# New interventions in cardiology

The last two decades have seen new treatments and techniques for managing cardiovascular disease emerge. These developments have led to a significant reduction in cardiovascular mortality and morbidity. **Drs Abhaya Gupta and Adrian Raybould** discuss how these new pharmacological approaches and interventions have altered the long-term management of cardiac conditions.

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Over the past 20 years, an improved understanding of the pathophysiology of Cardiovascular disease (CVD) has led to developments in the management of the condition. This in turn has led to a significant reduction in cardiovascular mortality, particularly amongst the middle age population.

However, the elderly have been poorly represented in clinical trials. Comprising only 16 per cent of the population, they represent a far greater proportion of those being treated for CVD. Indeed in the elderly, ischaemic heart disease is responsible for half of all deaths and a significant amount of morbidity[1]. Several treatments and interventions for CVD have been developed, and the knowledge obtained from recent clinical trials should also be incorporated into treating the elderly.

This article reviews the advances in pharmacotherapy and coronary intervention in recent years and their impact on management.

## Pharmacotherapy

### Antiplatelets

Aspirin has been established for a number of years in the treatment of atherosclerotic disease. This arises due to its property of limiting platelet activation through cyclo-oxygenase inhibition. Following atherosclerotic plaque rupture, platelets play a central role in the formation of an occlusive platelet rich thrombus. A similar role for aspirin exists following iatrogenic arterial injury during Percutaneous Coronary Intervention (PCI).

More recently clopidogrel was found to be useful in treating patients with coronary artery disease. Clopidogrel acts by inhibiting Adenosine-di-Phosphate-(ADP) mediated platelet activation and provides a platform for a two pronged dual platelet approach to inhibiting platelet activity. Clopidogrel was developed as a sister molecule to ticlopidine, which was effective in preventing thrombosis following coronary intervention but a potential for causing agranulocytosis saw it superseded by clopidogrel. The CREDO study using aspirin and clopidogrel (versus aspirin and placebo) for one year after coronary stenting resulted in a 27 per cent reduction in the combined endpoint of death, Myocardial Infarction (MI) and stroke[2].

In addition to its use post stenting, clopidogrel is also a helpful adjunctive therapy for patients with Acute Coronary Syndromes (ACS). The CURE study was a landmark trial and now most patients admitted with an ACS are being treated with aspirin and clopidogrel for six to 12 months.

The role of clopidogrel in acute ST Elevation MI (STEMI) has been less certain. However, recently, two large prospective randomised trials showed additional benefit with clopidogrel. With the publication of COMMIT[3] and CLARITY[4], clopidogrel is now increasingly being prescribed (for about six months) to patients presenting with acute STEMI along with aspirin and thrombolysis.

## IIb/IIIa antagonists

IIb/IIIa receptors exist on the surface of activated platelets and mediate platelet-platelet adhesion. Drugs inhibiting IIb/IIIa receptors are potent inhibitors of platelet activity by impeding the final common pathway of platelet aggregation. The drugs that have been used are abciximab, eptifibatide and tirofiban.

Several trials have assessed the role of these drugs in patients with ACS (unstable angina and NSTEMI)[5]. They seem most effective in those considered at highest risk (TACTICS-TIMI 18)[6] especially those with raised Troponin T and those undergoing PCI (PCI-CURE)[7]. Abciximab and eptifibatide during coronary artery stenting procedures can reduce the risk of MI, the need for urgent repeat PCI by up to 50 per cent and a reduction in mortality from two to one per cent[5]. Hence, early risk stratification is a key issue in the management of patients with ACS to identify those who may benefit from IIb/IIIa inhibitors and from early coronary intervention as per recommendations from the *European Society of Cardiology*[8] (ESC).

IIb/IIIa receptor antagonists have also been investigated as adjuncts to thrombolysis to improve patency rates in STEMI. A meta-analysis showed abciximab offered a survival advantage[9], but excess bleeding and lack of clear benefit has limited widespread use.

## Antithrombins

Low Molecular Weight Heparins (LMWH) such as enoxaparin have largely replaced unfractionated heparin in the treatment of patients with ACS. Improved bioavailability, reliable anticoagulation and lack of need for monitoring are reasons for their growth in use. A number of landmark studies provide evidence for their efficacy and safety[10]. Paradoxically, because its anticoagulant effect can be monitored, unfractionated heparin has traditionally been used during coronary intervention, but increasingly LMWH is being used and recent data supports the use of intravenously administered LMWH during PCI[11]. Bleeding complications remain the Achilles heel of antithrombotic therapy, and new agents are being studied to reduce bleeding complications whilst maintaining efficacy. The direct thrombin inhibitor bivalirudin has shown promise in this area. During PCI, this agent showed non inferiority with regard to ischaemic outcomes when compared to unfractionated heparin but had reduced bleeding complications (REPLACE-2)[12].

