Recent developments in acute coronary syndromes

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ABSTRACT – Coronary artery disease is the leading cause of death in the UK with a high clinical, social and economic burden. The management of acute coronary syndromes is rapidly evolving and clinicians are constantly challenged with incorporating new clinical pathways and guidelines into their practices. It is important for clinicians to have a sound working knowledge of acute coronary syndromes, and be updated on the emerging evidence to guide therapy and improve outcomes in these patients.

KEY WORDS: acute coronary syndromes, coronary artery disease, myocardial infarction

Introduction

Over recent years, there has been overwhelming trial data, which has had significant impact on our management of patients with acute coronary syndromes. There is greater emphasis on earlier reperfusion with different strategies in acute myocardial infarction (MI), development and greater use of novel antithrombotic agents, and greater emphasis on secondary prevention and cardiac rehabilitation. This review article serves to update physicians both in the primary and secondary care setting in this rapidly evolving field of acute coronary syndromes.

Trial acronyms.

ASSENT-4: ASsessment of the Safety and Efficacy of a New Thrombolytic-4

CAPTIM: Comparison of Primary Angioplasty and Pre-hospital Thrombolysis In Myocardial Infarction

CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance

CLARITY-TIMI 28: CLopidogrel as Adjunctive Reperfusion TherapY-Thrombolysis In Myocardial Infarction-18

COMMIT: CIOpidogrel and Metoprolol in Myocardial Infarction Trial

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

ESSENCE: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events

FINESSE: Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events

ISIS-2: International Study of Infarct Survival-2

MERLIN: Middlesborough Early Revascularization to Limit INfarction

REACT: REscue Angioplasty versus Conservative Treatment or Repeat Thrombolysis

TACTICS-TIMI 18: Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy

TIMI-11B: Thrombolysis In Myocardial Infarction-11B

Sources and selection criteria

A literature search was conducted using PubMed/Medline, EMBASE and Cochrane databases using coronary artery disease (CAD), acute coronary syndromes and MI as keywords. References of recent major articles and key reviews were also researched, and articles were accessed where necessary.

Classification

Acute coronary syndromes include unstable angina (USA), non-ST segment elevation MI (NSTEMI) and ST segment elevation MI (STEMI). Acute coronary syndromes with persistent STEMI generally require urgent reperfusion therapy. Those without persistent ST-elevation represent a continuum from USA to NSTEMI and can be further classified on the basis of troponin release, a biochemical marker of myocardial cell death (Fig 1).

Epidemiology

An estimated 2.7 million people in the UK have CAD which accounts for over 105,000 deaths per year. Approximately 1.3 million people in the UK have had a MI, 2 million people suffer from angina, and over 230,000 new MIs are diagnosed every year.[1] Over the last decade, the proportion of patients presenting with STEMI has fallen, while there has been an increase in USA and NSTEMI.[2] Explanations for this apparent change are probably multifactorial, but relate to advances in therapy, risk factor reduction, better primary and secondary preventative strategies and appropriate coronary revascularisation. In addition, the growing use of troponin assays, which have an increased overall diagnostic sensitivity for MI, has facilitated more effective early treatment.

Reperfusion therapy in STEMI

Thrombolysis

For over two decades, thrombolysis has been the cornerstone in the acute management of STEMI,

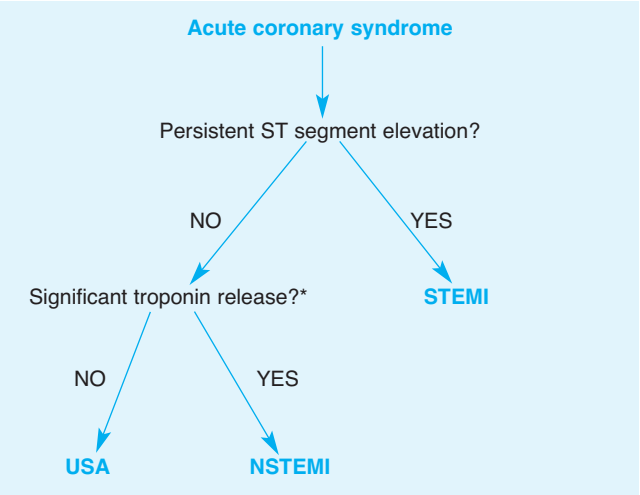

Fig 1. Acute coronary syndromes can be classified initially on the basis of the electrocardiogram. NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction; USA = unstable angina. *Non-ST segment elevation acute coronary syndrome represents a continuum from USA to NSTEMI. Differentiating NSTEMI from USA depends upon the troponin release being greater than the cut-off point. This varies between different laboratories and troponin assays used. Troponin levels should be measure after 12 hours from the onset of chest pain.

