Coronary artery disease

Coronary artery disease remains one of the leading causes of mortality in the UK, accounting for more than one in four of all deaths.[1] Since the prevalence of coronary artery disease increases with age, as our population grows older a larger number of people face living with this disease and its consequences.

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The pattern of coronary artery disease is changing. The overall mortality rate from cardiovascular disease has consistently declined for the past 50 years. This reduction may be explained in part by control of blood pressure and the introduction of lipid-lowering medication—although the downward trend predates these interventions. Recent research also suggests that the severity of myocardial infarction is declining,[2] which perhaps reflects changes in acute treatments, including antiplatelet therapies. The implication of these changes is that we have a growing burden of chronic coronary artery disease.

The underlying pathophysiology is loss of patency of epicardial coronary arteries, which results in myocardial ischaemia. Atherosclerosis is by far the most common cause, with deposition of fatty plaques in the arterial wall resulting in luminal occlusion: over time chronic stable angina develops. Acute coronary syndrome refers to presentation with sudden total or sub-total coronary artery occlusion. If there is associated myocardial necrosis, the diagnosis is of myocardial infarction.

When a patient presents with acute coronary syndrome, coronary angiography is usually performed to define coronary anatomy. Frequently, presentation is insidious, or with less specific symptoms—diagnosis of coronary artery disease therefore relies on clinical suspicion and diagnostic imaging. CT has recently been used to enhance risk stratification in suspected coronary artery disease, through the detection of coronary calcium (CT calcium scoring), and it offers an alternative to invasive angiography to assess coronary artery stenosis with CT coronary angiography.

Management of coronary artery disease falls into three broad categories:

- restoration of vessel patency;
- pharmacological alteration of the disease process;
- control of symptoms.

Recent clinical evidence has led to a change of emphasis in these treatment options. If occlusion is total, urgent restoration of blood flow is imperative with primary percutaneous coronary intervention offering the best outcome if available promptly. By contrast, if luminal obstruction is fixed and presentation less acute, the benefit of percutaneous intervention is uncertain.

Percutaneous coronary intervention targets only the presenting obstruction, not the underlying pathophysiology, thus all patients should receive disease modifying agents with more recent discussion focusing on primary prevention. Finally, both percutaneous intervention and disease modification may palliate, but often do not remove symptoms of coronary artery disease. Until recently control of symptoms has received little attention; however, new therapeutic strategies are becoming available.

Diagnosis of coronary artery disease

Diagnosis and imaging

If coronary artery disease is suspected, management is based on assessment of disease severity, which falls into two areas. Functional assessment consists of characterisation, including clinical history, type and stability of symptoms, and degree of limitation. This is supported by objective assessment of myocardial response to exercise (provided by exercise testing), myocardial perfusion imaging, and in some cases, stress echocardiography. If functional assessment indicates that significant coronary artery disease is likely, definition of the anatomical substrate has usually required invasive coronary angiography.

Non-invasive visualisation of coronary anatomy has become possible through cardiac CT angiography, which, like cardiac catheterisation, uses contrast to define coronary anatomy and can reliably rule out significant coronary artery disease in many patients. Multi-slice scanners, which are most commonly available, require a slow heart rate to allow adequate time for image capture. Additionally, the presence of significant coronary calcium can hamper assessment of stenosis, thus at present CT coronary angiography tends to be restricted to younger patients at intermediate risk of coronary artery disease in whom a rule-out test is most helpful. Rapid technological advances are addressing these limitations.

CT calcium scoring refers to the detection and quantification of coronary calcium deposits giving an age-corrected calcium score. Although an increased calcium score has been shown to be closely associated with subsequent development of coronary artery disease[3,4] the role of CT calcium scoring in the assessment of cardiovascular risk has yet to be fully clarified.[5]

The holy grail of cardiac imaging—the simultaneous definition of coronary artery anatomy and cardiac function remains elusive. Although MRI and positron emission scanning techniques are being developed, both are currently available in specialist centres only.

Biomarkers

The central feature of coronary artery disease is that acute events are unpredictable. Inflammation is known to accompany instability and several studies have found an association between increased cardiovascular risk and inflammatory markers such as fibrinogen, D-dimer, and homocysteine.[6–9] Although their ability to improve vascular risk prediction beyond thorough assessment of conventional risk factors has been questioned, this may not apply to all age groups. Elevated homocysteine levels have recently been shown to be superior to conventional Framingham risk assessment in predicting cardiovascular disease in healthy elderly individuals.[10]

