3 ACUTE CORONARY SYNDROMES

Everyone with an acute episode of coronary heart disease should receive high quality evidence based care.

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

There is a need to provide resuscitation training and/or refresher training across the community including the NHS, local government, the voluntary sector, and local business/enterprise. In addition, there is a need to provide resuscitation training to all schoolchildren and NHS staff. Such schemes need to be initiated in communities that have the highest levels of deaths under the age of 65 which occur before reaching hospital. [paragraph 2.7]

What are the best methods of resuscitation training?

The *statements*   The *evidence*

3.1 Prehospital resuscitation

3.1a. Opportunities for reducing fatality from acute coronary attacks lie mainly outside hospital[i-iii].

In a UK study, 54% of arrests were witnessed by a relative or bystander; **cardiopulmonary resuscitation** (CPR) was attempted in less than one third of these cases, but when it was attempted the success rate rose from 2% to 8% (p<0.001). The best result occurred when the arrest was witnessed by a paramedic equipped with a **defibrillator** (5% of cases) when the success rate increased to 40% (95% CI 28-53%)[i].

In a Netherlands study, family members were frequent witnesses of an arrest (44%) but seldom started basic CPR (52/408=13%)[ii].

Bystander CPR is associated with improved survival to discharge from hospital to home (2.9% vs. 0.8%, odds ratio for survival 3.7; 95% CI 1.7-8.8; p<0.001). CPR judged to be performed effectively has greater benefit (survival 4.6% vs. 2.0%. The odds ratio for CPR effectively compared to ineffectively performed was 3.9; 95% CI 1.1-14.0; p<0.04)[iii].

i. Norris RM; on behalf of the United Kingdom Heart Attack Study Collaborative Group. Fatality outside hospital from acute coronary events in three British health districts, 1994-5. *British Medical Journal* 1998; **316(7137)**: 1065-1070
http://bmj.bmjjournals.com/cgi/content/full/316/7137/1065 [accessed 22.12.03]
(Type IV evidence – two year community and hospital based study in the health districts of Brighton, South Glamorgan and York of 1,227 cardiac arrests outside hospital)

ii. Waalewijn RA, Tijssen JGP, Koster RW. Bystander initiated actions in out-of-hospital cardiopulmonary resuscitation: results from the Amsterdam Resuscitation Study (ARREST). *Resuscitation* 2001; **50(3)**: 273-279
(Type IV evidence – prospective study in Amsterdam in 1995-1997 of 922 bystander witnessed circulatory arrests resuscitated by emergency medical service personnel)

iii. Gallagher E, Lombardi G, Gennis P. Effectiveness of bystander cardiopulmonary resuscitation and survival following out-of-hospital cardiac arrest. *Journal of the American Medical Association* 1995;**274**:1922-25
(Type IV evidence - prospective cohort of 2,071 consecutive arrests, 662 receiving CPR, over a six-month period in New York)

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3 | ACUTE CORONARY SYNDROMES

| The *statements* | The *evidence* |

3.1b. The **interval** from collapse to cardiopulmonary resuscitation (CPR) is significantly associated with survival[i,ii].

The odds of one-month survival for bystander CPR given within 2 minutes was 8.35 (95% CI 6.3-10.8) and 2.9 (2.0-4.2) for a delay of more than 2 minutes compared to no CPR[i].

The effectiveness of bystander-initiated CPR could be successfully predicted based on the interval from collapse to CPR and initial ECG rhythm. When the initial ECG rhythm was ventricular fibrillation, a collapse to CPR interval of within 5 minutes was associated with an odds ratio for survival of 30.0 (95% CI 9.5-94.9) (compared to an odds ratio of one when the initial ECG rhythm was not ventricular fibrillation). For an interval of five minutes or more this ratio dropped to 5.4 (1.2-24.2). For other rhythms, the odds ratio was 1.2 (0.2-5.9) for a collapse to CPR interval of within 5 minutes compared to an odds ratio of 1.0 for an interval of five minutes or more[ii].

i. Holmberg M, Holmberg, Herlitz J; for the Swedish Cardiac Arrest Registry. Factors modifying the effect of bystander cardiopulmonary resuscitation on survival in out-of-hospital cardiac arrest patients in Sweden. *European Heart Journal* 2001; **22(6)**: 511-519

(Type IV evidence – survey of the Swedish Ambulance Cardiac Arrest Registry – 14,065 reports from 1990-1995. Bystander CPR was attempted in 3,572 patients; Information was known about the time from collapse to the start of cardiopulmonary resuscitation for 1,099 of these patients)

ii. Sekimoto M, Noguchi Y, Rahman M *et al*. Estimating the effect of bystander-initiated cardiopulmonary resuscitation in Japan. *Resuscitation* 2001; **50(2)**: 153-160

(Type IV evidence – study of 1,474 cardiac arrests in three Japanese regions during 1995-1999)

3.1c. **Dispatcher-assisted** (telephone-assisted) **bystander cardiopulmonary resuscitation** (CPR) may increase survival in cardiac arrest. Compared to no bystander CPR, the multivariate adjusted odds ratio of survival was 1.45 (95% CI, 1.21-1.73) for dispatcher-assisted bystander CPR and 1.69 (95% CI, 1.42-2.01) for bystander CPR without dispatcher assistance[i].

Caveat: Cardiac arrest cases receiving dispatcher assisted CPR were younger than those not receiving CPR. There may also be differences between US and UK procedures.

i. Rea RD, Eisenberg MS, Culley LL, Becker L. Dispatcher-assisted cardiopulmonary resuscitation and survival in cardiac arrest. *Circulation* 2001; **104**: 2513-2516

(Type IV evidence – evaluation of a population based cohort of emergency medical service attended cardiac arrests (n=7,265) from 1983 to 2000 in Washington County, US)

| 3 | ACUTE CORONARY SYNDROMES |

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3.1d. A **staged CPR training method** taking volunteers through bronze, silver and gold stages enhanced motivation to re-attend. 38% of the group attended for the third ('gold') session compared to 8% of the conventional group (who received repetitions of the first session in sessions two and three)[i]. In comparison to those who attended a single session only, the value of conventional retraining was only modest[ii]. *These and other strategies need further research*.
Caveat: There were some baseline differences between groups.

i. Chamberlain D, Smith A, Colquhous M, Handley AJ, Kern KB, Woollard M. Randomised controlled trials of staged teaching for basic life support. 2. Comparison of CPR performance and skill retention using either staged instruction or conventional training. *Resuscitation* 2001; **50**: 27-37
(Type II evidence – randomised controlled trial in the UK of 495 volunteers receiving either conventional (European Resuscitation Council, n=262) or staged CPR training (n=233) over three sessions)

ii. Chamberlain D, Smith A, Woollard M *et al*. Trials of teaching methods in basic life support (3): Comparison of simulated CPR performance after first training and at 6 months, with a note on the value of re-training. *Resuscitation* 2002; 179-187
(As above)

3.1e. **Active chest compression-decompression** (ACDR using a hand-held suction device) compared to standard manual cardiopulmonary resuscitation in patients with cardiac arrest is not associated with clear benefit. There were no significant differences in mortality immediately (relative risk, RR=0.98, 95% CI 0.94-1.03) or at hospital discharge (RR=0.99, 0.98-1.01) and a non-significant trend towards more frequent severed neurological damage in survivors of ACDR (RR=3.11, 0.98-9.83). However assessment of neurological outcome was limited and there were few patients with neurological damage [i].

i. Lafuente-Lafuente C, Melero-Bascones M. Active chest compression-decompression for cardiopulmonary resuscitation. (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (Most recent update 27 May 2002)
http://www.update-software.com/abstracts/ ab002751.htm [accessed 22.12.03]
(Type I evidence – systematic review, literature search to May 2002, and meta-analysis of 12 trials, including two in-hospital studies (n=826) and 10 out-of-hospital studies (n=4,162))

3.1f. Formidable evidence from animal model and other studies is emerging that new emphasis is required on the way in which **chest compression** is performed if improvements to the current survival rate for pre-hospital cardiac arrest are to be achieved[i].

i. Chamberlain D, Handley AJ, Colquhoun M. Time for change? *Resuscitation* 2003; **58**: 237-247
(Type V evidence – Editorial)

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The *statements*	The *evidence*

3.1g. Expert advice is available to assist with out-of-hospital decisions concerning the **termination** of resuscitation efforts for adults suffering nontraumatic cardiac arrest[i]. A poor prognosis is indicated for:

- Unwitnessed cardiac arrests with unknown downtimes, delayed initiation of CPR beyond six minutes, and delay to defibrillation of more than eight minutes
- No response after 20-30 minutes of advanced cardiac life support (ACLS)
- Patients in asystole or pulseless electrical activity. These patients are considered to be in terminal rhythms and cessation of resuscitation should be considered.

Caveat: This guidance was developed for the USA.

i. Bailey ED, Wydro CC, Cone DC; for the National Association of EMS Physicians Standards and Clinical Practice Committee. Termination of resuscitation in the prehospital setting for adult patients suffering nontraumatic cardiac arrest. *Prehospital Care* 2000; **4(2)**: 190-195

(Type V evidence – expert opinion and Position Statement)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

Key Aspects to the Immediate Care of a Patient who has Myocardial Infarction or a Cardiac Arrest" [paragraph 6.3]

- The availability of a defibrillator

What is the evidence for the best location and training programmes?

The *statements*	The *evidence*

3.2 Defibrillation

3.2a. **Defibrillation** and Basic Life Support (BLS) of patients with **out-of-hospital cardiac arrest** is associated with an increase in survival compared to BLS and no defibrillation[i,ii] (relative risk of mortality = 0.92, 95% CI, 0.88-0.96, $p<0.01$; for basic life support with defibrillation versus BLS without defibrillation)[ii].

Caveat: Meta-analyses are based on case series and weaknesses of individual studies also limit the reliability of the results.

i. Watts DD. Defibrillation by basic emergency medical technicians: effect on survival. *Annals of Emergency Medicine* 1995; **26**: 635-39.

(Type IV evidence - systematic review and meta-analysis of 1,827 patients in seven prospective case series)

ii. Auble TE, Menegazzi JJ, Paris PM. Effect of out-of-hospital defibrillation by basic life support providers on cardiac arrest mortality: a meta-analysis. *Annals of Emergency Medicine* 1995; **25**: 642-48.

(Type IV evidence - systematic review and meta-analysis of 4,017 patients in ten case series)

3 | ACUTE CORONARY SYNDROMES

The *statements*

The *evidence*

3.2b. Compared to **Basic Life Support** (BLS) & defibrillation, a **two-tier system** including BLS or BLS-defibrillation and **Advanced Life Support** (ALS) for out-of-hospital cardiac arrest is associated with increased survival[i].
Definitions: In this study BLS providers administered oxygen and CPR; BLS with defibrillation providers defibrillated patients using automated or manual methods and ALS providers were trained to perform endotracheal intubation and to administer IV medications.

For **sudden cardiac arrest**, survival was constant if the defibrillation response time interval was less than 6 minutes, decreased as the interval increased from 6 to 11 minutes and levelled off after 11 minutes (p<0.01). Compared with BLS with defibrillation (BLS-D), the odds of survival were: ALS, 1.71 (95% CI, 1.09-2.70, p=0.01); BLS plus ALS, 1.47 (95% CI, 0.89-2.42, p=0.07); and BLS-D plus ALS, 2.31 (95% CI, 1.47-3.62, p<0.01)[ii].

i. Nichol G, Detsky AS, Stiell IG, O'Rourke K, Wells G, Laupacis A. Effectiveness of emergency medical services for victims of out-of-hospital cardiac arrest: a meta-analysis. *Annals of Emergency Medicine* 1996;**27**:700-10.
(Type IV evidence - systematic review and meta-analysis of 23,313 cardiac arrests in 36 case series)

ii. Nichol G, Stiell IG, Laupacis A, Pham B, De Maio VJ, Wells GA. A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest. *Annals of Emergency Medicine* 1999; **34(4)**: 517-525
(Type IV evidence – systematic review, literature search to August 1997 of Medline and reference list follow up only; 37 case series describing 39 emergency medical service systems and including 33,124 patients)

3.2c. Conclusions from a systematic review were that the **automated external defibrillator (AED)** represents an efficient method of delivering defibrillation to persons experiencing out-of-hospital cardiac arrest and its use by both traditional and nontraditional first responders appears to be safe and effective. The rapidly expanding role of AEDs in traditional emergency medical systems is supported by the literature[i].

The PAD Trial is testing whether **volunteer, non-medical responders** can improve survival from out-of-hospital cardiac arrest (OOH-CA) by using automated external defibrillators (AEDs). Data collection is expected to be completed in late 2003 [ii].

i. Marenco JP, Wang PJ, Link MS, Homoud MK, Estes III NAM. Improving survival from sudden cardiac arrest: The role of the automated external defibrillator. *Journal of the American Medical Association* 2001; **285**: 1193-1200
(Type IV evidence - systematic review, literature search to December 2000, of 101 peered reviewed articles with a variety of research designs. No details are given of study types nor the critical appraisal techniques employed by the authors)

ii. Ornato JP, McBurnie MA, Nichol G *et al*. The PAD Trial Investigators. The Public Access Defibrillation (PAD) Trial: Study design and rationale. *Resuscitation* 2003; **56(2)**:135-147
(Ongoing randomised controlled trial at 24 field centers in the United States and Canada. Approximately 1,000 community units (e.g. apartment or office buildings, gated communities, sports facilities, senior centers, shopping malls, etc.) were randomized to treatment by trained laypersons providing either cardiopulmonary resuscitation (CPR) alone or CPR plus use of an AED, while awaiting arrival of the community's emergency medical services responders)

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National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

The management of CHD in Wales will require high-quality information in the form of leaflets and easily accessible advice. This source of advice might be based in a community setting (e.g. healthy living centres), general practices, or an LHG, a secondary care setting, or electronic access via public libraries or other Internet points. The establishment of such "resource centres" would provide easily accessible information and support to patients and their relatives and could be developed to provide a focus for:

■ rehabilitation programmes;
■ the management of those with CHD;
■ multifactorial risk assessment clinics;
■ training for resuscitation;
■ self-help groups. [paragraph 5.7]

What is the best location and type of activity?

Patients and carers must be offered leaflets, videos and other information about care by a tertiary centre. [paragraph 6.20]

What are the best provision methods? What is the best type of information?

The *statements*   The *evidence*

3.3 Information and advice

3.3a. Information and advice is available for **patients**[i,ii].

i. British Heart Foundation. *Heart Conditions*. **http://www.bhf.org.uk/hearthealth/index.asp? secondlevel=77** [accessed 22.12.03] (Type V evidence – expert opinion)

ii. NHS Direct Online Health Encyclopaedia. *Coronary Heart Disease*. Last updated July 2002. **http://www.nhsdirect.nhs.uk/en.asp?TopicID=625** [accessed 22.12.03] (Type V evidence – expert opinion)

3.3b. Guidelines are available to assist with the production and assessment of health information for members of the **public/patients**[i,ii].

i. Welsh Assembly Government. *Framework for Best Practice. The Production and Use of Health Information for the Public.* Cardiff: Welsh Assembly Government, 2002 **http://www.cmo.wales.gov.uk/content/publications/ reports/framework-for-best-practice-e.pdf** [accessed 22.12.03]

ii. The Centre for Health Information Quality. Help for Health Trust **http://www.hfht.org/chiq/guidelines.htm** [accessed 20.11.03]

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The *statements*	The *evidence*

3.3c. There is some evidence that **mass media interventions** may have an important role in influencing the use of health care interventions[i]. Two studies aimed at reducing delay in admission to hospital for patients with suspected myocardial infarction had mixed results although both found that the number of patients seen at the emergency department as a result of the campaigns increased, while the proportion of patients with suspected myocardial infarction remained relatively stable[i].

Caveat: The authors noted that the information on which these conclusions were based was limited.

i. Grilli R, Ramsey C, Minozzi S. Mass media interventions: effects on health services utilisation (Cochane Review) In. *The Cochrane Library*. Issue 1, 2003. Oxford: Update Software (Most recent substantive update: 16 November 2001)
    http://www.update-software.com/abstracts/ ab000389.htm [accessed 22.12.03]

    (Type IV evidence – systematic review, literature search to 1999, of 20 interrupted time-series analyses including two looking at myocardial infarction admissions)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

It is now possible to measure the cardiac Troponins T and I which are specific for cardiac muscle damage. [paragraph 6.1]

What is the evidence regarding different troponins and their value for the management of cardiac damage?

The *statements*	The *evidence*

3.4 Assessment of cardiac damage in the emergency department – Troponin and other markers

3.4a. **Risk stratification schemes** can categorise a patient's risk of death and ischaemic events and provide a basis for therapeutic decision making[i,ii,iii].