Box 1. Advantages and disadvantages of primary percutaneous coronary intervention (PPCI) compared to thrombolysis.

Advantages
- Greater patency rates of infarct-related artery (streptokinase: 55%, rt-PA: 60% and PPCI: >90% at 90 minutes)[8]
- Reduced re-occlusion and re-infarction rates
- Reduced haemorrhagic stroke
- Avoids the risk associated with thrombolysis, ie bleeding (including haemorrhagic stroke)
- Reduced mortality
- Better residual left ventricular function
- More rapid electrocardiographic normalisation
- Haemodynamic and coronary anatomy data from angiography
- Improved risk stratification with identification of patients suitable for coronary artery bypass surgery
- Can be performed where thrombolysis is contra-indicated (5–20% of patients)

Disadvantages
- High procedural costs
- Cardiac catherisation facilities not readily available
- Risks of cardiac catheterisation and percutaneous intervention

with streptokinase achieving a significant 19% reduction in mortality and a greater reduction in those treated early.[3] In ISIS-2, aspirin and streptokinase independently reduced mortality rates, with a greater reduction when used in combination.[4] The concept of fibrin-selective agents led to the development of recombinant tissue plasminogen activators (rt-PA). Initial studies without concomitant intravenous (iv) heparin therapy failed to show a survival benefit of rt-PA over streptokinase.[5,6] The importance of administering iv heparin with bolus lytic agents was demonstrated and rt-PA plus iv heparin was superior to streptokinase, with a greater reduction in 30-day mortality (6.3% *v* 7.3%, p<0.001).[7]

Primary percutaneous coronary intervention

Thrombolysis has important limitations (Box 1) and primary percutaneous coronary intervention (PPCI) offers an alternative by mechanically disrupting the occlusive thrombus and opening the underlying stenosis, rapidly restoring blood flow and achieving recannalisation rates greater than 90%.[8]

Pooled data from 23 trials has shown PPCI is superior to in-hospital thrombolysis at reducing short- and long-term mortality, re-infarction and stroke, independent of the thrombolytic agent used.[9] It is now widely regarded as the reperfusion strategy of choice in patients with STEMI with a fourfold increase in PPCI in England and Wales over the last two years (Table 1).[2] As only a minority of patients with STEMI present directly to PPCI centres, patients may either receive thrombolysis at the presenting centre or be transferred for PPCI. Even with transfer times up to three hours, PPCI remains superior to immediate in-hospital thrombolysis with a 42% reduction in the combined end-point of death, re-infarction and stroke (95% confidence interval (CI), 29–53%; p<0.001).[10]

Pre-hospital thrombolysis

Earlier thrombolysis is associated with reduced infarct size, better residual left ventricular function and improved survival.[5] The National Service Framework (NSF) states a target call to needle time of less than 60 minutes.[11] Many demographic and clinical factors may delay thrombolysis. Pre-hospital thrombolysis may be a more effective strategy in achieving this target. Compared to in-hospital thrombolysis, pre-hospital thrombolysis has been shown to reduce time to thrombolysis by one hour with a relative risk reduction in mortality of 17% and an absolute risk reduction of 1.6%, translating to one life saved for every 62 patients treated.[12] In England and Wales, there has been a sevenfold increase in the use of pre-hospital thrombolysis over the last two years, with 28 of the 31 ambulance services now able to provide treatment.[2]

The CAPTIM trial showed PPCI was not superior to pre-hospital thrombolysis, with no difference in 30-day mortality. Patients receiving thrombolysis within two hours from symptom-onset, however, had a significant reduction in cardiogenic shock with a strong trend towards lower 30-day mortality suggesting pre-hospital thrombolysis may be a valid alternative to PPCI, especially if administered early. Of those treated with thrombolysis, however, 26% had rescue PCI and 70% had PCI in the first 30 days.[14] This use of rescue or early PCI in addition to thrombolysis may explain why the results for the pre-hospital

Table 1. Data from the Myocardial Infarction Audit Project 2000–5. Trends in reperfusion strategies for ST segment elevation myocardial infarction.