## Statins

From early landmark studies, statins have been widely prescribed in the primary and secondary prevention of cardiovascular events. More recent studies suggest 'the lower the better' when it comes to targeting cholesterol levels (TNT trial)[13]. Indeed, even patients considered at relatively low risk from cardiovascular events can potentially benefit from cholesterol lowering (ASCOT)[14]. Their role in treating ACS by a plaque stabilisation effect has also been suggested and indeed studies support the use of statins early in ACS (PROVE-IT)[15].

Central to their effectiveness seems to be Low Density Lipoproteins (LDL)-cholesterol reduction. It is debated as to whether, for example, an accompanying fall in C Reactive Protein (CRP) is the cause of the additional benefit or a secondary effect of LDL reduction. Nevertheless different effects between statins has led some commentators to discuss as to whether all benefits remain a class effect or individual to a particular agent. No doubt research in this area will continue to advance our understanding of the atherosclerotic process.

## ACE inhibitors and angiotensin receptor blockers

Angiotensin Converting Enzyme (ACE) inhibitors have now become important agents in the prevention of cardiovascular events, irrespective of Left Ventricular (LV) function. The EUROPA study enrolled 13,655 patients with coronary artery disease but without LV dysfunction[16]. Patients were randomised to receive either placebo or perindopril and were followed for a mean of 4.2 years. A 20 per cent Relative Risk (RR) reduction in the perindopril group supported findings of the earlier HOPE study, which used ramipril[17]. These studies support the use of these agents in the prevention of cardiovascular events regardless of LV dysfunction.

Where these agents are contraindicated or not tolerated, Angiotensin Receptor Blockers (ARBs) provide a suitable alternative. Early use, based on theoretical benefits, are now increasingly supported by evidence from clinical trials. Indeed in the setting of heart failure, there is data confirming the benefit of these agents when added to standard treatment with ACE inhibition (CHARM trial)[18].

## Aldosterone receptor antagonists

Spironolactone has been 'rediscovered' as a treatment for heart failure, and the RALES study[19] confirmed a mortality benefit when patients were treated with this agent in addition to standard heart failure treatment. This was seen in patients with severe heart failure (NYHA class III–IV). A more recently developed agent, eplerenone, has shown promise post MI in patients with documented LV dysfunction and clinical evidence of heart failure in a trial with 3,319 patients followed for 16 months[20].

## Thrombolysis

This is the gold standard and it is used for most patients presenting with acute STEMI as it has been shown in several trials to reduce mortality significantly. The mortality is reduced by 30 patients per 1,000 presenting within 0 to six hours, and to be effective it needs to be given quickly. The *National Service Framework for Coronary Heart Disease* recommends thrombolysis within 60 minutes of call to needle time[21]. The Myocardial Infarction National Audit Project monitors the care delivered to MI patients in the UK. Since 2000, the number of patients receiving thrombolysis within 30 minutes of hospital arrival has doubled on average from 40 per cent to 81 per cent.

## Coronary intervention

The first coronary angioplasty was undertaken by Gruentzig in 1977. Since then there have been significant advances in both technology and techniques, and the number of PCIs undertaken in the UK is rising exponentially. Via a peripheral artery, various devices such as balloon and stents can be delivered to treat patients with coronary syndromes. This contrasts with the use of Coronary Artery Bypass Grafting (CABG) where numbers have remained static over the past few years, despite a sharp increase in the amount of coronary angiography undertaken.

With balloon angioplasty though, restenosis rates are high and up to 40 per cent in some series. Re-narrowing of the vessel occurs as a result of a restenotic process, involving smooth muscle cell proliferation and elastic recoil of the dilated artery. Coronary stents inserted at the time of angioplasty provide a scaffold and they have reduced restenosis rates significantly by preventing recoil of the artery. Therefore, the vast majority of procedures are now carried out with stenting, with balloon angioplasty reserved for difficult areas inaccessible to coronary stents (usually small and tortuous arteries with calcification making stent deployment difficult).

With coronary artery stenting, restenosis rates are improved but they still remain unacceptably high at around 15 to 20 per cent. Coronary stents have traditionally been made from stainless steel but in an attempt to reduce these restenosis rates, they have been coated with a variety of agents. This has heralded the advent of the Drug Eluting Stent (DES), where the antiproliferative agents Sirolimus (using Cypher® stent in RAVEL and SIRIUS trials)[22] and Paclitaxil (using Taxus® stent in TAXUS-IV trial)[23] have dramatically reduced the rate of restenosis. Long-term follow up data in humans is now available for both of these stents and show restenosis rates in the order of two to five per cent[24].