The seven **TIMI risk score predictor variables** were age 65 years or older, at least three risk factors for coronary heart disease, prior coronary stenosis of 50% or more, ST-segment deviation on electrocardiogram at presentation, at least two anginal events in prior 24 hours, use of aspirin in prior seven days, and elevated serum cardiac markers. Event rates (during the 14 days after randomisation) increased significantly as the TIMI risk score increased in the test cohort in TIMI IIB: 4.7% for a score of 1; 8.3% for 2; 13.2% for 3; 19.9% for 4; 26.2% for 5; and 40.9% for 6/7 (p<0.001 by c2 for trend)[i].

A troponin protocol allowed **earlier discharge** in low risk group compared to a low risk group under standard management (10 versus 30 hours, p<0.001) with no excess in adverse outcomes[ii].

i. Antman EM, Cohen M, Bernink PJLM *et al.* The TIMI risk score for unstable angina/non-ST elevation MI. A method for prognostication and therapeutic decision making. *Journal of the American Medical Association* 2000; **284(7)**: 835-842

    (Type IV evidence – development and evaluation of a risk score using data from the TIMI and ESSENCE trials. The three validation cohorts were the unfractionated heparin group from the ESSENCE trial and enoxaparin groups from both trials. Events included all-cause mortality, new or recurrent MI, or severe recurrent ischaemia prompting urgent revascularisation)

ii. Alp NJ, Bell JA, Shahi M. A rapid troponin-I-based protocol for assessing acute chest pain. *QJ Med* 2001; **94**: 687-694

    (Type II evidence – open label 30-day randomised controlled trial of 400 patients with acute chest pain admitted to a large acute hospital in the UK. Patients were randomised to standard diagnostic tests or a protocol based on the admission ECG and the troponon-l result 6 hours after the onset of chest pain.

iii. Braunwald E, Antman EM, Beasley JW *et al.* ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
     http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]

     (Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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The *statements*	The *evidence*

3.4b. Patients with acute coronary syndromes who have **troponin T or I** elevations show a substantial increase in risk during short and long-term follow-up[i,ii,iii].

Estimates of the odds ratio for death or myocardial infarction at 30 days for patients with elevated troponin at index presentation were 3.44 (95% CI 2.94-4.03, p<0.00001) in one review[i]. Another suggested 30 day odds ratios for death or myocardial infarction of 4.9 (3.9-6.2) and 4.6 (3.8-5.5) for troponin I and troponin T respectively[ii]. The prognostic value of a positive result was greater for cohort studies than for clinical trials[iii]. Odds ratios from cohort studies were 8.5 and 5.1 for elevated troponin I and troponin T respectively and the equivalent odds ratios from clinical trials were 2.6 (p=0.01) and 3.0 (p=0.2)[iii]. **Caveat**: The authors of reviews noted variations in assay methods and cut-off values used for diagnosis as well as variations in the reference materials used. Meta-analyses were carried out on the basis of *troponin +ve* and *troponin –ve* categories only.

i. Ottani F, Galvani M, Nicolini FA *et al*. Elevated cardiac troponin levels predict the risk of adverse outcomes in patients with acute coronary syndromes. *American Heart Journal* 2000; **140(6)**; 917-927
(Type IV evidence – systematic review, literature search to January 2000 of Medline and reference list follow-up, of 21 studies and 18,982 patients)

ii. Fleming SM, Daly KM. Cardiac troponins in suspected acute coronary syndrome. A meta-analysis of published trials. *Cardiology* 2001; **95(2)**: 66-73
(Type IV evidence – systematic review, Medline and reference list follow up (search date not given), of 22 prognostic studies (7,663 patients in all) of troponin I (n=5,759) and troponin T (n=5,483))

iii. Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: A meta-analysis. *Journal of the American College of Cardiology* 2001; **38(2)**: 478-485
(Type IV evidence – systematic review, literature search to 1999 of English language studies only, including data from seven clinical trials and 19 cohort studies reporting data for 5,360 patients for Troponin T and 6,603 patients for Troponin I)

3.4c. If the peak **troponin T or I** level measured at least 6 hours after the onset of chest pain symptoms is in the normal range in a patient with a normal electrocardiogram, it is very unlikely that the patient will die or have a nonfatal myocardial infarction in the next 30 days (negative likelihood ratio=0.07; probability of outcome=0.3% with a negative test, given a pretest probability of 4.4%). The initial troponin value is not as helpful as the peak value at least 6 hours after the onset of chest pain[i].
Caveat: The sensitivity and specificity varied widely for patients with unstable angina or non-Q-wave myocardial infarction depending on the inclusion criteria, cutoff used, timing of the blood draw, duration of follow-up and other factors.

i. Ebell MH, White LL, Weismantel D. A systematic review of troponin T and I values as a prognostic tool for patients with chest pain. *Family Practice* 2000; **49(8)**: 746-753
(Type IV evidence – systematic review, literature search to December 1999, of 28 published prospective cohort studies (with at least 80% follow-up))

3 | **ACUTE CORONARY SYNDROMES**

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3.4d. A **six hour rule out protocol** for myocardial infarction (serial measurements of creatine kinase MB mass and continuous ST segment monitoring for six hours with 12 leads) was accurate and efficacious. There were 18 false positive results and one false negative result. Sensitivity was 97.2% (95% CI, 95.0-99.0%), specificity 93.0% (90.0-96.0%), the negative predictive value 99.6% and the positive predictive value 66.0%[i].
Caveat: 68 early discharges were lost to follow-up and the outcome of the gold standard test was only available for 292 of the 383 patients. Rapid discharge strategies may not fully investigate the cause of the presenting pain.

Guidelines recommend that cardiac markers (including troponins), electrocardiogram and other measures should be monitored for at least 12 hours after the onset of pain[ii,iii].

i. Herren KR, Mackway-Jones K, Richards CR, Seneviratne CJ, France MW, Cotter L. Is it possible to exclude a diagnosis of myocardial damage within six hours of admission to an emergency department? Diagnostic cohort study. *British Medical Journal* 2001; **323(7309)** 372-374
http://bmj.bmjjournals.com/cgi/content/full/323/7309/372 [accessed 22.12.03]
(Type IV evidence – cohort study, during 1997-1998, of 383 consecutive patients aged over 25 years, with chest pain of less than 12 hours duration who were at low to moderate risk of acute myocardial infarction. The diagnostic test was compared to the gold standard consisting of either a 48 hour measurement of troponin T or screening for myocardial infarction according to the World Health Organisation's criteria. Outcome of the gold standard test was available for 292 patients)

ii. British Cardiac Society Guidelines and Medical Practice Committee, and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. *Heart 2001*; **85(2)**: 133-142
(Evidence based guidelines – narrative systematic review of the literature in peer reviewed journals, search to December 1999)

iii. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74
For the full guidelines see:
Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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3.4e. A simple, inexpensive, yet aggressive **critical pathway** that ulitises high-risk features from clinical history, electrocardiographic changes, and rapid point-of-care testing of three cardiac markers allows for accurate triaging of chest pain patients within 90 minutes of presenting to the emergency department. The pathway had 100% sensitivity and 94% specificity for myocardial infarction; a positive predictive value of 47% and a negative predictive value of 100%. Coronary care unit admissions decreased by 40%. 90% of patients with negative cardiac markers and a negative electrocardiogram at 90 minutes were discharged home. One patient returned with a myocardial infarction (0.2%) and 12 (2%) with unstable angina during the next 30 days[i]. **Caveats**: Since more than 98% of subjects were male and > 50% presented more than 6 hours after the onset of chest pain, these results may not be generalisable.

i. Ng SM, Krishnaswamy R, Morissey R, Clopton P, Fitzgerald R, Maisel AS. Ninety-minute accelerated critical pathway for chest pain evaluation. *American Journal of Cardiology* 2001; **88**: 611-617

(Type IV evidence – evaluation of a chest pain critical pathway in 1,285 consecutive patients with signs and symptoms of ischaemia to a US hospital from July 1998- April 1999. The critical care algorithm is provided in the text)

3.4f. **Out-of–hospital ECG** has moderate sensitivity (76%) and specificity (88%) for diagnosing acute cardiac ischaemia[i]. **Caveat**: This review also provides guidance on other diagnostic strategies but it only covers studies published up to 1998[i].

i. Lau J, Ioannidis JPA, Balk EM *et al*. Diagnosing acute cardiac ischemia in the emergency department: A systematic review of the accuracy and clinical effect of current technologies. *Annals of Emergency Medicine* 2001; **37**: 453-460

(Type IV evidence – systematic review, literature search to December 1998, of 106 diagnostic studies)

3.4g. In patients with clinically documented acute coronary syndrome who are treated with glycoprotein IIb/IIIa inhibitors, even small elevations of **troponins I and T** identify high-risk patients who derive a large clinical benefit from an early invasive strategy. Patients with a troponin I level of 0.1 ng/mL or more (n=1,097) experienced a significant reduction in the primary end point with the invasive versus conservative strategy (odds ratio=0.54, 95% CI 0.40-0.73). Patients with troponin I levels of less than 0.1 ng/mL had no detectable benefit from early invasive management. Directionally similar results were observed with troponin T[i].

i. Morrow DA, Cannon DP, Rifai N *et al*; For The TACTICs-TIMI 18 Investigators. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction. Results from a randomized trial. *Journal of the American Medical Association* 2001; **286(19)**; 2405-2412

(Type IV evidence – measurement of troponin levels within a randomised controlled trial of 2,220 patients with acute coronary syndrome assigned to early coronary angiography or a conservative strategy of medical treatment)

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3.4h. Several patient characteristics and electrocardiographic findings portend a worse prognosis in patients with suspected or diagnosed unstable angina including older age, male sex, past myocardial infarction, diabetes mellitus, and ST depression greater than 0.1 millivolt. Measurement of **troponin T or troponin I** provides additional independent prognostic information. A positive troponin finding increased the risk of subsequent death 5.3-fold at 4 weeks (95%CI, 3.6-7.9). A positive troponin finding also increased the risk of subsequent death or myocardial infarction 12.3-fold at 4 weeks (6.4-23.8) in patients with diagnosed unstable angina. The absolute increase in mortality was 3.9 percent (3.0-4.4) for patients with a positive troponin level. The predictive value of troponin T and troponin I was not significantly different[i].

i. *Prediction of Risk for Patients with Unstable Angina*. Evidence Report/Technology Assessment No. 31. Rockville MD: Agency for Healthcare and Research, December 2000 **http://hstat.nlm.nih.gov/hq/Hquest/screen/DirectAccess/db/3308** [accessed 22.12.03]

(Type IV evidence – guidance based on a systematic review, literature search to 1998)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

"Key Aspects to the Immediate Care of a Patient who has Myocardial Infarction or a Cardiac Arrest"

■ The time it takes to get the patient into contact with a person who is able to diagnose an MI and give clot bursting drugs (thrombolysis) if indicated

■ The time it takes to get the patient to a hospital from the time of call - Call to Door Time

■ The time it takes from the door of the hospital to giving Thrombolysis - Door to Needle Time [paragraph 6.3]

The standard set in this action plan is a maximum call to thrombolysis time of **sixty minutes** of which not more than **twenty minutes** should be door to thrombolysis time for those patients for whom thrombolysis is the treatment of choice. Thrombolysis is not indicated in all patients and any contra-indications must be addressed prior to the administration of the medicine. [paragraph 6.5]

By 2002/3 in cases of diagnosed MI, where administration of thrombolytic therapy is appropriate, a pain to thrombolysis time of sixty minutes should be achieved. The maximum times for each step of the pathway are as follows:

■ A maximum forty minute call to door time;

■ A maximum twenty minutes for door to needle time. [key action 16]

What is the latest evidence regarding the best indications for and types of thrombolysis?

Where a call to door time of thirty minutes is not achievable because of geography then thrombolysis must be delivered in settings other than the DGH. [paragraph 6.5]

What are the best settings for thrombolysis outside hospital?

There are strategies whereby the ambulance service can help reduce the delay of thrombolysis, including the possibility of the administration of thrombolytic agent on the paramedic's own initiative. [paragraph 6.7]

What are the best strategies for paramedic/other involvement?

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

The *statements*

The *evidence*

3.5   Thrombolysis

3.5a. **Thrombolytic therapy** improves survival in acute MI[i,ii,iii,iv], with greatest benefit in patients treated **within one hour of symptom onset**[i]. The benefit of fibrinolytic therapy was 65 (SD 14), 37(9), 26(6) and 29(5) lives saved per 1000 treated patients in the 0-1, 1-2, 2-3 and 3-6 hour intervals, respectively. Proportional mortality reduction was significantly higher in patients treated within two hours, 44% (95% CI 32-53%) than in those treated later, 20% (15-25%). No benefit was found for thrombolysis at 12-24 hours[i].

Fibrinolytic therapy was associated with an excess of deaths during days 0-1 (especially among patients presenting more than 12 h after symptom onset, and in the elderly) but this was outweighed by a much larger benefit during days 2-35. Among 45,000 patients presenting with ST elevation or bundle-branch block the relation between benefit and delay from symptom onset indicated highly significant absolute mortality reductions of about 30 per 1,000 for those presenting within 0-6 hours and of about 20 per 1,000 for those presenting 7-12 hours from onset[ii].

i. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; **348**: 771-75
(Type I evidence - systematic review and meta-analysis of 50,246 patients in 22 randomised controlled trials)

ii. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1,000 patients. *Lancet* 1994; **343**: 311-22
(Type I evidence - systematic review and meta-analysis of nine trials randomising >1,000 patients with suspected acute MI to fibrinolytic therapy or control; 58,600 patients in all)

3.5b. The results of a systematic review suggest that **thrombolysis begun before hospital admission** significantly decreases the time to thrombolysis and all-cause hospital mortality. Overall, 324 of 3,167 patients (10.2%) died in hospital when thrombolysis was begun in hospital and 280 of 3,257 patients (8.6%) when thrombolysis was begun before hospital admission (Odds ratio for prehospital versus in-hospital thrombolysis, OR= 0.83, 95% CI 0.70-0.98; Number Needed to Treat = 61, 95% CI 33-488)[i]. **Caveat**: The results were pooled for short term hospital mortality only. The authors couldn't combine the results for one- and two-year outcomes due to significant heterogeneity between trials. In a large European trial, mortality reduction was not significant at 30 days[ii].

i. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *Journal of the American Medical Association* 2000; **283(20)**: 2686-2692
(Type I evidence – systematic review, literature search to 1999, and meta-analysis of six randomised controlled trials (6,434 patients), and three follow-up studies)

ii. The European Myocardial Infarction Project (EMIP) Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *New England Journal of Medicine* 1993; **329**: 383-89.
(Type II evidence - randomised controlled trial of 2,750 patients with suspected acute MI home within six hours of symptom onset randomised to anistreplase prehospital with placebo in hospital, or placebo prehospital followed by anistreplase in hospital)

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3 | ACUTE CORONARY SYNDROMES

| The *statements* | The *evidence* |

Choice of thrombolytic

3.5c. Guidelines for intravenous thrombolysis are available[i].

NICE recommends that, in hospital, the choice of thrombolytic drug (alteplase, reteplase, streptokinase or tenecteplase) should take account of[i]:

- the likely balance of benefit and harm (for example, stroke) to which each of the thrombolytic agents would expose the individual patient
- current UK clinical practice, in which it is accepted that patients who have previously received streptokinase should not be treated with it again
- the hospital's arrangements for reducing delays in the administration of thrombolysis

The practicalities of administering thrombolytic drugs in **pre-hospital settings** (where this is considered a beneficial approach) mean that the bolus drugs (reteplase or tenecteplase) are recommended as the preferred option[i].

i. National Institute for Clinical Excellence. *Guidance on the Use of Drugs for Early Thrombolysis in the Treatment of Acute Myocardial Infarction*. Technology Appraisal Guidance No.52. London: NICE. Issue date October 2002. Review date October 2005
http://www.nice.org.uk/pdf/52_Thrombylosis_A4summary.pdf [accessed 22.12.03]
Full document:
http://www.nice.org.uk/pdf/52_Thrombolysis_full_guidance.pdf [accessed 22.12.03]
(Evidence-based guidance from an assessment report prepared by the Liverpool Reviews and Implementation Group, submissions from manufacturers, professionals, specialists, patients & carers) Summary:

3.5d. All **thrombolytic drugs** appear to be of similar efficacy in reducing mortality. For available comparisons (all alteplase vs. streptokinase, reteplase vs. streptokinase or alteplase, tenecteplase vs. alteplase), meta-analysis showed no significant differences in mortality at 30-35 days. The GUSTO-I study showed an apparent benefit of accelerated alteplase over streptokinase, but its inclusion or exclusion made little difference. Total stroke and haemorrhagic stroke rates were lower for streptokinase than for all alteplase combined (total stroke, OR 1.29, 95%CI 1.13-1.46; haemorrhagic stroke OR 1.83, 95%CI 1.14-2.93)[i].

i. Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: a systematic review. QJM 2003; **96(2)**: 103-113
(Type I evidence – systematic review. literature search to December 2001, of 14 randomised controlled trials comparing reteplase, tenecteplase, alteplase and streptokinase. Total study population 142 907)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

The *statements* | The *evidence*

Magnesium sulphate

3.5e. There is **no** evidence that the administration of **magnesium sulphate** to prehospital cardiac arrest patients presenting in **ventricular fibrillation** improves short or long-term survival[i]. In the ISIS trial there was no reduction in five week mortality attributed to the use of magnesium; 7.6% versus 7.2%[i].

i.   ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345**: 669-85

(Type I evidence – randomised controlled trial of 58,050 patients in a 2x2x2 factorial design comparing captopril, mononitrate and iv magnesium sulphate with placebo incorporating a meta-analysis of the results of ten earlier trials plus ISIS-4)

Guidelines for pre-hospital management

3.5f. Evidence-based guidelines for the **pre-hospital management** of acute myocardial infarction (MI) are available[i].

