 31% in men and 17% in women on the basis of population changes alone. The rise in GP visits during the same period would be 40% for men and 16% for women. Improving case fatality will further increase hospitalisations, up by 34% by 2020 on present trends. Moreover, there are more complex trends, not least in the prospects for increased obesity and diabetes.

Diabetes and obesity

Diabetes patients suffer from lipid problems aside from cardiovascular disease, and managing cholesterol in diabetes patients is an important part of the prevention of CVD.

"It has been estimated that 92% of individuals with type 2 diabetes, without cardiovascular disease (CVD), have a dyslipidaemic profile," according to a study of statin use in diabetics. Diabetics should be considered at high risk of CVD and treated with lipid-lowering therapy to reduce LDL cholesterol below 2.5mmol/l.[80]

The expected rise in diabetes over the next 25 years in Europe (as in the rest of the world), will have implications for the incidence of CVD and for cholesterol management in particular. Some projections suggest an epidemic expansion of diabetes prevalence in Europe[81] and a major challenge for clinicians in the 21st century.[82] Global rates are likely to rise from 2.8% of the total population in 2000 to 4.4% in 2030 and prevalence will shift to older age groups, over 65,[83] raising important questions about the lack of appropriate cholesterol management of this age group currently observed.

Targeting weight reduction and glucose control in the elderly will be important in preventing CVD.[84] A rise in insulin-dependent diabetes of 45-60% between 1990 and 2020 has been estimated in a Danish study,[85] while a British study suggests a 20% increase in type 2 diabetes by 2036, including a rapid rise in diabetes-related complications. Over coming decades there will be a steady increase in the relative cost of type 2 diabetes, exacerbated by the worsening dependency ratio of an ageing population.[86] The principal cause of diabetes mortality is cardiovascular disease, which can develop undetected as insulin resistance and hyperglycaemia worsen.[87] The neglect of cardiovascular risk factors in this group of patients is therefore of particular concern.

Type 2 diabetes is the disease most associated with obesity. Rising rates of obesity therefore have a direct link with diabetes and the elevated cholesterol that it implies and there is evidence that obese patients are not being screened sufficiently for the diseases most associated with their condition, including diabetes, elevated cholesterol and hypertension.[88] The Geneva-based World Heart and Stroke Forum, in its national and regional guidelines on CVD prevention, points to increasing obesity as an underlying risk factor for CVD in future years.[89]

Future challenges

In 2020 IHD will be the leading cause of disablement (calculated by disability-adjusted life years, DALYs).[90] The importance of appropriate treatment was highlighted by the WHO's MONICA project across 29 countries, including 16 in Europe. It concluded that one-third of the reductions in CHD mortality were attributable to declines in case fatality, where death occurred within 28 days of a coronary event.[91] Rising obesity and diabetes have the potential to present real challenges, offsetting more positive trends in improving risk factor profiles, and an ageing society will increase the proportion of the population in those age groups where CHD is most prevalent. An American study predicts a rise in CHD in the next 25 years of over 50% as baby boomers continue to swell the ranks of the older age groups, and European countries are ageing faster than the US. This will be exacerbated by a diabetes epidemic, driven in turn by an obesity epidemic, which will see many younger people succumb to the major CVD and CHD risk factors of raised cholesterol and high blood pressure.[92] The potential for further reductions in case fatality appears to be considerable. Together with appropriate secondary and primary prevention, there would appear to be the potential for a far larger reduction in Europe's most widespread cause of ill health and mortality.

Moreover, aside from questions of implementation at the clinical interface, there is also some question over whether targets for reductions of CVD mortality are sufficiently high, given the evidence base for even greater potential progress in the coming years. The UK government has called for a 40% decrease in CHD mortality by 2010.[93] The Medical Research Council (MRC) / British Heart Foundation (BHF) Heart Protection Study (HPS) concluded that allowing for the observed two-thirds compliance, 40mg simvastatin daily would probably reduce the rate of first major vascular events by about one-third. Hence, among the types of high-risk individuals studied, 5 years of simvastatin could safely prevent about 70-100 people per 1000 from suffering at least one major vascular event.[94] Critchley et al suggest that the target reduction in the UK could be met entirely through risk factor changes, and substantial improvements in treatment efficacy are also expected. There is, then, evidence that the government target of a 40% reduction by 2010 might be unambitious and a far more significant reduction might be possible. "Simple extrapolation from current trends suggests that the UK target is not testing."[95]