These results, however, come at significant financial cost and the *National Institute for Health and Clinical Excellence* (NICE) has given guidance to where it is appropriate to use a DES[25]. Essentially they should be used where the risk of restenosis is at its highest with small diameter, long stents (<3mm diameter/ >18mm long). Other agents that have been used in coated stents include everolimus and actinomycin.

Patients undergoing PCI versus CABG have a less invasive procedure and reduced hospital stay. Hence more and more patients with two and three vessel disease, advanced age, co-morbidity can be treated by PCI rather than CABG – thereby reducing the risk of CABG related surgical complications. Modern percutaneous techniques, however, can be used before and after CABG surgery.

Whilst PCI is established for single and multivessel disease, the debate continues over the appropriate treatment of diabetic patients with three vessel disease especially with LV impairment. Left main stem angioplasty is commonly undertaken but is another area for debate.

As with other areas of medicine, the elderly have often been excluded from clinical trials of coronary intervention; and in practice, they are often denied intervention on the true or perceived belief that the risks of intervention in this age group outweigh the potential benefits. This was addressed in the Trial of Invasive versus Medical therapy in Elderly patients (TIME), whereby 301 patients over 75 years of age were randomised to receive PCI/CABG or optimal medical therapy. The results showed a higher four year mortality and more angina in patients on medical therapy alone[26].

## Implantable devices

This type of therapy has become a sub-specialty within cardiology. This has been driven largely in two areas where new data is constantly being evaluated and guidance is changing.

The first area is Automatic Implantable Cardioverter Defibrillators (AICDs). This therapy can prevent sudden cardiac deaths with multicentre trials showing that AICDs reduce mortality in high risk patients with a history of MI and LVEF <30 per cent[27]. NICE, therefore, recommends use of ICDs for secondary and primary prevention of cardiac arrest. Patients with a history of sustained Ventricular Fibrillation (VF) leading to syncope or cardiac arrest due to VF or Ventricular Tachycardia (VT) may also be suitable. These devices are expensive and not without complications – hence should not be considered in cases where sustained VT is associated with minimal symptoms or in patients with syncope of unknown cause.

Dual chamber pacing has also been shown to be superior instead of ventricular pacing in AF in improving the quality of life[28]. LV assist devices produce chronic pressure and volume unloading of dilated LV in endstage heart failure but they have not shown any major survival benefits so far.

Another evolving therapy is the treatment of heart failure with cardiac resynchronisation therapy. This involves pacing right and (via the coronary sinus) left ventricles. In this way the dyssynchrony between the left ventricle and right ventricle seen in advanced heart failure can be corrected. This has shown promise in patients with class III/IV heart failure on maximum medical therapy and with broad >120ms QRS on the resting electrocardiogram. A subgroup of narrow QRS complex patients may benefit but need

## Key points

- Several drugs and techniques have revolutionised cardiology; thereby improving patient outcomes drastically.
- Early reperfusion following acute coronary occlusion is being achieved by a combination of several strategies.
- Novel cardiac drugs and techniques are continuing to evolve.
- With an ageing population, trials should reflect the population for whom it may be most useful.

evidence of ventricular dyssynchrony with detailed echocardiographic analysis.

## The future

The treatments and interventions discussed in this article will continue to evolve and expand their application in the future. PCIs are likely to have an expanding role in the treatment of coronary ischaemic lesions. In the future, cost, availability and deliverability of stents will determine their usage. Newer pharmacological agents are also on the horizon and offer the potential to improve the life of patients with established CVD. These include novel anti-anginal treatments such as drugs acting specifically on the sinoatrial node (ivabradine). Techniques to replace valves percutaneously have also been developed and are undergoing modification. Aortic valves have been replaced percutaneously and are also useful for patients when invasive cardiac surgery is contraindicated. This is most relevant to an increasingly elderly population where aortic stenosis is common with disabling co-morbidity. And of course no talk of the future of medicine would be complete without mention of the potential of stem cell research to heal the damaged heart.

## Conclusion

The past 20 years has seen great advances in our understanding of CVD and the treatments available to combat this prevalent and devastating illness. The use of current treatments is supported by a wealth of good evidence. Through modern technology, increasing imaging methods, wider indications, superior cardiac intervention techniques, patients are living longer. The future will continue with the evaluation of new and exciting treatments ■ GM

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