6.3   Ischaemic heart disease

See Background Paper 6.3 (BP6_3IHD.pdf)

Introduction

This chapter addresses cardiovascular disease (CVD) with a focus on the development, justification and evidence for the polypill in the secondary prevention of ischaemic heart disease (IHD). The reason for this is that the 2004 Priority Medicines Report highlighted this as a priority, leading to significant research funding being invested in this area, including the funding of two large-scale clinical trials. One of these studies (the UMPIRE trial) has since reported positive results, as outlined in more detail in Background Paper 6.3.

This report updates the information on this topic and therefore continues to focus on secondary prevention among patients who have already suffered a cardiovascular event. The majority of such patients have IHD, but a significant minority have cerebrovascular disease or peripheral vascular disease.

In addition to secondary prevention with the polypill, a number of other pharmacological approaches to prevention and treatment of IHD will need to be researched in order to provide more effective, safer and individualized intervention strategies. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; and regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD.

Background

The 2010 Global Burden of Disease Study reported that, in line with global trends, the largest single cause of death in the combined regions of Central, Eastern, and Western Europe was IHD (26.6% of all deaths), followed by cerebrovascular diseases with 11.0% of the total number of deaths.[1] For the world, IHD accounted for 13.3% of mortality again followed by stroke with 11% of global mortality. In 2010, in Europe, IHD accounted for 13.8% of the total European disease burden (DALYs).[2] For the world the equivalent figure was 5.2%. (See Table 5.8 of the Background Paper.)

Fifty-seven per cent of CVD deaths (19% of global deaths) can be attributed to eight risk factors associated with poor diet and low rates of physical activity: high blood pressure; high blood glucose; physical inactivity; overweight and obesity; high cholesterol; and low fruit and vegetable intake.[3] The 2010 Global Burden of Disease Study reported that the two leading risk factors for global disease burden overall were high blood pressure (9.4 million deaths and 7% of global DALYs) and tobacco smoking, including second-hand smoke (6.3 million deaths and 6.3% DALYs), both

of which are key factors in increasing the risk of CVD. In Europe, the leading risk factor was also high blood pressure, with smoking ranked either second or third (depending on the region of Europe).

Studies have shown that adherence to lifestyle guidelines advocating moderate physical activity, a cardio-protective diet and abstinence from smoking can reduce the incidence of CVD by more than 80% compared to the rest of the population. However, studies have also shown that neither the general population nor (more surprisingly) people with established CVD typically adhere to these recommended guidelines.

Evidence for the effectiveness of blood pressure lowering, cholesterol lowering and anti-platelet medications in preventing both initial and subsequent cardiovascular events is compelling, with hundreds of thousands of patients analyzed in meta-analyses and reviews over the last 10 years. Although most people with established CVD in high-income countries have been started on recommended medications, significant numbers of people in high-income countries [4,5,6] and even larger numbers in low- and middle-income countries either do not receive or do not remain adherent to these treatments in the long term[7,8,9] (see Figure 6.3.1).

Figure 6.3.1: PURE study: Number of drugs* taken by individuals with established cardiovascular or cerebrovascular disease by country economic status.
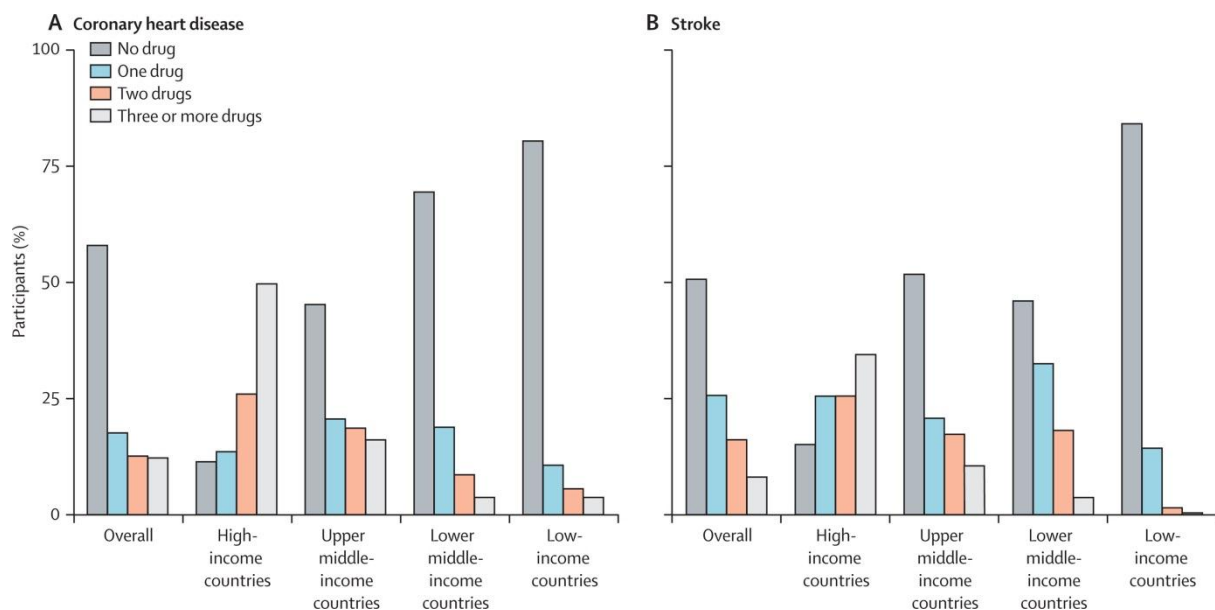
Source: Yusuf S et al. *Lancet*, 2011[9]