About 30,000 more deaths could be prevented annually in the UK by increasing treatment uptake, according to the study by Capewell et al.[96] CHD mortality fell in Scotland between 1975 and 1994 yet had age-specific mortality rates continued unchanged, over 6000 additional deaths could have been expected in 1994 than actually occurred (15,234 deaths occurred). But the scope for more improvement is substantial, with only around a third of eligible patients receiving appropriate therapy: a further 4078 deaths could be prevented or postponed in Scotland if 80% of eligible patients received appropriate treatment and by implication a further 30,000 in England and Wales. Over half this figure could be achieved by focusing on appropriate secondary prevention alone.

Key to predictions about future use are assessments of the gains to be made from ameliorating CHD and the part that might be played by cholesterol management in doing so. The study by Critchley et al points out than reductions in cholesterol seem to have greater potential to further reduce coronary heart disease mortality rates in the UK and elsewhere because CHD mortality it is reduced more by a 1% relative reduction in cholesterol than by a 1% mean reduction in blood pressure. It may also be that the principal gains from smoking cessation have

already been realised in the period of major reductions in smoking prevalence from the 1970s onwards.

An increase in the use of statins has been forecast and is expected within the UK. A study of statin use in the English NHS shows that their use has been among the fastest growing of all drugs. The Wanless review of 2002 projected an increase in the NHS spend on statins from £500 million to £2.1 billion by 2010, being made available to all people with at least a 15% risk of developing CHD in the subsequent decade, with a target compliance rate of 80%.[97]

Research has highlighted the potential of high risk (targeting those most at risk) and population (targeting the general population) approaches to reducing CVD risk. Emberson et al suggest that any major impact on CVD in the population will require wider use of high risk strategies as well as population wide reduction of major risk factors.[98]

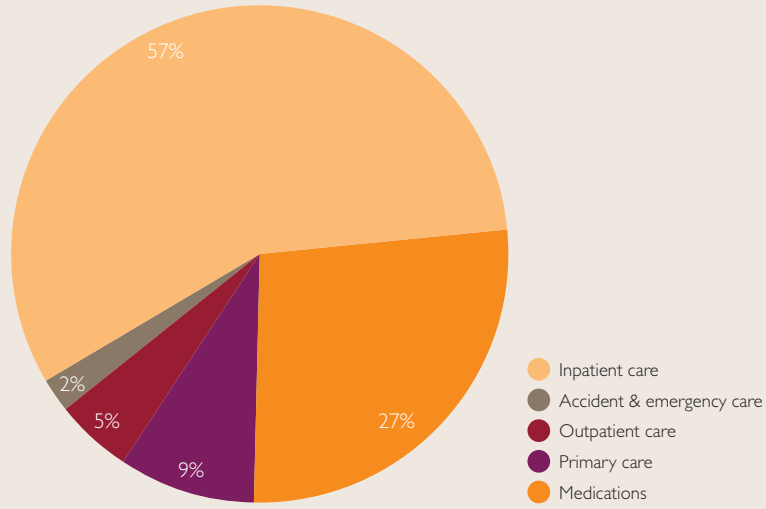
Ko et al concur with this view: "We found that prescription of statins diminished progressively as baseline cardiovascular risk and future probability of death increased. Since the benefits of a therapy are dependent on the baseline risk, the maximum benefits of statins may not be fully realised until implementation of therapy includes patients at highest risk." [99]

The incidence of elevated cholesterol is likely to worsen during the next decade if the observed treatment gap in the clinical management of elevated cholesterol is not addressed. The comprehensive guidelines that have been produced on the basis of decades of experience of cardiovascular diseases provide a sound basis for managing population health at the clinical level in the EU, yet clearly additional mechanisms are required to ensure their consistent and appropriate application. Demographic and other health trends do not augur well for Europe's health care systems, let alone its citizens, while such a failure to manage treatable conditions persists.

Costs of CVD and the potential of new cholesterol treatments

The ageing population and the rising rates of some underlying causes of CVD risk factors and elevated cholesterol in particular present a clear health challenge to the EU. There is also a substantial economic challenge given the cost burden of cardiovascular disease in the EU.