Following publication of the results of the JUPITER study[11] attention has focused on C-reactive protein. This large randomised controlled trial selected apparently healthy individuals (without hyperlipidaemia) in whom the inflammatory marker, highly sensitive C-reactive protein, was elevated. Over a median follow-up of 1·9 years there was a highly significant 43% reduction in cardiovascular events in those taking rosuvastatin 20 mg compared with placebo. Although the relative reduction in events was large, the absolute reduction in mortality was only 1·2%. This important result is the subject of considerable discussion, particularly from a public-health perspective. In effect, 125 patients would need to be treated for 2 years to prevent one myocardial infarction, stroke, or death from cardiovascular causes. Furthermore, on the basis of analysis of JUPITER's findings, one in five middle-aged and older adults in the USA would become eligible for statin therapy for the primary prevention of cardiovascular disease.[12]

Debate that statins might have a pleiotropic effect (ie, a benefit beyond their ability to reduce serum LDL cholesterol levels) is supported not only by the results of the JUPITER study, but also by two recent, inconclusive, studies of ezetimibe, a lipid-lowering agent that inhibits gastrointestinal absorption of cholesterol. In both studies, the combination of simvastatin and ezetimibe produced a greater fall in LDL-cholesterol levels than simvastatin alone.

However, there was no difference in the primary endpoint of arterial intima-medial thickness in patients with familial hypercholesterolaemia in the ENHANCE Study,[13] nor in the composite primary endpoint of aortic-valve and cardiovascular events in patients with mild-to-moderate aortic stenosis in the SEAS Trial.[14]Although the SEAS study found a 20% reduction in a secondary endpoint of ischaemic events, uncertainty exists over a significant increase in the risk of cancer seen in that study. IMPROVE IT, a study of the same treatment regimen in patients with recent acute coronary syndrome, is currently underway.[15] This will hopefully address both the safety and efficacy concerns.

Treatment of coronary artery disease

Acute coronary syndrome describes the emergent presentation of either partial or complete coronary luminal occlusion. This results from rupture or erosion of unstable (or vulnerable) plaque. Exposure of the thrombogenic plaque contents precipitates rapid platelet adhesion with organisation of thrombus in a process compared to the striking of a match.

Presentation with myocardial necrosis (cardiac enzyme elevation) in the absence of ST elevation is referred to as a non-ST elevation myocardial infarction and usually reflects sub-total coronary artery occlusion. By contrast, complete occlusion is followed rapidly by

myocardial necrosis and typical ECG changes of an ST elevation myocardial infarction. Total coronary artery occlusion mandates urgent attempts at restoring patency, either with thrombolysis or immediate angioplasty and stenting (primary percutaneous coronary intervention), which is increasingly recognised as superior to thrombolysis, both for safety and efficacy.

Optimum benefit from primary intervention is seen if done within 90 minutes.[16] Although such a target may be practical in urban areas, thrombolysis may be advantageous if administered within 15–20 minutes of onset of pain, in areas where access to primary intervention may take more than 90 minutes. A hybrid option of facilitated precutaneous intervention, whereby thrombolysis is given and intervention pursued semi-urgently has also been studied;[17] however, the current National Strategy has emphasised the need for greater access to round-the-clock centres capable of delivering primary percutaneous intervention to all.[18] The role of thrombolysis in rural areas currently seems unclear.

The benefit of restoring coronary artery patency after total occlusion is rapidly lost. Thus even after 3 days, attempts to open an occluded artery may be associated with harm.[19]

Chronic stable angina

By contrast with acute coronary syndrome in which plaque rupture precipitates sudden thrombus aggregation, chronic stable angina is a relatively static process. Progressive accumulation of atherosclerotic plaque results in gradual loss of coronary artery lumen. The patient presents either with typical angina (or occasionally dyspnoea) when the increased oxygen demand of exertion cannot be met by enhanced blood flow across the fixed stenosis. Pursuit of the idea that a better lumen equated with a better outcome led to the development of angioplasty, which initially involved dilation of the stenosis by the insertion and inflation of a balloon. Restenosis occurred in up to 40% of cases, due to the direct trauma to the arterial wall, thus this procedure was subsequently enhanced with the deployment of coronary artery stents, which, by providing metal scaffolding, sought (with only moderate effect) to reduce restenosis, which then tended to recur at the stent margins.

The solution appeared to be coating the stent with antiproliferative and antimitotic agents such as sirolimus and paclitaxel (drug-eluting stents) with the goal of suppressing the normal proliferative response to arterial wall trauma. While successfully reducing restenosis to about 6%, the drug coating also inhibits re-endothelialisation of the stent. Thus, patients treated with drug-eluting stents need to take aspirin and clopidogrel for at least 1 year after surgery.

Recent reports have raised concerns over late thrombosis when dual antiplatelet medication is stopped. Additionally, prolonged antiplatelet therapy increases the risk of gastrointestinal bleeding (possibly more so in older patients) and poses problems if therapy needs to be stopped for surgery.