Note: *For coronary heart disease (A), drugs counted were aspirin, β blockers, ACE inhibitors or ARBs, or statins. For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (e.g., β blockers, diuretics, and calcium-channel blockers). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.[9]

Within Europe, the EUROASPIRE III study[10] showed that the majority of coronary patients who required blood pressure lowering and lipid-lowering medications were

not receiving them on a long-term basis; and if patients were receiving them, they were not reaching their blood pressure and lipid targets, suggesting either poor adherence by the patient or inadequate prescriptions by physicians. Various factors may underlie the suboptimal treatment of high-risk patients, such as the need for doctors to navigate complex guidelines, low continuation rates by patients, inequities in health care, and resistance to costs by both doctors and patients.

Practical and affordable approaches are needed to close these treatment gaps. Combination pills or 'polypills' may have a role to play in closing these treatment gaps in ischaemic and cerebrovascular disease, and their use has been advocated for more than a decade. [11,12,13] The use of a polypill containing off-patent generic medicines would reduce the complexity, number and costs of medication regimens and could potentially improve adherence and reduce the number of cardiovascular events.

Developments since 2004

The 2004 Priority Medicines Report[14] strongly recommended that the EC should fund research into the development and testing of combination pills in secondary prevention of CVD. Since then, multiple short-term trials have been conducted on the use of various polypills compared with either a placebo or no treatment. While many of the patients involved in these trials suffered from IHD, some of the patients included were suffering from cerebrovascular disease. These trials have shown that the short-term reductions in CVD risk factors are of approximately the size expected from the individual agents, after taking into account loss to follow-up and non-adherence. Following on from these studies, the EC FP7-funded "Use of a multidrug pill in reducing cardiovascular events" (UMPIRE) trial was the first long-term trial reported that tested the impact on adherence to recommended medicines of a polypill in patients at highest risk of CVD. This 2000-patient randomized controlled trial compared the polypill to usual care and showed improvement in adherence of one-third, which corresponds to 4.6 patients needing to be treated with the polypill in order to gain one additional adherent patient. Reductions in SBP of 2.6 mmHg and LDL-cholesterol of 0.11 mmol/L in the polypill group were also seen and these were sustained throughout follow-up (see Background Paper 6.3).

