

Ischaemic Heart Disease

What is ischaemic heart disease?

Ischaemia is a shortage of blood-borne oxygen and fuel to an organ due to constriction or blockage (thrombosis) of the blood vessel feeding it. Ischaemic heart disease (IHD), or coronary heart disease, has two main forms: angina and myocardial infarction (MI). Ischaemia is usually due to the build-up of plaque and can affect the brain (stroke) or muscular tissue such as the legs (peripheral vascular disease), as well as the heart.

A heart attack, or MI, results when the blood (and hence oxygen) supply to part of the heart is suddenly reduced or stopped. Because the work load on the heart is extremely high, heart muscle deprived of oxygen soon begins to die. MI is most often caused by a blood clot lodging in one of the major arteries supplying the heart. A loss of normal heart rhythm with subsequent circulatory collapse is a significant risk in MI and rapid hospitalisation is required.

Angina is a consequence of a constriction rather than a blockage of an artery and may be due either to atherosclerosis or, less commonly, arterial spasm. In many people, it is stable over years and only occurs on exertion or exposure to cold, or after a heavy meal; in others, however, it progresses and may occur even at rest. This latter situation is called unstable angina and is serious, as it may be a warning of an impending heart attack.

Who does IHD affect?

It is estimated that over 1.8 million people in the EU have a heart attack in a given year and that approximately 8.5 million suffer from angina. In 1998, IHD is estimated to have caused at least 800,000 deaths in the EU. Angina and MI are uncommon below the age of 45, except where there is a family history of heart disease, but thereafter, incidence rises with age. Some eight per cent of men and seven per cent of women in the age range 65-74 experience angina in a given year and for those aged 75 or over, the corresponding figures are 11 per cent and ten per cent respectively. Between 40 and 50 per cent of patients experiencing a heart attack die within 20 days; in about 30 per cent of cases the patient dies before reaching hospital.

The risk of IHD can be reduced by modifying lifestyle choices (diet, exercise, not smoking), using medication to lower cholesterol and reduce plaque formation, maintaining a normal blood pressure, and through prophylactic use of anti-platelet medicines. People with diabetes are especially at risk and determined efforts to normalise blood sugar are necessary.

Ischaemic Heart Disease occurs when a blood vessel of the heart is too narrow or is blocked. Research has led to successful treatments such as: medicines that stop blood clotting, reduce high blood pressure and lower cholesterol. Researchbased companies are working to develop new agents to try and prevent the tragedy of people dying with the condition called 'Europe's numberone killer'.



Present treatments:

Treatment of stable angina involves management of acute symptoms by giving fast-acting aerosolised or sublingual glyceryl trinitrate (GTN), and longer-term prophylactic treatment with low-dose aspirin and an agent such as a nitrate or a nitrogen oxide-releasing substance, a beta-blocker, or a calcium antagonist, of which there is a large selection available. Slow-release forms of these preparations are often used, or transdermal patches in the case of GTN.

Surgical treatment may be considered instead of long-term medication and may be preferable in elderly patients. Angioplasty - the use of an inflatable catheter to widen narrowed arteries - and coronary artery bypass grafting (CABG) are the interventions used.

There are two major aspects in the management of MI - firstly, prevention and, secondly, emergency therapy if a heart attack occurs. In practice, prevention tends to mean 'secondary prevention' i.e. prevention of another heart attack once one has already occurred. Thus it represents an attempt to prevent further worsening of already established heart disease. Primary prevention consists both of identifying and treating those at especially high risk of IHD, e.g. because of an inherited predisposition, and educating and motivating the wider public to reduce as far as possible the lifestyle factors linked with the development of IHD.

Prevention of blood clot formation and plaque deposition inside blood vessels is a vital approach to reducing heart attacks and angina. Large studies showed that cholesterol-lowering medicines effectively reduce rates of death, stroke and coronary events when used for secondary prevention. At least part of this effect is due to their ability to stabilise existing plaques, as well as lowering cholesterol to prevent the formation of new plaque.



More recently, studies have shown that an angiotensin converting enzyme (ACE) inhibitor can significantly decrease stroke, MI and cardiovascular death rates and can also inhibit or reverse left ventricular hypertrophy (LVH), a thickening of the heart muscle in response to raised blood pressure that may lead to heart failure in patients with IHD. A diuretic and an angiotensin 2 receptor blocker (ARB) have been shown to be similarly effective against LVH. Thus, medical treatment for secondary prevention after MI might well involve taking a statin, a beta-blocker, an ACE inhibitor (or an ARB or diuretic) and low-dose aspirin.

