A review of emerging cardiac technologies

Their potential impact on cardiac services over the next 10 years

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Contents

Foreword

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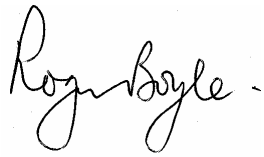
Cardiac services in England have improved enormously since the introduction of the Coronary Heart Disease National Service Framework in 2000. This set of evidence based standards, covering the entire patient pathway, was drawn up by clinicians and widely welcomed as a structure within which to pursue policy on heart disease. It is important that we maintain that momentum and work to plan heart disease services of the future. Cardiac disease remains common and is associated with very significant human and financial costs, which, as the population ages, will become increasingly challenging to tackle.

The technologies that can be used in the treatment of heart disease are diverse and represent some of the most exciting opportunities to improve the quality of cardiac care in England today. Successful identification, evaluation and implementation of these as they emerge presents a challenge to all those involved in shaping cardiac services of the future. The organising principles, outlined in this document, offer an indication of how, in the future, these technologies may contribute to better clinical outcomes for patients and efficiency savings for the NHS.

This document provides a summary of the best clinical and other evidence available on new and emerging technologies and forms part of the Department of Health review of the impact of the National Service Framework. It is intended to enable clinicians with an interest, commissioners and managers to understand what the technologies are, what they are used for and the extent to which they are likely to be available in the future. It does not make any specific recommendations on what local commissioners should or should not develop.

This piece of work has been undertaken by the Department of Health in close collaboration with many experts in cardiac technology, and I would like to thank all those who have contributed to the project.



Professor Roger Boyle, CBE
National Director for Heart Disease and Stroke

Introduction

Background and Context

1. The Coronary Heart Disease National Service Framework (CHD NSF)[1] was published in March 2000. Developed by clinicians, it set out a framework for action to prevent cardiovascular disease, tackle inequalities, save lives, and improve the quality of life for people living with heart disease. It has delivered substantial improvements in most areas of cardiovascular medicine. In order to learn the lessons of this approach work has been undertaken to evaluate the NSF and to look at the future burden of cardiovascular disease. This review forms part of the work and will support future policy developments, ensuring they are based on shared priorities for the future.

2. Cardiac services have improved enormously in England since the publication of the CHD NSF, with the aim of reducing the death rate from cardiovasuclar disease (CHD, stroke and related diseases) in people under 75 by at least 40 percent met early. However, cardiac disease is still common and is associated with significant human and financial costs. Cardiovascular diseases, such as CHD, heart failure, atrial fibrillation (AF) and stroke, remain the most common major cause of death in the UK, contributing to one third of all deaths registered in 2008, and costing around £14.4 billion in direct health care costs alone in 2006.[2] Furthermore, the proportion of people living in the UK aged 65 and over is projected to increase by around 50 per cent over the next 25 years[3], and since the prevalence of these diseases increases with age, their impact is likely to increase substantially. The clinically- and cost-effective management of these conditions therefore represents a significant opportunity. The burden of cardiovascular disease is considered in more detail in Appendix A.

3. Recent publications have reinforced the need for the NHS to adopt clinically- and cost-effective innovations in medical technologies[4]. Innovations are evolving at a rapid pace, and the NHS is well placed to introduce new technologies in a targeted manner, for those who have most to gain from them, in ways that provide fair and equal access and value for money. Moreover well established national audit programmes offer unrivalled opportunities to monitor the impact and cost-effectiveness of new technology.

4. In the current financial environment, local health economies need to focus on both quality of care and productivity. Organisations will need to be able to understand their local populations, identify and prioritise activities, which improve clinical outcomes as well as offering opportunities to make efficiency savings. This review considers both of these issues.

5. This document provides a summary of the best clinical and other evidence available on new and emerging technologies. It does not make any specific recommendations on what local commissioners should or should not develop.

Purpose

6. This report is the product of a multi-disciplinary horizon-scanning project. It is intended to identify the most promising emerging cardiac technologies and anticipate how they may influence the demand for and delivery of cardiovascular services in England over the next ten years. It focuses on the potential of technology to improve quality of care and takes account of clinical effectiveness,

[1] Coronary Heart Disease National Service Framework, Department of Health 2000
[2] 2006 figures, from Coronary Heart Disease Statistics 2008, published by the British Heart Foundation.
[3] National Population Projections, www.statistics.gov.uk/CCI/nugget.asp?ID=1352
[4] High quality care for all: NHS Next Stage Review final report, Department of Health 2008

while at the same time recognising the importance of value for money. It also highlights some organisational principles, which will help ensure that the full potential of these emerging technologies is realised.

7. It is aimed at clinicians, commissioners and all those involved in delivering, researching and managing heart disease services.

Scope

8. A discussion on cardiac technology could be wide-ranging and lack focus, we have therefore elected to undertake a selective review of the technologies available or emerging. A preliminary high-level multi-disciplinary scoping meeting identified the technologies for consideration and then those with the greatest potential to transform practice in the next ten years were selected.

9. Fetal and paediatric technologies, drug therapies (with the exception of newer anticoagulants) and long-established technologies that may currently be underutilised (for example 24-hour blood pressure monitoring) are outside the scope of this review but worthy of further consideration elsewhere.

Methods

10. There is by definition only a limited evidence-base for the clinical and cost effectiveness of emerging technology. The report is therefore based on a search of the literature combined with the opinions of acknowledged experts.

11. We included literature searches from Ovid Medline and the Cochrane Library. We sought the opinions of clinical experts, selected on the recommendations of the scoping group, and obtained their opinions through a series of structured interviews. At least two experts per technology were interviewed, wherever possible.

12. Agreement to the final draft was sought from each contributor, and the final document was comprehensively reviewed by a separate panel of clinical experts. Finally, the project was overseen by a senior clinical cardiologist.

13. A full list of contributors can be found at the end of this document.

General organisational principles

14. Maximising the benefit of emerging cardiac technologies and realising potential savings can only be achieved by adopting some key general organisational principles:

    - Successful forward planning depends on an effective horizon-scanning process that can identify, evaluate and co-ordinate the implementation of promising new technologies. The pathway by which new technologies pass from development into wider use needs to be planned prospectively, to ensure that all suitable patients can benefit from a new approach once it is of proven value. Closer links between commissioners, NICE, clinical leaders and industry may aid this process. Transcatheter Aortic Valve Implantation (TAVI) provides an example of how this might be achieved, and this process is outlined in Appendix E.

- Emerging technologies should be evaluated by clinicians and commissioners through coordinated collection of good quality cost and clinical effectiveness data. The NHS should involve itself in the early stages of the evaluation of new technologies so that it is well-placed to take a leading role in clinical trials.
- Comprehensive and robust national audits enable the impact of new technology to be assessed, and the identification of safety concerns.

- Differing needs of local populations should be recognised, and systems and processes should enable a flexible approach to changes in demand (both up and down) and the emergence of new technologies.

- Many developments in cardiology are driven by the results of large-scale trials and may result in interventions being rolled out on a national level. In order to ensure this is done in the most cost effective manner, efforts should be made to stratify patients and focus resources on those who are most likely to benefit (for example the use of fractionated ECG to assess the potential for individual benefit from an implantable cardiac defibrillator). This will ensure that expensive therapies are targeted at those who have most to gain from them.

- A co-ordinated national or central procurement and purchasing process may help to ensure best possible value for money in specialised services.

- Access to appropriate, high quality educational and training resources for clinicians will help to ensure that all eligible patients benefit from emerging technologies.

Key findings

15. This review provides background information, and discusses the clinical and cost effectiveness of each of the technologies most likely to impact on cardiac services. It describes current practice as well as seeking to anticipate developments over the next ten years, including those involving technologies likely to have the greatest impact such as percutaneous valve replacement, remote monitoring, point of care testing and pharmacogenetics.

16. The summary analyses of our findings are set out in the main body of the document (pages 8-16). These are set out in sections on Therapeutics and Diagnostics.

17. Full background, evidence and references are in the appendices to this document. Appendix B, for Therapeutics and Appendix C for Diagnostics. These are cross-referenced in the main body of the document for the main technologies addressed.

Therapeutics

(i) Transcatheter Aortic Valve Implantation (TAVI) (Appendix A, pp19-22)

- Aortic valve stenosis is estimated to affect 5% of adults over 75 years
- Severe aortic stenosis carries a poor prognosis, and is associated with significant morbidity, multiple hospital admissions and a marked reduction in quality of life
- Open valve replacement is a very effective therapy but involves a major operation and is not feasible in a significant number of very elderly patients, or those with severe co-morbidity.
- TAVI (percutaneous valve replacement) is now being used to treat patients with severe aortic stenosis in whom the risks of conventional aortic valve replacement are thought to be prohibitive. In the future it may be extended to patients who would otherwise undergo open heart surgery but pose a high operative risk.
- High quality world-wide observational data has shown that, in comparison with open surgery for these high risk patients, TAVI is both safe and effective.
- Over 700 procedures have been performed in the UK with good results. All patients have been included in a prospective national registry (Central Cardiac Audit Database) with the usual data collection by industry, as required for post marketing surveillance.

Future developments:

TAVI has an emerging evidence base and a great potential for patient benefit. An immediate population need of around 16 per million (around 800 TAVI procedures per year for England) has been estimated.

Within the next ten years, TAVI may be extended to patients who would otherwise undergo open heart surgery, with the potential for cost savings. However, such a move would need to be supported by high quality evidence. Potentially new resources would need to be identified to ensure that patients, currently too frail for open surgery might be considered for TAVI.

Support through the cardiac networks could enable TAVI to be implemented as a national programme, delivered through multi-disciplinary teams, with data from procedures being submitted to the national audit programme. It is important that clinicians should continue to maintain this registry(which now has data on >1000 patients), and support plans for a UK-based Randomised Controlled Trial to be undertaken in the future.

(ii) Transcatheter Mitral Valve Repair (TMVR) (Annex A, pp22-25)

- Mitral regurgitation is a common and heterogeneous condition that may be due to intrinsic diseases of the mitral valve apparatus. It also frequently complicates all forms of left heart failure, when it is termed “secondary” or “functional” mitral regurgitation; this is usually due to dilatation of the mitral valve ring (annulus) preventing normal coaptation (closure) of the mitral valve leaflets.
- A variety of percutanous mitral valve repair (TMVR) procedures designed to reduce mitral regurgitation are in development. The most advanced of these involves clipping parts of the valve leaflets together (MitraClip).
- TMVR development is some years behind TAVI, but it is already clear that these techniques can help selected patients with mitral regurgitation. Only 30 MitraClip procedures have been performed in the UK to date.

Future developments:

Initially, TMVR is likely to be used to treat patients with structural mitral valve disease who are considered to be too frail for conventional open surgery. However, depending on the availability of quality evidence, it may ultimately prove to be a useful adjunctive therapy for many types of heart failure and may impact on a significant number of people, with significant potential to reduce hospital admissions.

Lessons could be learned from the TAVI experience on how partners at national, regional and local levels could take this work forward.

(iii) Left atrial appendage occlusion devices (Annex A, pp25-27)

- Cardiac thrombo-embolism associated with atrial fibrillation is a common and preventable cause of stroke. The usual source of this thrombo-embolism is the left atrial appendage (LAA), a small hook-like chamber arising from the left atrium.
- The LAA can be obliterated permanently by implanting a device percutaneously; preliminary data suggest that this may be an effective means of preventing stroke in AF.
- The procedure is currently considered a good option for those patients with AF who are at high risk of an embolic stroke but in whom long term anticoagulation is contraindicated. Despite favourable evidence from a large scale randomised controlled trial, less than ten LAA occlusion procedures have been performed in England to date.
- The costs of the device (approximately £4000) must be set against the cost of long term anticoagulation and the considerable human and financial costs of a stroke (the cost of a stroke due to AF is estimated to be £11,900 in the first year alone).
- Minimally invasive surgical alternatives for LAA occlusion exist, and although at an earlier stage of development than the percutaneous option, may prove to be a more cost effective alternative.

Future developments:

It is suggested that, in the first instance, provision is made to deliver LAA occlusion therapy for selected patients at high risk of an embolic stroke who cannot tolerate long-term anticoagulation. The indications for LAA occlusion may expand considerably if the safety and efficacy of the procedures are substantiated. Future demand may be mitigated by the introduction of superior (but more expensive) anticoagulant strategies, for example dabigatran, and will be influenced by the results of ongoing trials.

(iv) Closure devices (Annex A, pp28-33)

Some abnormal communications in the circulation can be closed percutaneously, avoiding the need for major open-heart surgery. These include atrial septal defect and persistent foramen ovale.

(iv-i) Atrial Septal Defect (ASD)

- ASD is a common congenital heart defect, characterised by a hole in the atrial septum, which affects about 1 in a 1000 live births. It is typically associated with shunting of blood and progressive enlargement of the right heart.
- Unless the defect is very small and the patient is asymptomatic, closure is recommended to prevent future complications such as atrial arrhythmias (for example atrial fibrillation), stroke and heart failure.

- Percutaneous closure is feasible in 75-80% of people with ASD and is safe, effective and less invasive than open heart surgery. The procedure has been evaluated and recommended by NICE.

Future developments:

It is anticipated that over the next five to ten years the number of patients undergoing percutaneous ASD closure will grow modestly, and that this will be associated with a corresponding fall in the number of open surgical procedures, with minimal cost implications. Consideration will need to be given to rebalancing the necessary resources.

(iv-ii) Persistent Foramen Ovale (PFO)

- The fetal circulation allows oxygenated blood from the placenta to pass into the left heart through a hole in the atrial septum known as the foramen ovale. This usually closes spontaneously after birth; however, in as many as a quarter of people, it does not close completely and remains patent throughout life.
- A PFO is inconsequential for the vast majority of people; however, it can be implicated in the genesis of stroke (due to paradoxical embolism), migraine with aura, and decompression sickness in divers.
- Percutaneous closure of PFO is an increasingly common procedure with a well-established record of safety and long-term efficacy.
- Secondary stroke prevention is the main indication for closing a PFO. The optimum strategy for preventing recurrent strokes in people with PFO remains controversial, and will not be clear until trials comparing anti-thrombotic treatment with percutanous PFO closure are complete. However, observational data suggest that the treatment is likely to be of value in a significant proportion of younger stroke patients.
- There are approximately 600,000 people in the UK who suffer from migraine with aura; 60% of these patients are found to have a PFO and it has been suggested that closing this may reduce and even eliminate their migraine. The only published randomised controlled trial of PFO closure for migraine produced equivocal results and the results of a larger trial are awaited; a positive result could increase demand for PFO closure as a treatment for patients with severe migraine.
- All professional deep-sea divers are screened for PFO, which is implicated in decompression sickness. Less than 1% of all PFO closures are carried out for this reason and most of these are funded privately by the diver's employer. Routine screening and closure is not recommended for recreational divers.

Future developments:

Stroke: PFO closure is likely to become an increasingly important part of secondary stroke prevention. The optimum application of this therapy will depend on the outcome of ongoing trials and we suggest that at the moment resources should be focused on establishing high quality multi-disciplinary services for the evaluation of stroke patients who may benefit from PFO closure.

Migraine: demand for PFO closure to relieve migraine may increase significantly if the results of ongoing trials are positive. In that event, commissioners will wish to take account of as yet unavailable cost effectiveness data.

Deep-sea divers: no significant changes in the rates of PFO closure undertaken for this indication are anticipated.

(v) Cardiac Resynchronisation Therapy (CRT) (Annex A, pp34-35)

- CRT involves implanting a multi-lead pacing system to help synchronize the contractions of the heart and improve its pumping efficiency.
- There is compelling evidence that CRT improves survival and the quality of life of specified subgroups of heart failure patients at reasonable cost.
- There were 4,800 new CRT implants in the UK in 2008 and although intervention rates are rising, the UK lags behind many European countries. There are significant regional variations in the use of CRT, that are not related to need, and it has been estimated that providing CRT to every patient in England who has a recognised indication for the therapy would require a five-fold increase in implant rates.
- The application of this technology is broadening and it seems likely that CRT will be used to treat milder disease in the future. The appropriateness of this will be informed by the results of ongoing trials.

Future developments:

Consideration should be given to addressing the geographical variation in provision of CRT, and ensuring it is available to every eligible patient, according to current guidance.

(vi) Radiofrequency ablation for atrial fibrillation (Annex A, pp36-38)

- Radiofrequency (RF) ablation is a percutaneous procedure that aims to destroy aberrant electrical pathways in the heart, which are thought to be responsible for initiating and sustaining arrhythmias; it offers the prospect of a complete cure for some arrhythmias and is an attractive alternative to long-term drug therapy.
- Atrial fibrillation (AF) is the commonest arrhythmia in England and is thought to be responsible for as many as 12,500 strokes a year.
- Some forms of AF are amenable to RF ablation and almost 1,500 RF procedures for AF were carried out in England in 2009. Intervention rates are rising rapidly and the indications for RF ablation in AF are broadening.
- The clinical and cost effectiveness of RF ablation for AF is highly dependent on patient selection and better risk stratification is needed to identify those patients who have most to gain from the procedure.
- There are simpler ways of managing AF and the advent of new drug therapies and anticoagulant strategies may mitigate the growth in RF ablation for AF.

Future developments:

There will be a continued increase in demand for RF ablation for AF. The response to this should be guided by the results of ongoing trials and registry data.

(vii) Left Ventricular Assist Devices (LVADs) (Annex A, pp38-41)

- LVADs are used to support the pumping function of a failing heart, and can be used as a temporary or holding measure pending cardiac transplantation (bridge to transplant, BTT), in acute heart failure until recovery (bridge to recovery, BTR) or as a destination therapy for chronic heart failure (long term chronic support, LTCS).
- The technology is currently restricted to a few centres and, in the last three years, only 70 LVADs were implanted in the UK.
- When used both as a BTT and as LTCS there is some evidence of clinical benefit, but not of cost-effectiveness (in large part due to the cost of the device itself - around £40,000).

- This technology is unlikely to be adopted as mainstream therapy unless costs fall dramatically but will remain a focus for research and development.

Future developments:

It is suggested that funding for LVAD therapy continues on a case-by-case basis, and that the procedure is confined to a few specialist centres.

(viii) Inducing therapeutic hypothermia after cardiac arrest (Annex A, pp41-43)

- Approximately 57,000 people suffer an out of hospital cardiac arrest in England every year. Mortality is very high and survivors are often left with permanent brain damage.
- Cooling the body after a cardiac arrest helps reduce brain damage and increase survival, although the optimum initiation, method and duration of cooling are unclear.
- Despite strong evidence suggesting benefit, uptake of therapeutic hypothermia in routine clinical practice has been slow. This may reflect lack of awareness, fear of a novel therapy and inadequate resources.