Chart 5. CVD health care spending in the EU



As one of the three principal risk factors for cardiovascular disease, the management of cholesterol is a significant issue for European policy makers and the medical profession. The incidence of CVD in Europe is high, at a time when population ageing, and a worsening dependency ratio, is likely to make its economic consequences more severe. Historically, clinical care in CVD has been expensive and prolonged and is a major economic burden in Europe.[100] The lifetime costs of cardiovascular disease to Germany alone are estimated at $25 billion in direct health costs, and indirect costs in productivity at $48 billion.[101]

Total costs of CVD in the EU amount to €169 billion, of which €105 billion is for treating CVD and €64 billion is due to lost productivity and the cost of informal care. This accounts for around 12% of total health care spending in the EU. The majority of the health care costs, 57%, are for inpatient care. Outpatient care is estimated at 5%, primary care at 9% and medications at 27% of the total (see Chart 5).[102] The burden of undertreatment is therefore centred heavily on hospital budgets, with potential savings from more effective management of cardiovascular risk factors.

The introduction of statins in the late 1980s constituted a major advance in the treatment of elevated cholesterol. It played a large part in bringing the management of cardiovascular risk factors into the primary care setting, reducing the burden on secondary care. Despite important advances in the management of hypercholesterolemia in recent decades, many patients with lipid disorders remain unidentified or undertreated and so continue to have unfavourable levels of LDL cholesterol and an increased risk for coronary events.[103] Optimum doses of statins, which have demonstrated undisputed efficacy in the treatment of hypercholesterolaemia in clinical trials, are insufficiently used.[104]

However, as LDL-C goals in treatment guidelines have been reduced, it has become apparent that a significant number of patients still do not reach LDL-C target levels, even with high dose statin therapy. Additionally, higher more optimal doses of statins may not be used routinely in practice due to concerns over safety and the need for multiple dosage adjustments. In general, each dose doubling results in a 6% reduction in LDL-C. However, high doses can be associated with an increase in either hepatic or muscle toxicity.

This failure of treatment to achieve lipid management goals in clinical practice has made lipid-altering drugs an area ripe for the development of novel treatments.[105] New drugs that can be used in conjunction with statins, as well as new 'super' statins that are more efficacious for those with the worst lipid profiles, have been introduced. The variety of reasons that may underpin the lack of achievement of optimal lipid profiles in the majority of CVD patients in Europe may be ameliorated by such newer therapies.

New therapies target cholesterol more broadly than the traditional statins. Traditionally, statins have worked on the liver to inhibit cholesterol production, while new cholesterol absorption inhibitors work on lowering the absorption of dietary and biliary cholesterol by the intestine, from where cholesterol is absorbed into the bloodstream.

The cholesterol absorption inhibitor ezetimibe has been used successfully in clinical trials in conjunction with statins and has produced greater improvements in lipid profiles. Co-administration of ezetimibe with a statin has been shown to be more effective than statin monotherapy in lowering LDL cholesterol and improving other lipid parameters, and has allowed a greater number of patients to achieve treatment goals. This represents a new approach to lipid management and should assist in its clinical application.[106] Ezetimibe may be useful in the management of patients who respond poorly to, or are unable to tolerate, statins.[107] One study in Germany, Norway and Spain showed that between 40% and 76% of diabetic patients who had failed to achieve their lipid goals with statin treatment would be able to do so with co-administration of ezetimibe, representing an additional absolute 14% who will be able to reach their goal.[108] Another study found between 9.8% and 16.1% reduced risk for CHD patients with co-administration of ezetimibe,[109] and a further study observed a 12-21% further reduction of LDL cholesterol with statins and ezetimibe combined.[110]

Studies in the United Sates as early as 2001-2002 have shown that monotherapy with ezetimibe achieved maximum cholesterol lowering doses at between 10mg and 20mg daily. They have also established that co-administration with 10mg of ezetimibe together with a starting dose of a variety of statins produced a reduction in cholesterol levels equivalent to that seen with an eight-fold higher statin dose in phase II trials.[111]