Reperfusion therapy	Year (%)				
	2001/2	2002/3	2003/4	2004/5	2005/6
Pre-hospital lysis	0.5	1.2	1.3	5.3	9.5
In-hospital lysis	96.7	96.4	96.7	88.3	81.9
Rescue PCI	0.6	0.8	0.7	2.4	2.1
Primary PCI	2.3	1.6	1.3	4.2	6.5

PCI = percutaneous coronary intervention.

thrombolysis group in CAPTIM differ from those for pre-hospital thrombolysis groups in previous studies.[13] Pre-hospital thrombolysis may play a greater role in the future especially in conjunction with early angiography, which should be routine for all patients receiving thrombolysis.[15]

'Facilitated' PCI

This strategy aims to achieve early patency through early administration of thrombolytic agents and/or glycoprotein (GP) IIb/IIIa inhibitors followed by PCI. The rationale underlying this is that earlier treatment results in better myocardium salvage, higher patency rate of the infarct-related artery, improved microcirculatory flow, reduced re-occlusion and re-intervention rates and increased rates of procedural success.[16] Increased pre-procedural flows are associated with reduced late mortality after PCI.[17] Despite this theory, the ASSENT-4 trial comparing facilitated PCI using full-dose tenectaplase with PPCI, showed that facilitated PCI was associated with worse outcomes.[18,19] Thrombolysis leads to platelet activation promoting a prothrombotic milieu, which could explain this.

Many trials have previously explored different 'facilitating' regimens for PCI using GP IIb/IIIa inhibitors and/or reduced dose thrombolytic agents. Pooled data from studies comparing primary versus facilitated PCI shows a facilitated approach is associated with increased mortality, re-infarction, revascularisation rates, bleeding and stroke.[20] Interestingly, increased mortality was only seen when thrombolysis, alone, was used for facilitation. Thus while it may well be that the concept of 'facilitating' PCI is still valid, it seems this is not achieved with thrombolysis. The FINESSE trial is currently evaluating different 'facilitating' regimens with GP IIb/IIIa inhibitors either alone or in combination with thrombolysis in patients undergoing PPCI.[21]

Rescue PCI

When thrombolysis fails, patients may either have repeat thrombolysis or urgent angiography (rescue PCI). The MERLIN trial showed no difference in mortality between rescue PCI and conservative management.[22] However, rescue PCI was associated with significantly improved event-free survival, largely due to a reduction in subsequent revascularisation only. On the contrary, the REACT trial showed that rescue PCI was superior to repeat thrombolysis or conservative treatment with significantly improved event-free survival and a significant reduction in mortality, re-infarction and revascularisation.[23] Although there were important differences between the two trials, the conflicting results have led to controversy concerning the optimal management of failed thrombolysis. A recent meta-analysis supports the use of rescue PCI following failed thrombolysis, with a significant reduction in mortality and re-infarction, when compared to conservative therapy (10.8% *v* 16.8%; odds ratio = 0.60; 95% CI, 0.41–0.89; p=0.012).[24] If available, rescue PCI should be considered following failed thrombolysis.

Early revascularisation in USA and NSTEMI

Recent research has compared clinical outcomes associated with early invasive strategy versus an early conservative therapy in patients with USA or NSTEMI. An early conservative strategy involves aggressive medical therapy, with coronary angiography and revascularisation reserved only for patients with recurrent or inducible ischaemia. In an early invasive strategy, all patients undergo early coronary angiography, within 12–48 hours of presentation, and revascularisation if indicated. Current evidence suggests that a routine early invasive strategy in USA and NSTEMI is associated with better long-term outcomes, particularly in high-risk patients. In the TACTICS-TIMI 18 trial,[25] the benefits of an early invasive strategy were only observed in patients with high risk, defined as troponin elevation, ST segment deviation or Thrombolysis in Myocardial Infarction (TIMI) risk score ≥3. Pooled data from seven trials has shown that although a routine invasive strategy is associated with higher early mortality during initial hospitalisation, following discharge, it is associated with better long-term outcomes with a significant reduction in death, MI, recurrent angina and re-hospitalisation.[26] These benefits were only observed in patients at high risk with elevated cardiac biomarkers.

Antithrombotic therapy in acute coronary syndromes

Aspirin

In patients with acute coronary syndromes, aspirin is associated with an odds reduction in vascular events of 46%.[27] Aspirin has clearly and consistently demonstrated protection against cardiovascular disease in trials in all high-risk groups, with doses ranging from 30–1,500 mg daily. The benefits of aspirin were similar for doses ≥75 mg, but uncertainty remains about doses <75 mg. Gastrointestinal side effects and bleeding did not increase significantly with doses between 75–325 mg, but did increase with

doses >325 mg. Therefore the recommended aspirin dose for secondary prevention is between 75–325 mg/day.[27]

Clopidogrel

The CURE trial showed clopidogrel plus aspirin was superior to aspirin alone in patients with USA/NSTEMI.[28] The COMMIT[30] and CLARITY-TIMI 28[31] trials have shown clopidogrel plus aspirin is superior to aspirin alone in patients with STEMI. This benefit was not associated with an increase in major bleeding, providing a compelling case for the addition of clopidogrel to the routine management of patients with STEMI, starting as early as possible, including those receiving thrombolysis. Current recommendations for using clopidogrel are summarised in Box 2.