See also section 3.15 for more recent evidence-based guidelines for the management of patients with acute coronary syndromes

i.   Arntz H, Bossaert L, Carli P *et al*. The pre-hospital management of acute heart attacks. Recommendations of a Task Force of the European Society of Cardiology and the European Resuscitation Council. *European Heart Journal* 1998;**19**:1140-64

(Type V evidence - expert opinion)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

The work done in Wales by HeartStart Wales is one of the acknowledged initiatives. [paragraph 6.6]

The *statements* | The *evidence*

3.6 HeartStart Wales

3.6a. Information about **HeartStart Wales** is available from HeartStart BroTaf[i].

i.   Email da.morris@btconnect.com.

3 | ACUTE CORONARY SYNDROMES

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

All those with ACS need access to a bed in a Coronary Care Unit (CCU) or a monitored step-down bed. The agreed pathway for high-risk patients with ACS (unstable angina or non-Q-wave myocardial infarction) should include the use of low molecular weight heparin or therapeutic doses of unfractionated heparin, aspirin and glycoprotein IIb/IIIa inhibitors (where appropriate taking account of the most up to date research evidence as well as the NICE -Technology Appraisal Guidance. [paragraph 6.11]

What is the evidence regarding individual and combination treatments for patients with acute coronary syndrome?

The *statements* The *evidence*

3.7 Aspirin, clopidogrel and heparin for acute coronary syndromes *See also Section 3.21 re long term therapy*

3.7a. There is evidence from randomised controlled trials that in unstable angina and non-ST-segment elevation myocardial infarction that:

- **Aspirin** should be administered as soon as possible after presentation and continued indefinitely[i]
- **Clopidogrel** should be administered to hospitalised patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance[i,ii]
- In hospitalised patients in whom an early noninterventional approach is planned clopidogrel should be added to aspirin as soon as possible on admission and administered for at least one month[i].

An assessment of the effectiveness of **clopidogrel** in the treatment of non-ST-segment-elevation acute coronary syndrome is being carried out by the National Institute for Clinical Excellence. The expected date of issue is June 2004[iii].

i. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74

For the full guidelines see:

Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.

http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]

(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

ii. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal* 2003; **24**: 28-66

(Type V evidence – consensus guidelines)

iii. **http://www.nice.org.uk/cat.asp?c=66252** [accessed 22.12.03]

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

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3.7b. Treatment of patients with suspected or definite acute myocardial infarction with **antiplatelet therapy** is associated with reduced MI, stroke and vascular mortality at one month (% odds reduction 29% (SD 4%), Number needed to treat, NNT=26) and a significant reduction in non-fatal MI (% odds reduction 54%, SD 8%, NNT=83) and non-fatal stroke (% odds reduction 40%, SD 17%, NNT=50)[i]. Benefits of aspirin therapy are independent of, and additive to, thrombolytic therapy[ii] and early survival benefits are maintained for at least ten years[iii].

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994; **308**: 81-106.
http://bmj.bmjjournals.com/cgi/content/full/308/6921/81
[accessed 22.12.03]
(Type I evidence - systematic review and sub-group meta-analysis of 20,000 patients in nine trials of antiplatelet therapy in patients with acute MI.)

ii. ISIS-2 (Second International Study of Infarct Survival) 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
(Type II evidence - randomised controlled trial)

iii. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *British Medical Journal* 1998; **316**: 1337-43
http://bmj.bmjjournals.com/cgi/content/full/316/7141/1337 [accessed 22.12.03]
(Type II evidence - randomised controlled trial)

3.7c. **Aspirin** therapy is associated with **upper gastrointestinal complications** (UGIC) even when used at low doses or in buffered or enteric-coated formulations. The overall relative risk of UGIC associated with aspirin use was 2.2 (95% CI 2.1-2.4) for cohort and nested case-control studies and 3.1 (2.8-3.3) for non-nested case-control studies. Original studies found a dose-response relationship between UGIC and aspirin, although the risk was still elevated for doses lower than or up to 300 mg/day. The summary relative risk was 2.6 (2.3-2.9) for plain, 5.3 (3.0-9.2) for buffered, and 2.4 (95% CI 1.9-2.9) for enteric-coated formulations. The latter findings may be partially explained by channelling of susceptible patients to these formulations[i].

i. Rodriguez LAG, Hernández-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: Systematic review of epidemiologic studies. *British Journal of Clinical Pharmacology* 2001; **52(5)**: 563-571
(Type IV evidence – systematic review, Medline search to February 2001, of 17 cohort and case-control studies (12,140 cases and > 55,000 controls))

| 3 | **ACUTE CORONARY SYNDROMES** |

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3.7d. A very large randomised trial is underway in China to examine the effect of **clopidogrel plus aspirin, and/or metoprolol** among patients with suspected acute myocardial infarction[i].

i.   Second Chinese Cardiac Study (CCS-2) Collaborative Group. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. *Journal of Cardiovascular Risk* 2000; **7(6)**: 435-441

(Ongoing randomised controlled trial of up to 40,000 patients in 1,000 hospitals randomised to oral clopidogrel (75 mg/day) plus aspirin (162 mg/day) or placebo and/or metoprolol (200 mg/day) or placebo in a 2x2 study design. Medication will be given for up to four weeks. The trial was expected to be completed by 2003)

3.7e. Fixed dose **low molecular weight heparin** (LMWH) given subcutaneously compares favourably with **unfractionated heparin** (UFH) titrated to a target level of anticoagulation[i,ii]. Risk ratios (comparing LMWH with UFH) were 0.98 (95% CI 0.73-1.31) for death, 0.86 (0.74-1.01) for death or myocardial infarction (MI), 0.89 (0.74-1.07) for death, MI, recurrent angina or revascularisation and 1.01 (0.81-1.25) for major haemorrhage[i].

A Cochrane review of heparin versus placebo for acute coronary syndromes is in progress[ii].

i.   Le Nguyen M-T, Spencer FA. Low molecular weight heparin and unfractionated heparin in the early pharmacologic management of acute coronary syndromes: a meta-analysis of randomized controlled trials. *Journal of Thrombosis and Thrombolysis* 2001; **12(3)**: 289-295

(Type I evidence – systematic review, of Medline to 2000 and English language studies only, of five randomised controlled trials (13,320 patients). The trials included were: Gurfinkel, ESSENCE, FRIC, TIMI II B, FAXIS. No information is provided as to whether quality appraisal was carried out of the studies found)

ii. Magee K. Heparin versus placebo for acute coronary syndromes. (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised controlled trials, in progress)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

The *statements*

The *evidence*

3.7f. The short-term treatment of unstable coronary artery disease with the **low molecular weight heparin, enoxaparin**, is strongly recommended. There appears to be a cost-saving over unfractionated heparin although cost implications are likely to depend on local revascularisation procedures (both the proportion of patients undergoing revascularisation and the length of stay in hospital). No randomised controlled trials were found which were powered to compare dalteparin with unfractionated heparin and the one comparative trial was inadequate to reach a conclusion as to efficacy[i].

Studies based on Canadian[ii] and French[iii] scenarios from data in the ESSENCE trial suggest that enoxaparin is less costly and more effective than unfractionated heparin in patients hospitalised with unstable angina or non-Q-wave myocardial infarction[ii,iii].

At one year, the reduced risk and costs of revascularisation more than offset increased drug costs for enoxaparin, producing a cost saving (of Canadian dollars at 1997 prices) of $1485 (95% CI $-93 to $3167; p=0.06)[ii].

i. Nicholson T, Milne R, Stein K. Dalteparin and enoxaparin for unstable angina and non-Q-wave myocardial infarction: update. Development and Evaluation Committee Report No. 108. Southampton: Wessex Institute for Health Research & Development, 2000
http://www.hta.nhsweb.nhs.uk/rapidhta/ publications.htm [accessed 22.12.03]
(Type I evidence – systematic review and cost-utility analysis of three large published randomised controlled trials, ESSENCE & TIMI IIB (enoxaparin) and FRISC (dalteparin). The literature search was completed in March 2000)

ii. O'Brien BJ, Willan A, Blackhouse G, Goeree R, Cohen M, Goodman S. Will the use of low-molecular weight heparin (enoxaparin) in patients with acute coronary syndrome save costs in Canada? *American Heart Journal* 2000; **139**: 423-429
(Type IV evidence – cost-effectiveness analysis based on data from the ESSENCE trial)

iii. Detournay B, Huet Z, Fagnani F, Montalescot G. Economic evaluation of enoxaparin sodium versus heparin in unstable angina. A French sub-study of the ESSENCE trial. *Pharmacoeconomics* 2000; **18(1)**; 83-89
(Type IV evidence – cost-effectiveness analysis based on data from the ESSENCE trial)

3 | ACUTE CORONARY SYNDROMES

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3.7g. A recent review found that, in **aspirin-treated** patients with acute coronary syndrome without ST elevation, short-term **unfractionated heparin** or **low molecular weight heparin** (LMWH) halves the risk of myocardial infarction or death. There is no convincing difference in efficacy or safety between LMWH and unfractionated heparin. Long-term LMWH has not been proven to confer benefit additional to aspirin and there is no evidence to support its use after the first 7 days[i].

The summary odds ratio for myocardial infarction or death during short-term (up to 7 days) unfractionated heparin or LMWH compared with placebo or untreated control was 0.53 (95% CI 0.38-0.73, p=0.0001); during short-term LMWH compared with unfractionated heparin it was 0.88 (0.69-1.12; p=0.34); and during long-term LMWH (up to three months) compared with placebo or untreated control it was 0.98 (0.81-1.17; p=0.80). Long-term LMWH was associated with a significantly increased risk of major bleeding (OR=2.26, 95% CI 1.63-3.14, p<0.0001), or 12 major bleeds per 1000 patients treated[i].

There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that **anticoagulation** with subcutaneous low molecular weight heparin or intravenous unfractionated heparin should be added to antiplatelet therapy with ASA and/or clopidogrel[ii].

i. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; **355(9219)**: 1936-1942

(Type I evidence – systematic review and meta-analysis of 12 randomised controlled trials and 17,157 patients. No search date given but trials published up to 1999 were included.)

ii. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74

For the full guidelines see:
Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.

http://www.acc.org/clinical/guidelines/unstable/incorporated [accessed 22.12.03]

(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

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3.7h. **Direct thrombin inhibitors** are superior to heparin for the prevention of death or myocardial infarction (MI) during treatment in patients with acute coronary syndromes. Compared with heparin, direct thrombin inhibitors were associated with a lower risk of death or myocardial infarction at the end of treatment (4.3% vs 5.1%; odds ratio 0.85, 95% CI 0.77-0.94, p=0.001). This was due primarily to a reduction in myocardial infarctions (2.8% vs 3.5%, 0.80, 0.71-0.90, p<0.001) with no apparent effect on deaths (1.9% vs 2.0%, 0.97, 0.83-1.13, p=0.69). A reduction in death or MI was seen with hirudin and bivalirudin but not with univalent agents. Compared with heparin, there was an increased risk of major bleeding with hirudin, but a reduction with bivalirudin[i].

Caveat: The trials were completed before the current approach of glycoprotein IIb/IIIa inhibitors and stenting was available.

i. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: a meta-analysis based on individual patient data. *Lancet* 2002; **359**: 294-302

(Type I evidence – systematic review and meta-analysis, literature search date not given, of 11 randomised trials of individual patient data from 35,970 patients assigned up to seven days' treatment with a direct thrombin inhibitor (hirudin, bivalirudin, argatroban, efegatran or inogatran) or heparin and followed for at least 30 days)

3.8 **Glycoprotein IIb/IIIa inhibitors for acute coronary syndromes**

3.8a. The National Institute for Clinical Excellence (NICE) supports the use of **glycoprotein IIb/IIIa inhibitors** in acute coronary syndromes and has made the following recommendations[i]:

■ Glycoprotein IIb/IIIa (PG IIb/IIIa) inhibitors should be considered part of the management pathway for unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). This management pathway also includes other pharmacological interventions and, where appropriate, early coronary angiography with a view to revascularisation either by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)

i. National Institute for Clinical Excellence. *Guidance* on the use of *Glycoprotein IIb/IIIa Inhibitors* in the Treatment of Acute *Coronary Syndromes*. Technology Appraisal Guidance – No.47. London: NICE, September 2002. Review date: September 2005

Summary:

http://www.nice.org.uk/pdf/47_A4_summary.pdf

[accessed 22.12.03]

Full guidance:

http://www.nice.org.uk/pdf/Guidance_ GLYCOPROTNS.pdf [accessed 22.12.03]

(Evidence-based guidance from a systematic review and cost effectiveness analysis, submissions from manufacturers, professionals, specialists, patients & carers)

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3.8a continued from previous page

■ The intravenous use of small-molecule PG IIb/IIIa
inhibitor (eptifibatide or tirofiban) in addition to aspirin
and unfractionated heparin, is recommended as part
of the initial medical management of patients with
unstable angina or NSTEMI who are at high risk of
subsequent myocardial infraction (MI) or death.

■ Whilst early angiography is desirable for high-risk
patients, in situations where PCI does not occur or is
not immediately available, initial medical management
with PG IIb/IIIa inhibitors is still recommended

■ In determining who is at high risk, clinicians should
take into account risk factors such as: clinical history,
including age, previous MI, and PCI or CABG; clinical
signs, including continuing pain despite initial
treatment; and clinical investigations, such as ECG
changes, heamodynamic changes and raised cardiac
troponin levels

■ Treatment with small molecule PG IIb/IIIa inhibitors
should be initiated as soon as high risk status is
determined even though this may be before the result
of the troponin test is known.

■ If PCI is indicated….but it is delayed beyond the initial
medical management phase, use of a PG IIb/IIIa
inhibitor is recommended as an adjunct to the PCI
(currently only abciximab is licensed as an adjunct to PCI)

■ It is recommended that a PG IIb/IIIa inhibitor is
considered as an adjunct to PCI for all patients with
diabetes undergoing elective PCI, and for complex
procedures. In procedurally uncomplicated, elective
PCI, where the risk of adverse sequelae is low, use of a
PG IIb/IIIa inhibitor is not recommended unless
unexpected immediate complications occur

■ PG IIb/IIIa inhibitors are not currently licensed in the UK
for use as an adjunct to thrombolytic therapy in ST-
segment-elevation MI.

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the **supporting evidence** *for a consideration of all the implications of a recommendation.*

The *statements*

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3.8b. There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that:

- A platelet glycoprotein IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterisation and PCI are planned. The GP IIb/IIIa inhibitor may also be administered just prior to PCI.
- In patients for whom PCI is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least one month[i].

The following treatments are **contraindicated**:

- Intravenous fibrinolytic therapy in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block.
- Abciximab administration in patients in whom PCI is **not planned**[i].

Other systematic reviews also suggest a benefit in the use of **glycoprotein IIb/IIIa inhibitors** in patients with acute coronary syndromes[ii,iii] although a Cochrane review did not find a statistically significant reduction in deaths at six months[iii].

i. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74
For the full guidelines see:
Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

ii. 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**: 189-198
(Type I evidence – systematic review, using Medline only and reference list follow-up plus scientific abstracts, and meta-analysis of six randomised controlled trials published since 1990 (31,402 patients in all). The literature search date was not given. Trials included were: PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, GUSTO-IV ACS)

iii. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularisation, and unstable angina and non-ST-segment elevation myocardial infarction. (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (Most recent update 24 August 2001)
http://www.update-software.com/abstracts/ ab002130.htm [accessed 22.12.03]
(Type I evidence - systematic review, literature search to June 2001, and meta-analysis of 8 randomised controlled trials and 30,006 patients)

3 ACUTE CORONARY SYNDROMES

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3.9 Other post acute ACS therapies
■ Nitrates ■ glucose-insulin-potassium

3.9a. **Oral mononitrate** therapy started early in acute MI is **not** associated with a significant reduction in five-week mortality[i]. Meta-analysis of trials of oral and iv nitrates found a non-significant 3% odds reduction in short-term mortality[i].
Caveat: There was significant heterogeneity between the trials - effectiveness of nitrates remains unproven.

i. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669-85

(Type I evidence - randomised controlled trial of 58,050 patients in a 2x2x2 factorial design comparing captopril, mononitrate and iv magnesium sulphate with placebo, and meta-analysis of 23 randomised controlled trials of oral and iv nitrates in early MI)

3.9b. A trial noted a trend towards a reduction in major and minor in-hospital events in patients receiving **glucose-insulin-potassium** therapy and a significant reduction in mortality in 252 patients (61.9%) treated with reperfusion strategies (relative risk = 0.34, 95% CI 0.15-0.78, 2p=0.008)[i] and a systematic review also suggested a reduction of in-hospital mortality from 21% to 16.1% (p<0.01)[ii]. Another trial suggested that total mortality was higher in the GIK than the control group although there was no significant difference in cardiac mortality[iii].
Caveats: **No thrombolytic therapy** was given in all bar one trial in the systematic review[ii] so the review is out of date and the results of the more recent randomised controlled trials[i,iii] are contradictory.