Future developments:

It is suggested that this technology should be made available to all those who may benefit from it, in accordance with current UK and international guidelines. Consideration should be given to new International Liaison Committee on Resuscitation consensus statements which are expected to be published later in 2010.

(ix) Stem Cell Therapy (Annex A, p43)

- Stem cell therapy offers the prospect of repairing damaged hearts and has the potential to transform the management of heart failure and many other forms of heart disease.
- However, its complexity as a therapy and the need for long-term research means that it is likely to be many years before it might translate into routine clinical practice.

Future developments:

Stem cell therapy for heart disease is unlikely to have significant implications for NHS funding over the next ten years; nevertheless, significant resources are likely to be needed to support research and development.

Diagnostics

(i) Remote Monitoring of Cardiac Rhythm Management Devices
(Annex B, pp44-47)

- 275,000 patients in the UK are living with a permanent pacemaker (this figure is projected to exceed 324,000 by 2015), and 30,300 have an ICD or CRT device (projected to exceed 60,000 by 2015).
- Conventional device follow-up is performed in a booked out-patient clinic, interrogating the device using radio-frequency telemetry via a wand placed over the device. Follow-up has become increasingly complex and time-consuming due to the huge growth in the number and functionality of devices. Nevertheless, most clinic visits are scheduled and most of these do not result in changes in device re-programming or clinical care.
- Remote monitoring technology that allows data to be transmitted automatically to the clinical team, without the patient leaving home, is available in all new and many existing devices but is not widely used in England.
- Battery longevity, lead impedance and threshold for pacing can be monitored remotely; it is also possible to record the patient's heart rate and rhythm. Any significant change in rhythm can be detected rapidly, including the onset of atrial fibrillation; it is also possible to diagnose the early stages of myocardial infarction by monitoring ST segment shift.
- In addition, some implanted cardiac devices also have the capacity to monitor heart failure status – through such things as transthoracic impedance, patient activity and heart rate variability - which can give up to a week's warning of impending clinical deterioration.
- The clinical team can access data through a secure website at any time and, importantly, can be automatically alerted to any changes outside pre-specified limits so that early treatment can be given.
- European studies have confirmed that remote monitoring offers significantly earlier detection not only of device problems but also the onset of arrhythmias (such as atrial fibrillation) and incipient heart failure.
- Remote monitoring has the potential to improve patient safety and reduce healthcare costs. International cost effectiveness analyses have reported reduced numbers of clinic visits, reduced patient travel costs, increased clinic efficiency and earlier detection of clinically significant effects. Patient satisfaction is also enhanced.
- A centre in Newcastle has more than 200 ICD patients under remote follow up, and reports that it receives an average of two alerts per week (1% of patients) which require subsequent action. Cost effectiveness estimates from this centre are awaited, and should be available later in 2010.
- In addition to remote monitoring of cardiac rhythm devices, several other devices are being used to remotely monitor patients and facilitate tailored support to individuals in their own home. This technology is likely to play a particularly important role in the management of patients with heart failure.

Future developments:

Depending on the results of UK cost effectiveness data, this technology could become widespread over the next five years. In order for this to happen successfully further work is needed to facilitate and encourage the adoption of remote monitoring, perhaps through a co-ordinated cardiac network approach to develop a national remote monitoring programme, which could be in partnership with industry.

(ii) Imaging (Annex B, pp48-52)

- Radiography, ultrasound, scintigraphy, X-ray computed tomography (CT) and magnetic resonance (MR) can all be used to image the cardiovascular system and can provide overlapping or complementary anatomical and functional information. Each technique has advantages and disadvantages.

- Demand for all of these technologies is increasing, often based upon the evidence for the value of functional assessment of coronary atheroma alongside anatomical assessment, and of the integrity of downstream myocardium. Increasingly, the management of patients with coronary disease, particularly using invasive interventions, will require the assessment of both coronary function and the health of the myocardium.

- The technologies are advancing rapidly and future improvements are anticipated for them all. Technological advances are sometimes driven by academic and clinical practice within the NHS but may also be commercially driven.

- The choice of imaging modality often depends upon local expertise and equipment rather than upon robust comparative trials that use clinical outcome, cost effectiveness and safety as end-points. An important feature of practice in the next ten years will be to balance the desire to make new technology available to patients while guarding against premature use that might increase costs without improving outcomes.

- The prognostic power of functional abnormalities in patients with coronary disease is well established and is currently a valuable aid in their management. However, prognostic power applies to populations and the risk in individuals may differ. Assessment of coronary plaque stability may be a major advance for individual risk assessment and therapy if it can be achieved. Both invasive and non-invasive techniques could achieve this goal but they remain in the research phase and predicting their impact in the next ten years is difficult.

Future developments:

Cardiology units should have access to mainstream imaging modalities with sufficient capacity to provide both anatomical and functional imaging according to accepted professional guidelines. There is a need to train more sub-specialists in cardiac imaging; this can be approached both from the cardiology and imaging specialties and will require close collaboration between them. Where the capabilities of the imaging techniques overlap, comparative studies of real world effectiveness and cost-effectiveness using relevant clinical outcome measures would be helpful. NICE is considering this as a potential piece of their work.

Technological advances and their application should be encouraged in specialist centres but initially as part of a coordinated system of technology appraisal. Wider implementation should be based upon proven effect on costs and outcomes. Imaging techniques aimed at assessing the stability of individual

coronary plaques have the potential to have a major impact upon the management of coronary disease but are still in development.

(iii) Point of Care (POC) Testing (Annex B, pp53-56)

(iii-i) Biochemical markers of cardiac damage

- Acute chest pain is responsible for around 700,000 patient attendances per year in England and Wales; many of these patients have a benign cause of chest pain but are detained in hospital in order to rule out an acute coronary syndrome by measuring troponin a minimum of 12 hours after the episode of chest pain.
- The introduction to emergency departments of a reliable point of care (POC) test for early markers of myocardial damage could prevent as many as 500,000 hospital admissions a year by allowing earlier diagnosis (<4 hours) and hence earlier discharge. Nevertheless, it is important to stress that competent clinical evaluation remains paramount.
- A variety of novel markers have been identified and validated that could be used in a POC test for patients with possible cardiac pain. Systems that use an array of several tests are likely to be the most accurate and are expected to cost around £25 per test. Involvement of a central chemical pathology service is important for quality assurance.
- The RATPAC Trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) is a UK multi-centre randomized controlled trial that was designed to assess the cost and clinical utility (including patient satisfaction), of a point-of-care cardiac marker panel. The findings will be published in 2010, and may have a major impact on the assessment of chest pain.

Future developments:

The advent of new and proven point of care tests for the evaluation of chest pain should be anticipated within the next five years. These have the potential to deliver important cost savings with good clinical outcomes, particularly if they are introduced as part of a co-ordinated national plan.

(iii-ii) Home monitoring of International Normalised Ratio (INR) and self-management of anticoagulant therapy

- INR measurements (for the monitoring of warfarin dosage) can be performed in a patient's own home using a POC device, thereby eliminating the need for clinic visits; this allows patients to participate in their own care in the same way that diabetics monitor their blood glucose.
- Devices cost around £450 each with between £2.50 and £2.70 for each test strip.
- Self-management of anticoagulant therapy using a POC INR device is associated with cost savings to the health care system and the patient, some improvement in control (the time within the therapeutic range), and better quality of life. However, some concerns over quality assurance have slowed the introduction of this technology.

Future developments:

It is suggested that consideration should be given to addressing the anomaly whereby INR POC devices cannot be prescribed on the NHS but the test strips can.

The NHS will need a coordinated approach to the introduction of INR self-monitoring, taking account of emerging evidence of clinical and cost-effectiveness as well as the potential impact of newer anticoagulants, eg Dabigatran.

(iii-iii) BNP testing in heart failure

- Measuring BNP is a well-validated means of excluding heart failure and risk stratifying those with confirmed heart failure. Using BNP in this way is very cost effective but only around a quarter of GPs currently have access to BNP testing in any form.

Future developments:

Evidence suggests that, when managed appropriately, provision of BNP testing in primary care is a cost effective diagnostic tool. Current guidelines for diagnosis of heart failure now recommend this.

(iii-iv) Highly selective C-Reactive Protein (Hs-CRP) as a marker of cardiovascular risk

- There is compelling evidence to show that hs-CRP is a predictor of cardiovascular risk but the test is expensive (approximately £27) and seems to add little to existing risk assessment tools. Moreover, there is no clear advantage to making measurements at the point of care instead of within a central laboratory.

Future developments:

New UK evidence-based guidelines for the primary prevention of cardiovascular disease, which focus on lifetime risk, are being drawn up (the 3rd Joint British Society Guidelines) and are expected to be published in 2011. Consideration should be given to these when they are published.

(iv) Genomics (Annex B, pp56-58)

- Genetic testing has enormous potential and very wide applications. In future, it will probably be used to confirm diagnoses, to screen healthy individuals for the presence of important disease causing genes, and to determine the likely course of illness and response to therapy.
- The most pressing issue facing the NHS in the next ten years is likely to be the need to guard against adoption of genetic testing before its use in predicting risk and guiding therapy has been fully validated.

Future developments:

Evidence-based genetic testing to guide anti-platelet prescribing is likely to become more commonplace over the next ten years. If this is the case, consideration will need to be made of the need to access tests of platelet function.

GPs and other clinicians will need to ensure they keep up to date with the advice from NICE and their professional bodies about clinical practice.

Appendix A

The burden of disease: four important cardiac conditions

Coronary heart disease

1. Around 2.6 million people in the UK are living with coronary heart disease (CHD), and it kills more than 110,000 people a year in England, of whom more than 41,000 are under the age of 75. CHD is the most common cause of premature death in the UK accounting for 19% of premature deaths in men and 22% of premature deaths in women[5] .

2. As well as the human cost of CHD, it is also associated with a significant financial burden. CHD accounts for about 3% of all hospital admissions in England with direct costs to the UK NHS of £3.3 billion per year (2.7% of total health care expenditure in 2006), and total costs (including health care costs, loss in productivity and informal care) of almost £9 billion per year[6].

Heart failure

3. Heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the heart's ability to function efficiently as a pump to support the circulation. There are approximately 700,000 people in the UK with heart failure[7], and the prevalence rises steeply with age: while around 1 in 35 people aged 65–74 years has heart failure, this increases to about 1 in 15 of those aged 75–84 years, and to just over 1 in 7 in those aged 85 years and above[8]. The incidence of heart failure is increasing; this is due to the effects of an ageing population combined with improved survival (with residual heart dysfunction) rates after a heart attack. The prognosis of heart failure has improved in recent years, however newly diagnosed patients still have a 14% chance of dying (from all causes) within six months of diagnosis[9].

4. Estimates suggest that the direct costs of heart failure are £628.6 million per year, the majority of this (£378.6 million) made up by hospital inpatient care[10]. These figures do relate, however to the year 2000, and as such are likely to have increased. Anecdotal evidence suggests that the current annual expenditure on heart failure (direct costs) is closer to £900 million.

Stroke

5. There are approximately 110,000 strokes and 20,000 transient ischaemic attacks (TIAs) per year in England alone. Stroke is the single largest cause of adult disability: around 300,000 people are living with moderate to severe disabilities as a result of stroke[11]. Modelling suggests that stroke prevalence in England will increase over the next ten years: from an estimated 2.5% in 2010 to

[5] Coronary Heart Disease National Service Framework, Department of Health 2000
[6] Ibid
[7] Ibid
[8] Davies M, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet 2001;358:439–44.
[9] Mehta PA, et al. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. Heart. 2009 Nov; 95(22):1851-6.
[10] Cost of heart failure to the National Health Service 2000, www.heartstats.org
[11] The National Stroke Strategy, Department of Health 2007

2.6% in 2015, and 2.7% in 2020[12]. Although the majority of people who have a stroke are elderly, 25% are under the age of 65[13]. Indeed, 10,000 people under the age of 55 and 1,000 people under the age of 30 suffer a stroke every year[14].

6. It is estimated that, in 2008-09, the direct care cost of stroke was at least £3 billion annually, within a wider economic cost of about £8 billion[15]. Furthermore, in 2005 it was estimated that 4% of health care expenditure is spent on the direct costs of managing patients with stroke[16].

Atrial fibrillation

7. Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting at least 600,000 (1.2%) people in England[17]. The incidence and prevalence of AF increases with age and it is estimated that one in four people over the age of 40 will develop AF at some time in their life[18]. The age-adjusted mortality rates for people with AF are approximately double those of the general population. AF is a major preventable cause of stroke, with 16,000 strokes annually in patients with AF of which approximately 12,500 are thought to be directly attributable to AF[19].

8. The prevalence of AF is expected to increase 2.5-fold during the next 50 years[20]: this is largely as a result of an ageing population and an increased longevity resulting from improved medical care for chronic cardiac conditions, which predispose to AF.

9. The management of AF imposes a considerable financial burden on the NHS: the annual direct cost of AF in the UK was reported to have reached £459 million in 2000 (approximately €655 million at the then exchange rate), which was equivalent to 0.97% of the total NHS budget[21], and is expected to increase as the prevalence of AF increases.

[12] Modelled estimates of prevalence of stroke for PCTs in England, Eastern Region Public Health Observatory, October 2008, DH
[13] The National Stroke Strategy, Department of Health 2007
[14] Oxford Vascular Study, figures extrapolated to give UK estimates. Raw data in Stoke Statistics 2009 (chapter 2), www.heartstats.org/datapage.asp?id=8615
[15] Progress in Improving Stroke Care, National Audit Office Report 2010
[16] Saka RO, McGuire A, Wolfe CDA. Economic burden of stroke in England. King's College, London: NAO, 2005
[17] Atrial fibrillation in primary care: making an impact on stroke prevention. Heart and Stroke Improvement 2009
[18] Lloyd-Jones DM, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation (2004) 110:1042–1046
[19] Atrial fibrillation in primary care: making an impact on stroke prevention. Heart and Stroke Improvement 2009
[20] Go AS, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370–5
[21] Stewart S, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 2004;90:286–92

Appendix B

Therapeutics

Percutaneous Valve Surgery for valvular heart disease

1. Valvular Heart Disease (VHD) increases with advancing age (particularly over the age of 75) and aortic stenosis (AS) and mitral regurgitation (MR) make up the bulk of disease. Males and females are equally affected. Mitral stenosis (MS), which is highly prevalent in populations affected by rheumatic disease, is now uncommon in economically developed countries[22],[23],[24].

2. In an American study, the population prevalence of moderate to severe valvular disease was 11.7% of those aged 75 years and older[25]. There are currently no equivalent data for the UK population but extrapolation from the American figures would give an estimate of around one million affected individuals over the age of 65 years.

3. Predicting the future need for treatments for valvular heart disease requires consideration of two different types of patients – firstly those who are currently too frail for conventional surgery (surgical 'turn downs') and who therefore currently receive only supportive care, and those in whom conventional surgery is possible but high risk, where percutaneous surgery would offer an effective alternative. The former group has greater potential to impact service provision in the short term.

[22] Nkomo VT, et al. Burden of valvular heart disease: a population based study. Lancet 2006;368:1005-1011
[23] Nkomo VT. Epidemiology and prevention of valvular heart disease and infective endocarditis in Africa. Heart 2007;93:1510-1519
[24] Marijon E, et al. Prevalance of rheumatic heart disease detected by echocardiographic screening. N Engl J Med. 2007;35:470-6
[25] Nkomo VT, et al. Burden of valvular heart disease: a population based study. Lancet 2006;368:1005-

(i) Transcatheter Aortic Valve Implantation (TAVI)

Background

4. Aortic valve stenosis is the most commonly acquired valvular disorder, accounting for 43% of valvular heart disease[26]. It is usually caused by a degenerative, age-related process of valve calcification and destruction. Severe aortic stenosis carries a poor prognosis and is associated with significant morbidity, multiple prolonged hospital admissions and a marked reduction in quality of life. Once AS becomes symptomatic, life expectancy decreases dramatically: the mortality of untreated symptomatic severe aortic stenosis is high (84% at five years, compared to 78% survival in those treated by surgery, in one series)[27].

5. Until now, the only effective treatment for severe or symptomatic aortic stenosis has been aortic valve replacement on cardiopulmonary bypass. In England, 6,300 open aortic valve replacements were performed in 2008[28]. However, it is estimated that 50-60% of people with symptomatic AS are currently not referred for surgery because they are thought to be too frail, elderly or with complex co-morbidities that make conventional aortic valve surgery too high risk. Percutaneous and minimally invasive treatments therefore represent a very attractive option for this group of patients and their clinicians.

Technology

6. The procedure is performed through a catheter, which is inserted into either a blood vessel at the top of the leg (transfemoral approach), in the armpit or below the clavicle (subclavian or axillary approach), or into the apex of the heart (transapical approach). Transfemoral cases (all done in the cardiac catheterisation laboratory) may now be done without the need for a general anaesthetic, using sedation only. The diseased valve is dilated by inflating a large balloon in its orifice and a replacement valve is positioned and deployed in its place. Sophisticated cardiac imaging is fundamental to both pre-procedural assessment and peri-procedural monitoring. The main technological challenge has been developing sufficiently small and flexible delivery systems. The Corevalve (Medtronic) device is already 18F gauge and from early 2010, the Edwards-Sapien (Edwards Life Sciences) valve will be the same size allowing percutaneous closure without the need for a surgical cutdown. Further reductions to size 16F or even 14F gauge are likely to occur in the near future.

7. Figures from The Edinburgh Heart Centre estimate the cost per procedure to be £17,040 for the transfemoral approach and £18,240 for the transapical approach (including the device, pre-operative imaging, surgical consumables and post-operative care). The Edwards-Sapien valve costs £12,500 if the centre orders around 20 devices per annum and this price may fall as market competition increases and bulk orders can be placed. However, several waves of new generation devices will be associated with increased costs, and a significant fall in device cost may not be seen for a few years. So far, the cost of training specialists to carry out this procedure has been borne by industry.