Box 2. A guide to prescribing clopidogrel.

- Clopidogrel may be used as an alternative to aspirin those with aspirin intolerance
- Following NSTEMI, all patients should be prescribed clopidogrel in combination with aspirin. Clopidogrel should continue for at least three months and possibly up to one year. Aspirin therapy should continue life long[28,29]
- Following STEMI, all patients should be prescribed clopidogrel in combination with aspirin. Clopidogrel should continue for at least one month. Aspirin therapy should continue life long[30,31]
- All patients following PCI with stent insertion will require dual anti-platelet therapy. Aspirin therapy should continue life long. The duration of clopidogrel therapy depends upon the type of stent used. Bare metal stents usually require clopidogrel for one to three months.[32] Current guidelines recommend clopidogrel for 12 months following drug-eluting stents.[33] Life-long aspirin and clopidogrel may be appropriate in selected high-risk patients
- Clopidogrel should not be routinely added to aspirin in patients with stable cardiovascular disease or those with multiple risk factors for cardiovascular disease[34]

NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction.

Unfractionated heparin

Unfractionated heparin (UFH) accelerates the ability of antithrombin III to inactivate factors IIa, Xa and IXa. Its unpredictable anticoagulant effect requires regular monitoring with activated partial thromboplastin time (APTT). A weight-adjusted iv bolus followed by continuous infusion is recommended.[35] Pooled data shows that combining UFH with aspirin reduces the rate of death or MI by 53% when compared to aspirin alone, in USA/NSTEMI (p=0.018).[36]

Low-molecular-weight heparin (LMWH)

Low-molecular-weight heparin (LMWH) is derived by cleavage of UFH to yield smaller chains with greater Xa:IIa inhibition and does not require laboratory monitoring.[35] LMWHs are potential replacements to UFH in the management of acute coronary syndromes. Pooled data has shown that LMWHs are at least as effective as UFH,[37] but the ESSENCE[38] and TIMI-11B[39] trials demonstrated superiority of enoxaparin over UFH in USA/NSTEMI, with no significant increase in major haemorrhage. All patients with USA/NSTEMI should be anticoagulated although LMWHs may be preferable, especially in those at high-risk. Anticoagulation should be continued for at least 48 hours with the absence of spontaneous ischaemia for 24 hours and should be discontinued after successful intervention.

Unfractionated heparin is used as adjunctive therapy with bolus thrombolytic agents. The superiority of enoxaparin over UFH for adjunctive therapy with thrombolysis has recently been demonstrated.[40]

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors are a novel class of anti-platelet agents, which block the GP IIb/IIIa receptor – the final pathway in platelet aggregation. Oral GP IIb/IIIa inhibitors are associated with worse outcomes.[41–43] Intravenous GP IIb/IIIa inhibitors have only been extensively evaluated and three agents have been developed to be administered with adjuvant UFH/LMWH: abciximab (Reopro®), tirofiban (Aggrastat®) and eptifibatide (Integrilin®). Initially developed for use with PCI to reduce procedure-related thrombotic complications, more recent studies have focused on GP IIb/IIIa inhibitors in the primary medical management of USA/NSTEMI. Patients at high-risk with elevated troponin or those undergoing early PCI derive greater benefit from GP IIb/IIIa inhibitors.[44] Even in patients with USA/NSTEMI who were not scheduled for early coronary revascularisation, the greatest benefit was seen in patients with elevated troponin.[45] GP IIb/IIIa inhibitors are of greatest benefit in patients with USA/NSTEMI, who have early PCI. They are of questionable benefit in patients who are managed medically without intervention, but may be selectively useful in the conservative management of high-risk patients (Box 3).

Current evidence suggests that early administration of GP IIb/IIIa inhibitors in STEMI improves coronary artery patency and is associated with a significant reduction in death, MI and urgent revascularisation.[47,49] The FINESSE trial will provide further data on the use of GP IIb/IIIa inhibitors in the early management of patients with STEMI.[20]

Fondaparinux

Fondaparinux, a synthetic pentasaccharide, causes rapid and predictable inhibition of factor Xa. It is more effective than enoxaparin in preventing venous thrombosis in surgical patients.[50] Recent trials have shown fondaparinux is as effective as enoxaparin in USA/NSTEMI and UFH in STEMI, particularly in those not undergoing PPCI, without increasing the risk of major bleeding.[51,52] These studies demonstrate the safety and efficacy of fondaparinux when compared to standard therapy in patients with acute coronary syndromes. Fondaparinux is not currently licensed for use in acute coronary syndromes but may represent a potential alternative or replacement to UFH or LMWH.