In addition, new more potent statins have been developed, such as rosuvastatin and pitavastatin, which have been shown to reduce LDL cholesterol effectively at relatively low doses. In the future, agents combining statins and nicotinic acid may produce greater LDL reduction.[112] Rosuvastatin can produce reductions in LDL cholesterol of up to 55%, through which 80% of patients would reach European LDL treatment targets at a dose of 10mg/day. Rosuvastatin has been shown to produce significantly greater reductions in LDL-C levels compared with atorvastatin, simvastatin, and pravastatin, and allows more patients to meet lipid goals.[113]

Possible future directions may include both more combination therapy or higher doses of monotherapy, and various studies have focused attention on one or the other as the more likely scenario. Combination lipid-lowering therapies are of particular relevance to older populations, especially where there is a prevalence of metabolic syndrome as a target for secondary intervention. Regimens involving statins in concert with niacin, fibric-acid derivatives, or bile acid resins may be increasingly required. Such regimens may facilitate superior efficacy and lower risk of adverse events compared with higher doses of monotherapy.[114]

Current guidelines might result in under treatment and new guidelines from the Joint European Societies are expected that will contain treatment targets of 2mmol/l and 4 mmol/l for LDL and total cholesterol respectively. This may result in larger numbers of people receiving lipid lowering therapy in Europe.[115] Both rosuvastatin and pitavastatin may also have a higher potency to lower triglycerides and raise HDL cholesterol, compared to traditional statins.[116] It has been suggested that use of a more efficacious statin is preferable to combination therapy because it may be more effective, cost effective and simple for the patient.[117] Several studies have demonstrated that the most efficacious statins are the most cost-effective in terms of patients achieving their recommended LDL-C goals.[118] Use of more efficacious doses may result in cost savings through fewer GP visits and a reduction in laboratory costs. In the ACCESS trial in the United States, the extent of LDL-C reduction at the initial dose of statin treatment correlated strongly with the proportion of patients who maintained LDL-C goals.[119]

Options for improving lipid management include dose titration, combination therapy or prescribing a more efficacious statin. LDL-C reductions are generally modest when patients' current statin dose is titrated.[120] Yet because the principal barrier to achieving cholesterol treatment goals appears to be the failure of prescribers to titrate statin therapy to a dose sufficient to achieve goals, both combination therapy and more potent statins present treatment options that directly challenge the nature of current treatment failure. New therapies represent a significant improvement in ease of use for those requiring above 10mg doses. Rather than up-titration to 20, 40 and 80mg, co-administration with ezetimibe at 10mg has been shown to achieve the greater reductions in LDL cholesterol that require much higher doses of statins. Dual inhibition via co-administration of ezetimibe with a statin provides the superior efficacy required to get patients to a lower LDL-C level.[121]

New therapies therefore have the potential to overcome one of the principal barriers to cholesterol goal attainment, which is the compliance with treatment regimens by patients and the continuing need for management through up-titrations by physicians. A number of studies have found that most patients who begin treatment with a statin remain at the initial dose.[122] Consequently lipid management strategies that reduce the need for dose titrations offer considerable advantages.[123] New therapies may considerably assist clinicians in achieving recommended LDL-C and HDL-C levels for their patients.[124] The new therapies should enable a larger number of patients to achieve more ambitious cholesterol goals, thereby reducing the risk of cardiovascular events,[125] creating cost savings elsewhere in the health care system.[126]

New therapies are also focusing on some higher risk groups, including those with diabetes and metabolic syndrome. According to one Glasgow study, while statin therapy reduces their risk, their absolute risk still remains higher than in other individuals and:

"There is a clear need to target other aspects of lipoprotein metabolism, notably low HDL-C and hypertriglyceridaemia, to further reduce CHD risk. Combining statin therapy (targeting LDL-C) with interventions that also modify low HDL-C and elevated triglycerides could be a useful strategy to optimise CHD risk reduction… this European Consensus Panel recommends the combination of nicotinic acid and a statin, together with lifestyle modification, as a useful strategy to lower CHD risk in patients with diabetes and metabolic syndrome."[127]

More effective treatment through better patient compliance with regimens as well as more effective therapies have the potential to save on the costs of the treatment of coronary events in secondary care. The financial burden of CVD is decreased by prevention of coronary heart disease. Part of the costs of statin therapy can be covered in every situation by cost savings through the avoidance of coronary heart disease.[128]

The benefits of combination therapy or more effective statins to overcome some of the hurdles in goal attainment by patients ought to have a real influence on the cost effectiveness of lipid lowering therapies in the years to come.