A trial looking at glucose-insulin-potassium therapy in patients treated with **primary angioplasty** in acute myocardial infarction did not find a significant mortality reduction in all patients at 30 days. In the subgroup of 856 patients without heart failure a significant reduction was noted (relative risk 0.28, 95% CI 0.1-0.75). The effect of GIK infusion in patients with signs of heart failure (Kippi class ≥ 2) at admission is uncertain (RR 1.44, 95% CI 0.65-3.22)[iv]. *Further research is required*.

i. Díaz R, Paolasso EA, Piegas LS *et al;* on behalf of the ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. Metabolic modulation of acute myocardial infarction. The ECLA glucose-insulin-potassium pilot trial. *Circulation* 1998; **98**: 2227-2234

(Type II evidence – randomised controlled trial of 407 patients with suspected AMI admitted within 24 hours of symptom onset allocated to receive high or low dose GIK or control. High-dose GIK = 25% glucose, 50 IU soluble insulin per liter and 80 mmol KCl per liter at an infusion rate of 1.5 mL/kg/h. Low-dose GIK = 10% glucose, 20 IU soluble insulin per liter and 40 mmol KCl per liter an an infusion rate of 1.0 mL/kg/h)

ii. Fath-Ordoubadi F, Markides V, Beatt KJ. Meta-analysis of glucose-insulin-potassium therapy for myocardial infarction. *Cardiology Review* 1998; **15(4)**: 41-44

(Type I evidence – systematic review, literature search to 1996, of nine trials and 1932 patients)

iii. Ceremuzynski L, Budaj A, Czepiel A *et al*. Low-dose glucose-insulin-potassium is ineffective in acute myocardial infarction : results of a randomised multicenter Pol-GIK trial. *Cardiovascular Drugs* 1999; **13**: 91-99

(Type II evidence – randomized controlled trial of 954 patients with acute myocardial infarction randomized to low-dose GIK (1000 mL 10% dextrose, 32-20 U insulin and 80 mEq K+) or control)

iv. van der Horst ICC, Zijlstra F, Van't Hof AWJ *et al*. Glucose-insulin-potassium infusion in patients treated with primary angioplasty for acute myocardial infarction. The Glucose-Insulin-Potassium Study: A randomized trial. *Journal of the American College of Cardiology* 2003; **42**: 784-791

(Type II evidence – randomized controlled trial of 940 patients randomly assigned, by open label, to either a continuous GIK infusion for 8-12 hours or no infusion)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

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3.9c. An **advice and relaxation tape** reduces cardiac misconceptions but does not confer any other benefits over a music tape[i].

i. Lewin RJP, Thompson DR, Elton RA. Trial of the effects of an advice and relaxation tape given within the first 24 h of admission to hospital with acute myocardial infarction. *International Journal of Cardiology* 2002; **82(2)**; 107-114

(Type II evidence – randomised controlled trial of 243 subjects randomised to receive either the advice and relaxation tape or a music tape of their choice within 24 h of sustaining a myocardial infarction)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

Treatment with Glycoprotein inhibitors will also apply to patients undergoing acute or elective percutaneous coronary intervention when appropriate. [paragraph 6.11]

What are the latest indications for treatment?

The *statements*	The *evidence*

3.10 Glycoprotein IIb/IIIa blockers in percutaneous coronary intervention

3.10a Intravenous glycoprotein IIb/IIIa blockers reduce the risk of death at 30 days and markedly that of death or MI at 30 days and six months in patients submitted to percutaneous coronary revascularisation at a price of moderate increased risk of severe bleeding. Mortality was decreased at 30 days (odds ratio = 0.71, 95% CI 0.52-0.97) but not at six months (OR = 0.85, 95% CI 0.66-1.11). Mortality or infarction was decreased both at 30 days (OR = 0.62, 95% CI 0.55-0.70) and at six months (OR = 0.65, 95% CI 0.58-0.73) but severe bleeding was increased (10 per 1000, OR = 1.38, 95% CI 1.04-1.85)[i].

The National Institute for Clinical Excellence (NICE) has made the following recommendation regarding the use of glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention[ii]:

■ It is recommended that a PG IIb/IIIa inhibitor is considered as an adjunct to PCI for all patients with diabetes undergoing elective PCI, and for complex procedures. In procedurally uncomplicated, elective PCI, where the risk of adverse sequelae is low, use of a PG IIb/IIIa inhibitor is not recommended unless unexpected immediate complications occur

See also statement 3.8a.

continued

i. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularisation, and unstable angina and non-ST-segment elevation myocardial infarction.
(Cochrane Review). In: The Cochrane Library, Issue 1 2003. Oxford: Update Software. (Most recent update 24 August 2001)
http://www.update-software.com/abstracts/ ab002130.htm [accessed 22.12.03]

(Type I evidence - systematic review, literature search to June 2001, and meta-analysis of 14 randomised controlled trials and 17,788 patients)

ii. National Institute for Clinical Excellence. *Guidance on the use of Glycoprotein IIb/IIIa Inhibitors in the Treatment of Acute Coronary Syndromes*. Technology Appraisal Guidance – No.47. London: NICE, September 2002. Review date: September 2005
Summary:
http://www.nice.org.uk/pdf/47_A4_summary.pdf
[accessed 22.12.03]
Full guidance:
http://www.nice.org.uk/pdf/Guidance_ GLYCOPROTNS.pdf [accessed 22.12.03]

(Evidence-based guidance from a systematic review and cost effectiveness analysis, submissions from manufacturers, professionals, specialists, patients & carers)

3 | ACUTE CORONARY SYNDROMES

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3.10a continued from previous page

There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that intravenous platelet **glycoprotein** IIb/IIIa inhibitor should be given to patients with unstable angina or non-ST-segment elevation myocardial infarction undergoing PCI[iii].

iii.   Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

3.10b. In patients undergoing stent implantation, at 6 months **tirofiban** provided a similar level of overall protection to abciximab against the composite of death, myocardial infarction, and any target-vessel revascularisation. The composite end-point occurred in 356 (14.8%) of patients who received tirofiban and 345 (14.3%) patients who received abciximab (hazard ratio 1.04, 95% CI 0.90-1.21, p=0.591)[i].
Caveats: TARGET was funded by Merck and several authors were Merck employees. However, the masked data were collected and adjudicated by an independent company.

Abciximab use compared with **tirofiban** resulted in greater suppression of periprocedural myonecrosis, although a survival benefit was not demonstrated. In this group of patients, abciximab resulted in lower rates of myocardial infarction at 30 days (5.8% vs 8.5%, p=0.004) and six months (7.2% vs 9.8%, p=0.013) although six month mortality rates were identical (1.39% in both groups, p=0.99). Patients with stable coronary syndromes may have equivalent or better outcomes with tirofiban relative to abciximab, with fewer incidences of thrombocytopenia[ii].
Caveat: This is a post-hoc analysis of the data.

A formal cost-effectiveness analysis is pending.

i.   Moliterno DJ, Yakubov SJ, DiBattiste PM *et al*. Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: The TARGET follow-up study. *Lancet* 2002 ; **360(9330)**: 355-360
(Type II evidence – multicentre randomised controlled trial of post-ACS (n=3,025) and non-ACS patients (n=1,784) in a randomised controlled trial of 4809 patients undergoing planned stenting randomised to abciximab or tirofiban. An intention to treat analysis was used)

ii.   Stone GW, Moliterno DJ, Bertrand M *et al*. Impact of clinical syndrome acuity on the differential response to 2 glycoprotein IIb/IIIa inhibitors in patients undergoing coronary stenting. The TARGET trial. *Circulation* 2002; **105(20)**: 2347-2354
(Type II evidence – post-hoc analysis of patients in the TARGET trial. See above)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

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3.10c. The **NICE 4** study collected data on the combination of the low molecular weight heparin (LMWH), enoxaparin and the GPIIb/IIIa inhibitor abciximab in non-ST-elevation acute coronary syndrome patients undergoing PCI, and both safety and efficacy data compared well with historical data collected on the use of unfractionated heparin (UFH) with abciximab. The more recent **NICE 3** study extended this finding to the combination of enoxaparin with abciximab, tirofiban or eptifibatide. In addition, a **GUSTO IV** substudy found that dalteparin had equivalent safety to UFH when co-administered with abciximab in patients not undergoing PCI. The NICE 3 and 4 trials were not randomised comparisons, and as such these results must be interpreted with caution[i].

An ongoing randomised controlled trial (**SYNERGY**) is investigating the efficacy of the combination of enoxaparin with abciximab versus that of UFH and abciximab in 8000 non-ST-elevation acute coronary syndrome patients treated with an early invasive strategy[ii].

The *evidence*

i. Cohen M. Combination of low molecular weight heparins with antiplatelet agents in non-ST elevation acute coronary syndromes: an update. *Drugs* 2002; **62(12)**: 1755-70
(Type V evidence – expert review of recent trials)

ii. Mahaffey KW. The SYNERGY trial: Study design and rationale. *American Heart Journal* 2002; **143(6)**: 952-960
(Ongoing trial)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

The decision regarding the revascularisation method to be used in individual patients should be made in a multidisciplinary way involving the cardiologists, cardiac surgeons, nurses and the patient. This will ensure that the method of revascularisation will match the needs of each patient without any unnecessary waiting [paragraph 6.11]

Revascularisation can be done either by angioplasty with or without stenting or by CABG. A decision about the most appropriate mode of revascularisation for an individual patient should be made jointly by the cardiologists and the cardiac surgeon after they have together reviewed the results of the patient's investigations. [paragraph 6.19]

What are the current recommendations?

3 | ACUTE CORONARY SYNDROMES

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3.11 Angioplasty versus thrombolysis

3.11a. The National Institute for Clinical Excellence (NICE) has made the following recommendations[i]:

■ **Glycoprotein IIb/IIIa** (PG IIb/IIIa) inhibitors should be considered part of the management pathway for unstable angina or non-ST-segment-elevation myocardial infarction (NSTEMI). This management pathway also includes other pharmacological interventions and, where appropriate, early coronary angiography with a view to revascularisation either by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)

■ Whilst early angiography is desirable for high-risk patients, in situations where PCI does not occur or is not immediately available, initial medical management with PG IIb/IIIa inhibitors is still recommended

For a full summary of the NICE guidance, *see statement 3.8a*

i.   National Institute for Clinical Excellence. *Guidance on the use of Glycoprotein IIb/IIIa Inhibitors in the Treatment of Acute Coronary Syndromes.* Technology Appraisal Guidance – No.47. London: NICE, September 2002. Review date: September 2005
Summary:
http://www.nice.org.uk/pdf/47_A4_summary.pdf
[accessed 22.12.03]
Full guidance:
http://www.nice.org.uk/pdf/Guidance_GLYCOPROTNS.pdf
[accessed 22.12.03]
(Evidence-based guidance from a systematic review and cost effectiveness analysis, submissions from manufacturers, professionals, specialists, patients & carers)

3.11b. There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that an **early invasive strategy** in patients with unstable angina or non ST segment elevation myocardial infarction without serious comorbidity and who have any of the following high risk indicators:

■ Recurrent angina/ischemia at rest or with low level activities despite intensive anti-ischaemic therapy
■ Elevated TnT or TnI
■ New or presumably new ST-segment depression
■ Recurrent angina/ischaemic with congestive heart failure symptoms, an S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
■ High-risk findings on non-invasive stress testing
■ Depressed LV systolic function
■ Hemodynamic instability
■ Sustained ventricular tachycardia
■ PCI within six months
■ Prior CABG[i].

i.   Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74
For the full guidelines see:
Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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3.11c In patients with unstable angina and myocardial infarction without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the use of an **early invasive strategy** significantly reduced the incidence of major cardiac events. At six months, the rate of the primary end point (death, non fatal myocardial infarction or rehospitalisation for acute coronary syndrome within six months) was 15.9% with use of the early invasive strategy and 19.4% with use of the conservative strategy (odds ratio=0.78, 95% CI 0.62-0.97, p=0.025). The rate of death or non fatal myocardial infarction at six months was similarly reduced (7.3% vs. 9.5%, OR=0.74, 0.54-1.00, p<0.05) although there was no difference in the death rate when considered alone[i].

i. Cannon CP, Weintraub WS, Demopoulos LA *et al*. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *New England Journal of Medicine* 2001; **344(25)**: 1879-1887

(Type II evidence – randomised controlled trial of 2,220 patients. Patients were randomly assigned to an early invasive or a more conservative (selectively invasive) strategy in which catheterisation was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test)

3.11d **Primary percutaneous transluminal coronary angioplasty (PTCA)** is more effective than **thrombolytic therapy** for the treatment of ST-segment elevation acute myocardial infarction.

Primary PTCA was better than thrombolytic therapy at reducing overall short-term death (7% [n=270] vs 9% [360]; p=0.0002), non-fatal reinfarction (3% [80] vs 7% [222]; p<0.0001), stroke (1% [30] vs 2% [64]; p=0.0004), and the combined endpoint of death, non-fatal reinfarction, and stroke (8% [253] vs 14% [442]; p<0.0001). The results seen with primary PTCA remained better than those seen with thrombolytic therapy during long-term follow-up, and were independent of both the type of thrombolytic agent used, and whether or not the patient was transferred for primary PTCA[i].

i. 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(9351)**: 13-20

(Type I evidence – systematic review, literature search date and information on quality assessment not provided, of 23 trials and 7,739 thrombolytic-eligible patients with ST-segment elevation AMI assigned to primary PTCA (n=3,872) or thrombolytic therapy (n=3,867). Streptokinase was used in eight trials (n=1,837), and fibrin-specific agents in 15 (n=5,902). Most patients who received thrombolytic therapy (76%, n=2,939) received a fibrin-specific agent)

3 | ACUTE CORONARY SYNDROMES

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3.12 Choice of operative technique
See Section 2.17 for trials of operative techniques for patients with stable angina, most of which include patients with unstable angina/acute coronary syndrome.

3.12a. There is general agreement that the following **operative procedures** are indicated:

- CABG for patients with significant left main coronary artery disease[i,ii]
- CABG for patients with three-vessel disease; the survival benefit is greater in patients with abnormal LV function (ejection fraction <0.50)[i,ii]
- CABG for patients with two-vessel disease with significant proximal left anterior descending coronary artery disease and either abnormal LV function (ejection fraction <0.50) or demonstrable ischaemia on noninvasing testing[i,ii]
- PCI for patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function and without diabetes[i].

i.   Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74
     For the full guidelines see:
     Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
     http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]
     (Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

ii. British Cardiac Society Guidelines and Medical Practice Committee, and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. *Heart* 2001; **85(2)**: 133-142
     (Evidence based guidelines – narrative systematic review of the literature in peer reviewed journals, search to December 1999)

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3.12b. Findings from a recent trial suggested that **percutaneous coronary intervention** is an alternative to CABG for patients with medically refractory myocardial ischemia and a high risk of adverse outcomes with CABG. The 30-day survivals for CABG and PCI were 95% and 97% respectively. Survival rates for CABG and PCI were 90% versus 94% at six months and 79% versus 80% at 36 months (p=0.46)[i].

Caveats: Surgical and medical methods evolved during the course of the study (1995-2000). There were many exclusions including a number of clinically eligible patients who were not entered into the study by their clinicians and the results may not be generalisable.

i. Morrison DA, Sethi G, Sacks J *et al*. for the Investigators of the Department of Veternas Affairs Cooperative Study #385, the Angina with Extremely Serious Operative Mortality Evaluation (AWESOME). Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: A multicentre, randomized trial. *Journal of the American College of Cardiology* 2001; **38(1)**: 143-149

(Type II evidence – five year randomised controlled trial of 454 patients. 58% of clinically eligible patients (n=781) entered the study. Analysis was by intention to treat)

3.12c. In a **high risk** group with multivessel disease, **percutaneous transluminal coronary revascularisation** (PCTR) with stent implantation showed better survival and freedom from myocardial infarction than **coronary artery bypass** graft surgery (CABG). At follow up (mean 18.5 ± 6.4 months), survival was 96.9% in PTCR versus 92.5% in CABG (p<0.017). Freedom from myocardial infarction was also better in PTCR compared to CABG patients (97.7% vs. 93.4%*, p<0.017). Repeat revascularisation procedures were higher in the PTCR than the CABG group (16.8% versus 4.8%, p<0.002)[i].