Until recently the use of coronary artery stenting, and particularly drug-eluting stents, had expanded rapidly on the basis of the assumption that longer-term outcome would improve. This has now been challenged by the COURAGE trial,[20] which compared optimum medical therapy with precutaneous intervention in a large population with objective evidence of myocardial ischaemia and significant coronary artery disease at angiography. The majority of patients received bare-metal stents, with drug-eluting stents approved for use only in the last 6 months of the trial. After 4·6 years of follow-up no significant differences were seen in the primary outcome of all cause death or non-fatal myocardial infarction. Quality of life improved significantly in both groups with a small advantage in favour of percutaneous coronary intervention disappearing after 3 years. In effect, the COURAGE study showed that aggressive optimum medical therapy was both safe and effective for patients with chronic stable angina. Only if optimum medical therapy fails to control symptoms does intervention need to be considered.

Disease modification

Optimum medical therapy as emphasised by the COURAGE study had two goals: disease modification and symptom control. Other than in the acute management of myocardial infarction, the prevention of morbidity and mortality in anyone with proven, or suspected, coronary artery disease relies on attenuation of the underlying pathophysiology through the optimum measurement and treatment of cardiovascular risk factors. A large body of recent evidence from randomised controlled trials supports the benefit of the combination of angiotensin-converting enzyme inhibitor, statin, and aspirin to deliver target blood pressure and lipid control. This should be supported by uptake of exercise, cessation of smoking, and adequate control of blood sugar. Irrespective of other interventions optimum disease modification is the fundamental component of the management of vascular disease.

Symptom control

The COURAGE study[20] clearly identifies a role for percutaneous intervention for controling the symptoms of chronic stable angina when medical treatment has failed. Yet, this area has received little attention until recently. Although calcium antagonists, β-blockers and nitrates are recommended for treating angina, there is no convincing evidence that they reduce the incidence of myocardial infarction or prolong survival. However, nicorandil, a potassium channel activator, was shown to reduce admissions to hospital because of angina.[21]

Earlier anti-anginal agents, for example nitrates and calcium antagonists, focused on vasodilation, although β-blockade is thought to reduce ischaemia both directly through sympathetic inhibition, as well as through bradycardia, which may facilitate myocardial recovery time and prolong exercise duration by delaying time to tolerated tachycardia.

Although β-blockade is effective for reducing the symptoms of angina, it is frequently either not commenced because of concerns over contraindications, or discontinued because of side-effects. By contrast, ivabradine, which inhibits the I*f* pacemaker current in the sino-atrial node, produces a pure bradycardia with few side-effects. Although currently licensed for angina, the influence on clinical outcomes remains uncertain. Despite effective heart-rate reduction when used alone or in addition to β-blockade, ivabradine failed to improve the primary endpoint in the BEAUTIFUL study[22] (cardiovascular death, admission to hospital for acute myocardial infarction, or worsening heart failure) in patients with proven coronary artery disease and systolic left ventricular dysfunction. This may reflect a confounding effect of comorbid ventricular impairment, since subsequent analyses found benefit in those with higher ejection fraction and those with a baseline heart rate of more than 70 bpm.

Given the lack of prognostic benefit with vasodilators, recent research has also focused on the cellular metabolic response to ischaemia, which has been shown to be associated with an increase in the late sodium current, resulting in intracellular calcium accumulation and possibly diastolic cellular dysfunction in myocardial ischaemia.[23] Ranolazine, an inhibitor of the late sodium current is currently licensed for the management of angina in the USA. Studies to date have demonstrated improvement of symptoms with no impact on cardiac outcome.

Conclusion

Cardiovascular medicine faces the challenge of an ageing population with multiple comorbidities. Additionally, the pattern of coronary artery disease is changing, with a decline both in overall cardiovascular mortality and severity of myocardial infarction, contributing to an increase in the prevalence of coronary artery disease, which remains a leading cause of death. The detection and prevention of coronary artery disease thus remains a priority.

Treatment of coronary artery disease has three objectives: restoration of vessel patency; pharmacological alteration of the disease process; and control of symptoms. Recent research has clarified these objectives. In the early acute phase, percutaneous intervention is increasingly the management of choice and provides prognostic benefit, but that should not distract from the benefits of disease modifying medications. For non-acute cases, optimum medical treatment, consisting of disease modification and symptom control is indicated, with percutaneous intervention available for relief of refractory symptoms. Of the objectives, control of symptoms has previously seemed a lesser priority. Coronary artery disease will become a central part of the complex pattern of disorders of the elderly.[24] To meet this challenge requires new ways to manage the symptom burden of angina.

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