[26] Iung B, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European Heart Journal 2003 24(13):1231-1243
[27] Pellikka PA, et al. Outcome of 622 adults with asymptomatic, haemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290-5
[28] The Society for Cardiothoracic Surgery in Great Britain and Ireland; Sixth National Annual Cardiac Surgical Database Report 2008

Evidence - *Clinical effectiveness*

8. Early experience of TAVI was analysed in the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) study[29]. Anatomical and procedural success using the transfemoral technique exceeded 90% with a low 30-day mortality (less than 10%). There was an impressive improvement in aortic valve area and mean aortic gradient, which was maintained at follow-up. A further study[30] reported a valve implantation success rate of 86% with a 30-day mortality of about 12%. These initial results were influenced by a marked learning curve and procedural success increased to 96% when experience was gained.

9. The largest series of trans-apical procedures has been performed by Walther et al[31], who reported a similar success rate to the transfemoral procedure (exceeding 90%) with a small risk of complications requiring urgent femoro-femoral cardiopulmonary bypass. The mortality rate is slightly higher using the trans-apical approach, probably because trans-apical TAVI patients tend to have more peripheral vascular disease (a marker for atheroma burden) and a higher baseline risk.

10. Access site complications can be serious and occur in 10-15% of cases, according to the device used; this problem is likely to improve as the devices become smaller and more flexible[32]. The risk of embolism from the aortic valve, causing stroke is relatively low and varies from 2-4%. Atrioventricular block occurs relatively rarely after Edwards-Sapien valve implantation (5%) but is more frequent with self-expanding devices (e.g. Corevalve) with a need for pacemaker implantation in up to 20%[33]. Severe aortic regurgitation after valve implantation is very rare; although mild to moderate para-valvular regurgitation with no haemodynamic consequence is frequently observed.

11. Data on nearly 1000 patients from the UK TAVI Registry, presented in abstract form at the EuroPCR meeting in Paris, and at the British Cardiovascular Society meeting in Manchester (June 2010) confirm the excellent clinical outcomes with TAVI, with a 30-day mortality one third of that predicted by Logistic EuroSCORE. After TAVI, there is a conversion in symptoms of breathlessness from 78% in NYHA class 3/4 (breathlessness at rest or minimal exertion) to 93% in NYHA class 1/2 (no symptoms or only on significant exertion) at one year of follow-up. Outcomes have steadily improved as the devices and techniques have evolved.

12. TAVI has the potential to revolutionise the treatment of AS but randomised clinical trial data are still lacking. The PARTNER-IDE study (Placement of AoRTic traNscathetER valves) is a randomized controlled trial comparing standard surgical AVR with TAVI (using the Edwards-Sapien valve) and optimal medical treatment with TAVI in patients who are deemed inoperable. Recruitment for the study in the US and Canada has been completed and one year results are anticipated in late 2010.

13. A UK study is also proposed. In a nested design, all patients considered by an experienced multidisciplinary team to be eligible for either TAVI (using any device) or conventional AVR will be randomised to either procedure in a 1:1 ratio. Those considered unsuitable for randomisation will be followed in procedural registries for both TAVI and high risk AVR. Similarly, patients undergoing TAVI outside the trial structure will be followed via the CCAD mechanism. Projected trial numbers are approximately 700-800 and recruitment will take approximately three to five years. Future commissioning in the UK is likely to be based upon the findings of this study.

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[29] Cribier A, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol, 2006; 47:1214-1223

[30] Lichtenstein SV, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007; 116:755-63

[31] Walther T, et al. Transapical minimally invasive aortic valve implementation: multicenter experience. Circulation 2007;116:1240-5

[32] Webb J, et al. A New Transcatheter Aortic Valve and Percutaneous Valve Delivery System. J Am Coll Cardiol, 2009; 53:1855-1858

[33] Grube E, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis. J Am Coll Cardiol 2007;50:69-76

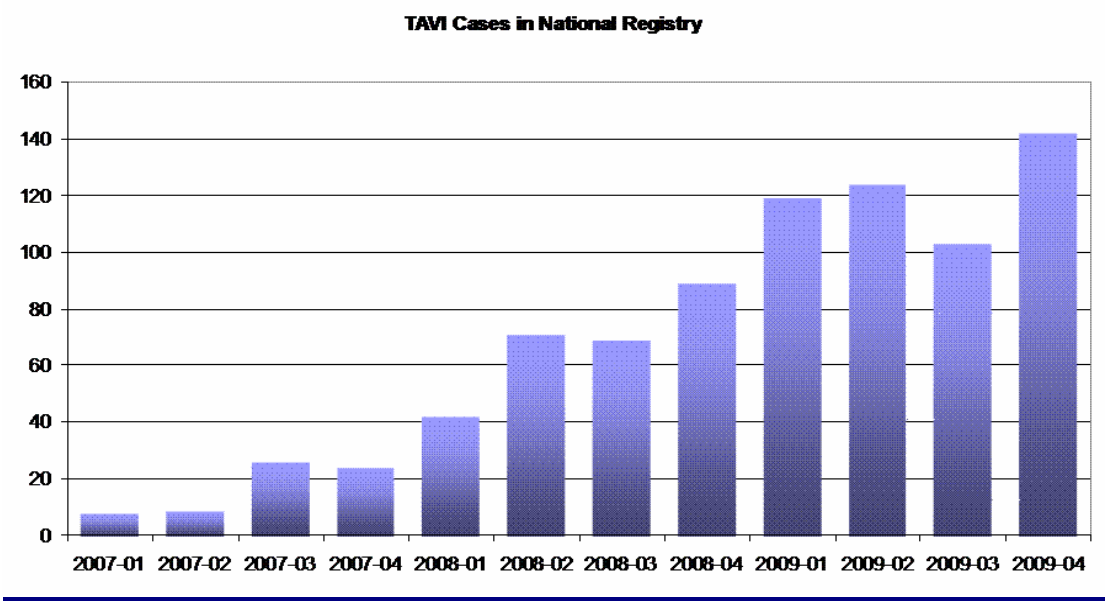
Evidence - *Cost effectiveness*

14. There are potentially significant cost savings to be had from this technology, and the projected cost per QALY is likely to fall below the NICE threshold of £20-30,000. However, no data are currently available to support this. Although many people with atrial stenosis and refused surgery die in the subsequent months to years, the economic burden on the health care system is considerable. The vast majority of such patients are repeatedly hospitalised, often with prolonged lengths of in-hospital stay and when discharged to the community, consume additional resources from primary and social care. The quality of life enjoyed by these patients is poor with a high mortality. If these sick, older patients could have TAVI, they might have a much-improved quality of life with a significantly reduced burden on health care resources. Furthermore, compared to conventional aortic valve replacement, it is expected that percutaneous and minimally invasive aortic valve replacement will result in a reduced requirement for intensive care unit support, assisted ventilation, and haemodialysis. Once discharged, these patients are less likely to require subsequent hospitalisation with symptoms attributable to aortic stenosis and one would anticipate an improved quality of life as a consequence. It is likely that there will also be a reduced need for concomitant medical therapy and involvement of the specialist community heart failure nurse in the care of the patient outside hospital.

Current activity

15. TAVI is currently indicated in patients with severe symptomatic, calcific AS who are deemed unfit for conventional, surgical AVR based on one of the current risk scoring systems (EuroSCORE or STS Score). Particular co-morbidities which are not adequately reflected by the risk scores, such as porcelain aorta, difficulties with surgical access and severe respiratory disease, are seen as additional indications. A total of >1000 procedures have been performed in the UK so far (835 to the end of 2009).

Figure 1: Quarterly number of TAVI procedures entered into CCAD database (UK)



16. Currently, TAVI represents an exciting treatment option for very symptomatic patients who would previously have been too unfit for anything other than medical management. It is difficult to know how big the size of this group is; however, it is estimated that 50-60% of people with symptomatic AS are currently not referred for surgery because they are thought to be too frail. There may therefore be a significant 'hidden' cohort of people who would benefit from TAVI.

Future developments

17. TAVI is exponentially increasing around the world, and in the medium term is likely to become a mainstream intervention for high-risk surgical patients. There is currently a lack of epidemiological data to determine population need, but a population need of around 16 per million (around 800 TAVI procedures per year for England) has been estimated[34]. This number was deemed a minimum number based on current indications. If the indication for TAVI increases to include the 'moderate-risk' surgical cohort, the number will be greater than this. This will need to be considered by commissioners in light of any recommendations from NICE as to the cost-effectiveness of the procedure.

18. The ultimate impact of TAVI is potentially very far reaching because, subject to the outcome of randomised trials, it may be offered to lower risk (and possibly even the vast majority of) surgical patients, with the prospect of shorter hospital stays, earlier return to normal activities and low complication rates.

19. An important factor for success appears to be a multidisciplinary team approach to patient selection, which should involve both cardiac surgeons and imaging specialists, as well as interventional cardiologists. Techniques (and, in turn, outcomes) will improve with operator experience and further progress will be driven by advancing technology and the accumulation of a robust evidence base. Support through improvement agencies and the cardiac networks will assist the national roll out of TAVI and ensure that data from all procedures are submitted to the national audit programme. It is important that clinicians continue to maintain the registry and consideration should be given to conducting a UK-based Randomised Controlled Trial. Experience of implementing TAVI in England is described in Appendix E.

(ii) Valve-in-valve technology

20. Work is being undertaken to adapt the TAVI device to the treatment of failing aortic bioprosthetic valves[35]. One series reported the cases of four patients who had previously undergone AVR with a bioprosthetic valve that subsequently failed[36]. All of the subjects were poor candidates for open repair because of co morbidities and therefore underwent TAVI. All procedures were technically successful, with immediate improvements in valvular haemodynamics and no periprocedural deaths. Used in this way, TAVI could potentially benefit several thousand patients whose existing prosthetic valves have worn out.

(iii) Transcatheter Mitral Valve Repair (TMVR)

Background

21. Mitral regurgitation (MR) is a common and heterogeneous condition that can be due to intrinsic valve disease but may also complicate many types of heart disease including coronary heart disease and all forms of left heart failure. Mitral valve (MV) surgery is the second commonest valve operation performed in the developed world[37]. Conventional surgical therapies (predominantly mitral valve replacement), while clinically effective, may not be suitable for sicker, older patients. Percutaneous alternatives to the conventional procedure have been developed for the treatment of

[34] Sethi S et al. A commissioning framework for transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis. March 2009
[35] Walther T, et al. Valve-in-a-valve concept for transcatheter minimally invasive repeat xenograft implantation. J Am Coll Cardiol 2007;50:56-60
[36] Khawaja, M et al. Transcatheter Aortic Valve Implantation for Failing Bioprosthetic Valves. J. Am. Coll. Cardiol. 2010;55;97-101
[37] Mitral valve repair and replacement patients: Incidence of Complications Summary (2008). STS U.S. Cardiac Surgery Database, www.sts.org

MR. These are distinct from, and should not be confused with, balloon valvuloplasty, which is a long established and very effective therapy for rheumatic mitral stenosis.

Technology

22. There are two main techniques for the percutaneous repair of MR: edge-to-edge repair and prosthetic ring annuloplasty, the most established of which is an edge-to-edge reconstruction while the heart is beating - the MitraClip system. This comprises a transcatheter delivery system that enables placement of a clip on opposing mitral valve leaflets resulting in permanent leaflet approximation. To access the left heart, standard trans-septal catheterisation is performed. The guide catheter is then percutaneously inserted into the femoral vein. The delivery catheter is then inserted into the guide and the MitraClip device is positioned above the mitral valve. Manipulation of the steering mechanism on the handles of the guide and delivery catheter positions the MitraClip device on the mitral valve. The MitraClip device is actuated (i.e., opened and closed, locked, deployed) through manipulation of levers on the handle of the delivery catheter.

23. The procedure is performed in the cardiac catheterisation laboratory with echocardiographic and fluoroscopic guidance while the patient is under general anaesthesia.

24. Figures from the Edinburgh Heart Centre estimate the cost of the procedure per patient to be £19,340, based on a device cost of £14,500 (which may be reduced based on volume commitment), pre-operative imaging, post-operative inpatient care and post-discharge follow up.

25. An alternative procedure to MitraClip involves the percutanous insertion of an annuloplasty ring around the diseased valve. This technique, although promising, is at a considerably less advanced stage of development than MitraClip. Several other techniques are in development.

Evidence - *Clinical effectiveness*

26. The MitraClip system has been evaluated in two clinical trials in 47 US and Canadian centres: EVEREST I[38], and EVEREST II[39].

27. EVEREST I was a feasibility trial in 55 patients of median age 71 years with a median left ventricular ejection fraction of 62%, 46% of whom were in NYHA class III or IV. In this study group, along with 60 patients from the roll-in phase of EVEREST II, the 30-day freedom from clinical events was 91%, with 1 non-clip-related death, 1 stroke after 72 hours, 2 requiring surgery for trans-septal complications, and 4 requiring more than two units blood transfusion. At 12 months, 92% of patients were in NYHA class I-II; 77% showed an improvement in NYHA class, 17% had no change, and 6% were worse. In terms of LV remodelling, there was a significant reduction in LV end-diastolic volume (LVEDV) from 174 to 151 ml ($p<0.001$) and in LV end-systolic volume (LVESV) from 72 to 64 ml ($p<0.01$) in all patients. In those with LV dysfunction (LVEF<55%), the LVEDV fell from 207 to 171 ml, and the LVESV from 109 to 86 ml (both $p<0.001$). At three years follow-up, 96% of patients were still alive with 82% free from cardiac surgery.

28. EVEREST II is a randomized controlled trial including over 300 patients with eligible patients randomised to MitraClip or surgery. Patients not suitable for randomisation due to high risk of surgery were included in a 'High risk registry'. The EVEREST II trial has completed recruitment and is expected to report late in 2010. Data from the high-risk registry arm of EVEREST II have been reported: in this registry, the 30-day mortality was reported at 7.7% (no procedure-related deaths) compared to an estimated mortality of 18.2% had the patients undergone conventional mitral valve

[38] Feldman T, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol 2005;46:2134-40

[39] Kar, S, on behalf of the EVEREST investigators. Experience with Mitraclip therapy in the EVEREST II high risk registry. Eurointervention 2009;5

surgery. Furthermore, at 30 days, 82% of patients had mitral regurgitation of 2+ or less which was sustained out to one-year follow-up in parallel to an improvement in symptoms. However, caution needs to be exercised, as the high-risk registry is a retrospective comparison group, with small patient numbers and limited duration of follow-up (1 year). In addition, data from this study have not yet been published.

29. MitraClip has been awarded a CE mark, and is now being introduced into a small number of centres in Europe. The largest European experience is at the University Hospital Hamburg[40]. A series of 26 patients (73% with functional mitral regurgitation, 61% grade 3, 39% grade 4 MR severity) have been reported, 70% of whom fell outside the EVEREST I and II trials in terms of adverse anatomy, namely an LVEF <20% (31%), and LVESD > 60 mm (38%) and a coaptation length <2 mm (27%). This high-risk population had a EuroSCORE of 37±24 compared to 15±25 in the minority with favourable features. Despite these adverse variables, 96% had a successful clip procedure (12% required a second clip) with a mean device procedure time of 112 minutes with no major in-hospital complications. There was a reduction in MR by at least one echocardiographic class in all patients (59% grade 1, 25% grade 2 and 16% grade 3 MR severity).

30. In EVEREST I, 70% of the data came from the centres' first, second or third procedures thus comprising a data set from the learning curve of the technique. Despite this, the procedure-related mortality to date in over 400 patients is 0% with a successful implantation in over 90% of patients with MR reduction in over 90%, and no mitral stenosis reported after two years of follow-up[41]. These data demonstrate the MitraClip is a device that can be implanted as part of a low risk procedure in patients with degenerative MR and may be associated with significant benefit to patients.

Evidence - *Cost effectiveness*

31. There is very little cost effectiveness data available for MitraClip. Data from the high-risk registry arm of EVEREST II demonstrates 45% reduction in rate of re-hospitalisation. It estimates the savings resulting from reduced admissions are €18,144 (approximately £16,544) per year versus the cost of the Mitraclip procedure, estimated to be €23,472 (approximately £21,402). It estimates therefore that the cost to treat is recovered in 1.3 years. As above, caution needs to be exercised with this unpublished data.

Current activity

32. Of the various techniques for transcatheter mitral valve repair, MitraClip is at the most advanced stage. There are currently three centres in the UK who have performed 31 MitraClip procedures in total. Percutaneous techniques cannot yet match the sophistication of conventional surgical techniques and are therefore reserved for those whose co-morbidity prevents conventional surgery.

Future developments

33. The development of transcatheter mitral valve repair (TMVR) is currently some way behind TAVI and there are fewer patients not suitable for conventional mitral valve surgery. Like TAVI, TMVR repair may initially provide an option for otherwise inoperable patients.

34. It seems unlikely that percutaneous mitral valve repair will be able to match the excellent results of conventional surgical repair in the foreseeable future; however, the procedure may become a useful adjunct to the treatment of heart failure associated with dilatation of the left heart and functional mitral regurgitation.

[40] Franzen O. Mitraclip therapy in Europe: initial experience in patients with heart failure. J Am Coll Cardiol 2009;53
[41] Hermann HC, et al. Effect of percutaneous mitral valve repair with the Mitraclip device on mitral valve area and gradient. Eurointervention 2008;4:1-6

35. It is recommended that that in the first instance NHS resources should be targeted towards the development of specialist multidisciplinary teams who can evaluate the technology and its utility, and on the creation of a national UK-based registry into which all TMVR cased should be entered.

(iv) Percutaneous pulmonary valve procedures

36. Pulmonary stenosis accounts for about 8% of all congenital heart disease and can be treated effectively with percutaneous balloon valvuloplasty. Current indications for percutaneous pulmonary valve implantation are limited to patients who have pulmonary valve stenosis and/or regurgitation in a right ventricle-to-pulmonary artery conduit. This represents a very small group of patients, and so is not discussed further in this document.

(v) Percutaneous tricuspid valve procedures

37. Tricuspid stenosis is a rare valve disease almost always caused by rheumatic fever and coexistent with mitral stenosis. Severe tricuspid stenosis can also be treated percutaneously with good long-term results and a very low rate of re-stenosis/regurgitation. This also represents a very small group of patients, and so is not discussed further in this document.

Left atrial appendage occlusion devices

(i) Percutaneous occlusion of the left atrial appendage

Background

38. Cardiac embolism associated with atrial fibrillation (AF) is a common and preventable cause of stroke. The usual source of thromboembolism in AF is the left atrial appendage (LAA), a small hook-like structure arising from the left atrium, and the resulting stroke is commonly disabling or fatal.