* This figure is given as 93.4% in abstract and 93.7% in the body of the paper.

i. Rodriguez A, Bernardi V, Navia J *et al*; for the ERACI II Investigators. Argentine randomized study: Coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple-vessel disease (ERACI II): 30-day and one-year follow-up results. *Journal of the American College of Cardiology* 2001; **37**: 51-58

(Type II evidence – randomised controlled trial of 450 patients with coronary artery disease (from 2,759 patients screened). 92% had unstable angina. Analysis was by intention to treat)

3 | ACUTE CORONARY SYNDROMES

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3.12d. Guidance from NICE on the use of **coronary artery stents** including **drug eluting stents** are that[i]:

■ Stents should be used routinely where percutaneous coronary intervention (PCI) is the clinically appropriate procedure for patients with either stable or unstable angina or with acute myocardial infarction.

■ It is recommended that when considering the use of a bare-metal stent (BMS) or a drug-eluting stent (DES) the decision should be based on the anatomy of the target vessel for stenting and the symptoms and mode of presentation of the disease.

■ The use of either a Cypher (sirolimus-eluting) or Taxus (paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic coronary artery disease (CAD) in whom the target artery is less than 3 mm in calibre (internal diameter) or the lesion is longer than 15 mm. This guidance for the use of DES does not apply to people who have had an MI in the preceding 24 hours, or for whom there is angiographic evidence of thrombus in the target artery.

■ If more than one artery is considered clinically appropriate for stenting then the considerations above apply to each artery.

■ This guidance specifically relates to the present clinical indications for PCI and excludes conditions (such as many cases of stable angina) that are adequately managed with drug therapy.

A recent metaanalysis suggests that routine coronary stenting is safe but probably not associated with important reductions in rates of mortality, acute myocardial infarction, or coronary artery bypass surgery compared with standard PTCA with provisional stenting[ii] (see also Statement 2.17a).

i. National Institute for Clinical Excellence. *Guidance on the Use of Coronary Artery Stents*. Technology Appraisal 71. London: NICE, October 2003

http://www.nice.org.uk/pdf/TA71_coronaryarterystents_fullguidance.pdf [accessed 22.12.03]

(Evidence-based guidance from a systematic review and cost effectiveness analysis, submissions from manufacturers, professionals, specialists, patients & carers)

ii. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Annals of Internal Medicine* 2003; **138(10)**: 777-86

(Type I evidence – systematic review, literature search to June 2002, of 29 published trials involving 9918 patients. Patients with myocardial infarction were excluded)

3.12e. The primary success rate of **direct stenting** was 88.3% versus 97.8% for stenting preceded by **balloon dilatation** (P=0.01). However, compared to stenting preceded by balloon predilatation, direct stenting was associated with similar six-month restenosis and major event rates. Procedural but not overall six-month costs were reduced by direct stenting[i].

i. Ijsselmuiden AJJ, Serruys PW, Scholte A *et al*. Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events: Six month results of a randomized trial. *European Heart Journal* 2003; **24(5)**: 421-429

(Type II evidence – randomised controlled trial of 400 patients with stable or unstable angina and coronary stenoses in a single native vessel allocated to direct stenting or stenting after predilatation)

*This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the **supporting evidence** for a consideration of all the implications of a recommendation.*

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3.12f. In a small trial of patients with acute myocardial infarction, a reperfusion strategy based on stenting with **abciximab** produced more myocardial salvage than the combination of fibrinolysis plus abciximab (median 13.6% [Inter Quartile Range 5.9-23.9] vs 8.0% [2.5-16.0] of the left ventricle; p=0.007). *Larger studies are needed to see whether these effects translate into clinical benefit*[i].

i. Kastrati A, Hemilli J, Dirschinger J *et al*. for the Stent versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI-2) Study. Myocardial salvage after coronary stenting plus abciximab versus fibrinolysis plus abciximab in patients with acute myocardial infarction: a randomised trial. *Lancet* 2002; **359**: 920-925

(Type II evidence – randomised controlled trial of 162 patients with acute myocardial infarction within 12 hours of onset of symptoms to stenting plus abciximab or alteplase plus abciximab)

3.12g. A Cochrane review is underway to examine the evidence, in patients with non-complex lesions of the coronary arteries, for the safety, effectiveness, tolerability and cost of **percutaneous transluminal coronary rotational atherectomy (PTCRA)** compared to percutaneous transluminal coronary angioplasty (PTCA)[i].

i. Villanueva EV, Petherick ES, Wasiak J. Percutaneous transluminal rotational atherectomy for atheromatous lesions of the coronary arteries. (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised controlled trials, in progress)

3.13 Influenza vaccination

3.13a. Influenza vaccination may reduce the risk of death and ischemic events in patients suffering from infarction and those recovering from angioplasty during flu season. This response could be related to a humoral immune response with positive consequences during flu seasons.

The relative risk with vaccine as compared with controls was 0.25 (95% CI 0.07-0.86; p = 0.01). The triple composite end point (cardiovascular death, nonfatal MI or severe ischaemia) occurred in 11% of the patients in the vaccine group compared with 23% in controls (P=0.009)[i].

Caveat: The rationale and method of single rather than double-blinding was unclear. *This was a pilot study and further research is needed.*

i. Gurfinkel EP, De la Fuente RL, Mendiz O, Mautner B. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: The FLU Vaccination Acute Coronary Syndromes (FLUVACS) study. *Circulation* 2002 ; **105(18)** : 2143-2147

(Type II evidence – Pilot randomised controlled trial of 200 myocardial infarction patients and 101 planned angioplasty/stent (PCI) patients in a prospective, multicenter log during the winter season. Patients were allocated to a unique intramuscular influenza vaccination or a control group)

3	ACUTE CORONARY SYNDROMES

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

An essential part of a DGH cardiology service is a comprehensive and efficient electrophysiological measurement department. This department provides ECGs, echocardiography, and exercise testing for all those who need investigation either because they are suspected as having CHD, have stable angina or have acute coronary syndrome. Those with acute coronary syndrome need rapid access to investigations in a way that does not delay treatment. [paragraph 6.12]

What is the latest evidence on these techniques?

The *statements*   The *evidence*

3.14   Non-invasive investigation

3.14a. **Exercise ECG testing** for patients stabilised after an episode of unstable coronary artery disease or after myocardial infarction has some value at a low cost (£30-£160 per test). The negative predictive value of testing is quite high (ie patients who have a negative test are unlikely to suffer a further cardiac event and will probably not benefit from angiography). Conversely, the positive predictive value is quite low. Not all patients with a negative exercise test will avoid angiography. The timing of testing is crucial and clinical flexibility is required[i].

i.   Chase D, Milne R. Exercise testing following unstable coronary artery disease or myocardial infarction. Development and Evaluation Committee Report No. 92. Bristol: NHS Executive South and West, 1998. **http://www.hta.nhsweb.nhs.uk/rapidhta/ publications.htm** [accessed 22.12.03]

(Type IV evidence – systematic review of four observational studies with one-year follow-up (in unstable coronary artery disease) and one meta-analysis plus two long-term observational studies (after myocardial infarction). Literature searches completed in June 1998)

3.14b. In post myocardial infarction patients, echocardiographic assessment of **atrioventricular plane displacement** showed a strong, independent prognostic value. The combined mortality/heart failure hospitalisation incidence was 43.8% in the lowest and 14.6% in the combined upper three quartiles (risk ratio = 3.0, p<0.0001)[i]. **Caveat**: This technique is not widely used in the UK.

i.   Brand B, Rydberg E, Dricsson G, Gudmudsson P, Willenheimer R. Prognostication and risk stratification by assessment of left atrioventricular plane displacement in patients with myocardial infarction. *International Journal of Cardiology* 2002; **83**: 35-41

(Type IV evidence – echocardiographic assessment of 271 consecutive patients with acute myocardial infarction attending a hospital in Sweden between May 1997 and March 1998. The mean prospective follow-up was 628 days)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

The *statements*

The *evidence*

3.14c **Exercise treadmill testing** alone is poorly diagnostic of post-PTCA restenosis, while **stress nuclear** and **stress echocardiographic imaging** perform better. Nuclear imaging has a sensitivity of 87% (95% CI 74-100%) and a specificity of 78% (95% CI 74-81%). Echocardiographic imaging has a sensitivity of 63% (95% CI 15-100%) and a specificity of 87% (95% CI 72-100%). However, the value of routine post-PTCA functional testing to detect restenosis is declining because restenosis rates are decreasing due to an increase in stent use. A decline in restenosis rate from 30% to 10% leads to an increase in the false positive rate of stress imaging from 37% to 77%[i].

i.   Garzon P, Eisenberg MJ. Functional testing for the detection of restenosis after percutaneous transluminal coronary angioplasty: a meta-analysis. *Canadian Journal of Cardiology* 2001; **17(1)**: 41-48

(Type IV evidence – systematic review, literature search to 2000, of 13 diagnostic studies. Restenosis was defined for comparative purposes as a coronary artery diameter narrowing of >50%)

3.14d A NICE technology appraisal of **myocardial perfusion scintigraphy** (MPS) recommends that[i]

MPS using single photon emission computed tomography (SPECT) is recommended for the diagnosis of suspected coronary artery disease (CAD) in the following circumstances:

■ As the initial diagnostic tool for people with suspected CAD for whom stress electrocardiography poses particular problems of poor sensitivity or difficulties in interpretation, including women, patients with cardiac conduction defects (for example, left bundle branch block), and people with diabetes, and for people for whom treadmill exercise is difficult or impossible

■ As part of the investigational strategy for the diagnosis of suspected CAD in people with lower likelihood of CAD and of future cardiac events. The likelihood of CAD will be based on the assessment of a number of risk factors including age, gender, ethnic group, family history, associated comorbidities, clinical presentation, physical examination, and results from other investigations (for example, blood cholesterol levels or resting electrocardiogram).

MPS using SPECT is recommended as part of the investigational strategy in the management of established CAD in people who remain symptomatic following myocardial infarction or reperfusion interventions.

i.   National Institute for Clinical Excellence. *Coronary Imaging: Myocardial Perfusion Scintigraphy for the Management of Angina and Myocardial Infarction* (No. 73). London: NICE, November 2003
http://www.nice.org.uk/cat.asp?c=94600
[accessed 22.12.03]

(Evidence based guideline – based on a systematic literature review completed in May 2003)

3 ACUTE CORONARY SYNDROMES

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3.15 Guidelines and audit standards for the management of acute coronary syndromes

3.15a. Guidelines for the management of patients with acute coronary syndromes are available[i,ii,iii,iv].

i. British Cardiac Society Guidelines and Medical Practice Committee, and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. *Heart* 2001; **85(2)**: 133-142

(Evidence based guidelines – narrative systematic review of the literature in peer reviewed journals, search to December 1999)

ii. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-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). *Journal of the American College of Cardiology* 2002; **40(7)**: 1366-74

For the full guidelines see:

Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.

http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]

(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

iii. Van de Werf F, Ardissino D, Betriu A *et al*. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal* 2003; **24**: 28-66

(Type V evidence – consensus guidelines)

iv. Bertrand ME, Simoons ML, Fox KA *et al*. Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal* 2002; 23(23): 1809-1840

(Type V evidence – consensus guidelines)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

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3.15b. The **Myocardial Infarction Audit Project (MINAP),** is the response of the profession to the audit requirements of the National Service Framework for Coronary Heart Disease. Through close collaboration with Central Cardiac Audit Database (CCAD) group a core set of data from acute trusts is collected and analysed. 100% of hospitals in England and 84% hospitals in Wales are contributing data, and have the facility to view online their hospital's performance of NSF targets compared to national aggregate data[i].

i. Myocardial Infarction Audit Project (MINAP). Royal College of Physicians. Prepared on behalf of the National Service Framework for Coronary Heart Disease.
http://www.rcplondon.ac.uk/college/ceeu/ceeu_ami_home.htm [accessed 22.12.03]
(Web page)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001
Rehabilitation must be provided in an agreed way across primary, secondary and tertiary care, and should be accessible and acceptable to the patients. [paragraph 1.11]
Rehabilitation programmes should continue to be the subject of research evaluation.
All cardiac rehabilitation programmes should be based on evidence (NB the guidelines and standards outlined by the British Association of Cardiac Rehabilitation). A cardiac rehabilitation programme needs to be provided for all those who have had an episode of acute coronary syndrome, some of whom will have had a revascularisation procedure. This rehabilitation must be provided in an agreed way across primary, secondary and tertiary care, and should be accessible and acceptable to the patients. This action plan recommends that a specialised nurse/health care professional be appointed in each LHG to work with the DGHs and tertiary centres to identify all suitable/at risk individuals and encourage them to take part in a locally based programme. These nurses would organise local programmes in collaboration with the DGH multidisciplinary rehabilitation team, building on the expert programmes already in place in parts of Wales. [paragraph 6.14]
What is the current evidence for the effectiveness of cardiac rehabilitation programmes and how should these be organised?

The *statements*	The *evidence*

3.16 Cardiac rehabilitation

3.16a. **Guidelines** endorsed by the **British Association of Cardiac Rehabilitation** (BACR) are available for cardiac rehabilitation[i].
Caveat: Some large recent trials that have been published since the literature search was carried out for these guidelines.

i. Scottish Intercollegiate Guidelines Network. *Cardiac Rehabilitation*. SIGN Publication No. 57. Edinburgh: SIGN, January 2002
http://www.sign.ac.uk/guidelines/fulltext/57/index.html
[accessed 22.12.03]
(Evidence based guidelines from a systematic review, literature search to September 2000)

3 | ACUTE CORONARY SYNDROMES

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3.16b. A multicentre randomised controlled trial of programmes of **comprehensive cardiac rehabilitation** of patients following acute myocardial infarction by multi-disciplinary teams demonstrated **no** effect on mortality, cardiac or phycological morbidity, cardiac risk factors, activities or quality of life[i].
Caveat:This study has been published as an abstract only to date and no quality appraisal was possible.

i. West, R. Rehabilitation after myocardial infarction: Multicentre randomised controlled trial. NHS Executive, Northern & Yorkshire Research & Development Directorate, September 2002 [Abstract]
http://www.doh.gov.uk/research/rd3/nhsrandd/ timeltdprogs/cvd/rm19.htm [accessed 22.12.03]
(Two year randomised controlled trial published as abstract only to date – 1813 patients in 14 hospitals in England and Wales were randomised to comprehensive cardiac rehabilitation or former 'usual care')

Exercise based rehabilitation

3.16c. Exercise-based cardiac rehabilitation appears to be effective in reducing cardiac deaths. It is not clear whether exercise only or a comprehensive cardiac rehabilitation intervention is more beneficial. The pooled effect estimate for total mortality for the exercise only intervention showed a 27% reduction in all cause mortality (random effects model odds ratio (OR)=0.73, 95% CI 0.54-0.98). Similarly, comprehensive cardiac rehabilitation reduced all cause mortality compared to usual care, but not significantly (OR=0.87, 95% CI 0.71-1.05). Total cardiac mortality was reduced by 31% (random effects model OR=0.69, 95% CI 0.51-0.94) and 26% (random effects model OR=0.74, 95% CI 0.57-0.96) in the exercise only and comprehensive cardiac rehabilitation intervention groups respectively when compared to usual care. Neither intervention had any effect on the occurrence of non-fatal myocardial infarction[i].