Box 3. Guidelines for using glycoprotein (GP) IIb/IIIa inhibitors. Reproduced with permission of NICE.[46] Another tool to identify high risk is the Thrombolysis in Myocardial Infarction (TIMI) score (Reference 82).

- GP IIb/IIIa inhibitors should be used in the initial medical management of USA/NSTEMI in patients who are at high-risk*
- Though, early angiography is desirable for high-risk patients, in situations where PCI does not occur or is not immediately available, initial medical management with GP IIb/IIIa inhibitors is still recommended
- GP IIb/IIIa inhibitors should be initiated as soon as high-risk status is determined even though this may be before the result of troponin becomes available
- GP IIb/IIIa inhibitors are not currently licensed in the UK for use as an adjunct to thrombolysis in STEMI
- If PCI is indicated as part of the early management of USA/NSTEMI, but it is delayed, GP IIb/IIIa inhibitor is still recommended as an adjunct to PCI
- GP IIb/IIIa inhibitor should be considered as an adjunct to PCI for elective PCI for
  (a) all patients with diabetes
  (b) multi-vessel PCI
  (c) insertion of multiple stents
  (d) vein graft PCI
  (e) PCI for bifurcation lesions
- Tirofiban and eptifibatide should be used in the initial medical management of USA/NSTEMI
- Only abciximab is licensed for use as an adjunct to PCI
- All GP IIb/IIIa inhibitors should be given with adjuvant heparin therapy

NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction; USA = unstable angina. *In determining high risk, clinicians should take into account a combination of risk factors, clinical signs (ongoing chest pain, haemodynamic instability), dynamic changes on the electrocardiogram and an elevated troponin.

Bivalirudin

Bivalirudin, a direct thrombin inhibitor, is a novel iv anticoagulant currently licensed for use during elective PCI. It has many advantages over heparin: heparin cannot inactivate fibrin-bound thrombin, bivalirudin can; heparin can lead to platelet activation and heparin induced thrombocytopenia, bivalirudin has antiplatelet action through inhibition of thrombin; bivalirudin has a predictable response given its short half-life, thus avoiding the need for monitoring and haemorrhagic complications are rare.[53] Trials have shown bivalirudin to be as effective as GP IIb/IIIa inhibitors plus heparin in high-risk patients undergoing PCI, but with a significantly reduced risk of bleeding, thus demonstrating a net clinical benefit.[54,55] Bivalirudin is a potential alternative to GP IIb/IIIa inhibitors plus heparin in high-risk patients undergoing PCI, especially in those where heparin cannot be given or those at increased bleeding risk.

Other drug therapies

β *blockers*

β blockers should be started early in patients with acute coronary syndromes in the absence of contraindications.[29] Peripheral vascular disease and obstructive airways disease are relative contraindications, and if necessary, these patients may be given a β blocker with a short half life (eg metoprolol) or a greater β_1-selective agent (eg bisoprolol) and observed closely for adverse effects. In patients who have survived a MI and have obstructive airways disease β blockers are associated with a 40% reduction in total mortality.[56] There is considerable evidence for using β blockers (eg bisoprolol, metoprolol and cardvedilol) in patients with stable heart failure.[57-60]

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors decrease morbidity and mortality in patients with established left ventricular dysfunction and in patients with left ventricular dysfunction post MI.[61] More recently, ACE inhibitors have shown benefit in patients with CAD and preserved left ventricular systolic function.[62] ACE inhibitors should be started in all patients with acute coronary syndromes, provided there are no contraindications, even in those with preserved left ventricular function.[63] In those who cannot tolerate ACE inhibitors, angiotensin II antagonists can be used.[64,65]

Statins

Numerous landmark trials have shown the benefits of statins in high-risk patients with or without clinical evidence of CAD in all sex and age groups, irrespective of initial cholesterol levels. Statins reduce recurrent ischaemic events in patients with acute coronary syndromes.[66–68] Recent studies using intracoronary ultrasound show that statins reduce the progression of atherosclerosis[69] and may even cause regression of atherosclerotic plaques.[70]

Current evidence demonstrates that more aggressive lipid lowering is better.[67] This has had an impact on current guidelines with lower targets for optimal cholesterol. Low-dose statins are now available over the counter in UK, and the National Institute for Health and Clinical Excellence have recently issued new guidelines for prescribing statins, which will make an additional 3.3 million people eligible for statin therapy (Box 4). It is anticipated that revisions will be made to the Quality and Outcomes Framework within the general medical services (GMS) contract, which is currently based on targets of total cholesterol <5.0 mmol/l. Despite a considerable increase in prescription for statins in UK, a large primary care-based audit showed that in 2004–05 only 60% of patients with CAD reached the target cholesterol of 5 mmol/l.[73] If cholesterol targets were lowered, an even greater proportion of patients not meeting target cholesterol values would be expected. Prescription data for statins shows that 30–68% are available for the lowest dose, thus a considerable potential for dose titration.[74]