39. Obliterating the LAA with a device that is implanted percutaneously offers the prospect of permanently eliminating the most important source of embolism in AF and is therefore a potential alternative to long-term therapy with warfarin or other anticoagulants.

Technology

40. A multidisciplinary approach to patient selection is valuable and ideally, the team should include a stroke physician and a specialist in cardiac imaging as well as an interventional cardiologist. The procedure is performed in a cardiac catheterization laboratory under general anaesthesia with fluoroscopic and transoesophageal echo guidance. The combination of interventional cardiologist, anaesthetist and echocardiographer is the same as the team assembled for a number of other cardiological procedures.

41. Detailed cardiac imaging is used to measure the size of the LAA orifice. After passage of a catheter into the right atrium via the femoral vein, a transeptal puncture is performed to access the left atrium. The implant is then deployed into the LAA to close the appendage. Patients normally spend one night in hospital following the procedure and an echo to confirm position is performed prior to discharge.

42. At present, there are two commercially available LAA occlusion devices (Watchman and AGA), with others in development. The devices currently cost about £4000 each but are likely to become cheaper through market forces.

Evidence - *Clinical effectiveness*

43. The Embolic Protection in Patients with Atrial Fibrillation (PROTECT–AF) trial[42] is a multicentre, randomised but unblinded trial of the Watchman-Atritech LAA occlusion device. 707 patients were randomly assigned to conventional warfarin therapy or the Watchman device plus short-term (45 days) warfarin therapy (2:1 - device: closure) and followed for up to 4 years. In total 463 patients were randomised to device closure and 244 patients to warfarin alone.

44. The aim of the trial was to demonstrate equivalence (non-inferiority) of the LAA occluder (Watchman device) to long-term warfarin therapy using the composite primary endpoint of ischaemic and haemorrhagic stroke, cardiovascular and unexplained death, and systemic embolism.

45. However, after 900 patient years of follow up the primary event rate was 32% lower in the LAA occluder group. In particular the risk of a haemorrhagic stroke was much lower in the LAA occluder group (0.2% vs 1.8%), with a reduced overall stroke rate (2.6% vs 3.5%).

46. The procedure related hazards of device implantation were significant. Pericardial effusion needing drainage or surgery was reported in 5% of patients. A peri-procedural stroke was observed in 1.1% of patients and almost 1% of the devices dislodged and had to be removed surgically. As might be expected the frequency of these complications reduced as the participating centres became more experienced. The projected rate of major complications in experienced hands is less than 2%, but nevertheless still very significant.

47. Although there was a higher rate of adverse events in the intervention group than in the control group, events in the intervention group were mainly a result of peri-procedural complications. The study concluded that occlusion of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

Evidence - *Cost effectiveness*

48. Cost effectiveness calculations for LAA have been made based on the following assumptions: the cost of a stroke due to AF is £11,900 in the first year[43] (assumed to be per year) and the cost of one year of anticoagulation with dabigatran is £1500[44]. The cost of a LAA device is £4000. These figures have been incorporated into three different scenarios:

49. Scenario 1: High-risk stroke patient (10% annual chance of stroke but unable to be anticoagulated because of bleeding problems). In this highly selected population, the device cost for ten patients (£40,000) is recouped in just over three years, as the natural history of ten untreated patients will cost £11,900 per year (one preventable stroke per year in ten patients).

50. Scenario 2: medium to high-risk patients where LAA device is used as an alternative to long-term anticoagulation. The cost of anticoagulation (with Dabigatran) is £1500 per year. The cost of a LAA device is recouped if three to four years of anticoagulation is avoided. This strategy would need more clinical evidence to be feasible.

51. Scenario 3: LAA occlusion in addition to anticoagulation to prevent stroke in high-risk patients. This strategy would need a large trial to demonstrate benefit and the cost effectiveness would be based on stroke prevention to demonstrate benefit. For example warfarin/ Dabigatran reduces absolute

[42] Holmes DR, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet.2009 Aug 15; 374(9689):534-42
[43] Department of Health Atrial Fibrillation cost benefit analysis. Marion Kerr, 2008
[44] British National Formulary. According to the BNF, the current costs for dabigatran 110mg is £2.10 per capsule; this equates to about £1500 for a year's course when given twice daily

risk of stroke from 5-10% per year to 2-3% per year. A LAA occluder could reduce the absolute risk from 2-3% per year to perhaps 1% per year. So 100 patients would need devices costing a total of £400,000 to prevent one stroke costing £11,900 per year. This strategy requires more evidence of clinical and cost-effectiveness.

Current activity

52. Although, the procedure is already commonplace in some European centres (for example in Frankfurt and Berne) less than ten percutaneous closures of the LAA have been carried out in England to date.

53. Currently LAA occlusion is thought to be a good option for a small number of patients with AF who are at high risk of an embolic stroke in whom long term anticoagulation is problematic. Recurrent bleeding with warfarin or Dabigatran is likely to be the main reason why some patients are unable to be maintained on these drugs in the long term. It should be remembered that short term anticoagulation (45 days) was used in patients undergoing LAA occlusion in the PROTECT-AF study.

Future developments

54. The indications for LAA occlusion may expand considerably if the safety and efficacy of the procedure improves. The costs of the device must be set against the cost of long term treatment with warfarin (including monitoring) or Dabigatran (see Appendix D). Moreover, the cost of the different treatment strategies will need to be weighed against the enormous human and financial costs of a stroke due to AF, estimated to be £11,900 per stroke in the first year alone[45].

55. It is anticipated that LAA occlusion will become an important treatment for a small number of highly selected patients in the next five years. As the technology improves, and the procedure becomes safer and perhaps less expensive, the indications may expand to offer an alternative to long-term anticoagulation in many patients. However, any increase in demand may be mitigated by the emergence of newer anticoagulant strategies (see Appendix D).

(ii) Minimally invasive surgical approach to LAA occlusion

56. An alternative to the percutaneous approach is the minimally invasive surgical approach. It has been found that the Gillinov-Cosgrove LAA exclusion system, the Atriclip (manufactured by Atricure), offers a safe and effective way to exclude the LAA from the epicardial aspect of the heart.[46,47] The procedure is undertaken under general anaesthetic, through a small incision in the chest wall and the device is implanted under thoracoscopic guidance. Post-operative length of stay is approximately two to three days, usually requiring just ward-based care. The Atriclip can be used for both open and thoracoscopic occlusion of the LAA and can be combined with open or thoracoscopic AF surgery as well as other forms of open surgery (for example mitral valve surgery).

57. The price in the UK is £650 each including the sizing device – this represents a considerable cost reduction when compared to percutaneous closure devices. One centre in England has implanted 15 to date, three of which have been done thoracoscopically. All of these procedures have been done as part of another procedure - the thoracoscopic procedures were done as part of a thoracoscopic AF ablation. This approach may prove to be very cost effective and further debate about its role in relation to the percutaneous alternatives is warranted.

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[45] Department of Health Atrial Fibrillation cost benefit analysis. Marion Kerr, 2008

[46] Salzberg SP, et al. Surgical left atrial appendage occlusion: evaluation of a novel device with magnetic resonance imaging. Eur J Cardiothorac Surg. 2008;34:766-70

[47] Salzberg SP, et al. Left atrial appendage clip occlusion: Early clinical results. J Thorac Cardiovasc Surg. 2009 Oct 30. [Epub ahead of print]

Closure devices

58. Some abnormal communications in the circulation can be closed percutaneously by deploying a carefully sized device delivered over a guide wire introduced through a vein or artery. These procedures are usually carried out in a cardiac catheterization laboratory, often under general anaesthesia, by specialist teams. They can be used to treat a variety of congenital and acquired defects that would otherwise require major surgery.

(i) Atrial Septal Defect

Background

59. Atrial septal defect (ASD) is one of the commonest congenital heart defects (with an incidence of 1 in a 1000) and results in 'shunting' of blood from the left to the right atrium. The flow of blood through the lungs is increased and there is progressive enlargement of the right side of the heart. The condition is often asymptomatic in early life and is often detected as a result of routine examination. If left untreated, pulmonary hypertension, atrial fibrillation, heart failure, and stroke may supervene. Unless the size of the defect is very small and the patient asymptomatic, closure is advised in order to minimise symptoms and avoid long-term complications. About 75-80% of ASDs can be closed percutaneously. Open-heart surgery remains the best option for patients with very large defects (where there is no rim to anchor the closure device) and those with associated abnormalities such as mitral regurgitation due to a cleft mitral valve.

Technology

60. Endovascular closure of an atrial septal defect is usually carried out in a cardiac catheterisation laboratory under general anaesthesia with transoesophageal echocardiography and fluoroscopic guidance. A guidewire and delivery sheath are passed through the defect, via a femoral vein; an appropriately sized occlusion device is then introduced and deployed across the defect. The closure is usually effective for the patient's lifetime.

61. The three commercially available devices for percutaneous ASD closure in adults cost approximately £3,000 each.

Evidence - *Clinical effectiveness*

62. This procedure has been evaluated and recommended by NICE[48]. Endovascular closure is successful in 97% of cases but a small proportion of patients are left with a residual shunt. Complication rates are low and include malposition of the device requiring surgical retrieval (1%); stroke (0.1%) and cardiac tamponade (0.1%)[49].

Evidence - *Cost effectiveness*

63. The increase in device cost associated with percutaneous ASD closure is likely to be offset by a shorter hospital stay, however little published cost-effectiveness data exists.

[48] NICE Interventional Procedure Guidance 96 (Oct 2004)
[49] Ibid

Current activity

64. The procedure rates reported to CCAD for the UK show that total number of ASD closure have fallen in recent years (figure 2), with an overall increase in the number of percutaneous procedures performed over the last ten years, and corresponding fall in surgical procedures (figure 3).

Figure 2: Total number of ASD closures entered into CCAD database (UK):

Year	Total ASD closures
2000	742
2001	750
2002	857
2003	1056
2004	1048
2005	1190
2006	1251
2007	1200
2008	1058

Figure 3: ASD closures by surgical (open) and catheter (percutaneous) procedures entered into CCAD database (UK):

Year	*Surgical*	*Catheter*
2000	*458*	*284*
2001	*496*	*254*
2002	*479*	*378*
2003	*555*	*501*
2004	*526*	*522*
2005	*629*	*561*
2006	*645*	*606*
2007	*612*	*588*
2008	*549*	*509*

Future developments

65. It is predicted that over the next five to ten years the numbers of patients undergoing percutaneous ASD closure may grow modestly. This is likely to be offset by a fall in the number of open surgical procedures with minimal cost implications. Consideration will need to be given to re-balancing the necessary resources.

(ii) Persistent Foramen Ovale

Background

66. The fetal circulation allows oxygenated blood from the placenta to pass into the left heart through a hole in the atrial septum known as the foramen ovale. This usually closes spontaneously after birth; however, in as many as a quarter of people, the foramen ovale does not close completely and remains patent throughout life. In most people, the persistence of a patent foramen ovale does not cause any complications. However, the defect may operate as a flap valve opening when intrathoracic pressures rise during coughing, sneezing or straining at stool. This can result in intermittent shunting of de-oxygenated blood from the right to the left atrium and even paradoxical embolism (thrombi from the venous system crossing into the systemic circulation).

67. PFO can be implicated in the pathogenesis of
    - stroke
    - migraine with aura
    - decompression sickness in divers.

68. These problems are more likely to occur if the PFO is large or occurs in association with an aneurysm of the atrial septum and, in some cases, may merit percutaneous closure.

Technology

69. Diagnosis is usually confirmed by transthoracic or transoesophageal contrast echocardiography. The procedure is similar to ASD closure (see above), takes around an hour and is usually undertaken as a day case in the cardiac catheterisation laboratory under general anaesthesia with fluoroscopic and echo guidance.

70. There are currently seven commercially available devices available in the UK costing approximately £3000 each.

Current activity

71. Percutaneous closure of PFO is an increasingly common procedure (see figure 4), with a well established record of safety and long-term clinical efficacy.

    Figure 4: Number of PFO closures in adults entered into CCAD database (UK)

Year	Procedures (adult)
2000	1
2001	7
2002	13
2003	39
2004	104
2005	231
2006	410
2007	517
2008	461

    NB Coverage is not complete and growth rates may have been overestimated due to initial under-reporting.

72. In a German series of 1,349 patients[50] the primary indication for PFO closure was stroke prevention in all but a handful of cases:
    - stroke in 696 (51.6%),
    - transient ischemic attack in 610 (45.2%),
    - paradoxical embolism (not to the brain) in 22 (1.6%),
    - decompression sickness in 13 (0.9%),
    - others, including migraine, in 6 (0.4%)

73. The three main indications for PFO closure (stroke, migraine with aura and decompression sickness in divers) are considered below.

[50] Staubach S, et al. New onset atrial fibrillation after patent foramen ovale closure. Catheter Cardiovasc Interv. 2009 Nov 15;74(6):889-95

(ii-i) Stroke

Background

74. Stroke prevention is the main indication for closing a PFO, estimated to account for almost 97% of PFO closures[51]. The lifetime risk of stroke in people with a PFO is less than 1/1000 and does not justify the cost and risk of routine closure. However, there is a strong case for closing the defect in patients who have already had a stroke and are thought to be at a high risk of recurrent stroke due to paradoxical embolism. About 40% of stroke patients (mainly younger patients) have no recognized cause of stroke (cryptogenic stroke) and approximately 40% of these patients will have a PFO. In one series the prevalence of PFO was significantly greater among patients with cryptogenic stroke compared to those with stroke of known cause in both younger (43.9% vs 14.3% for those less than 55 years old) and older patients (28.3% vs 11.9% for those aged 55 or more)[52]. There is a particularly strong association between cryptogenic stroke and the presence of a PFO with concomitant atrial septal aneurysm; moreover, the risk of recurrent stroke in such patients has been reported to be as high as 15.2% at 4 years[53].

Evidence - *Clinical effectiveness*

75. The optimum strategy for preventing recurrent strokes in people with PFO remains controversial and will not be clear until trials comparing antithrombotic treatment with transcatheter PFO closure are complete.

76. One study[54] followed 620 patients who had PFO repair with the Amplatzer device for secondary prevention of paradoxical embolism: contrast transesophageal echocardiography at 6 months showed complete closure in 91% of patients, whereas a minimal, moderate, or large residual shunt persisted in 6%, 2%, and 1%, respectively. During a mean follow-up period of 3.0 +/- 1.9 years (median: 2.6 years; total patient-years: 1,871), 5 ischemic strokes, 8 transient ischemic attacks, and no peripheral emboli were reported. Freedom from recurrent ischemic stroke, transient ischemic attack, or peripheral embolism was 99% at 1 year, 99% at 2 years, and 97% at 5 years. Five procedural complications were noted (0.8%): four arteriovenous fistulae requiring elective surgical correction, and one transient ischemic attack.

77. The UK/European study PC-Trial compares the efficacy of percutaneous closure of PFO using the Amplatzer PFO occluder device with medical treatment (aspirin, clopidrogrel or dypyridamole) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale. This randomized, multi centre clinical trial, is expected to report in 2011, but involves only 414 patients and may prove to be underpowered.

78. The NMT Medical sponsored CLOSURE I trial in the USA is a prospective, multicentre, randomised, controlled trial to evaluate the safety and efficacy of the STARFlex closure system in patients with a stroke and/or transient ischemic attack due to presumed paradoxical embolism through a PFO. It has recruited around 900 patients and compares best medical therapy (aspirin or warfarin) with device closure and is expected to report in April 2010.

79. Unfortunately these trials may be outmoded by the advent of new antithrombotic therapies such as Dabigitran (see appendix D).

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[51] Staubach S, et al. New onset atrial fibrillation after patent foramen ovale closure. Catheter Cardiovasc Interv. 2009 Nov 15;74(6):889-95

[52] Handke M, et al. Patent Foramen Ovale and Cryptogenic Stroke in Older Patients. Lancet 2007; 357 : 2262-8

[53] Mas JL, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm or both. New England J Medicine 2001; 345: 1740-6

[54] Wahl A, et al. Late results after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism using the amplatzer PFO occluder without intraprocedural echocardiography: effect of device size. JACC Cardiovasc Interv. 2009 Feb;2(2):116-23

Evidence - *Cost effectiveness*

80. Limited data of cost effectiveness is available until trials currently underway report.

Current activity

81. In England, practice is currently extremely variable, with significant inequalities in access, and a five-fold difference in utilization of PFO closure for stroke between regions. This probably reflects differences in the approach to the assessment and treatment of stroke patients and strengthens the case for establishing a well-resourced and consistent approach to the evaluation of cryptogenic stroke.

Future developments

82. There are strong grounds to believe that percutaneous closure of a PFO will become an important component of secondary prevention in a proportion of stroke patients. The precise indications for closure and the potential number of patients who might benefit from this therapy will depend on the outcome of trials that are due to report shortly.

83. In the next five years, resources should be focused on establishing appropriate mechanisms to detect patients who are at high risk of recurrent stroke due to PFO. This may lead to a significant (possibly two fold) increase in the number of patients who are referred for percutaneous closure. It is suggested that new funding for PFO closure should be conditional on the provision of clinical audit programmes and a multidisciplinary approach to the selection of patients for PFO closure.

84. Longer-term demand for PFO closure following stroke will depend on the results of on-going clinical trials but is likely to be substantial. Moreover, it is conceivable, that the technique may also be used for the primary prevention of stroke among healthy people who are found to have a PFO as a result of an incidental finding or screening test, although it is felt this is unlikely to happen on a large scale in the next ten years.

(ii-ii) Migraine with aura

Background

85. There are approximately 600,000 people who suffer from migraine with aura in the UK, 60% of patients who experience migraine with aura are found to have a PFO. This is often quite large, and it seems likely that right to left shunting of blood may trigger migraine by exposing the brain to microscopic emboli or chemicals that are normally denatured in the lungs, Accordingly, it has been hypothesised that closure of PFO may lead to a reduction in the frequency and intensity of migraine attacks.

Evidence - *Clinical effectiveness*

86. There are many anecdotal reports of improvement or even abolition of migraine following closure of a PFO. However, the only completed randomized controlled trial produced equivocal results.

87. The Migraine Intervention with STARflex Technology (MIST) trial[55] is a prospective, randomized, double blind, placebo-controlled study of PFO closure for migraines, sponsored by device manufacturers NMT medical. 147 patients were randomized to receive the device or undergo a sham procedure. To qualify for enrollment, patients were required to have experienced migraine

[55] Dowson A, et al. Migraine Intervention With STARFlex Technology (MIST) Trial. Circulation. 2008;117:1397-1404

with aura and suffered from frequent migraines (5+ days/month) for at least 1 year. They also were required to have a moderate to large PFO and to be refractory to two types of migraine medication.