Among those trials that reported cholesterol levels, there was a significant net reduction in total (-0.57 mmol/l, 95% CI –0.83 to –0.31) and LDL (-0.51 mmol/l, 95% CI –0.82 to –0.19) cholesterol in the comprehensive cardiac rehabilitation group[i].
Caveat: A great deal of heterogeneity was present within these trials and this may limit the validity of the pooled effect estimate. Many trials were carried out before the introduction of modern therapies.

i. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease.
(Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (most recent update 22 November 2000)
http://www.update-software.com/abstracts/ ab001800.htm [accessed 22.12.03]
(Type I evidence – systematic review, literature search to December 1998, and meta-analysis of 32 randomised controlled trials including 7683 patients (2582 in exercise only and 5101 in the comprehensive cardiac rehabilitation group))

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

The *statements*

The *evidence*

3.16d. A three year **exercise programme** resulted in a non-significantly reduced mortality risk early in the follow-up period but the benefits diminished with time. All cause mortality risk estimates (95% CIs) in the exercise group compared with controls were 0.69 (0.39-1.25) after an average follow-up of three years, 0.84 (0.55-1.28) after 5 years, 0.95 (0.71-1.29) after 10 years, 1.02 (0.79-1.32) after 15 years and 1.09 (0.87-1.36) after 19 years[i].
Caveat: No data were provided on relevant non-fatal cardiac events or quality of life.

i. Dorn J, Naughton J, Imamura D, Trevisan M; for the NEHDP Project Staff. Results of a multicenter randomized clinical trial of exercise and long-term survival in myocardial infarction patients. The National Exercise and Heart Disease Project (NEHDP). *Circulation* 1999; **100**: 1764-1769

(Type II evidence – three year randomised controlled trial of 651 men (aged 30-64) randomised to exercise or normal routines. The treatment group exercised for eight weeks in a laboratory. Thereafter they jogged, cycled or swam in a gymnasium/pool setting guided by an individualised target heart rate. Men were followed-up until death or for 19 years. Analyses were by intention-to-treat)

3.16e. Stable post-CABG patients who receive a detailed **exercise prescription** to follow at home do as well as those in supervised rehabilitation. Following six months of exercise training there were substantial improvements in peak VO2, peak workload, and peak MET levels in both the supervised and unsupervised groups (p<0.0001)[i].
Caveats: This was a retrospective review with one post-intervention sampling point only. *A randomised controlled trial is recommended.*

i. Kodis J, Smith KM, Arthur HM, Daniels C, Suskin N, McKelvie RS. Changes in exercise capacity and lipids after clinic versus home-based aerobic training in coronary artery bypass graft surgery patients. *Journal of Cardiopulmonary Rehabilitation*. 2001; **21(1)**; 31-36

(Type IV evidence – retrospective database review of 1,042 patients who took part in exercise rehabilitation following CABG between 1992 and 1998. Of these, 713 patients took part in supervised exercise and 329 were in an unsupervised home-based group)

Smoking cessation

3.16f. Studies comparing a **nursing intervention for smoking cessation** to control or usual care found intervention to significantly increase the odds of quitting (odds ratio = 1.50, 95% CI 1.29-1.73). There was heterogeneity between study results but pooling using a random effects model did not alter the estimate of benefit. There was limited evidence that interventions were more effective for hospital inpatients with cardiovascular disease than for inpatients with other conditions. The challenge will be to incorporate smoking cessation intervention as part of standard practice so that all patients are given an opportunity to be queried about their tobacco use and to be given advice to quit along with reinforcement and follow-up[i].

i. Rice VH, Stead LF. Nursing interventions for smoking cessation. Cochrane Review. (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (most recent update 15 May 2001.
http://www.update-software.com/abstracts/ ab001188.htm [accessed 22.12.03]

(Type I evidence - systematic review, search to April 2001, and meta-analysis of 16 randomised trials with a follow-up of at least six months)

3 | ACUTE CORONARY SYNDROMES

The *statements*   The *evidence*

3.16g. **High intensity behavioural interventions** that include at least one month of follow-up contact are effective in promoting smoking cessation in hospitalised patients. Intensive intervention (inpatient contact plus follow-up for at least one month) was associated with a significantly higher quit rate compared to control (odds ratio = 1.82, 95% CI 1.49-2.22). There was insufficient evidence to judge the effect of interventions delivered only during the hospital stay[i].

i. Rigotti NA, Munafo MR, Murphy MFG, Stead LF. Interventions for smoking cessation in hospitalised patients. (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (most recent update 27 August 2002).
http://www.update-software.com/abstracts/ab001837.htm [accessed 22.12.03]
(Type I evidence - systematic review, literature search to July 2000, of 15 randomised or quasi randomised studies with follow-up of at least six months)

3.16h. A Cochrane review is underway to examine by how much and how quickly **smoking cessation** reduces the risk of mortality among patients with coronary heart disease[i].

i. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software
(Type I evidence - systematic review and meta-analysis of randomised controlled trials, in progress)

The *statements*

The *evidence*

Psychoeducational programmes

3.16i. Evidence concerning **pyschoeducational programmes** is mixed[i,ii,iii,iv].

A systematic review of publications to 1998 suggested that psychoeducational programmes yielded a 34% reduction in cardiac mortality, a 29% reduction in the recurrence of MI, and significant positive effects on blood-pressure, cholesterol, body weight, smoking, behaviour, physical exercise, and eating habits. No effects of psychoeducational programmes were found in regard to coronary bypass surgery, anxiety or depression[i].
Caveat: No unpublished studies were sought, nor was information given about the selection of papers for inclusion.

A recent large trial found that **cognitive behaviour therapy** (supplemented with SSRI therapy when indicated) improved depression and feelings of social isolation at six months but this was less than expected due to substantial improvement in usual care patients and there were **no differences in survival** between groups after an average follow-up of 29 months. At six months the mean (± standard deviation) change in the HSRD score was –10.1 (7.8) in the depression and psychosocial intervention group versus –8.4 (7.7) in the depression and usual care group (p<0.001); Mean (SD) change in the ESSI score was 5.1 (5.9) in the LPSS and psychosocial intervention group versus 3.4 (6.0) in the LPSS and usual care group (P<0.001)[ii].
Caveat: Very large numbers of patients excluded from the trial following screening and this may limit the generalisability of the results.

Two other large trials of psychological rehabilitation offer little objective benefit to patients in terms of depression, anxiety and mortality[iii,iv] and one trial suggested a possibly harmful impact on women[iv].
Caveat: In the latter trial[iv], the intervention was unclear; nurses were trained in coronary care but had no mental health training. Monthly telephone screening and interventions in the home may have increased distress

i.   Dusseldorp E, van Elderen T, Maes S, Meulman J, Kraaij V. A meta-analysis of psychoeducational programs for coronary heart disease patients. *Health Psychology* 1999; **18**: 506-519

(Type I evidence – systematic review, literature search to 1998, of 28 randomised controlled trials and 9 quasi randomised studies (9,081 participants))

ii. Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The ENhancing Recovery In Coronary Heart Disease patients (ENRICHD) randomized trial. *Journal of the American Medical Association* 2003; **289**: 3106-3116

(Type II evidence – randomised controlled trial of 2,481 myocardial infarction patients (1,084 women, 1,397 men) from eight clinical centres randomised within 28 days to cognitive behaviour therapy, supplemented with a selective serotonin reuptake inhibitor (SSRI) antidepressant when indicated, or usual care. Depression was measured by the Hamilton Rating Scale for Depression (HRSD) and low perceived social support (LPSS) by a score (ESSI), based on validated social support scales, developed for the trial)

iii. Jones DA, West RR. Psychological rehabilitation after myocardial infarction: multicentre randomised controlled trial. *British Medical Journal* 1996; **313**: 1517-1521

http://bmj.bmjjournals.com/cgi/content/full/313/7071/1517 [accessed 22.12.03]

(Type II evidence – one year randomised controlled trial of 2,328 unselected myocardial infarction patients at six UK district general hospitals assigned to seven weeks of psychological rehabilitation or usual care)

iv. Frasure-Smith N, Lespérance F, Prince RH *et al*. Randomised trial of home-based psychosocial nursing intervention for patients recovering from myocardial infarction. *Lancet* 1997; **350**: 473-479

(Type II evidence – one year randomised controlled trial (M-HART) of 1,376 post myocardial infarction patients (903 men, 473 women) in 10 Montreal hospitals assigned to a home-based psychological nursing intervention or usual care)

3 | ACUTE CORONARY SYNDROMES

The *statements*	The *evidence*

3.16j. A Cochrane review of **stress management training** following myocardial infarction or cardiac surgery is in progress[i].

i. Rees K, Bennett P, Vedhara K, West R, Davey Smith G, Ebrahim S. Stress management for coronary heart disease. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised controlled trials, in progress)

Outcome measurement and auditing of cardiac rehabilitation programmes

3.16k. Multidisciplinary programmes integrating **primary and secondary care** in the provision of rehabilitation services in the UK have been evaluated[i,ii] and *further randomised controlled research is awaited*[i]. See also Section 3.20, particularly 3.20e.

i. Dalal HM, Evans PH. Achieving national service framework standards for cardiac rehabilitation and secondary prevention. *British Medical Journal* 2003; **326**: 481-484

http://bmj.bmjjournals.com/cgi/content/full/326/7387/481 [accessed 22.12.03]

(Type IV evidence – 12 month audit of an integrated cardiac rehabilitation scheme for 106 patients who had survived an acute myocardial infarction)

ii. Anonymous. *The Heart Manual*. York: Department of Health Studies, University of York, undated.

http://www.cardiacrehabilitation.org.uk/heart_manual/HeartManual.htm [accessed 22.12.03]

3.16l. A number of measures show significant potential for **routine outcome assessment**. *Formal assessment of these instruments is recommended to inform final recommendations about instrument selection for audit and evaluation purposes in cardiac rehabilitation*[i].

i. McGee HM, Hevey D, Horgan JH. Psychosocial outcome assessments for use in cardiac rehabilitation service evaluation: a 10-year systematic review. *Social Science & Medicine* 1999; **48**: 1373-1393

(Type IV evidence – a systematic overview of 32 studies of instruments, published from 1986-1995.

3.16m. A **minimum data set** for auditing cardiac rehabilitation has been developed[i].

i. British Heart Foundation Rehabilitation Research Unit, University of York; Northern & Yorkshire Public Health Observatories. *Coronary Heart Disease National Service Framework: Cardiac Rehabilitation – Meeting the Information Needs*. Occasional Paper No. 4. York: University of York, April 2002

http://www.nepho.org.uk/reference/occ_paper/OC04.PDF [accessed 22.12.03]

(Type V evidence – expert consensus guidance based on a systematic review of the literature)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 │ ACUTE CORONARY SYNDROMES

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

All those with ACS must be risk stratified to discharge using as appropriate: [key action 19]

■ Troponin T or I ■ Exercise testing ■ Echocardiology ■ Radionuclitide scanning

What is the evidence for risk stratification at discharge?

The *statements*	The *evidence*

3.17 Risk stratification at discharge (see also Section 3.14)

3.17a. **Troponin T** and **troponin I** show similar prognostic significance for acute myocardial infarction or death in patients with unstable angina[i,ii]. Meta-analysis suggested risk ratios of 4.2 (95% CI 2.7-6.4, p<0.001) for troponin I and 2.7 (2.1-3.4, p<0.001) for troponin T. The sensitivities and specificities for both markers were similar (57% and 68% respectively for troponin T; 63% and 71% for troponin I)[i].

i. Olatidoye AG, Wu AH, Feng YJ, Waters D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. *American Journal of Cardiology* 1998; **81**: 1405-1410

(Type IV evidence – systematic review, using Medline to 1997 plus reference list follow up and meeting abstracts. 12 studies of Troponin T (2,847 patients) and 9 studies of Troponin I (1,901 patients) were included. Results were validated in 123 patients with unstable angina

3.17b. A **risk stratification strategy** has been developed to enable identification of acute coronary syndrome survivors who remain at very high risk despite statin therapy, and who may be appropriately considered for other interventions. The independently significant risk factors included total and high density lipoprotein cholesterol, age, gender, smoking status, qualifying ACS, prior coronary revascularisation, diabetes, hypertension and prior stroke[i].
Caveat: No external validation of the tool was carried out.

i. Marschner IC, Colquhoun D, Simes RJ *et al*. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study. *Journal of the American College of Cardiology* 2001; **38(1)**: 56-63

(Type IV evidence – prognostic risk assessment model developed using patient data from the LIPID randomised controlled trial (n=8,557))

3 | ACUTE CORONARY SYNDROMES

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The *evidence*

3.17c. A large study carried out in 1992 found that, post myocardial infarction, patients ≥ **75 years of age** were significantly less likely than patients 65 to 74 years of age to have either cardiac catheterisation (17% vs 43%) or any test for coronary artery disease severity (24% vs 53%). They were also less likely to have a test for left ventricular function (61% vs 76%). Even after adjustment for baseline characteristics, older patients remained less likely than younger patients to have an assessment of coronary artery disease severity (odds ratio, 0.44) or left ventricular function (odds ratio, 0.65)[i].

A smaller but more recent UK study suggested that, despite having indications for intervention identical to those of younger patients, older patients (> 75 years) and women, independently, were significantly less likely to undergo exercise tolerance testing and cardiac catheterisation. The similar trends for age and access to CABG did not reach significance. The authors calculated that the cost implications of addressing these inequities in service provision would be considerable[ii].

i.   Alexander KP, Glalnos AN, Jollis JG, Stafford JA, Peterson ED. Post-myocardial infarction risk stratification in elderly patients. *American Heart Journal* 2001; **142(1)**: 37-42

(Type IV evidence – retrospective case-record study in the US following 192,311 Medicare patients (age ≥ 65 years) for 60 days after admission for myocardial infarction between January and November 1992)

ii. Bowling A, Bond M, McKee D *et al*. Equity in access to exercise tolerance testing, coronary angiography, and coronary artery bypass grafting by age, sex and clinical indications. *Heart* 2001; **85 (6)**: 680-686

(Type IV evidence – case-record study, tracking 1,790 patients with a cardiac ICD inpatient code at discharge, 12 months backwards and 12 months forward. The study took place in a single UK district hospital over a 12 month period in 1996-1997)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

Angioplasty must only be undertaken in a tertiary centre with surgical services on site. [key action 23]

What is the most recent evidence concerning angioplasty services?

3 | ACUTE CORONARY SYNDROMES

The *statements* The *evidence*

3.18 Effect of centre size on angioplasty outcomes

3.18a. There is some evidence that mortality is significantly lower at **high volume** versus low volume hospitals for some interventions. In individual, high quality studies, the odds of mortality (low volume vs high volume) for coronary artery bypass surgery (n=12,448) were 1.39 (95% CI 1.16-1.67); for **coronary angioplasty** (n=62,670) were 1.33 (1.10-1.61) and for cardiac transplantation (n=7,893) were 2.06 (1.69-2.50)[i].

Caveat: It is unclear whether the quality criteria used to judge the best study for each intervention were from a validated scheme. Definitions of high volume varied between studies. Unpublished studies were not sought and publication bias cannot be excluded.

i. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals. Estimating potentially avoidable deaths. *Journal of the American Medical Association* 2000; **283(9)**: 1159-1166

(Type IV evidence – results from selected 'best' studies based on a systematic review of the literature looking at the effects of referral to low volume versus high volume hospitals on various interventions)

3.18b. Among hospitals in the United States that have full interventional capabilities, a **higher volume** of **angioplasty procedures** is associated with a lower mortality rate among patients undergoing primary angioplasty. In-hospital mortality was 28% lower among patients who underwent primary angioplasty at hospitals with the highest volume (>33 per annum) than those with the lowest volume (5-11 per annum) (adjusted relative risk = 0.72, 95% CI 0.60-0.87, p<0.001). There was no association between volume and mortality for **thrombolytic** therapy. Reperfusion was carried out sooner in the high volume hospitals and this may have influenced the outcomes[i].

i. Canto JG, Every NR, Magid DJ *et al*; for the National Registry of Myocardial Infarction 2 Investigators. The volume of primary angioplasty procedures and survival after myocardial infarction. *New England Journal of Medicine* 2000; **342**: 1573-1580

(Type IV evidence – analysis of data from the US National Registry of Myocardial Infarction, June 1994 – March 1998, examining hospitals with ≥ 5 angioplasty procedures per year. Data on 257,602 angioplasty patients in 450 hospitals and 277,156 thrombolysis patients in 516 hospitals were examined. Patients transferred from other hospitals were not included and referral bias was unlikely to be a problem)

3 | **ACUTE CORONARY SYNDROMES**

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3.18c. **Angioplasty** is developing in some district general hospitals (DGH). This has become a realistic option because of the improvements in technology, including stenting and glycoprotein IIb/IIIa inhibitors[i]. PCI services should only be developed in the DGH if they can satisfy the recent guidelines produced by the British Cardiac Society and the British Cardiovascular Intervention Society[ii]. This requires a high level of facilities, a fully trained team, adequate numbers of operators, and appropriate arrangements for surgical cover[ii].

The European guidelines recommend that only hospitals with an established interventional cardiology programme should use primary PCI as a routine treatment option for patients with the symptoms and signs of acute myocardial infarction[iii].

i. Anon. Fifth report on the provision of services for patients with heart disease. *Heart* 2002; **88(suppl.III)**: iii1-iii59 **http://heart.bmjjournals.com/cgi/content/full/88/ suppl_3/iii1** [accessed 22.12.03]
(Type V evidence – expert consensus opinion)

ii. British Cardiac Society. British Cardiovascular Intervention Society. Coronary angioplasty: guidelines for good practice and training. Joint working group on coronary angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society. *Heart* 2000; **83**: 224-235
(Type V evidence – expert consensus opinion)

iii. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal* 2003; **24**: 28-66
(Type V evidence – consensus guidelines)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

It is also crucially important that all patients who have suffered myocardial infarction undergo assessment of their heart's function (usually by echocardiography) in order to identify those who should be commenced on ACE inhibitors, to prevent the subsequent development of heart failure… Patients with significant left ventricular dysfunction following myocardial infarction should also be followed up closely since the development of heart failure can be rapid. [paragraph 7.6]

What is the evidence for the best assessment and treatment of heart failure post MI?