Myocardial Infarction National Audit Project

The NSF was launched in 2000 to improve the management of CAD: a 10-year programme aiming to reduce cardiovascular deaths by 40% by 2010.[11] The Myocardial Infarction National Audit Project (MINAP) was launched in parallel with NSF to monitor the achievement of its standards, and has shown a considerable improvement over the last six years (Fig 2).

Cardiac rehabilitation

Cardiac rehabilitation programmes bring together medical treatment, patient education and counselling, risk factor modification and exercise training to optimise patient function, limit psychosocial effects and reduce the risk of recurrent cardiac events. Exercise-based cardiac rehabilitation programmes are associated with a 27% reduction in all-cause mortality.[75] Despite a steady increase in cardiac rehabilitation services, its provision in the UK remains low. Only small proportions of patients with MI are offered or take up cardiac rehabilitation. A survey by the Healthcare Commission has shown that 63% of cardiac patients treated in NHS trusts had not received any formal rehabilitation.[76] There appears to be a chronic understaffing in this area, with only 1 in 4 centres having purpose-built facilities and half do not hold their budgets.[77] Historically, cardiac rehabilitation classes have been held in hospitals. Community centre or home-based rehabilitation programmes appear to be safe and effective, and may improve access to cardiac rehabilitation.[78,79]

Secondary prevention in primary care

Evidence-based approach to managing CAD has led to greater strategies for secondary prevention, resulting in an increased workload for physicians both in primary and secondary care. The Quality and Outcomes Framework in the GMS contract for general practitioners (GPs) provides an opportunity to improve the management of cardiovascular disease in the community.[80] Achieving quality markers allows GPs to accumulate clinical points linked to financial rewards. In relation to CAD, managing hypertension, smoking and cholesterol equates to a total of 242 points, 44% of the total clinical points available. This poses a tremendous workload for GPs, and potentially expands the role for practice nurses. The concept of an 'atheroma clinic' has been proposed, where patients with cardiovascular disease have their risk factors recorded, treated and monitored providing a more robust strategy for secondary prevention.[81]

Box 4. UK guidelines for managing cholesterol.

- **National Service Framework for coronary heart disease**[11]
  TC <5.0 (or reduced by 20–25%, whichever is greater)
  LDL <3.0 (or reduced by 30%, whichever is greater)
- **British Hypertension Society guidelines**[71]
  TC <4.0 (or reduced by 25%, whichever is greater)
  LDL <2.0 (or reduced by 30%, whichever is greater)
- **Joint British Societies guidelines**[71]
  TC <4.0 (or reduced by 25%, whichever is greater)
  LDL <2.0 (or reduced by 30%, whichever is greater)
- **National Institute for Health and Clinical Excellence guidelines**[72]
  Statins should be prescribed for all patients with clinical evidence of cardiovascular disease. Statins are recommended for primary prevention for adults who have a 20% or greater 10-year risk of developing cardiovascular disease*

LDL = low-density lipoprotein (mmol/l); TC = total cholesterol (mmol/l).
*Cardiovascular risk can be calculated using an appropriate risk calculator.

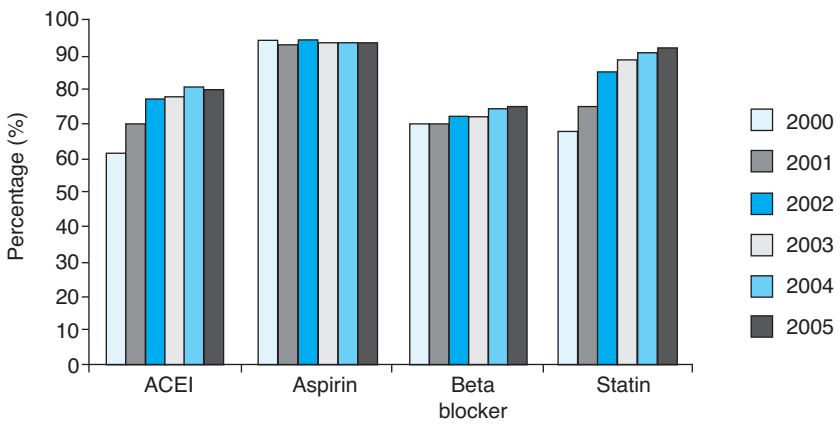

Fig 2. Data from the Myocardial Infarction Audit Project 2000–5. Trends in discharge medications following acute coronary syndromes. ACEI = angiotensin converting enzyme inhibitors.