88. Although the study failed to reach its primary endpoint of complete elimination of migraine in 40% of closure patients, it demonstrated a statistically significant reduction in headache. Thus, patients who received the PFO closure implant demonstrated a 37% reduction in headache burden from baseline, while those who received the sham procedure showed a 17% reduction in headache burden, a difference that was statistically significant (*P* = 0.033). In addition, 42% of those in the implant group, compared with 23% in the sham group, demonstrated a 50% reduction in headache days (*P* = 0.038). Furthermore, diagnostic data from the trial appeared to confirm the link between migraine and large PFO shunts. A second trial, MIST II, is now underway; this has a longer follow-up period and a larger patient population but there are fears publication may be delayed by allegations of irregularities in the reporting of data from the first trial.

Evidence - *Cost effectiveness*

89. Data on cost effectiveness is awaited, and will largely depend on the outcome of the MIST II trial.

Current activity

90. Currently less than 0.4% of PFO closures are for migraine prevention[56].

Future developments

91. Screening migraine sufferers for PFO and closing the defects that are discovered could cost as much as £3 billion. Patient demand is bound to increase if the results of MIST II are positive and in that event NICE will need to issue guidelines, that take account of cost-effectiveness, for NHS practitioners. It is possible that only patients with severe and frequent migraine, refractory to drug therapy, will be offered PFO closure

(ii-iii) Diving

92. PFOs, particularly large defects, are implicated in some forms of decompression sickness. Bubbles of nitrogen gas are thought to pass across the PFO into the systemic circulation as the diver ascends and can trigger a wide variety of problems including severe and persistent neurological damage.

93. Less than 1% of all PFO closures are carried out for the prevention of decompression sickness in deep-sea divers. All professional divers are screened for PFO and treated preventatively, with private funding. A significant increase in the number of closures is not anticipated, and it is expected that this activity will continue, for the most part, to be funded privately. Routine screening and closure is not recommended for recreational divers because the risk of procedural complications usually outweighs the potential benefit.

[56] Staubach S, et al. New onset atrial fibrillation after patent foramen ovale closure. Catheter Cardiovasc Interv. 2009 Nov 15;74(6):889-95

Cardiac resynchronisation therapy

Background

94. Certain people with heart failure may benefit from cardiac resynchronisation therapy (CRT) to help synchronise the contractions of the heart and improve its pumping mechanism.

Technology

95. CRT involves implantation in the upper chest of a pulse generator from which three leads descend via veins into the heart. Leads are placed in the right atrium and the right ventricle, and a third lead (the left ventricular lead) is usually placed via the coronary sinus. Most patients who undergo a planned CRT procedure will spend two days in hospital.

96. CRT pacing (CRT-P) devices allow both regulation of atrioventricular delay and restoration of synchronous contraction by pacing the right atrium and both ventricles. A cardioverter defibrillator function can be included with the pulse generator to defibrillate the heart internally should a malignant ventricular arrhythmia occur, and in this case the device is known as a CRT defibrillator (CRT-D) device.

97. The estimated cost of the CRT-P device (and leads) is €5,808 (£5,296) compared to €19,977 (£18,218) for the CRT-D hardware[57].

Evidence - *Clinical effectiveness*

98. CRT is a highly effective treatment for a subgroup of patients with heart failure and in these patients improvements in both morbidity and mortality are seen when CRT is used in addition to optimal medical therapy.

99. The Cardiac Resynchronization-Heart Failure (CARE-HF) trial demonstrated that CRT improves cardiac function, symptoms, quality of life, and prognosis[58]. It noted these benefits are additive to, and similar or greater in magnitude than, those of pharmacological therapy. Longer-term follow up in this cohort of patients demonstrated that these benefits in morbidity and mortality persisted during a mean follow-up of 37.4 months. Reduction in mortality was due to fewer deaths both from worsening heart failure and from sudden death[59].

100. The COMPANION trial demonstrated that in patients with advanced heart failure and a prolonged QRS interval, cardiac-resynchronization therapy decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality[60]. Observations from the REVERSE trial also suggest that CRT prevents the progression of disease in patients with asymptomatic or mildly symptomatic LV dysfunction[61].

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[57] Calvert MJ, et al. Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. European Heart Journal (2005) 26, 2681–2688

[58] Cleland J, et al: Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. New Engl J Med 2005;352: 1539-49

[59] Cleland J, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure, the Cardiac Resynchronization-Heart Failure (CARE-HF) trial extension phase. European Heart Journal doi:10.1093/eurheartj/ehl099

[60] Bristow MR, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure for the COMPANION trial (The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), N Engl J Med 2004; 350:2140-50

[61] Daubert C, et al. REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE). J Am Coll Cardiol 2009;54:1837–46

101. Moderate or severe adverse events related to the implantation procedure occurred in 10% of patients in the pacemaker group and 8% of those in the pacemaker–defibrillator group. Included in these events were coronary venous dissection (0.3% in the pacemaker group and 0.5% in the pacemaker–defibrillator group), coronary venous perforation (1.1% and 0.8%, respectively), and coronary venous tamponade (0.5% and 0.3%, respectively)[62].

Evidence - *Cost effectiveness*

102. In a prospective within-trial cost-effectiveness analysis from the CARE-HF trial, one series estimated the incremental cost-effectiveness of CRT-P therapy (in addition to optimal medical therapy) to be €19,319 (£17,618) per QALY[63]. Another series suggested that long-term treatment with CRT-P appeared cost-effective compared with MT alone, and furthermore that from a lifetime perspective, CRT–D may also be considered cost-effective when compared with CRT-P + MT[64]. In this study, from a lifetime perspective in a 65-year-old patient, the incremental cost-effectiveness of CRT-P compared with MT was €7,538 (95% CI €5,325–€11,784) per QALY gained and €7,011 (95% CI €5,346–€10,003) per life year gained. The incremental cost-effectiveness of CRT–ICD compared with CRT-P is €47,909 (95% CI €35,703–€79,438) per QALY gained, and €35,864 (95% CI €26,709–€56,353) per life year gained. In addition, the positive impact on heart failure hospitalization observed in the COMPANION study suggests that, despite the high cost of these devices, they will be cost-effective in the long term.

Current activity

103. Currently, CRT is recommended as a treatment option for people with heart failure who continue to have severe symptoms (NYHA class III–IV), evidence of electrical dysynchrony on ECG and poor cardiac output, despite optimal medical therapy.

104. There is a good evidence base for the effectiveness of CRT but it is under-utilized according to current guidelines. This appears to be due to both low capacity (both in terms of skills and resources) and low referral rates.

105. In 2008, 4,800 CRT devices were implanted in the UK, a significant rise from previous years. This places the UK behind many European countries in terms of CRT implant rate: seventh out of 15 countries surveyed[65].

Future developments

106. In the future CRT will probably be used to treat patients with milder heart failure (NYHA class I/II), and as a rescue therapy for patients with acutely decompensated heart failure.

107. If every patient, who might benefit from CRT, as judged by the current NICE guidelines, is offered treatment this could lead to a five-fold increase in uptake.

[62] Bristow MR, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure for the COMPANION trial (The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), N Engl J Med 2004; 350:2140-50
[63] Calvert MJ, et al. Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. European Heart Journal (2005) 26, 2681–2688
[64] Yao G, et al. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. European Heart Journal (2007) 28, 42–51
[65] Heart Rhythm Devices: UK National Survey 2008

Radiofrequency ablation for atrial fibrillation

Background

108. Arrhythmias are initiated and sustained by abnormal electrical pathways or circuits in the heart. Drug therapy can control arrhythmias by altering the properties of these pathways but is unreliable and sometimes hazardous. Eliminating or destroying the pathway altogether offers the prospect of a complete cure and this is the goal of percutaneous Radiofrequency Ablation (RFA) procedures. These techniques involve placing catheters in the heart, mapping the electrical circuits, and then selectively destroying the abnormal tissue or pathway with radiofrequency energy.

109. RFA was initially used to treat arrhythmias associated with the Wolff Parkinson White syndrome, which is characterised by short-circuiting through a congenital accessory pathway bypassing the AV node. This pool of patients is decreasing as they have been successfully treated and the focus of RFA has shifted to treating other arrhythmias particularly atrial fibrillation (AF). Well over a third of all RFA procedures are now for the treatment of AF and this proportion is rising steadily.

110. RFA is primarily used as a means of achieving rhythm control and can benefit patients by reducing or even eliminating the need for anti-arrhythmic drug therapy.

Technology

111. RFA for AF is carried out in the cardiac catheterisation laboratory with the patient under sedation or general anaesthesia with most patients staying in hospital overnight. Catheters are guided into the heart and used to destroy or ablate the tissues that are thought to trigger and sustain AF. One goal is to 'isolate' the pulmonary veins from the left atrium and a wide range of techniques can be used. The procedure usually takes 3-4 hours, and effectively occupies the cardiac catheterisation lab, a cardiologist, technician, nurse, and radiographer for half a day. Simpler technologies in early clinical use (e.g. multi-electrode catheters, mesh catheters, freezing balloons), may reduce procedure time to less than two hours, enabling greater patient volumes to be undertaken.

112. The cost is approximately £2000 per case but there are additional costs related to developing the skill base and maintaining evolving infrastructures.

Evidence - *Clinical effectiveness*

113. There is some uncertainty about the efficacy and safety of percutaneous RFA for AF: it is quite a new technique that continues to evolve and heterogeneity has made it difficult to interpret trial and registry data. Defining success is also not straightforward; complete abolition or reduction in the frequency of the arrhythmia, elimination or mitigation of symptoms, and minimising the need for potentially hazardous anti-arrhythmic drug therapy and/or anticoagulation are all important end points but these are not always easy to measure.

114. The published literature suggests that about 75% of patients who undergo ablation for AF remain free of arrhythmia for 12 months with about 70% of patients reporting a marked improvement in symptoms following a single intervention; most of the rest will report some improvement and about 10-15% will require a second procedure[66]. There is no doubt that results are critically dependent on patient selection with the best outcomes being achieved in young patients with paroxysmal AF and structurally normal hearts.

[66] National Institute for Health Research HTA 2008; 12: 1-220

115. It is reasonable to suppose that correcting or preventing AF will improve the outcome, by avoiding the unwanted effects of drug therapy and reducing the long-term risk of heart failure and stroke due to embolism. However, this is not necessarily true because it is possible that some of the excess morbidity and mortality associated with AF is attributable to underlying or associated heart disease and not AF itself.

116. Good long-term trial and registry outcome data are obviously very desirable and all practitioners should therefore be required to collect and submit follow up information. The NIHR-funded Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is designed to test the hypothesis that in patients with new-onset AF a treatment strategy of catheter ablation is superior to rate control or anti-arrhythmic drug therapy to reduce mortality. Up to 3000 patients will be enrolled in this trial and will be followed for an estimated duration of five years. The trial recruited its first patient in November 2009 but will not report for several years.

117. Adverse events and complications are rare but can be significant. Peri-procedural mortality is less than 0.1% and is often due to perforation of the heart. Complications such as pulmonary vein stenosis and atrio-oesophageal fistulae are now less likely to occur with increased experience but continuing risks of stroke and a range of other severe but less common complications remain of concern.

Evidence - *Cost effectiveness*

118. The existing evidence regarding the cost-effectiveness of RFA for AF is rather sparse. The conclusions of the recent HTA '[that RFA] appears to be cost-effective if the observed quality of life benefits are assumed to continue over a patient's lifetime'[67] will clearly need support and ratification in the light of further emerging data.

119. The completion of properly designed prospective, randomized trials or (medical, economic, quality of life) outcome observational studies which would quantify the long-term effects of this therapy will delineate in which patients catheter ablation can exert tangible beneficial effects at an acceptable cost and will provide valuable evidence to optimize the organization of modern laboratories and maximize efficiency in health-care provision.

Current activity

120. RFA is now an established and very useful procedure for treating a small number of patients with AF, particularly young patients with paroxysmal AF and a structurally normal heart. However, the criteria for patient selection are widening; procedure rates are increasing:

Figure 5: number of RFA procedures for AF entered into CCAD database (UK)

Year	Cases
2001	2
2003	19
2004	26
2005	170
2006	332
2007	874
2008	1171
2009	1466

121. There is marked geographical variation in the utilisation of AF ablation.

[67] National Institute for Health Research HTA 2008; 12: 1-220

Future developments

122. It is anticipated that current trends will be maintained and the number of AF ablations in England will continue to rise. However, there are simpler, easier to apply, initially less expensive ways of managing AF, and the emergence of new anti-arrhythmic drugs and pharmaceutical alternatives to warfarin may reduce the impact of this technology. Developing the ability to effectively sub-stratify patients with AF in order to target those who are most likely to benefit from ablation will be of critical importance and can only be achieved through good audit and research.

Left ventricular assist devices

Background

123. Left ventricular assist devices (LVADs) were first used to support transplant candidates with rapidly failing circulation who were considered unlikely to survive until a suitable organ could be found (known as bridge to transplantation (BTT)) or to support acutely unwell patients until recovery of the heart (bridge to myocardial recovery (BTR)).

124. LVADs may also be used as long-term chronic support (LTCS), a destination therapy for people with end-stage heart failure (ESHF). Cardiac transplantation is accepted as the most effective surgical treatment for suitable patients with ESHF. However, the availability of heart transplantation is severely limited by the shortage of suitable donor hearts. In addition, patients undergoing heart transplantation are prone to rejection of the donor organ and to opportunistic infection, so that they are maintained on a range of immunosuppressive and prophylactic drugs for life.

Technology

125. Implantation of an LVAD is done under general anaesthesia through a chest incision; surgery usually takes several hours. The inflow pipe of the LVAD is inserted into the left side of the heart, usually the left ventricle, and the outflow pipe is inserted into the systemic arterial system, usually the aorta. The LVAD pumps oxygenated blood from the failing left ventricle into the systemic arterial system under pressure[68].

126. Over 30 types of VADs have been developed and have been termed first, second or third generation. These are expensive devices. In a study looking at BTT patients[69] mean VAD implantation cost, including device, was £63,830, with costs of VAD support for survivors of £21,696 in month one and £11,312 in month two. The cost of the device itself varies, but an estimate of the cost of one third generation device is £40,000.

Evidence

127. The clinical effectiveness of LVADs for their three main indications have been considered by NICE[70] and are summarised below.

[68] Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE guidance IPG177
[69] Sharples L, et al. Evaluation of the ventricular assist device programme in the UK NICE Health Technology Assessment 2006; Vol. 10: No. 48
[70] Clegg AJ, et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. NICE Health Technology Assessment 2005; Vol. 9: No. 45

Clinical effectiveness of LVADs as a bridge to transplant (BTT)

128. Despite relatively poor quality evidence, LVADs compared with other treatment options appear to be beneficial for patients with ESHF when assessed in terms of patient survival, functional status and quality of life. When compared with inotropic agents, LVADs appeared to provide a benefit in patient survival that increased with the length of support (difference in survival: 1 month 3%; 3 months 17%) and extended beyond heart transplantation (difference in survival: 1 year 24%; 4 years 30%).

129. Comparisons of the use of LVADs with usual care were less certain, with outcomes varying from no difference in survival to, or after, heart transplantation, to improved survival for LVADs patients to heart transplantation (survival difference: range 14–59%) and post-transplantation (difference in survival: 1 and 2 years 100%). Patients supported by an LVAD appeared to have an improved functional status compared with those on usual care. Also, patients with an LVAD experienced an improvement in their quality of life from before implantation of the device to the period during support.

130. The use of LVADs as a BTT is associated with risks of adverse events, with patients suffering mechanical device failures, bleeding, thromboembolic events, infections and re-operations. Adverse event rates varied between different LVADs and studies. The second-generation devices appear to perform better than the first generation ones but there is little or no long-term data to support this contention.

Clinical effectiveness of LVADs as a bridge to recovery (BTR)

131. Evidence of the clinical effectiveness of LVADs as a BTR for people with acute heart failure is also limited. Studies appear to show that the LVADs provide benefit in supporting patients until myocardial recovery. As there are no direct comparisons of different interventions, it is not possible to assess whether the LVADs are more effective than other alternatives or specific devices. No evidence was found to judge the effects of the devices on the quality of life or functional status of patients. Limited information on adverse events has been reported, although infections and bleeding are the main concerns.

Clinical effectiveness of LVADs as long-term chronic support (LTCS)

132. Limited evidence exists on the clinical effectiveness of LVADs as LTCS for people with ESHF. There is some evidence to suggest that LVADs provide benefits for patients in terms of improved survival, functional status and quality of life. The REMATCH trial provided good-quality evidence that the first generation HeartMate LVAD was associated with a statistically significant 48% reduction in the risk of death from any cause when compared with optimal medical management.

133. Actuarial survival was significantly higher for patients with the HeartMate LVAD compared with optimal medical management at one year (52% versus 25%) and two years (23% versus 8%) follow-up. Improvements in one-year survival were evident for patients aged under 60 years and those aged 60–69 years. However, the HeartMate LVAD was associated with twice as many serious adverse events than optimal medical management, with significantly higher rates of non-neurological bleeding and neurological dysfunction. Despite these adverse events, the benefits of these LVADs appear to outweigh limitations.

Evidence - *Cost-effectiveness*

134. An economic evaluation of LVADs for people with ESHF within the UK was undertaken by NICE in 2005[71]. It demonstrated that neither LVAD indication considered (BTT and LTCS) was a cost-effective use of resources.

135. Using a combined LVAD device and operation cost of £87,877, for the HeartMate device used as a BTT, the cost per QALY was £65,242. The BTT indication approaches cost-effectiveness only when the one-off costs associated with an LVAD fall considerably.

136. When used as LTCS, the NICE analysis showed that this is also not cost-effective. The baseline cost per QALY of the first-generation HeartMate LVAD was £170,616. Although the analyses recognise the benefits in terms of survival and quality of life, these were outweighed by associated increases in cost.

Current activity

137. Very few patients in the UK have received an LVAD and this has declined in recent years:

Figure 6: number of LVAD procedures entered into CCAD database (UK)

Year	Cases
2000	18
2001	10
2002	11
2003	20
2004	11
2005	18
2006	33
2007	47
2008	18
2009	5

Future developments

138. Uncertainty remains about the potential need and demand that may exist for this technology. With the limited and declining availability of donor hearts for transplantation, it appears that the future of this technology in its current form lies in its use as LTCS. The limited research available showed some clinical benefit for patients receiving LVADs as LTCS, but the economic evaluation suggested that they are currently not a cost-effective option.