Figure 6.3.2: Systolic blood pressure and LDL-cholesterol by treatment group over follow-up in the FP7-funded UMPIRE trial*
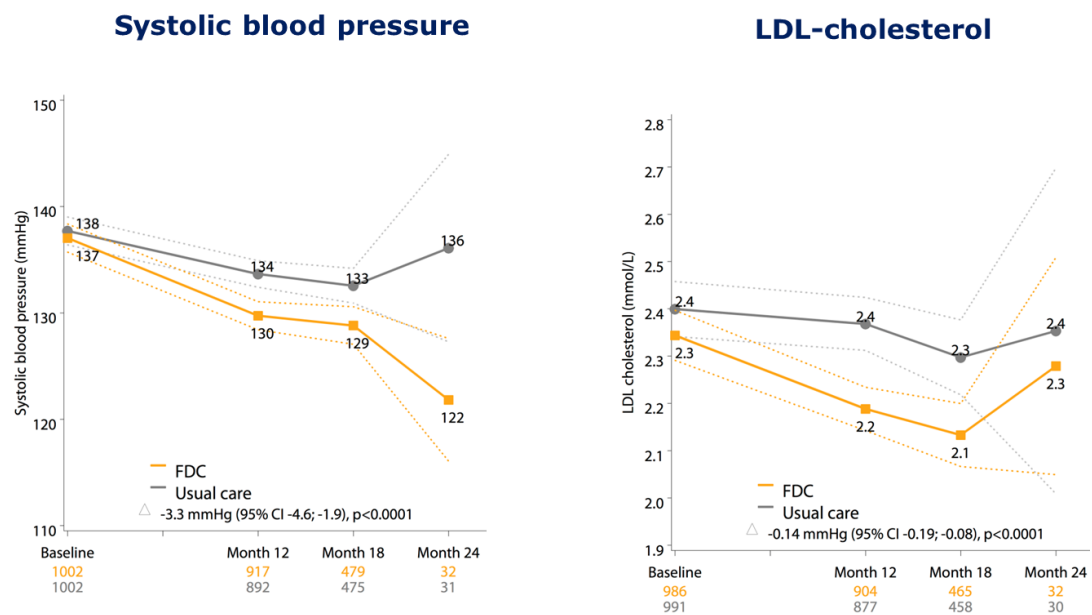
Source: personal communication, S Thom

Note: * Systolic blood pressure (panel A) and LDL-cholesterol (panel B) values shown at baseline, during follow-up and at end of study (EOS) in the polypill and usual care groups.

These improvements were seen even though the trial population had higher than average usage rates for the individual classes of medication at baseline and the "newer" statins (atorvastatin or rosuvastatin) comprised over 70% of the statins prescribed in the usual care comparison group. Even larger benefits were seen in the small group of patients who were not adherent to all three medication classes at baseline.

Remaining challenges

The recommendations of the 2004 Priority Medicines Report have led to advancements in polypill research over the past nine years and demonstration of the effectiveness of such a strategy in improving adherence. However, there is now a need for committed funding to assess the size of the benefits and risks of implementing a polypill strategy on a large scale.

The scale of funding required to further develop the evidence base that has already been achieved in the area of polypill research is unlikely to be committed to by major pharmaceutical companies as their focus lies in the development of newer patent-protected products which are likely to have higher profit margins. Meanwhile, generic pharmaceutical companies do not have the research budgets that would enable them to invest in such large-scale clinical trials. Major public funding commitment is therefore needed to ensure that what has been achieved so far is built upon and to provide the evidence necessary for regulatory approval in both Europe

and worldwide. The potential benefits (both in economic and health gains) of the widespread use of polypills for secondary prevention are enormous.

Research needs related to the polypill

Many of the factors involved in scale-up are system-level (including training, education, task shifting, and electronic decision support), and many of the patients, clinicians and environments most in need of adherence-improving strategies are those least likely to join a standard clinical trial. Therefore the area would be well served with a very large implementation trial or a series of sister trials. The UMPIRE trial showed improvements in risk factor reductions that would be expected to result in a 10% to 15% reduction in cardiovascular events in that trial population. However, that benefit might be at least twice as great among a group not already taking all the indicated medications. This would require trials involving tens of thousands of participants in order to reliably assess cardiovascular outcomes and assess consistency in different patient groups and in different health systems.

Other issues that require further research in this area (as part of the above-mentioned implementation research or as separate trials) include:
- Potential additional benefits from newer agents now off-patent
- Careful attention to new evidence on the side-effects of statins
- Number of dose versions
- Low-dose versus high-dose polypills
- Specific populations (e.g. diabetes polypill, hypertension polypill)
- Use in acute care (e.g. immediately after a heart attack versus use in chronic care).

Other research needs related to ischaemic heart disease.

As mentioned in the introduction, there are many other areas of research into pharmacological approaches to IHD that may need to be supported. These include the development of new lipid-lowering drugs; pharmacological means to address novel mechanistic concepts of vessel wall damage and protect against conditions such as chronic inflammation and local angiogenesis; as well as regenerative medicine/cell therapy approaches. Similarly, new pharmacological treatment strategies need to be developed for heart failure and arrhythmias, frequent consequences of IHD. While these areas have not been investigated in the background paper or in this chapter, opportunities for research may exist that are not being addressed by the pharmaceutical industry.

References

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