Emergency treatment of a heart attack or unstable angina involves measures in the first few hours to dissolve the blood clot that is causing ischaemia, re-establishing blood flow to the heart, to prevent or reverse arrhythmias, and subsequently to prevent formation of new clots. Clot-dissolving agents, which transform plasma-derived plasminogen into clot-dissolving plasmin are given intravenously over a period of time while the heparin derivatives and anti-platelet agents are given to prevent new clot formation.

What's in the development pipeline?

Several new compounds are in early development that enhance production of nitric oxide in muscle cells, bringing about a relaxation of blood vessels that reduces resistance to blood flow and hence the work done by the heart. This in turn raises the threshold at which angina begins to be felt. An anti-platelet agent, already approved for use after a stroke or MI, has also shown benefit in unstable angina, reducing the risk of MI, stroke and death by about 20 per cent. Scientists are developing a gene therapy approach in an attempt to stimulate the growth of new blood vessels around areas of blockage in chronic angina.

Increasingly, people with unstable angina are undergoing angioplasty. This may include placing a stent (a small wire tube) inside the affected artery to keep it open.

In more than ten per cent of cases, this stent later becomes blocked. There is clinical development of impregnated stents that can inhibit this process.

Paradoxically, the re-establishment of blood flow in ischaemia can lead to an inflammatory reaction called reperfusion injury. Activation of the complement system which is part of the body's defence against infection has been shown to be involved in this. Research is underway to study a complement-inhibiting antibody fragment in angioplasty and CABG to see if this can reduce heart muscle damage. Patients undergoing CABG may also benefit from compounds known as sodium-hydrogen-exchange inhibitors.

Medical treatments for secondary prevention of MI and other cardiovascular events have now reached the point where advances are mostly being made through the optimal use of existing medications, rather than from the development of further new compounds. This emphasis on better understanding the capabilities of existing medications does not, however, preclude new developments.

An anti-platelet agent of the GP 2b/3a type, that has been shown to be effective in preventing MI after stent insertion, and which is authorised for prevention of MI in patients with unstable angina, is now being developed for use in the treatment of acute MI. Other developments include a new plasminogen activator in Phase 3 trial as an injectable clot-buster to be given rapidly in the early stage of MI. Also underway is a trial of an anti-platelet immunoglobulin being studied for its ability to reduce blood clot formation in people being treated for acute MI. Furthermore, there is research on an endothelin receptor antagonist in Phase 2.

The longer-term future:

Cardiovascular disease has been an area of intense new product development by the pharmaceutical industry over much of the past 40 years and the range of medications now available is impressive. Nevertheless, treatment of acute ischaemic conditions is still associated with significant mortality and morbidity, some of it related to the period of time before intensive care treatment can be started. Research-based companies are continuing to devote large resources to improving therapy in the battle against Europe's number one killer.

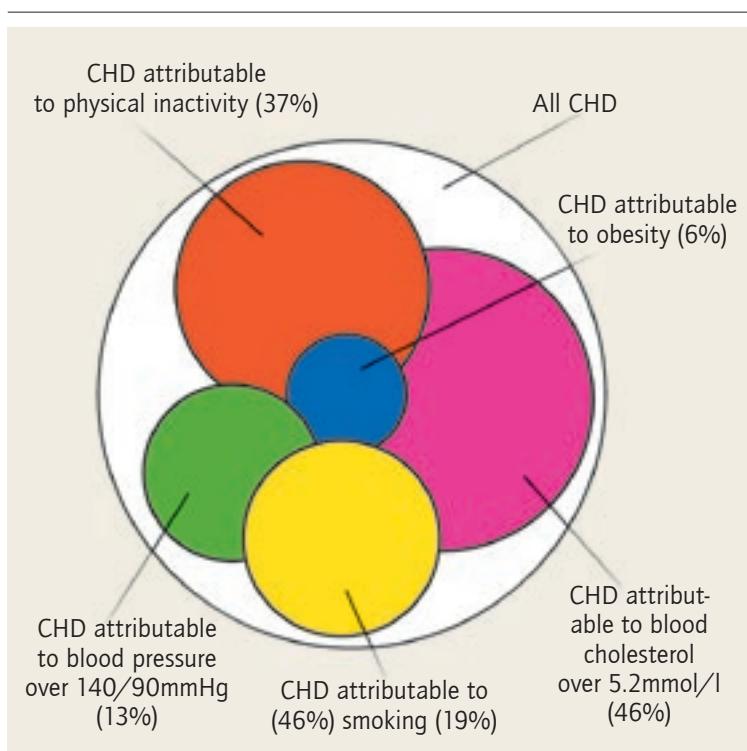


FIGURE 1: Proportion of all CHD attributable to five different risk factors
Courtesy of the National Heart Foundation

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