139. In addition, as primary percutaneous coronary intervention (PPCI) becomes an increasingly common treatment for heart attack and more patients with cardiogenic shock are stabilised, the demand for temporary assist devices (as a bridge to myocardial recovery) may increase significantly. Currently this type of temporary assist is usually delivered by using an intra-aortic balloon pump (IABP); this offers a simple but less effective way of supporting the circulation. In addition, if LVAD technology becomes less expensive and easier to use, it may have a role in the treatment of this (potentially large) group of patients.

[71] Clegg AJ, et al. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. NICE Health Technology Assessment 2005; Vol. 9: No. 45

140. Although currently not cost effective, device costs will probably fall and with the possible addition of percutaneous VAD technology, it is conceivable that LVADs will become a cost effective option for the treatment of end stage heart failure within five to ten years.

Inducing therapeutic hypothermia after cardiac arrest[72]

Background

141. Approximately 57,000 people suffer an out of hospital cardiac arrest (OHCA) a year. Of all patients where resuscitation is attempted, 14% to 40% achieve return of spontaneous circulation and are admitted to hospital. Of those that survive to leave hospital, over 50% are left with permanent neurological sequelae[73].

142. Good quality cardiopulmonary resuscitation (CPR) and prompt defibrillation are key to the return of spontaneous circulation (ROSC). Following ROSC the aim is to limit further neurological decline and minimise subsequent morbidity and mortality, and one suggested intervention is the induction of mild therapeutic hypothermia (MTH).

Technology

143. The optimum initiation, method and duration of cooling are unclear[74]. Both invasive (eg endovascular cooling catheters, haemofiltration and coronary bypass) and non-invasive (eg cold fluids and ice packs) cooling methods have been developed and whole-body and brain-only cooling methods have been trialled. MTH is currently carried out almost exclusively in the intensive care setting, although some evidence suggests cooling should be commenced as early as possible after the return of spontaneous circulation, and that this can be safely achieved in the field using cold intravenous fluid. The three phases of therapeutic hypothermia include induction, maintenance and re-warming. For all phases, monitoring accurate core body temperature accurately is essential. The optimum length of time for which MTH should be maintained remains unknown, but previous studies have suggested maintenance periods of 12-48 hours.[75,76]

Evidence - *Clinical effectiveness*

144. Over 20 non-randomized studies examining MTH in OHCA have been published. The target temperature has consistently been 32°-34°C using a variety of cooling techniques. Reported favorable neurological outcome rates vary from 25 to 68%.

145. One systematic review published in 2006 reviewed the data from four RCTs representing 436 patients. Inclusion criteria were adults with primary OHCA who remained comatose after ROSC. The review concluded MTH had an NNT of five to improve neurological outcome and an NNT of seven to save a life. However, the review failed to draw conclusions on the optimum cooling

[72] With thanks to Clegg GR et al. Therapeutic Hypothermia in the Emergency Department following Out-Of-Hospital Cardiac Arrest – A Review. Accepted for publication in EMJ
[73] de Vreede-Swagemakers JJ, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997; 30(6):1500-1505
[74] Nolan JP, et al. Controversial Topics from the 2005 International Consensus Conference on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 2005; 67(2-3):175-179
[75] The Hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. N Engl J Med 2002; 346:549-56
[76] Bernard SA, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346:557-63

method, rate or duration of cooling. No evidence of treatment-limiting side effects was reported[77].

146. A recent Cochrane review[78] (examining five randomized trials with data on a total of 481 cardiac arrest survivors) agreed that inducing MTH improved survival and neurological outcome in cardiac arrest survivors within the first hours of restoration of spontaneous circulation. Again, no cooling specific adverse events were reported. The reviewers recommended further research evaluating practical methods for pre-hospital cooling, widening of inclusion criteria and comparisons of earlier (pre-hospital) with late (hospital) cooling. Safety reporting should include known and unexpected adverse events, and cost-benefit analysis.

147. There is strong evidence to support the use of MTH in the hospital setting after OHCA where the initial cardiac rhythm was Ventricular Fibrillation (VF).[79,80] The evidence supporting MTH use in other presenting cardiac rhythms is less clear and further studies are required. These data support the most recent recommendations from international guidelines[81]: 'unconscious adult patients, with spontaneous circulation, after out-of-hospital VF cardiac arrest should be cooled to 32-34°C for 12-24 h. Mild hypothermia may also benefit unconscious adult patients, with spontaneous circulation, after out-of-hospital cardiac arrest from a non-shockable rhythm or after cardiac arrest in hospital'. There are no robust data from randomised trials exploring the safety and effectiveness of inducing MTH in the pre-hospital setting, although trials are underway.

148. Whatever the cooling technique employed the degree of hypothermia induced is important; overcooling is potentially hazardous and careful core body temperature monitoring is mandatory. The risks of overcooling include infection, coagulopathy and cardiac arrhythmias[82].

Evidence - *Cost effectiveness*

149. Little cost effectiveness data exist, although the cost of cooling is likely to be offset by shorter ITU stays and a reduction in long-term need for health and social care.

Current activity

150. Despite strong evidence suggesting benefit, uptake of therapeutic hypothermia in routine clinical practice has been slow[83]. Lack of awareness, fear of a novel therapy and unknown side effects, as well as lack of equipment, have been cited as barriers to MTH implementation[84].

Future developments

151. Inducing MTH after OHCA offers the possibility of more patients surviving to leave hospital with good neurological function. The development of this technique over the next ten years depends on wider awareness, increased provision of equipment, and further research to evaluate safety and

[77] Cheung KW, et al. Systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. CJEM 2006; 8(5): 329-337
[78] Arrich J, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No: CD004128
[79] With thanks to Clegg GR et al. Therapeutic Hypothermia in the Emergency Department following Out-Of-Hospital Cardiac Arrest – A Review. Accepted for publication in EMJ
[80] The Hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. N Engl J Med 2002; 346:549-56
[81] Nolan JP, Morley PT, Hoek TL, et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advanced Life support Task Force of the International Liaison committee on Resuscitation. Resuscitation. 2003;57:231-5
[82] Merchant RM, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med 2006; 34(12 Suppl):S490-S494
[83] Merchant RM, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. Crit Care Med 2006; 34(7):1935-1940
[84] Acosta P, Varon J. Therapeutic hypothermia - from the bench to the bedside: are we there yet? Resuscitation 2008; 79(2):183-184

effectiveness of MTH induced in the ambulance. In line with international guidelines, it is suggested that this technique should be made available to every patient who would benefit within the next five years. Consideration should be given to new International Liaison Committee on Resuscitation consensus statements which are expected to be published later in 2010.

Stem cell therapy

152. Stem cell therapy offers the exciting prospect of repairing damaged hearts and has the potential to transform the management of heart failure and many other forms of heart disease. However, it is unlikely to become a mainstream activity in the next ten years (if at all). This is because we anticipate that it will take at least five years to complete proof of concept studies and initial clinical trials; moreover, even if such studies are positive they will have to be validated by one or two large scale, multi-centre, controlled trials.

153. There are currently no clinical trials in heart failure using embryonic stem cells and most investigators are using bone marrow derived cells. If England is going to contribute to worldwide research and development in this field, some cardiac centres will need access to facilities for generating the necessary stem cells. The haematology services may be able to contribute to this work but it may be preferable to develop a central facility.

154. Stem cell therapy for heart disease is unlikely to have significant implications for funding or health service delivery in the next ten years but will remain an important research activity.

Appendix C

Diagnostics

Remote monitoring of cardiac rhythm management devices

Background

1. Remote monitoring of cardiac rhythm management (CRM) devices is the transfer of follow-up information from the device to the physiologist and cardiologist without the patient leaving their home.

2. In recent years the number and complexity of CRM devices implanted into patients has increased exponentially, along with the evidence showing improvements in quality of life and reduction in mortality. Now each year in Europe, more than 900 pacemakers per million population are implanted for bradycardia, 130 implantable cardioverter defibrillators (ICDs) per million are implanted to prevent sudden cardiac death from ventricular tachy-arrhythmias and more than 90 devices per million are implanted to electrically resynchronise the heart and treat heart failure.

3. Following up the patient and their device is an integral part of this process and is required to maintain patient safety and optimise device performance. Follow-up has become increasingly complex and time-consuming due to the huge growth in the number and the functionality of devices.

4. Remote monitoring technology is available in new and many already implanted devices. The patients with most to gain are those whose clinic visits can be safely reduced e.g. elderly, immobile patients living far from the clinic with a pacemaker implanted for bradycardia with which there are no problems, and those who would benefit from closer monitoring e.g. a heart failure bi-ventricular

defibrillator (CRT-D) patient with difficult to control symptoms or frequent arrhythmias. Other patient groups with clear benefit are younger working patients where taking time off work is problematic and older patients who need either ambulance transport or transport from a relative to attend the clinic.

Technology

5. For some devices, the process requires the patient to initiate the remote follow-up by placing a wand over their device on a planned date or because of symptoms. Other devices can be monitored automatically through wireless technology. Data are transmitted over a standard telephone line or mobile telephone network to a secure website, which can be accessed by the clinical team at any time.

6. Battery longevity, sensing of intrinsic heart rhythm, lead impedance and threshold for pacing can all be monitored in this way; it is also possible to record the patient's intrinsic heart rate, significant heart rhythm abnormalities (eg. paroxysms of VT or AF) and important ECG changes (eg. ST elevation). Moreover, some implanted cardiac devices have the capacity to monitor heart failure status as well as cardiac rhythm and functioning of the device – through such things as transthoracic impedance, patient activity and heart rate variability - which can give up to a week's warning of impending clinical deterioration. Importantly, the clinical team can be automatically alerted to any data outside pre-specified limits.

7. It is difficult to give an accurate figure for the cost of remote monitoring because companies charge for it in a variety of ways, and negotiate separate rates with each user. Most now offer a price for a device which includes remote monitoring for the lifetime of that device. For example ICDs with wandless remote monitoring are estimated to cost 10-15% more then previous models with older technology, no wireless connectivity and no remote monitoring. One company has a model costing £10 per month per patient (a total of about £800 during the expected lifetime of an ICD).

Evidence - *Clinical effectiveness*

8. There is very little UK data on the utility of this technology. However, European studies have reported that it offers significantly earlier detection not only of device problems[85] but also the onset of arrhythmias such as atrial fibrillation[86]. Detecting AF at its onset allows early initiation of heart rate control and anticoagulation thereby potentially reducing subsequent admissions with heart failure or stroke.

9. Heart failure devices (CRT) can also monitor patients' physical activity, fluid status and/or haemodynamic parameters allowing early intervention in heart failure and thereby reducing emergency admissions. There are also new implantable devices for patients without rhythm management indications which can monitor these parameters in the same way. Patient surveys have demonstrated a preference for routine remote monitoring, with visits to the clinic limited to the occurrence of clinical or device problems.

Evidence - *Cost effectiveness*

10. Remote monitoring has the potential to use healthcare provider time more efficiently because it allows screening of data by less highly trained personnel with problems passed to specialists who can review data at a convenient time. The technology also reduces the need for clinic visits and frees time for the care of patients who need direct contact. International cost effectiveness analyses

[85] Nielsen JC, et al. Automatic home monitoring of implantable cardioverter defibrillators. Europace. 2008; 10:729-35
[86] Ricci RP, et al. Remote control of implanted devices through Home Monitoring technology improves detection and clinical management of atrial fibrillation. Europace 2009;11:54-61

have reported reduced numbers of clinic visits[87], reduced patient travel costs[88] and increased clinic efficiency[89]. The anticipation of patient decompensation by remote monitoring from an implanted CRM or monitoring-only device also has the potential to avoid emergency admissions. This will improve patient safety and reduce healthcare costs. An on-going multi-centre cost-effectiveness study (EuroEco) should provide further European data in the next two years.

11. The published cost savings are based on reduction in patient travelling expenses and are highly sensitive to the price charged by industry for access to the technology. For example, a French study[90] showed a reduction of two visits per patient per year which resulted in $2149 savings over five years. In this model the cost of the technology was recouped within 17 months for patients living 150km from the hospital and 52 months for those living less than 50km away.

Current activity

12. In the UK, usual practice is to follow-up patients with pacemakers soon after implant then annually until the pacemakers are nearing the end of battery life, and defibrillator and CRT patients six-monthly. Conventional device follow-up is performed in a booked outpatient clinic, interrogating the device using radio-frequency telemetry via a wand placed over the device. Most clinic visits are scheduled and most of these do not result in changes in device programming or clinical care.

13. Many of the cardiac rhythm devices implanted in the last three years can be remotely monitored, and some manufacturers are working to make older devices compatible with remote monitoring. However, few centres in England have moved to remote monitoring of rhythm management devices. A centre in Newcastle has more than 200 ICD patients under remote follow up, and reports that it receives an average of two alerts per week (1% of patients) which require subsequent action. Cost effectiveness estimates from this centre are awaited, and should be available later in 2010.

14. Currently the Payment by Results tariff for outpatient cardiology attendances reimburses trusts £94 per adult in-clinic follow-up attendance. New 2010/11 guidance[91] has clarified that the same tariff is payable for in-clinic and remote follow-up (previously only £23 was paid for non face-to-face appointments).

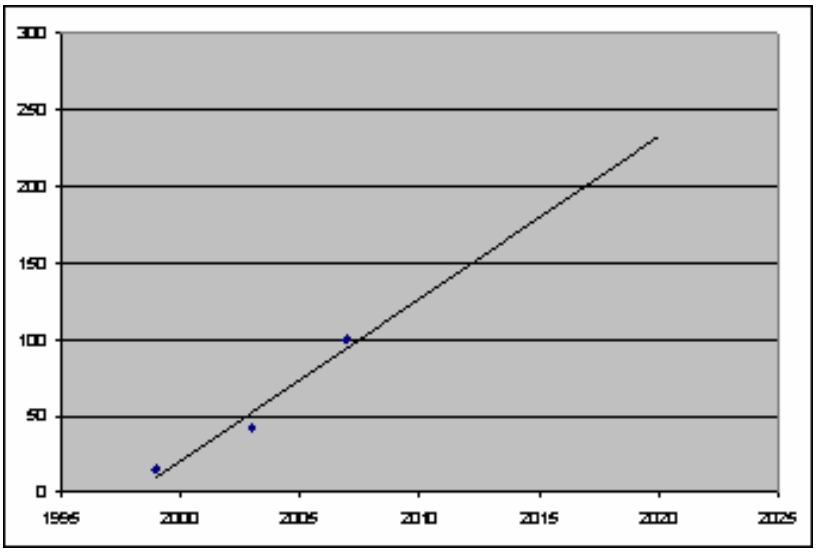
Future developments

15. 275,000 patients in the UK are living with a permanent pacemaker (this figure is projected to exceed 324,000 by 2015[92]), and 30,300 have an ICD or CRT device (projected to exceed 60,000 by 2015[93]). Further projections for ICD and CRT device implant rates are shown in *figure 7*:

[87] Heidbüchel H, et al. Potential role of remote monitoring for scheduled and unscheduled evaluations of patients with an implantable defibrillator. Europace. 2008;10:351-7
[88] Fauchier L, et al. Potential Cost Savings by Telemedicine-Assisted Long-Term Care of Implantable Cardioverter Defibrillator Recipients. PACE 2005;28:S255-9
[89] Ricci R, et al. Home monitoring in clinical practice. Europace 2008;10:164-70
[90] Fauchier L, et al. Potential Cost Savings by Telemedicine-Assisted Long-Term Care of Implantable Cardioverter Defibrillator Recipients. PACE 2005;28:S255-9
[91] Payment by Results 2010-2011 Guidance
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112284
[92] Figures from CCAD. The new implant rate is increasing, as is the number of deaths each year as the pacemaker patient population gets older. These figures are approximate, and do not take into account the increased demand for pacemakers due simply to the increased average age of the general population
[93] Figures from CCAD. These numbers are subject to some assumptions. Definite life status is not known for every patient, so total numbers are extrapolated from the 80% where life status is known for certain. 77% of ICD and CRT patients who were ever implanted are still alive, whereas for pacemaker patients the percentage still alive is only 50%

Figure 7: current and projected ICD and CRT-D implant rate (CCAD database (UK).

These projections give an ICD + CRT-D implant rate of approximately 100/million/year now, increasing to 175/million/year in 2015 and 230/million/year in 2020:



NB above projections are an estimate. It is difficult to be precise as implant rates are rapidly changing at present.

16. Almost all of these patients could benefit from remote monitoring of their devices. At present, there is no commercially available system which allows remote reprogramming of devices. However, the technology exists to do this and safety evaluations are underway. This has the potential to reduce in-clinic follow-up further by limiting it to wound and other physical problems.

17. Remote device follow-up is an important new technology, which has the potential to improve patient care and safety while at the same time increasing the efficiency of hospital device services. It allows a radical shift in the way patient care is delivered - from device follow-up to disease monitoring – moving from regular attendance at clinics to frequent unobtrusive device, patient and disease monitoring, and allowing early intervention to prevent decompensation and emergency hospital admission. This also has significant efficiency advantages: patient travelling is reduced, clinic time is reduced and patients can transmit data at a time convenient for them with data reviewed off-line in a “virtual clinic” at an efficient time by the most appropriate person.

18. Furthermore, it has the potential to enable a greater proportion of patients to be cared for by a specialist in heart failure. It is, however, important not to underestimate the administrative support for setting up and maintaining an efficient remote monitoring service. Further work is necessary to determine the optimum combination of data and how to present this (and how often) to the healthcare team in the best way to improve the outcome for patients. Additionally, the data obtained through remote monitoring could provide extremely valuable audit and research information.

Other roles of telecare

19. In addition to remote monitoring of cardiac rhythm devices, several other devices for telecare ranging from simple alarms and safety monitors to symptom, weight, blood pressure, and electrocardiogram monitoring devices are being used to remotely monitor patients and facilitate tailored support to individuals in their own home.

20. Telecare is likely to play an increasing role in the management of patients with heart failure, as outlined in NICE heart failure guidelines[94] on the need for patient monitoring and the need for management to be seen as a shared responsibility between patient and health care professionals. Indeed, improved utilisation of telecare in heart failure may enable more patients to receive specialist input, with a recent audit suggesting that 80% of patients admitted to hospital with heart failure have no subsequent contact with anyone with special interest or expertise in their condition[95]. Many PCTs are making plans to incorporate this technology into their traditional model of care. Further work is required to determine the best use of such technology: who to monitor, how to do this, for how long, and how this best fits with the conventional model of healthcare are key questions.