The *statements*   The *evidence*

3.19 **Assessment and treatment of heart failure post ACS**

3.19a. Data from 10,655 acute coronary syndrome patients suggests that **heart failure** is a frequent complication (15% in ST elevated myocardial infarction, 16% in non ST elevated MI and 9% in unstable angina). Heart failure was associated with less frequent use of percutaneous procedures, a reduced use of beta-blockers, a more than threefold increase in hospital death and a prolonged hospital stay[i].

i. Steg PG, Dabbous O, Cohen-Solal A *et al*; for the GRACE Investigators. Determinants and outcomes of congestive heart failure complicating acute coronary syndromes: Observations from the Global Registry of Acute Coronary Events. [Abstract] *Journal of the American College of Cardiology* 2002; **39(5)**: 154A
(Type IV evidence – results from a prospective registry enrolling acute coronary syndrome patients from 94 hospitals in 14 countries (GRACE). Patients admitted to GRACE hospitals are stratified according to the presence or absence of coronary heart failure (Killip class 2 or 3). Patients with a prior history of heart failure or in cardiogenic shock are excluded. **Abstract** only)

The *statements*   The *evidence*

ACE inhibitors to prevent heart failure

3.19b. Angiotensinogen converting enzyme (ACE) inhibitor therapy started early in acute MI is associated with a one-month odds reduction in mortality of 7%; 95% CI 2%-11%; p= <0.004, equivalent to 5 (SD 2) fewer deaths/1000 treated. Survival benefit seems to persist for at least one year[i].

In a further analysis of these trial data, both **aspirin** and **ACE inhibitors** (ACEi) are beneficial in acute myocardial infarction (MI). A systematic review of trial data support the early use of ACEi in acute MI (0-36 hours from symptom onset) irrespective of whether or not aspirin is being given. Overall 30-day mortality was 7.1% among patients allocated to ACEi and 7.6% among those allocated to control; a 7% proportional reduction (95% CI 2%-11%, p=0.004). ACEi was associated with similar proportional reductions in 30-day mortality among the 86,484 patients who were taking aspirin (a 6%, standard deviation 3%, reduction) and among 10,228 patients who were not (10%, standard deviation, 5%)[ii].

i. ACE inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction. Circulation 1998;**97**:2202-12

(Type I evidence - systematic review and meta-analysis of 98,496 patients in four randomised controlled trials ACE inhibitor treatment in acute phase MI)

ii. Latini R, Tognoni G, Maggioni AP *et al.*; on behalf of the Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin. Systematic overview of individual data from 96,712 randomized patients *Journal of the American College of Cardiology* 2000; **35(7)**:1801-7.

(Type I evidence – systematic review of data on concomitant ASA use, available for 96,712 of 98,496 patients in four eligible trials (and for none of 1,556 patients in the one other eligible trial). All trials involving more than 1000 patients were included)

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3.19c. There is only weak evidence of any reduction in the benefit of **ACE-inhibitor** therapy when added to **aspirin**.

Results from analyses of all trials, except SOLVD, did not suggest any significant differences between the proportional reductions in risk with ACE inhibitor therapy in the presence or absence of aspirin for the major clinical outcomes (death, myocardial infarction, stroke, hospital admission for congestive heart failure, or revascularisation, p=0.15) or in any of its individual components, except myocardial infarction (p=0.01)[i].

The benefit of **ACE inhibitors and aspirin** in **elderly people** is consistent with what would be expected from overall results of randomized trials; prescribed together, the effect is slightly greater than with either one alone, but not significantly or substantially so[ii].

In the multivariate analysis, patients who received both aspirin and ACE inhibitors alone had a significantly lower one-year mortality (adjusted risk ratio, ARR=0.86, 95% CI 0.78-0.95 versus 0.85, 0.77-0.93 respectively) compared with patients who received neither therapy at discharge. The ARR for patients prescribed both aspirin and ACE inhibitors was 0.81 (0.74-0.88)[ii].

Caveats: There were a large number of exclusions from this observational study and some potential confounders.

i. Teo KK, Yusuf S, Pfeffer M *et al*. ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin : a systematic review. *Lancet* 2002 ; **360(9339)**: 1037-1043
(Type I evidence – systematic overview of data for 22,060 patients from six long-term randomised controlled trials of ACE inhibitors)

ii. Krumholz HM, Chen Y-T, Wang Y, Radford MJ. Aspirin and angiotensin-converting enzyme inhibitors among elderly survivors of hospitalisation for an acute myocardial infarction. *Archives of Internal Medicine* 2001; **161**: 538-544
(Type IV evidence – cohort study of 14,129 patients aged over 65)

3.19d. There is evidence from randomised controlled trials and general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that **long term medical therapy** for patients should include **ACE-inhibitors** for patients with congestive heart failure, LV dysfunction (ejection fraction <40%), hypertension or diabetes[i].

i. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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3.19e. A trial is underway to compare the efficacy and safety of **long-term treatment** with the angiotensin receptor blocker **valsartan**, the ACE-inhibitor **captopril**, and their combination in high-risk patients after myocardial infarction[i]. This trial will report in Spring 2004.

i. Pfeffer MA, McMurray J, Leizorovicz A *et al*. Valsartan in acute myocardial infarction trial (VALIANT) : rational and design. *American Heart Journal* 2000; **140(5)**: 727-750
(Ongoing randomized controlled trial, n=14,500)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

A variety of non pharmacological therapies such as exercise training, surgical revascularisation, biventricular pacing and cardiac transplantation are also of proven value in selected cases. [paragraph 7.7]

Which patients would benefit from these alternative treatments?

See Chapter Four (heart failure)

| The *statements* | The *evidence* |

3.20 Secondary prevention

Discharge policies for secondary prevention

3.20a. A **review of treatment strategies** of unstable angina and myocardial infarction without ST elevation is warranted in the UK to ensure that patients are receiving optimum treatment. Results from a prospective registry show that aspirin was given to 87% and heparin to 72% of patients in hospital. Patients with total cholesterol 6.0-7.0 and ≥ 7.0 mmol/L had a 52% and 47% probability respectively of not receiving a statin over a six-month follow-up. The six-month rate of coronary angiography was 27% and any revascularisation, 15%[i].

A **Global Registry of Acute Coronary Events** (GRACE) has been established to explore and improve the quality of hospital care for acute coronary syndrome patients, with six month follow-up (http://www.outcomes/org.grace). A total of 18 cluster sites in 14 countries in North America, South America, Europe, Australia and New Zealand are currently involved[ii].

i. Collinson J, Flather MD, Fox KAA *et al*; for the PRAIS-UK Investigators. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *European Heart Journal* 2000; **21(17)**: 1450-1457

(Type IV evidence – prospective registry, with six-month follow-up, for patients admitted to 56 UK hospitals (n=1046, May 1998-February 1999). A history of acute cardiac chest pain was required plus ECG changes consistent with myocardial ischaemic and/or prior evidence of coronary heart disease)

ii. The GRACE Investigators. Rational and design of the GRACE (Global Registry of Acute Coronary Events) project: A multinational registry of patients hospitalised with acute coronary syndromes. *American Heart Journal* 2001; **141(2)**; 190-199

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3.20b. Implementation of **guideline-based tools** for acute myocardial infarction may facilitate improvement among a variety of institutions, patients and caregivers. Increases in adherence to key treatments pre- and post-intervention were seen in the administration of aspirin (81% vs 87%, p=0.02) and beta-blockers (65% vs 74%; p=0.04) on admission and use of aspirin (84% vs 92%; p=0.002) and smoking cessation counselling (53% vs 65%; p=0.02) at discharge. For most of the other indicators, nonsignificant but favourable trends towards improvement in adherence to treatment goals were observed[i].

Compared with the control group, Medicare patients in GAP hospitals showed a significant increased in the use of aspirin at discharge (5% vs 10%; p<0.001). Use of aspirin on admission, ACE inhibitors at discharge, and documentation of smoking cessation also showed a trend for greater improvement among GAP hospitals compared with controls although none of these were statistically significant. Evidence of tool use noted during chart review was associated with a very high level of adherence to most quality indicators[i].

Caveats: Baseline measurement occurred more than one year before the initiative was implemented, thus results compared to the control hospitals will be the most realistic. However, control hospitals were also engaged in quality improvements. The use of GAP tools was only identified in a minority of case-notes and greater use of these tools may have improved the results.

i.   Mehta RH, Montoye CK, Gallogly M *et al*. Improving quality of care for acute myocardial infarction. The Guidelines Applied in Practice (GAP) initiative. *Journal of the American Medical Association* 2002; **287(10)**: 1269-1276

(Type IV evidence – an American College of Cardiology quality improvement initiative. A random sample of Medicare and non-Medicare patients at baseline (July 1998- June 1999, n=735) and following intervention (September-December 2000, n=914) admitted to 10 study centres were compared with a random sample of Medicare patients admitted to 11 control hospitals (Baseline data collected from January-December 1998, n=513; Remeasurement March-August 2001, n=388). Quality indicators in patients with no contraindications to these treatments were examined. (GAP tool kits are available at **http://www.acc.org/gap/mi/ami_gap.htm** [accessed 22.12.03]). Similar projects are in progress for heart failure and stable angina)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

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Primary care management of secondary prevention

3.20c. The **Healthwise survey** showed that even in well organised general practices there is ample scope for improvement in the detection, recording and intervention for the major cardiac risk factors among patients with established heart disease. A quarter of the total study population still smoked. Blood pressure was less well managed among diabetic than with non-diabetic patients and most patients were hypercholesterolaemic (47% of men and 40% of women) or had never been tested (35% of men and 52% of women). Only a few were taking statins despite current evidence of efficacy. Few patients with previous myocardial infarction were taking beta-blockers but around half were prescribed ACE-inhibitors[i].
Caveat: The authors note that the survey may have a bias, representing larger practices with computerised systems in place by 1997.

i. Brady AJB, Oliver MA, Pittard JB. Secondary prevention in 24,431 patients with coronary heart disease: survey in primary care. *British Medical Journal* 2001; **322(7300)**; 1463 **http://bmj.bmjjournals.com/cgi/content/full/322/7300/1463** [accessed 22.12.03]
(Type IV evidence – survey in 1997/1998 of 548 UK practices (of 653 invited to take part) with computerised records who had not recently undergone an audit of coronary heart disease. The Healthwise survey)

3.20d. There is a collective failure of medical practice in Europe to achieve the substantial potential among patients with coronary heart disease to reduce the risk of recurrent disease and death. Between the two **EUROASPIRE** surveys the prevalence of smoking remained almost unchanged at 19.4% vs 20.8%. The prevalence of obesity (body-mass index ≥ 30 kg/m2) increased substantially from 25.3% to 32.8%. The proportion with high blood pressure (≥ 140/90 mm Hg) was virtually the same (55.4% vs 53.9%). However, the prevalence of high total cholesterol concentrations (≥ 5.0 mmol/L) decreased substantially from 86.2% to 58.8%[i].

i. EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001; **357 (9261)**: 995-1001
(Type IV evidence – Two surveys undertaken in nine European countries in 1995-6 (n=3,569) and 1999-2000 (n=3,379). The surveys were undertaken in the same selected geographical areas and hospitals in the Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, Solvenia and Spain. Consecutive patients (men and women ≤ 70 years of age) were identified after coronary-artery bypass graft or percutaneous transluminal coronary angioplasty, or a hospital admission with acute myocardial infarction or ischaemia, and were interviewed at least six months later. Smoking and diabetes were self reported. Other measures were taken directly)

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3.20e. An intervention to **coordinate preventive care in general practice** of patients with newly diagnosed heart disease promoted follow-up but did not improve health outcomes. The authors concluded that simply coordinating and supporting existing NHS care is insufficient, and that angina and MI patients merit the same systematic approach to secondary prevention as given to other chronic conditions such as diabetes[i].
Caveats: There was some evidence of small but clinically important reductions in total cholesterol, blood pressure and smoking but also some evidence of increased anxiety in the intervention practices' patients. None of these results were statistically significant.

i.   Jolly K, Bradley F, Sharp S *et al*. Randomised controlled trial of follow-up care in general practice of patients with myocardial infarction and angina: Final results of the Southampton Heart Integrated Care Project (SHIP). *British Medical Journal* 1999; **318**: 706-711
http://bmj.bmjjournals.com/cgi/content/full/318/7185/706 [accessed 22.12.03]

(Type II evidence – randomised controlled trial (by stratified random allocation) of all 67 practices in Southampton and southwest Hampshire, England. The intervention was a programme to coordinate preventive care led by specialist liaison nurses which sought to improve communication between hospital and general practice to encourage GP nurses to provide structured follow-up. 597 adult patients were involved (422 with MI and 175 with a new diagnosis of angina. Data were analysed on an intention to treat basis)

3.20f. **Postal prompts** to patients who had had acute coronary events and to their general practitioners in a locality where guidelines for coronary heart disease had been disseminated **did not** improve prescribing of effective drugs for secondary prevention or self reported changes to life style. The prompts did increase consultation rates related to coronary heart disease and the recording of risk factors in the practices. Effective secondary prevention of coronary heart disease requires more than postal prompts and the dissemination of guidelines[i].

i.   Feder G, Griffiths C, Eldridge S, Spence M. Effect of postal prompts to patients and general practitioners on the quality of primary care after a coronary event (POST): randomised controlled trial. *British Medical Journal* 1999; **318**: 1522-1526
http://bmj.bmjjournals.com/cgi/content/full/318/7197/1522 [accessed 22.12.03]

(Type II evidence – randomised controlled trial of 328 patients in 52 general practices in East London, 44 of which had received facilitation of local guidelines for coronary heart disease)

3.20g. Setting up a **register and recall** system in **general practice** improved patient assessment at 18 months follow-up but was not consistently better than audit alone in improving treatment or risk factor levels. Adequate assessment of all three risk factors (blood pressure, cholesterol and smoking status) was much more common in the nurse and GP recall groups (85%, 76%) than the audit group (52%) but these differences were not reflected in clinical outcomes which varied little between the three groups[i]. Understanding the reasons for this is the key next step in improving the quality of care of patients with coronary heart disease[i].
Caveat: Results may not be generalisable. Practices that did not wish to be involved in the study were smaller, less likely to employ a practice nurse, and less likely to be involved in training.

i.   Moher M, Yudkin P, Wright L *et al*; for the Assessment of Implementation Strategies (ASSIST) Trial Collaborative Group. *British Medical Journal* 2001; **322(7298)**: 1338-1345
http://bmj.bmjjournals.com/cgi/content/full/322/7298/1338 [accessed 22.12.03]

(Type II evidence – randomised controlled trial of 21 General Practices in Warwickshire, UK randomised to three methods of promoting secondary prevention of coronary heart disease in primary care: Audit of notes with summary feedback to primary health care team (audit group); assistance with setting up a disease register and systematic recall of patients to general practitioner (GP recall group); assistance with setting up a disease register and systematic recall of patients to a nurse led clinic (nurse recall group))

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

The *statements*

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3.20h. Disease management programmes improve processes of care, reduce admissions to hospital, and enhance quality of life or functional status in patients with coronary heart disease. Patients randomised to these programmes were more likely to be prescribed efficacious drugs - risk ratios = 2.14 (95% CI 1.92-2.38) for lipid lowering drugs, 1.19 (1.07-1.32) for beta-blockers and 1.07 (1.03-1.11) for antiplatelet agents. Summary risk ratios were 0.91 (0.79-1.04) for all cause mortality, 0.94 (0.80-1.10) for recurrent myocardial infarction, and 0.84 (0.76-0.94) for admission to hospital. Five of eight trials evaluating quality of life or functional status reported better outcomes in the intervention arms. Only three reported costs and there were cost savings in two cases, but no formal cost-effectiveness analysis was carried out. The programmes' impact on survival and recurrent infarctions, their cost-effectiveness and the optimal mix of components remain uncertain[i].

i. McAlister FA, Lawson FME, Teo KK, Armstrong PW. Randomised trials of secondary prevention programmes in coronary heart disease: systematic review. *British Medical Journal* 2001; **323(7319)**: 957-962

http://bmj.bmjjournals.com/cgi/content/full/323/7319/957 [accessed 22.12.03]

(Type I evidence – systematic review, literature search to 2000, of 12 trials (9,803 patients with coronary heart disease) of secondary prevention programmes)

3.20i. Nurse run clinics proved practical to implement in general practice and effectively increased secondary prevention in coronary heart disease. Most patients gained at least one effective component of secondary prevention and, for them, future cardiovascular events and mortality could be reduced by up to a third. There were significant improvements in aspirin management (odds ratio 3.22, 95% CI 2.15-4.80), blood pressure management (5.32, 3.01-9.41), lipid management (3.19, 2.39-4.26), physical activity (1.67, 1.23-2.26) and diet (1.47, 1.10-1.96). There was no effect on smoking cessation (0.78, 0.47-1.28). Of six possible components of secondary prevention, the baseline mean was 3.27. The adjusted mean improvement attributable to intervention was 0.55 of a component (0.44-0.67). Improvement was found regardless of practice baseline performance[i].

i. Campbell NC, Ritchie LD, Thain J, Deans HG, Rawles JM, Squair JL. Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. *Heart* 1998; **80(5)**: 447-52

(Type II evidence – One year randomized unblinded controlled trial of 19 general practices (1,173 patients under 80 years with working diagnoses of coronary heart disease, but without terminal illness or dementia and not housebound)

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3.20j. **Feedback of prescribing practice** can increase the proportion of patients with ischaemic heart disease receiving prescribed daily aspirin by 9%. Such prescribing rose from 47.8% to 58.2% in the intervention group of practices compared with 48.6% to 50.5% in the control group[i].

i. McCartney P, Macdowell W, Thorogood M. A randomised controlled trial of feedback to general practitioners of their prophylactic aspirin prescribing. *British Medical Journal* 1997; **315**: 35-36

http://bmj.bmjjournals.com/cgi/content/full/315/7099/35

[accessed 22.12.03]

(Type II evidence – randomised controlled trial of 28 General Practices in North London with computerised records on ischaemic heart disease and repeat prescribing. Practices were randomised to receive feedback on their prescribing, either of aspirin for patients with ischaemic heart disease or of hormone replacement therapy for women who had had hysterectomies. Prescribing data were collected at baseline (when feedback and educational input were provided) and at follow-up, at least three months later)

3.20k. The evidence suggests that **HRT** should **not be** used with an expectation of cardiovascular or cerebrovascular benefit in women with **established disease**[i,ii,iii].