Cardiovascular disease and EU policy

As the role of the European Union in the health of its citizens expands, the importance of cardiovascular disease cannot be overlooked. CVD represents one of the most widespread areas of ill health and mortality

amenable to effective treatment, as well as one of the most stark areas of inequality between European countries and regions and a particular gulf exists between the new member states of Central and Eastern European (CEE) and Western member states.

The Commission Programme of Community action in the field of Health and Consumer Protection 2007-2013, states that there is an EU role to contribute to reducing the incidence of major diseases such as CVD, through specific actions, including support for secondary prevention through screening and early detection.

The Cork Health Council of June 2004 focused specially on CVD as a modern health scourge across the EU. The Council invited the Commission to:

"consider the identification of best practice guidelines, in consultation with Member States, to enhance…prevention policies and programmes";

"examine the economic cost of cardiovascular disease against the improved health status arising from a comprehensive public health strategy";

"study ways of promoting better cardiovascular health";

"consider bringing forward further proposals on health determinants of major importance for the promotion of cardiovascular health."

Current predictions suggest that in 2020 CHD will remain the leading cause of disablement (calculated by disability-adjusted life years, DALYs).[129] It has been calculated that if all forms of major CVD were eliminated, life expectancy would rise by seven years.[130] The potential to improve life expectancy in the CEE countries by targeting cardiovascular disease will clearly be greater still. Acting on the major CVD risk factors has the potential to contribute substantially to the improvement in quality of life and life expectancy of European citizens. Management of cholesterol in those with elevated cholesterol is one of the principal means of achieving this goal. Indeed acting on cholesterol appears to have greater potential to further reduce coronary heart disease mortality rates because CHD mortality it is reduced more by a 1% reduction in cholesterol than by a 1% mean reduction in blood pressure.[131] It may also be that the principal gains from smoking cessation have already been realised in the period of major reductions in smoking prevalence from the 1970s onwards.

In the context of comprehensive guidelines for the prevention and treatment of CVD at the European level, as well as the widely documented failure of such guidelines to be adequately implemented in clinical care across all EU member states, Europe's institutions have an unprecedented opportunity to act to prioritise the prevention of cardiovascular disease, which remains the greatest health scourge for European citizens, across member states.

Methodology

This paper is a review of the substantial literature produced around cholesterol management and the use of lipid-lowering medications in European countries. It draws principally on academic literature in journals, as well as on some literature produced by research institutes, governments and other relevant organisations. Key word searches of PubMed/MEDLINE were undertaken, with supplementary searches in the International Bibliography of the Social Sciences (the IBSS) and Google Scholar. The literature search was supplemented, as appropriate, with targeted searches of international and national institutions. Principal search terms used were: 'cholesterol', 'cholesterol risk', 'cholesterol treatment', 'cholesterol management', 'cholesterol risk factors', 'new cholesterol therapies', 'cholesterol absorption inhibitors', 'statins', 'statin use' / 'use of statins', 'demographics', 'age-profile', 'ageing population'. Additional search terms were combined with these to reduce the hit rate where necessary, including: 'population', 'cost effectiveness', 'burden of disease', 'avoidable mortality', 'primary / secondary prevention', 'impact of statins' 'prescription of statins'. Named countries, institutions, organisations and publications were sometimes used to narrow searches further where necessary. Further references and materials were identified through references and bibliographies of search material found, as well as through 'related articles' links on the search engines.

Notes

CHOLESTEROL: THE PUBLIC POLICY IMPLICATIONS OF NOT DOING ENOUGH

1 Source: European Heart Network

2 J L Y Liu1, N Maniadakis, A Gray and M Rayner, *The economic burden of coronary heart disease in the UK*, *Heart* 2002;88:597-603 – available at: http://heart.bmjjournals.com/cgi/content/full/88/6/597

3 Source: U.S. Census Bureau, Population Division, International Programs Center – available at: http://www.census.gov/ipc/www/idbpyr.html

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A COMPREHENSIVE REVIEW OF THE EXISTING LITERATURE ON CHOLESTEROL MANAGEMENT

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