Conclusions

The recent years have seen great changes to the management of acute coronary syndromes. There has been a considerable increase in PPCI and pre-hospital thrombolysis. Pre-hospital thrombolysis may play a greater role in the future, especially with early coronary angiography. Facilitated PCI with thrombolytics is associated with worse outcomes and other facilitating regimens are being evaluated. Novel anti-thrombotic agents have been developed, and may play an increasing role in the future. β blockers, ACE inhibitors, statins and cardiac rehabilitation are important in secondary prevention. It is hoped that the GMS contract will provide an effective strategy for secondary prevention.

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References

Only the first 30 references are shown. A full reference list is available from the author upon request.

1 British Heart Foundation. *Coronary heart disease statistics fact sheet 2006: United Kingdom*. London: BHF, 2006. www.heartstats.org
2 Myocardial Infarction National Audit Project core data set. www.rcplondon.ac.uk/college/ceeu/ceeu_ami_home.htm
3 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397–402.
4 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349–60.
5 GISSI-2 and International Study Group. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto. Six-month survival in 20,891 patients with acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *Eur Heart J* 1992;13:1692–7.
6 ISIS-3 Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753–70.
7 The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–82.
8 Grech ED, Ramsdale DR. Acute coronary syndrome: ST segment elevation myocardial infarction. *BMJ* 2003;326:1379–81.
9 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13–20.
10 Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003;108:1809–14.
11 Department of Health. *The National Service Framework for coronary heart disease*. London: DH, 2000. www.doh.gov.uk/nsf/coronary.htm
12 Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA* 2000;283:2686–92.
13 Bjorklund E, Stenestrand U, Lindback J *et al*. Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006;27:1146–52.
14 Bonnefoy E, Lapostolle F, Leizorovicz A *et al*; CAPTIM study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;360:825–9.
15 Fernandez-Aviles F, Alonso JJ, Castro-Beiras A *et al*; GRACIA (Grupo de Analisis de la Cardiopatia Isquemica Aguda) Group. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;364:1045–53.
16 Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;348:771–5.
17 Stone GW, Cox D, Garcia E *et al*. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001;104:636–41.
18 ASSENT-4 PCI investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;367:569–78.
19 Van de Werf F. Assessment of the safety and efficacy of a new treatment strategy for acute myocardial infarction: 90-day clinical outcomes. American Heart Association (AHA) Scientific Sessions, Dallas, TX, 13–16 November 2005.
20 Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006;367:579–88.
21 Ellis SG, Armstrong P, Betriu A *et al*. Facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention: design and rationale of the FINESSE trial. *Am Heart J* 2004;147:E16.
22 Sutton AG, Campbell PG, Graham R *et al*. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the MERLIN trial. *J Am Coll Cardiol* 2004;44:287–96.
23 Gershlick AH, Stephens-Lloyd A, Hughes S *et al*. REACT Trial Investigators. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005;353:2758–68.
24 Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006;48:1326–35.
25 Cannon CP, Weintraub WS, Demopoulos LA *et al*; TACTICS-TIMI 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879–87.
26 Mehta SR, Cannon CP, Fox KA *et al*. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908–17.
27 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
28 Yusuf S, Zhao F, Mehta SR *et al*; CURE Trial Investigation. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
29 Braunwald E, Antman EM, Beasley JW *et al*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002;106:1893–900.
30 Chen ZM, Jiang LX, Chen YP *et al*; COMMIT collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607–21.

31 Sabatine MS, Cannon CP, Gibson CM *et al*; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–89.

32 National Institute for Clinical Excellence. *Clopidogrel in the treatment of non-ST-segment elevation acute coronary syndrome*. London: NICE, 2004.

33 British Cardiovascular Intervention Society. *BCIS council statement on stent thrombosis and drug eluting stents*. London: BCIS, 2007.

34 Bhatt DL, Fox KA, Hacke W *et al*; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706–17.

35 Hirsh J, Warkentin TE, Raschke R *et al*. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1998;114: 489S–510S.

36 Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000;36:970–1062.

37 Eikelboom JW, Anand SS, Malmberg K *et al*. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936–42.

38 Cohen M, Demers C, Gurfinkel EP *et al*. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. ESSENCE Study Group. *N Engl J Med* 1997; 337:447–52.

39 Antman EM, McCabe CH, Gurfinkel EP *et al*. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593–601.

40 Antman EM, Morrow DA, McCabe CH *et al*; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354:1477–88.

41 Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. The SYMPHONY Investigators. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet* 2000;355:337–45.