Imaging technologies

Non-invasive imaging in Coronary Artery Disease (CAD)

21. This topic is updated briefly here, and is discussed in detail in a report of the British Cardiovascular Society Working Group[96].

Acute coronary syndromes

22. The management of these patients is well established and imaging strategies are unlikely to change over the next ten years (PPCI for STEMI and angiography with the option of follow-on PCI for intermediate and high risk NSTEMI).

Chronic stable angina

23. Coronary angiography (CA) is the standard for determining the anatomical severity, extent and prognosis of coronary atheromatous disease. However, newer imaging techniques offer advantages that may make them more appropriate investigations for some patients.

(i) Established non-invasive imaging techniques: Myocardial Perfusions Scintigraphy (MPS) and Stress Echo (SE)

24. Both MPS and SE are well-established clinical tools. While each has strengths and weaknesses for most purposes they are interchangeable in expert hands. Each provides information about inducible ischaemia, previous infarction, myocardial viability and left ventricular function. In particular, a normal study using either method predicts a very low risk of serious cardiac events (<1% per year) and obviates further coronary investigation in the majority of cases. Either technique should currently be considered as the first or second-line imaging investigation in patients with chest pain although this may change in some patients with newer NICE guidance.

(ii-i) Myocardial Perfusion Scintigraphy (MPS)

25. MPS is an established test that is accurate for the detection of coronary disease and for assessing its prognostic value. Patients undergoing this test are subject to modest radiation exposure (approx 6-10mSv for a technetium study) but (as with CT), the trend will be for reducing exposure with new

[94] NICE guideline CG5: Chronic heart failure.
[95] Healthcare Commission. Pushing the boundaries: Improving services for people with heart failure. Service Review. Commission for Healthcare Audit and Inspection; 2007
[96] Gershlick, T, et al. Role of non-invasive imaging in the management of coronary artery disease: an assessment of likely change over the next 10 years. A report from the British Cardiovascular Society Working Group. Heart 2007 93: 423-431

solid-state gamma camera technology. MPS is usually led by a cardiologist, radiologist or nuclear physician and requires a gamma camera, and facilities to handle radiopharmaceuticals and stress patients. These are available in most hospitals.

(ii-ii) Stress echo (SE)

26. SE has similar accuracy to MPS for the detection of coronary disease in good hands. An advantage is that it does not involve ionising radiation, however the quality of the test is user dependent and skilled echocardiographers are not available in many hospitals. A standard echo machine is used.

Future developments (MPS and SE)

27. This is an area where there is limited investment. According to NICE, the demand for MPS is currently 4000/million pa, however only a proportion of this number of MPS scans are undertaken, despite the potential to reduce the need for CA by up to 50% (or perhaps more realistically by no more than 25%).

28. As with all of the technologies, scintigraphic imaging is evolving and important changes will be decreased imaging time, decreased radiation exposure and a possible shift from SPECT towards PET if suitable tracers and cameras fulfil their potential. Developments that are likely to affect practice can be summarised as follows:

- Robust attenuation correction techniques using X-ray transmission imaging will reduce artefact and add greater objectivity to image interpretation
- Tomographic reconstruction techniques such as iterative reconstruction with scatter correction and resolution recovery will improve image quality and/or allow equivalent information to be obtained with reduced radiation exposure or shorter acquisitions. Dose reductions of half to a quarter are realistic.
- SPECT-CT and PET-CT cameras will provide simultaneous assessment of coronary anatomy and function and will provide more precise mapping of perfusion abnormalities to coronary territories.
- Sensitive solid-state cameras with rapid dynamic acquisitions will lead to further dose reductions, and dynamic imaging may provide reliable quantification and measurements of myocardial perfusion reserve for better assessment of small vessel function.
- Affordable dedicated cardiac PET cameras will provide access to higher resolution and quantifiable techniques in routine practice, if they can be combined with a suitable PET perfusion tracer.
- Rubidium-82 generators for myocardial perfusion PET may become more widely available, but a fluorine-18 labelled perfusion tracer is currently entering phase III trials and, if successful, may drive the nuclear cardiology field from SPECT to PET using lower cost dedicated cardiac PET cameras.
- Imaging of sympathetic innervation using iodine-123 mIBG has prognostic value in patients with heart failure, and trials are currently underway to assess its value in predicting response to resynchronisation and implanted defibrillator therapy.
- Phase imaging of inter- and intra-ventricular synchrony using either myocardial or blood pool labelling may also develop a role in predicting response to resynchronisation pacing.
- Radio-labelled tracers of plaque components with either external imaging or non-imaging intravascular radiation detectors are attractive in a research setting for assessing plaque evolution and stability but they are unlikely to have a clinical impact within 5 years.

29. There are two recent major technology advances in echocardiography that can improve diagnostic accuracy and reduce operator dependent variability in SE: intravenous (transpulmonary) contrast agents and real-time three-dimensional echocardiography (3DE). Recent national and international

guidelines[97] recommend the use of contrast agents during SE. Implementation requires upgrades to standard echocardiography machines (image acquisition and post processing) but is currently available on premium machines. The cost of contrast agents is £20-50 per patient. Real time 3DE is a technological advance that has a number of applications. In SE, single beat application of the entire left ventricle with (semi-automated) offline multi-segment analysis has been shown to improve quantitative assessment of LV function. 3DE is discussed in more detail in the non-CAD imaging section below.

(ii) Non-invasive imaging techniques in development

Cardiac Magnetic Resonance (CMR)

30. CMR is a technique free of ionising radiation. It is currently the standard for quantifying ventricular function, and it is increasingly becoming the standard for determining myocardial viability. CMR is valuable in the assessment of cardiomyopathy and heart failure. Stress perfusion CMR imaging has spread into mainstream clinical use with performance similar to MPS[98], with particular advantages in patients with prior revascularisation or infarction, but long-term outcome data is currently limited compared to MPS.

31. Availability is limited with only a few centres swapping completely from MPS in the UK at this time. Issues of staffing, machine time and throughput may need to be overcome to allow perfusion imaging to achieve its potential. The development of newer contrast agents with properties more akin to microspheres may allow alternative and novel ischaemic imaging strategies. CMR is valuable for assessment of coronary anomalies but will not impact on coronary atheroma imaging in the foreseeable future given its lower resolution compared with CT. Plaque imaging and sub-typing in the aorta and carotid arteries is a potentially important development but it is currently some way from having clinical relevance. The inability to scan patients with a permanent pacemaker/ implantable cardioverter defibrillator is a problem although device manufacturers are currently addressing this.

Future developments

32. CMR may challenge the established non- invasive tests, particularly MPS, in patients with established disease, if its cost effectiveness can be established. It is likely to reduce the need for CA by up to 25% over the next 10 years. It is unlikely to replace CA when images of coronary anatomy are required.

X-ray Computed Tomography (CT)

33. Currently CT is the best non-invasive test for demonstrating coronary anatomy with real potential to improve as the number of detector rows increases and other technological advances arise. Important current applications include imaging of coronary grafts and anomalous coronary arteries. The high negative predictive value of a normal coronary CT scan effectively excludes coronary disease in low risk patients. It provides limited functional data—for example, LV wall thinning and systolic function—although developments are ongoing.

Coronary Calcium Scoring:

34. Levels of coronary calcification can be assessed by prospectively gated CT with a low radiation dose. Calcium scoring has been promoted as an initial screening investigation in those patients considered at low risk of suffering from ischaemic heart disease. Patients judged to be at low risk of

[97] www.bsecho.org
[98] Schwitter J, et al. MR-IMPACT study. European Heart Journal 2008. 29, 480-489

having CAD, would undergo a CT from which a calcium score would be obtained. The negative predictive value of this test is very high (approaching 99%).

Coronary CT angiography (CCTA):

35. The additional use of IV contrast allows an accurate assessment of the coronary lumen and the extent and severity of coronary atheroma. Unlike invasive angiography the vessel wall is imaged providing additional information on the nature and extent of plaque. In the future assessment of plaque morphology may play a more important role in the management of coronary disease.

36. While cardiac gated CT may expose patients to a significant dose of radiation, newer techniques reduce this exposure to levels below those of invasive angiography. The confounding effects of significant calcification is an important drawback for CT, as are the potential nephrotoxic effects of iodinated contrast and the need for a low heart rate when performing prospectively gated scans. CT alone does not give any indication of ventricular function under stress, so patients with an abnormal CCTA or significant coronary calcification may need some form of functional assessment before or during intervention.

Future developments

37. Calcium scoring is recommended as a first line investigation for patients with chest pain and a low pre-test probability of coronary disease (NICE chest pain guideline CG95, published March 2010). Patients without coronary calcium would have no further investigations. Those with an intermediate calcium score would go on to have CCTA. Patients at intermediate risk of having CAD, would undergo non-invasive functional imaging, with MPS, SE or CMR. Patients in whom the pre-test probability is high, or those who have abnormal CCT, will undergo invasive coronary angiography or non-invasive functional imaging. If calcium score using MDCT becomes a first line investigation then this modality will expand considerably.

38. There is concern to ensure that the use of CT at a very early stage in the investigation of patients presenting with chest pain does not lead to increasing numbers of other investigations. While it has been proposed that the exercise test be partially replaced by the CT determined calcium score, many would suggest that the ETT is still important as part of the investigation of patients who may have coronary artery disease.

Future developments (coronary artery imaging in general)

39. The prediction of future demand for non-invasive coronary artery imaging is difficult to estimate because of rapid technological advances, but there is likely to be a significant increase, particularly in CT and CMR. Each technique has its advantages and disadvantages and no modality is likely to dominate. The newer techniques of CMR and CT may have advantages in terms of resolution and speed, but at present they lack long-term prognostic data. They do however appear to have similar accuracy for detecting coronary disease as existing techniques.

40. It is important that every cardiology unit has access to the different imaging modalities. There is a need for more consultants to be trained in cardiac imaging and this should cover all modalities, and be approached jointly by cardiologists, radiologists and nuclear physicians. Professional groups need to develop new training curricula that might be open to trainees from both cardiology and imaging backgrounds.

Imaging in non-Coronary Artery Disease (CAD)

41. The major modalities of imaging in cardiac conditions not directly related to CAD (including heart failure/heart muscle disease, heart valve disease and congenital heart disease) are echocardiography, CMR and CT. The mainstay of non-CAD cardiac imaging is echocardiography. CMR and CT provide high quality imaging in specific settings but their utility and application is far less widespread.

42. Future developments in CMR and CT are discussed in the previous section.

Future Developments in Echocardiography

43. Advances in conventional ultrasound technologies that improve echocardiographic image quality and new data processing techniques such as speckle tracking, strain and torsion analysis, and automated quantification, will be incorporated into premium echocardiography machines in an evolutionary fashion. These technologies are not discussed in detail in this document. Other new techniques (i.e. new equipment, expertise and implementation) include real-time three-dimensional echocardiography (3DE), intracardiac echocardiography (ICE) and miniaturised probes.

44. 3DE has been shown to improve the accuracy of quantitative assessment of left ventricular (LV) size and function. Evidence-based applications include the regional and global assessment of LV function and dyssynchrony in heart failure. 3DE (in particular using transoesophageal imaging) enhances the assessment of structural heart conditions, including heart valve disease. Since this technology can be used during cardiac surgery and/or catheter-based procedures, 3DE facilitates improved imaging during mitral valve repair and some percutaneous ASD/PFO closure techniques. 3DE is therefore almost certain to be more widely utilised in hospital based echocardiography departments**.** Set up costs include the addition of 3DE ultrasound processing (approximately £30,000, in addition to the cost of the echocardiography machine), 3DE probes (TTE and TOE, approximately £10-20,000 each) and 3D analysis software (approximately £10,000).

45. Advances in technology involving miniaturisation of ultrasound probes that are capable of full cardiac imaging (two-dimensional echocardiography, colour flow mapping and spectral Doppler) are utilised in Intracardiac Echocardiography (ICE) and Nasogastric Echocardiography (NGE).

46. ICE is a recently established technique that utilises 9-10 French ultrasound probes introduced via the femoral vein and advanced into the heart, giving high-resolution images of near field intracardiac structures (especially the atrial septum and pulmonary veins). This approach, during catheter-based procedures, can be used for ultrasound guidance of percutaneous procedures such as PFO closure, LA appendage occlusion and ablations (with consequent reduction in radiation exposure etc.). It obviates the need for TOE (and hence general anaesthesia) when used during interventional procedures and has proven to be both clinically and cost effective in this setting. ICE is used with conventional echocardiography machines. Its main limitation is the single-use nature of the ICE catheter probes, which currently cost approximately £1200 each. ICE is likely to become more widely utilised in major cardiac units performing complex cardiac interventions.

47. The use of miniaturised ultrasound probes, designed initially for use in paediatric TOE, can be regarded as a potential new technological advance. The indications for use are likely to include ultrasound guidance of catheter-based procedures (see above – ICE). Utilising a miniaturised multiplane TOE probe, inserted via the nasogastric route, would obviate the need for general anaesthesia in the prone patient undergoing cardiac catheterisation. It has potential advantages over ICE in this setting - a wide field of view and reusable (sterilisable) probes. Nasogastric echocardiography is not currently available commercially - cost is likely to be approximately £20,000 per probe. This may become a more cost effective alternative to ICE in major cardiac units performing complex cardiac interventions.

Point of care testing

(i) Biochemical markers of cardiac damage in emergency care

Background

48. Acute chest pain is responsible for around 700,000 patient attendances per year in England and Wales, and around a quarter of all emergency hospital admissions[99]. Many of these patients have a benign cause of chest pain but are detained in hospital in order to rule out an acute coronary syndrome by measuring troponin a minimum of 12 hours after the last episode of chest pain.

49. Three innovations offer the prospect of more efficient, more rapid and more reliable risk stratification of patients with chest pain; they are
    - point of care testing (obviating the need to involve a central lab)
    - using new markers that are released more rapidly than troponin
    - assaying multiple markers simultaneously (greater sensitivity and specificity)

50. It is important to stress that clinical evaluation remains paramount and that the results of biochemical assays can only be interpreted in the light of the clinical findings.

51. Nevertheless, a point of care (POC) test using markers of myocardial damage to deliver faster results and avoid unnecessary hospital admissions would save valuable health service resources as well as finding favour with the patient.

Technology

52. POC involves testing blood samples from patients taken at arrival in the emergency department and then again, 90 minutes later, in order to detect markers of myocardial damage, which are released from damaged tissue at different times after injury. There is some disagreement as to which marker of myocardial damage should be included in the POC test – there is currently only one validated POC test in England which uses creatine kinase MB (CK-MB), myoglobin (myo), troponin I (Tn I) and lactate dehydrogenase (LDH). Other markers of cardiovascular risk including BNP and hs-CRP have been used in some countries, however as these assays remain under patent the cost is high. Heart fatty acid-binding protein (H-FABP) has also been advocated[100].

53. POC testing can be carried out using a device in the emergency department, for around £26 per patient (which includes two tests, baseline and 90 minutes later). However, the cost is likely to fall as a result of market forces. This model is more expensive than a lab based system, and also requires those using it to be well trained. In an emergency department, with rapid change over of medical staff, this can be difficult to achieve, and the involvement of the hospital's central chemical pathology service will be vital to quality control.

Evidence

54. The RATPAC Trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) is a multi-centre randomized controlled trial, which is due to be published in 2010 (results are not yet in the public domain). It has evaluated the effectiveness of a point-of-care cardiac marker panel, comprising CK-MB, myoglobin and troponin I. Further blood samples have been stored and used to test alternative markers to explore whether these might be more effective or

[99] Goodacre S, at al. The health care burden of acute chest pain. Heart 2005;91:229-230
[100] Kilcullen N, et al. Heart-Type Fatty Acid-Binding Protein Predicts Long-Term Mortality After Acute Coronary Syndrome and Identifies High-Risk Patients Across the Range of Troponin Values. J Am Coll Cardiol, 2007; 50:2061-2067

cost-effective than the current panel. As well as looking at cost and clinical outcome data, this trial has also measured patient satisfaction. If this study confirms that POC testing can substantially and safely speed up the risk stratification of patients with acute chest pain, roll out across England and Wales could prevent many thousand admissions per year.

Future developments

55. The value of POC testing lies in its negative predictive value, a rapid ACS rule out, to enable a patient to be safely and quickly discharged from the emergency department. If results from forthcoming trials prove favourable, rapid testing to assess biochemical markers of cardiac damage should be adopted by all hospitals within the next five years. In most cases this will be in the form of POC testing in the Emergency Department, however in some units, the test could be more efficiently processed in a 24-hour central hospital laboratory. It is suggested that co-ordinated plans to introduce this on a national level could enable the technology to be purchased at a reduced rate.

(ii) Home monitoring and self-management of INR

Background

56. The international normalised ratio (INR) is a measurement of the bleeding time of a patient on warfarin. Regular measurements are needed to ensure that the INR remains in the therapeutic range, and the patient is maintained on the most appropriate dose of warfarin.

57. INR measurements can be performed in a patient's own home using a POC INR device, eliminating the need for laboratory visits. Self-management allows the patient to participate in and manage their therapy in a similar way to glucose self-monitoring and diabetes management.

Technology

58. The POC INR device requires a small finger-prick blood sample and produces an INR result within one minute, enabling timely drug dose adjustment. Ongoing quality assurance (laboratory-meter comparisons) is performed every 6-12 months or after changing the test strips (cartridges) to reassess device accuracy and the integrity of the test strips.

59. Bought individually, the INR POC devices cost at least £550 each according to one international online provider[101] and the test strips for these machines cost between approximately £2.50 and £2.70 each[102].