42 Cannon CP, McCabe CH, Wilcox RG *et al*. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149–56.

43 O'Neill WW, Serruys P, Knudtson M *et al*. Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. EXCITE Trial Investigators. Evaluation of Oral Xemilofiban in Controlling Thrombotic Events. *N Engl J Med* 2000; 342:1316–24.

44 Boersma E, Harrington RA, Moliterno DJ *et al*. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359:189–98.

45 Morrow DA, Antman EM, Snapinn SM *et al*. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes. Application of the TIMI Risk Score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J* 2002;23:223–9.

46 National Institute for Clinical Excellence. *Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes*. London: NICE, 2002.

47 Montalescot G, Barragan P, Wittenberg O *et al*; ADMIRAL Investigators. Abciximab before direct angioplasty and stenting in myocardial infarction regarding acute and long-term follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 2001;344:1895–903.

48 Brener SJ, Barr LA, Burchenal JE *et al*. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. RAPPORT Investigators. *Circulation* 1998;98:734–41.

49 Neumann FJ, Kastrati A, Schmitt C *et al*. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 2000;35:915–21.

50 Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2002;162:1833–40.

51 Yusuf S, Mehta SR, Chrolavicius S *et al*; Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464-76.

52 Yusuf S, Mehta SR, Chrolavicius S *et al*; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295:1519–30.

53 Reed MD, Bell D. Clinical pharmacology of bivalirudin. *Pharmacotherapy* 2002;22:105S–111S.

54 Lincoff AM, Bittl JA, Harrington RA *et al*; REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853–63.

55 Stone GW, McLaurin BT, Ware JH *et al*. Prospective, randomized comparison of heparin plus IIb/IIIa inhibition and bivalirudin with or without IIb/IIIa inhibition in patients with acute coronary syndromes: the ACUITY trial. Program and abstracts from the American College of Cardiology 55th annual scientific session, Atlanta, GA, 11–14 March 2006. Abstract 402-12.

56 Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;339:489–97.

57 Poole-Wilson PA, Swedberg K, Cleland JG *et al*; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the COMET: randomised controlled trial. Lancet 2003;362: 7–13.

58 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.

59 Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.

60 Packer M, Coats AJ, Fowler MB *et al*; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–8.

61 Flather MD, Yusuf S, Kober L *et al*. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;355:1575–81.

62 Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2006;47:1576–83.

63 National Institute for Clinical Excellence. *Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation*. London: NICE, 2001.

64 Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet* 2002;360:752–60.

65 Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP *et al*; Valsartan in Acute Myocardial Infarction Trial

Investigators.Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893–906.
66 Schwartz GG, Olsson AG, Ezekowitz MD *et al*; MIRACL Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711–8.
67 Cannon CP, Braunwald E, McCabe CH *et al*; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.
68 Athyros VG, Papageorgiou AA, Mercouris BR *et al.* Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002;18:220–8.
69 Nissen SE. Halting the progression of atherosclerosis with intensive lipid lowering: results from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. *Am J Med* 2005; 118(Suppl 12A):22–7.
70 Nissen SE, Nicholls SJ, Sipahi I *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295:1556–65.
71 British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91(Suppl 5): v1–52.
72 National Institute of Health and Clinical Excellence. *Cardiovascular disease-statins: guidance.* London: NICE, 2006.
73 de Lusignan S, Hague N, Belsey J, Dhoul N, van Vlymen J. The 'rule of halves' still applies to the management of cholesterol in cardiovascular disease: 2002–2005. *Br J Cardiol* 2006;13:145–53.
74 de Lusignan S, Dzregah B, Hague N. Chan T. Cholesterol management in patients with IHD: an audit-based appraisal of progress towards clinical targets in primary care. *Br J Cardiol* 2003;10:223–8.
75 Jolliffe JA, Rees K, Taylor RS *et al.* Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2001;1:CD001800.
76 Healthcare Commission. *Coronary heart disease: survey of patients, 2004.* London: Healthcare Commission, 2005. www.healthcarecommission.org.uk
77 Swanton RH. The National Service Framework: six years on. *Heart* 2006;92:291–2.
78 Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J. Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. *BMJ* 2003;326:84.
79 Bethell HJ, Mullee MA. A controlled trial of community based coronary rehabilitation. *Br Heart J* 1990;64:370–5.
80 Mead M. Cardiology and the new GMS contract for GPs. *Br J Cardiol* 2003;10:329–31.
81 Kirby M. Applying the evidence: guidelines in primary care. *Heart* 2004;90(Suppl 4):6–8.
82 Antman EM, Cohen M, Bernink PJ *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42.