Evidence - *Clinical effectiveness*

60. In clinical trials involving adults who required long-term oral anticoagulant therapy, self-management of anticoagulant therapy using a POC INR device is associated with cost savings to the health care system as well as to the patient.[103] Self-management of anticoagulation also confers moderate improvement in the time within the therapeutic range, and improvements in patients' quality of life[104]. In addition, POC testing and self-management has the potential to reduce adverse clinical outcomes (thromboembolism, bleeding).[105]

[101] www.inrtest.com
[102] Drug Tariff, January 2010
[103] Douketis JD. Patient self-monitoring of oral anticoagulant therapy: potential benefits and implications for clinical practice. Am J Cardiovasc Drugs 2001;1(4):245-51
[104] Ansell J, et al. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. International Journal of Cardiology 2005;99(1):37-45
[105] Heneghan C, et al. Self-monitoring of oral anticoagulation: A systematic review and meta-analysis. Lancet 2006;367(9508):404-11

61. Numerous studies have assessed the accuracy and precision of POC INR devices. The accuracy and precision of POC devices are inconsistent and less accurate when an INR is above the therapeutic range (i.e., INR >3.5) or, for some devices, when a patient has antiphospholipid antibodies. In general, when comparisons are made between laboratory-based and POC-based INR measurements within the usual therapeutic range, the difference between values are <15%. Such a difference is acceptable as it is similar to that of INR results from different laboratories[106].

Evidence - *Cost effectiveness*

62. There is little published data. However, the majority of the £383 per year that it costs to maintain a patient on warfarin is made up by monitoring costs. There is potential for these to be reduced by self monitoring and management of INR.

Current activity

63. Most patients on warfarin regularly attend their GP surgery or a hospital outpatient monitoring service for regular monitoring of INR. Currently INR POC devices cannot be prescribed on the NHS, however the test strips for these machines can.

Future developments

64. Further data is needed to support the cost-effectiveness of this technology. A co-ordinated approach to the introduction of this clinically effective technology should be considered over the next five years; however, demand may be weakened by the advent of new anticoagulant strategies (for example, Dabigatran – see Appendix D).

(iii) BNP as a test for chronic heart failure

65. B-type natriuretic peptide (BNP) is a cardiac neurohormone that is released from the ventricles in response to volume or pressure overload. Laboratory measurements of BNP are a well-validated means of excluding heart failure and risk stratifying those with confirmed heart failure; the investigation can therefore be used to target resources effectively.

66. Applied early in the diagnostic process a negative BNP test can help rule out CHF and avoid unnecessary referral for echocardiography and specialist assessment; using BNP in this way is very cost effective.[107,108] Unfortunately, concerns over quality control have limited the introduction of POC (community) testing for BNP.

67. Only 25-30% of GPs have access to BNP testing in any form. It is suggested that over the next five years this capacity should be expanded so all GPs have access to BNP testing. Current guidelines for diagnosis of heart failure now recommend this. Furthermore, it is recommended that consideration should be given to any recommendations on BNP in the NICE Heart Failure (partial review) when it is published in August 2010.

(iv) Highly sensitive CRP as a marker of cardiovascular risk to guide primary prevention

68. A number of markers (for example highly sensitive CRP) are being advocated to help identify select patients for treatment as primary prevention of cardiovascular disease. For example, the Jupiter

[106] Ng VL, et al. Failure of the International Normalized Ratio to generate consistent results within a local medical community. Am J Clin Pathol 1993;99(6):689-94
[107] Mueller C, et al. NEJM 2004;350:647
[108] Mant et al. NICE HTA Assessment on Diagnosis of Heart Failure, HTA 2009:13:32

study demonstrated that rosuvastatin significantly reduced the incidence of major cardiovascular events in healthy patients without hyperlipidemia but with elevated highly -sensitive C-reactive protein levels[109]. Nevertheless, this has no implications for primary prevention policies in the UK because the baseline risk of the people who participated in the trial was well below the current threshold for intervention. This is an expensive test (approximately £27 per assay). Moreover, there is no clear advantage to making measurements at the point of care instead of within a central laboratory.

69. New UK evidence-based guidelines for the primary prevention of cardiovascular disease, which focus on lifetime risk, are being drawn up (the 3rd Joint British Society Guidelines) and are expected to be published in 2011. Consideration should be given to these when they are published.

Genomics

Genetic screening for cardiac conditions

(i) Population screening for monogenic conditions

70. Sudden cardiac death (SCD) occurs in approximately 50,000–70,000 people annually in the UK, and several individual genes have been implicated. National programmes to screen all children who undertake competitive sport to detect these rare mutations are currently undertaken in some European countries, most notably in Italy. There is pressure from third sector organisations to implement such a programme in the UK, however the National Screening Committee has judged such an approach to be premature. One issue is that the genetics are not yet sufficiently refined, either in terms of identifying most of the causative genes, or in understanding genotype-phenotype correlations. In addition, little is known on prevalence or natural history of such rare disorders. However, given the rate at which genetics is moving, it is conceivable that some form of screening may be implemented in England over the next ten years. It is estimated that less than 0.1% of those screened would test positive under such a scheme; they would then undergo a tailored risk management programme, which may include fitting an ICD. Cardiac Risk in the Young (CRY) is currently piloting a screening programme in London.

(ii) Population screening for polygenic conditions

71. Polygenic diseases are diseases in which a variety of genes are implicated, each with a small individual effect, to a greater or lesser extent, in development of the disease, for example hypertension and atherosclerosis. It is likely to take at least ten years to determine the value, if any, of genetic testing in place of, or in addition to, risk prediction using conventional risk factors.

72. However, there are commercial organisations already marketing genetic testing to predict risk of cardiovascular disease. Consequently, it will be important over the next ten years to guard against adoption of genetic testing before its use in predicting risk has been validated. This technology is being introduced in an unregulated way in the private sector, leading to un-validated and inaccurate risk predictions, which may then fall to the GP to interpret. GPs and other clinicians will need to ensure they keep up to date with the advice from NICE and their professional bodies about clinical practice.

[109] Ridker PM, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. NEJM 2008:359:2195-2207

Pharmacogenomics to optimise drug therapy

73. This describes the practice of using genetic testing to optimise drug therapy and is likely to become an important component of modern healthcare. Genetic polymorphisms may influence both the efficacy and hazards of drug therapy and screening patients for such polymorphisms may help to avoid a wide range of unwanted problems. For example, genetic testing can be used to predict which patients are likely to develop myositis in response to statin therapy. There are also grounds to believe that genetic testing may help to optimise antiplatelet therapy.

Genetic testing as a guide to prescribing to Clopidogrel

74. Clopidogrel is an oral anti-platelet drug that is widely used, often in conjunction with aspirin, as an evidence-based secondary preventive agent for patients with cardiovascular disease; it is particularly valuable in patients who have had a coronary stent implanted. Unfortunately, individual responses to Clopidogrel are rather variable because it is a pro-drug that is metabolised by CYP enzymes whose activities are determined by a variety of genetic polymorphisms. Approximately 30% of patients prescribed standard doses of Clopidogrel are deemed low responders[110]. There is compelling evidence that these patients are at higher risk of adverse cardiovascular events, notably stent thrombosis, than their counterparts. For example, one study has shown that patients with a specific CYP2C19 polymorphism are five times more likely to suffer stent thrombosis when given standard doses of Clopidogrel.[111] Prescribing a higher dose of Clopidogrel to everyone offers a crude solution to the problem of variable response since some individuals may still not respond well to the higher dose whilst others may be unnecessarily exposed to a higher risk of bleeding complications[112].

75. There are two new antiplatelet medications (Prasugel and Ticagrelor) that have been shown to be effective in phase three trials[113,114,] and have a more predictable response than Clopidogrel. However, Ticagrelor is not yet licensed and both are likely to be much more expensive than Clopidogrel (which is now available in relatively cheap generic forms). Of particular importance was the finding that Ticagrelor, compared to Clopidogrel, progressively reduced cardiovascular and total mortality over the course of treatment for up to 12 months. This creates a strong case for using Ticagrelor instead of Clopidogrel in higher risk patients with acute coronary syndromes.

76. One approach would be to monitor the therapeutic effects of Clopidogrel by assessing changes in platelet reactivity. Several assays are available but none have been well validated. Clopidogrel responsiveness can now be monitored by a bedside POC test. The most promising bedside device is the VerifyNow P2Y12 system which costs approximately £5000 for the device and £40 per test for disposables. An alternative device is the Multiplate system which costs approximately £12000 for the device and £8 per test for disposables. However, assaying platelet reactivity remains imprecise, and there remains no consensus on the optimal threshold of platelet responsiveness nor of the platelet assay that should be used. Ongoing studies should support the development of a consensus on platelet function testing within the next 2 years.

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[110] Cannon CP, et al. Safety, tolerability, and initial efficacy of AZD6140 (Ticagrelor), the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol. 2007;50:1844-1851

[111] Collet JP, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. The Lancet 2009; 373 (9660): 309 – 317

[112] CURRENT OASIS-7: Benefit to doubling clopidogrel dose in ACS patients undergoing PCI http://www.theheart.org/article/995967.do

[113] Wiviott SD, et al for the TRITON–TIMI 38 Investigators. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. NEJM (2007); 357:2001-15

[114] Wallentin L, et al. for the PLATO investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. NEJM (2009); 361:1045-1057

77. Another solution may lie in using genetic testing to identify the common genetic mutations that influence Clopidogrel response (known as CYP2C19 *1/*2), thereby identifying some patients who will respond poorly to Clopidogrel with a view to giving them a higher dose of the drug or an alternative (more expensive) antiplatelet agent. The limitation of this approach is that genetic testing will not identify all the poor responders so it is likely that genetic testing will complement platelet function testing to determine Clopidogrel response.

78. It is possible that genetic testing to guide Clopidogrel prescribing will become commonplace within the next ten years. It is anticipated that all cardiac centres will want to have the capacity to predict and monitor effectiveness of antiplatelet therapy in this way. It seems likely that this will need to be supported by access to tests of platelet function.

Appendix D

New anticoagulants for management of atrial fibrillation

1. Atrial fibrillation (AF) is the most common sustained arrythmia, affecting at least 600,000 (1.2%) people in England alone. Approximately 12,500 strokes a year are thought to be directly attributable to AF. Appropriate anti-coagulation of all patients with recognised AF would prevent approximately 4,500 strokes per year and prevent 3,000 deaths[115]. A Department of Health cost benefit analysis[116] suggests that
   - the treatment of AF with warfarin reduces risk of stroke by 50-70%;
   - the estimated total cost of maintaining one patient on warfarin for one year, including monitoring, is £383;
   - the cost per stroke due to AF is estimated to be £11,900 in the first year after stroke occurrence.

2. Currently, Vitamin K antagonists (for example warfarin) are recommended for stroke prevention in patients with AF. Warfarin has a narrow therapeutic window, thus regular monitoring to maintain appropriate concentrations for anticoagulation is required. Achieving target international normalized ratio (INR) levels is often difficult, and studies have demonstrated that in patients on warfarin only half their time was spent within target blood levels[117]. Subtherapeutic INR levels substantially increase risk of stroke or arterial thromboembolism. Bleeding is a concern with anticoagulants; data suggest that the average annual frequency of major and minor bleeding with warfarin is approximately 3% and 10%, respectively.

3. Poor control may be for a wide variety of reasons including significant inter-patient and intra-patient variability in dose-response, narrow therapeutic index, and numerous drug and dietary interactions, especially among elderly people who are both at higher risk for thrombotic events and are likely to be taking multiple medications. Patient and physician concern about the use of warfarin has resulted in its underutilization, particularly among elderly individuals who are at the greatest risk for cardiovascular and cerebrovascular events: it is suggested that 46% of those who would benefit from warfarin are not receiving it[118].

4. These difficulties have led to a search for alternative ways of managing AF. As well as the technological advances discussed in this report (in particular radiofrequency ablation and percutaneous left atrial appendage occlusion devices) several pharmaceutical alternatives to warfarin are being developed. The most advanced of these achieve their anticoagulant effect by inhibiting a single activated clotting factor, either thrombin (factor IIa) or factor Xa, and represent a step forward in the care of patients with AF. These agents are expected to offer advantages of enhanced or similar efficacy without an increased risk of major bleeding compared with warfarin. Dabigatran, a thrombin inhibitor, appears to be safer and easier to use than warfarin and may represent an alternative to warfarin that does not require frequent monitoring.

[115] Atrial fibrillation in primary care: making an impact on stroke prevention. Heart and Stroke Improvement 2009
[116] Department of Health Atrial Fibrillation cost benefit analysis. Marion Kerr, 2008
[117] Boulanger L, et al. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. Int J Clin Pract 2006;60:258–64.
[118] The management of atrial fibrillation costing report, NICE 2006

5. Dabigatran was shown to be at least as effective as warfarin in preventing strokes, particularly haemorrhagic strokes, in people with AF who are at moderate or high risk of strokes.[119] This finding, taken together with no greater risk of major bleeding, suggests a possible role as an alternative to warfarin in such patients. Dabigatran may also be an appropriate option for those patients who cannot take warfarin, or undergo the monitoring required, or where control of anticoagulant status is poor, despite best efforts. However longer term data are lacking. Furthermore, novel anticoagulants may offer a better balance of safety and efficacy in patients with acute coronary syndromes or following PCI (who often receive warfarin combined with antiplatelet drugs, leading to a particularly high risk of bleeding[120]) – again, further studies are required to support such use.[121] A NICE appraisal of Dabigatran in AF is expected to begin during early March 2010, in order to be available at or around the expected launch of Dabigatran later in the year, should its license be approved.

6. While these novel anticoagulants will certainly be more expensive than warfarin (the projected costs of therapy with Dabigatran are estimated to be £1,500 per year[122] versus £383 per year for warfarin including monitoring costs[123]), definitive cost-effectiveness analyses will have to account for the reduced number of strokes as well as the lack of routine anticoagulant monitoring associated with warfarin. However, many of the costs associated with current warfarin services will be fixed due to the need to maintain the existing infrastructure for patients well established on warfarin. Therefore it seems unlikely that in the short term there will be real cost savings associated with the development of alternatives to warfarin.

7. However, it is likely that the clinical benefits and convenience for patients will mean that within the next five years significant numbers of patients will begin using one of the newer anticoagulants, including new patients, some already on warfarin and those intolerant to it. The increased use of newer anticoagulants is likely to reduce the impact of some of the technologies discussed in this horizon-scanning document: particularly percutaneous left atrial appendage occlusion devices, radiofrequency ablation for atrial fibrillation and point of care monitoring of INR.

[119] Connolly SJ, et al with RE-LY investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM 2009; 361:1139-1151
[120] Sorensen R, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet. 2009; 374 (9706):1967-74.
[121] Grove EL and Storey RF. The right oral antithrombotics in acute coronary syndromes. Lancet. 2009; 374 (9706):1947-8
[122] British National Formulary. According to the BNF, the current costs for dabigatran 110mg is £2.10 per capsule; this equates to about £1500 for a year's course when given twice daily
[123] Department of Health Atrial Fibrillation cost benefit analysis. Marion Kerr, 2008

Appendix E

Implementing a new technology:
the TAVI experience

Dr Huon Gray

Advances in new cardiac technology can transform clinical practice and save lives; intracoronary stents and implantable cardiac defibrillators are good examples. It is understandable that when new devices become available the specialists practising in these fields will all wish to take part in their implementation. However, for less common cardiac conditions the number of cases requiring the use of a new device may be small, and it would not be appropriate for all relevant specialists to be undertaking small numbers of procedures. This is particularly true when the place of the technology is yet to be clear, when registry and trial data are emerging, and when clinicians are gaining important early experience in their use. Under these circumstances it would be logical for experience to be concentrated in the hands of fewer operators and centres, at least until their experiences can be evaluated, with a view to introducing a phased roll out when appropriate. In the past, this has not occurred, and the uptake of new technology has been somewhat unstructured.

On the one hand, it is of great importance that enthusiasts for a technique or device are supported and their motivation is harnessed (in the interests of service development and improved patient care) but on the other hand, enthusiasm should not be the sole determinant of uptake. Some regard needs to be taken for geographical distribution of centres and operators involved in the early uptake of a device, to ensure equity of access, and centres close to one another competing for limited resources and experience. In other words, there are some benefits to be gained from some form of strategic planning.

The implementation of transcatheter aortic valve implantation (TAVI) is a recent example of how the uptake of new technology might be better structured. TAVI technology is described in more detail in Appendix B, and summarised here. The conventional treatment for severe aortic stenosis is surgical aortic valve replacement, but some patients may not be suitable for such open heart surgery, due to very advanced age or co-morbidity. TAVI involves insertion of a balloon catheter to dilate the aortic valve and a prosthetic valve is then positioned using a metal stent. The early international experience with TAVI showed benefit for the small number of patients considered too high risk for conventional cardiac surgery, and even though only low numbers were implanted in 2008, most UK cardiac surgical centres had either already performed some procedures or were making plans to do so. There were concerns that a complex and potentially high risk interventional procedure would be undertaken in too many centres, with too low numbers of procedures per centre and per operator, for early results to be optimum and for its more widespread use to be determined.

In June 2008, NICE issued guidance on TAVI, highlighting the complexity of the procedure, the need for multi-specialty involvement (cardiology, cardiac surgery, radiology, cardiac anaesthesia) and recommended that procedures should only be undertaken in centres performing cardiac surgery. The NICE guidance also recommended that all patients undergoing TAVI were entered in a registry. The Department of Health Vascular Programme met with NICE, representatives of the relevant professional societies (particularly the British Cardiovascular Intervention Society and the Society of Cardiothoracic Surgeons) and Commissioners, to establish a TAVI dataset within the Central Cardiac Audit Database (CCAD). In December 2008, a meeting was arranged, under the chairmanship of the National Director for Heart Disease, at which there was representation from interested cardiac surgical centres, NICE, Specialist Societies, and Commissioners. From this emerged a consensus and the publication by Commissioners in March 2009 of a “Commissioning Framework for TAVI for Severe Aortic Stenosis”. A

TAVI Steering Group was established, with broad representation, to support national data collection and monitoring, the development of a grant application to the HTA for a randomised clinical trial, and to support the work of the National Specialist Commissioners' Group. The TAVI registry was established and is now the biggest in the world.

Such was the perceived value to all parties of this more coordinated approach to the implementation of a new technology that the key stakeholders (Commissioners, NICE, Specialist Societies, the MHRA and the DH) have established a "New Technology Advisory Group". This group will undertake some horizon scanning, offer advice to stakeholders on which emerging cardiac technologies are most likely to have a sustained impact on patient care and to support their work in evaluating and implementing new devices.

This group is currently advising on the potential impact of interventional devices (such as MitraClip) for the management of some patients with mitral regurgitation. Experience gained from the implementation of TAVI has greatly assisted this new work, and has demonstrated that the implementation of new technology can be achieved with some strategic oversight and consensus between stakeholders.

Appendix F

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(Footnote: Martin Rothman contributed to the section on ventricular assist devices and declared a potential conflict of interest. He is vice-president of medical affairs at Medtronic, however this division does not deal in ventricular assist devices.)

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