During an average follow-up of 4.1 years, treatment with HRT **did not** reduce the overall rate of CHD events in postmenopausal women with **established coronary disease**. The treatment increased the rate of venous thromboembolic events (relative hazard = 2.89, 95% CI 1.50-5.58). There were more CHD events in the hormone group than the placebo group during year one but fewer in years 4-5[i].

A recent trial found that neither estrogen alone, nor estrogen plus medroxyprogesterone acetate affected the progression of **coronary atherosclerosis** in women with **established disease**[ii].

Estradiol valerate does not reduce the overall risk of further cardiac events in postmenopausal women who have survived a myocardial infarction (rate ratio for treatment versus placebo = 0.99, 95% CI 0.70-1.41, p=0.97)[iii].

The American Heart Association recommend that HRT should not be initiated for the secondary prevention of cardiovascular disease[iv].

i. Hulley S, Grady D, Bush T *et al*. Randomised trial of estrogen and progestin for secondary prevention of coronary heart disease in postmenopausal women. *Journal of the American Medical Association* 1998; **280**: 605-613

(Type II evidence – the HERS randomised controlled trial of 2,763 women with coronary disease, younger than 80 years and postmenopausal with an intact uterus. The mean age was 66.7 years. Women were assigned to 0.625 conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate daily or placebo. 82% of those assigned hormone treatment were taking it at the end of one year and 75% at the end of three years. An intention-to-treat analysis was used)

ii. Herrington DM, Reboussin DM, Brosnihan KB *et al*. Effect of estrogen replacement on the progression of coronary artery atherosclerosis. *New England Journal of Medicine* 2000; **343(8)**: 522-529

(Type II evidence – randomised controlled trial of 309 women with angiographically verified coronary disease to receive 0.625 mg of conjugated estrogen per day, 0.625 mg of conjugated estrogen plus 2.5 mg of medoxyprogesterone acetate per day, or placebo. The women were followed for a mean (±SD) of 3.2±0.6 years)

iii. The ESPRIT Team. Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. *Lancet* 2002; **360**: 2001-2008

(Type II evidence – 24 month randomised controlled trial of 1017 women aged 50-69 years, who had survived a first myocardial infarction, assigned to 2 mg oestradiol valerate or placebo daily for two years)

iv. Mosca L, Collins P, Herrington DM *et al*. Hormone replacement therapy and cardiovascular disease. A statement for healtcare professionals from the American Heart Association. *Circulation* 2001; **104**: 499-503

(Type V evidence – expert consensus opinion)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

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3 | **ACUTE CORONARY SYNDROMES**

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3.21 Aspirin/clopidogrel for secondary prevention

3.21a. Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischaemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischaemia, peripheral arterial disease or atrial fibrillation. Overall, antiplatelet therapy reduced any serious vascular event by one quarter, non-fatal myocardial infarction by one third, non-fatal stroke by one third and vascular mortality by one sixth. In each of these high risk categories, the absolute benefits substantially outweighed the absolute risks of major extracranial bleeding.

Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, *but more research into this strategy is needed*[i].

i. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *British Medical Journal* 2002; **324(7329)**: 71-86

http://bmj.bmjjournals.com/cgi/content/full/324/7329/71

[accessed 22.12.03]

(Type I evidence – systematic review, literature search to 1997, of 287 studies involving 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 in comparisons of different antiplatelet regimens)

3.21b. There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that **long term medical therapy** for patients should include:

■ aspirin 75 to 325 mg per day in the absence of contraindications

■ clopidogrel 75 mg daily (in the absence of contraindications) when ASA is not tolerated because of hypersensitivity or gastrointestinal intolerance[i].

i. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.

http://www.acc.org/clinical/guidelines/unstable/ incorporated [accessed 22.12.03]

(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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3.21c. The available randomised evidence shows that the **thienopyridine derivatives** are modestly but significantly more effective than **aspirin** in preventing serious vascular events in patients at high risk (and specifically TIA/ischaemic stroke patients), but there is uncertainty about the size of the additional benefit. Allocation to a thienopyridine was associated with a modest, yet statistically significant, reduction in the odds of a serious vascular event (12.0% vs 13.0%; odds ratio=0.91, 95% CI 0.84-0.98, 2p=0.01), corresponding to the avoidance of 11 (95% CI 2-19) serious vascular events per 1000 patients treated for about two years. There was also a reduction in stroke (5.7% vs 6.4%; OR=0.88, 95% CI 0.79-0.98; 7 [95% CI 1-13] strokes avoided per 1000 patients treated for two years).

The thienopyridines are also associated with less gastrointestinal haemorrhage and other upper gastrointestinal upset than aspirin, but an excess of skin rash and diarrhoea. The risk of skin rash and diarrhaea is greater with ticlopidine than with clopidogrel. Ticlopidine, but not clopidogrel, is associated with an excess of neutropenia and of thrombotic thrombocytopenic purpura[i].

Clopidogrel reduced serious vascular events by 10% (SE 4%) compared with aspirin, which was similar to the 12% (7%) reduction observed with ticlopidine. Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Among patients at high risk of immediate coronary occlusion, short term addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin prevented a further 20 (4) vascular events per 1,000 (p<0.0001) but caused 23 major (but rarely fatal) extracranial bleeds per 1,000[ii].

Ticlopidine is not used in UK practice.

i. Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software. (most recent update 24 August 1999). **http://www.update-software.com/abstracts/ab001246.htm** [accessed 22.12.03]

(Type I evidence – systematic review and meta-analysis of four high-quality, comparable, randomised controlled trials involving a total of 22,656 patients. Aspirin was compared with ticlopidine in three trials (3471 patients) and with clopidogrel in one trial (19,185 patients))

ii. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *British Medical Journal* 2002; **324(7329)**: 71-86 **http://bmj.bmjjournals.com/cgi/content/full/324/7329/71** [accessed 22.12.03]

(Type I evidence – systematic review, literature search to 1997, of 287 studies involving 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 in comparisons of different antiplatelet regimens)

3 | ACUTE CORONARY SYNDROMES

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3.21d. **Clopidogrel** has beneficial effects in **aspirin-treated patients** with acute coronary syndromes without ST-segment elevation (relative risk of clopidogrel vs placebo = 0.80, 95% CI 0.72-0.90, p<0.001). However, the risk of bleeding is increased among patients treated with clopidogrel (relative risk vs placebo = 1.38, p=0.001) but there were not significantly more patients with episodes of life-threatening bleeding or hemorrhagic strokes[i].
Caveat: Although follow-up was excellent (99.9%) temporary discontinuation rates (for more than 5 days) were high at 46.2% in the clopidogrel and 45.4% in the aspirin group.

i.   The Colpidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New England Journal of Medicine* 2001; **345(7)**: 494-502

(Type II evidence – randomised controlled trial, the CURE trial, of 12,562 acute coronary syndrome patients who had presented within 24 hours after onset of symptoms to clopidogrel (300 mg immediately, followed by 75 mg once daily, n=6,259) or placebo (n=6,303) in addition to aspirin for 3-12 months. An intention to treat analysis was used)

3.21e. Increased prescription of **aspirin** for secondary prevention of coronary heart disease is attractive from a **cost-effectiveness** perspective. Because **clopidogrel** is more costly, its incremental cost effectiveness if currently unattractive, unless its use if restricted to patients who are ineligible for aspirin. An estimate of treatment from 2003-2027 at US prices is $11,000 per QALY for aspirin and $130,000 per QALY for clopidogrel (or $31,000 per QALY for the 5% of patients ineligible for aspirin)[i].

i.   Gaspoz J-M, Coxson PG, Goldman PA *et al*. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *New England Journal of Medicine* 2002; **346(23)**: 1800-1806

(Type IV evidence – cost-effectiveness analysis comparing four strategies in patients over 35 years of age with coronary disease: Aspirin for all eligible patients (ie those who are not intolerant or allergic to aspirin), clopidogrel for all patients, and the combination of aspirin for all eligible patients plus clopidogrel for all patients)

3.21f. The National Institute for Clinical Excellence (NICE) are carrying out a review to determine the clinical and cost effectiveness of **clopidogrel and modified-release dipyridamole**, used alone or in combination with aspirin, for the prevention of occlusive vascular events in individuals with established peripheral arterial disease. The expected date of issue is June 2004[i].

i.   National Institute for Clinical Excellence. *Vascular Disease – Clopidogrel and Dipyridamole for the Prevention of Occlusive Vascular Events*. London: NICE **http://www.nice.org.uk/cat.asp?c=34136** [accessed 22.12.03]

(Ongoing technology appraisal)

3 | ACUTE CORONARY SYNDROMES

The *statements*   The *evidence*

3.22 Cholesterol control for secondary prevention
See also Section 2.5 (cholesterol lowering interventions) for primary prevention

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3.22a. **Statin therapy** is effective for **secondary prevention**[i,ii,iii].

The relative reductions in total and CHD mortality were 21% (95% CI, 14-27%) and 26% (95% CI, 17-34%) respectively[i].

i. Ebrahim S, Davey Smith G, McCabe C *et al*. What role for statins? A review and economic model. *Health Technology Assessment* 1999; **3(19)**
http://www.hta.nhsweb.nhs.uk/fullmono/mon319.pdf
[accessed 22.12.03]
(Type I evidence – systematic review (Medline only searched from 1993-1997 plus personal contact). Five major trials of statins were identified. Data from these and from another 18 RCTs were included in the analysis)

ii. Sacks FM, Pfeffer MA, Moye LA *et al;* for the Cholesterol and Recurrent Events (CARE) Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New England Journal of Medicine* 1996; **335**: 1001-09
(Type II evidence - randomised controlled secondary prevention trial of 3,583 men and 576 post menopausal women aged 21-75 years, with previous MI, and total cholesterol levels <6.2mmol/l and LDL cholesterol 3.0 to 4.5 mmol/l, randomised to double blind treatment with pravastatin 40mg daily or placebo, median five year follow-up)

iii. Schwartz GG, Olsson AG, Ezekowitz MD *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: A randomized controlled trial. *Journal of the American Medical Association* 2001; **285**: 1711-1718
(Type II evidence – international, double-blind, randomised controlled trial of 3,086 adults (aged 18+) with unstable angina or non-Q-wave acute myocardial infarction in 122 Centres. Patients were stratified by Centre and randomly assigned to atorvastatin (80 mg/d) or matching placebo between 24 and 96 hours after hospital admission. >95% follow-up was achieved and an intention to treat analysis was used)

3.22b. There is general agreement from the American College of Cardiologists/American Heart Association (ACC/AHA) that long term medical therapy for patients should include **lipid-lowering agents and diet** with low density lipoprotein (LDL) cholesterol of greater than 130 mg per dl[i].

i. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction.
http://www.acc.org/clinical/guidelines/unstable/incorporated [accessed 22.12.03]
(Evidence Based Guidelines. Literature search strategy, including date of search completion, and critical appraisal methods for included papers unclear)

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3.22c. Based on observational data from the SYMPHONY trials there was **no relationship** between **early statin initiation after acute coronary syndromes** and improved outcome. However, subset analysis suggested that results may vary with cholesterol level and that clinicians should use caution in starting statin therapy during the acute phase of ACS in patients who did not meet current treatment guidelines (LDL-C levels >130 mg/dL [>3.4 mmol/L][i]. *The results of adequately powered randomised clinical trials are awaited*[i].
Caveats: This study was based on a retrospective analysis and there were baseline differences between patients prescribed and not prescribed statins as might be expected.

In contrast, the importance of starting statin therapy for myocardial infarction patients **at or before discharge from hospital** was suggested by a large prospective cohort study in Sweden. This found that the relative risk for all-cause mortality at one year in the statin vs no statin group was 0.75 (95% CI 0.63-0.89, p=0.001)[ii].
Caveats: Cholesterol levels at baseline, and mortality from cardiovascular causes alone, were not assessed.

i. Newby LK, Dristinsson A, Bhapkar MV *et al*. Early statin initiation and outcomes in patients with acute coronary syndromes. *Journal of the American Medical Association* 2002; **287(23)**: 3087-95

(Type IV evidence – observational data from the SYMPHONY and 2nd SYMPHONY randomised controlled trials to compare patients who started statin therapy early (median 2.0 days) after ACS (n=3,952) or survived more than 5 days and never received statin therapy (n=8,413). 91% adherence to statin therapy at 90 day follow up was noted)

ii. Stenestrand U, Wallentin L; for the Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following acute myocardial infarction and 1-year survival. *Journal of the American Medical Association* 2001; **285**: 430-436

(Type IV evidence – prospective cohort study of patients with first registry recorded acute myocardial infarction who were younger than 80 years and who were discharged alive from hospital, including 5,528 who received statins at or before discharge and 14,071 who did not. Patients admitted from 1995-1998 were studied)

3.22d. Active **hospital-based programmes** to ensure routine LDL-C measurements in patients admitted for acute myocardial infarction increased the use of appropriate lipid lowering therapy. The measurement during hospitalisation increased from 14% preintervention to 48% post intervention. Hospitals lacking standard policies averaged only 23% compared to those with policies who averaged a 70% test rate[i].
Caveat: The lack of a no-intervention control is a potential confounder since practice may well have changed in the hospitals during this period irrespective of the educational intervention.

i. Malach M, Quinley J, Imperato PJ, Wallen M. Improving lipid evaluation and management in Medicare patients hospitalized for acute myocardial infarction. *Archives of Internal Medicine* 2001; **161**: 839-844

(Type III evidence – pre & post intervention study of a collaborative educational intervention in 20 New York hospitals. The treatment of 406 preintervention patients discharged alive from the hospital after a confirmed acute myocardial infarction (in 1996) and 498 postintervention patients (in 1999) was studied)

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3.22e. **Statin therapy** for secondary prevention is **cost effective**[i,ii,iii].

The **cost-effectiveness of pravastatin** therapy in survivors of myocardial infarction with average cholesterol levels compares favourably with other interventions. Based on US dollars at 1996 prices, pravastatin therapy increased quality-adjusted life expectancy at an incremental cost of $16,000 to $32,000 per QALY gained. In subgroup analyses, therapy was more cost-effective for patients > 60 years of age and for these with pre-treatment low-density lipoprotein cholesterol levels >125 mg/dL[i].

The cost-effectiveness of statins depends on the cost of the statin used and the CHD risk in the population treated. Gross, discounted estimates based on CHD risk in the trials considered ranged from £5,400 to £13,3000 per life-year gained at levels of risk expected in primary prevention, and from £3,800 to £9,300 at levels of risk consistent with secondary prevention. Use of low cost statins had the potential to reduce gross costs by 60%. Targeting statin treatment at people aged 55 years and older would further improve cost-effectiveness. Although statins are less cost-effective than other treatments, there is consensus that their use in secondary prevention is acceptable because they achieve effects additional to those of other treatments[ii]

i.   Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. *American Heart Journal* 2001; **141(5)**: 727-734

(Type IV evidence – cost-effectiveness analysis modelled on trial data in Markov models. Full adherence to medication was assumed.

ii. Ebrahim S, Davey Smith G, McCabe C *et al*. What role for statins? A review and economic model. *Health Technology Assessment* 1999; **3(19)**

http://www.hta.nhsweb.nhs.uk/fullmono/mon319.pdf

[accessed 22.12.03]

(Type I evidence – systematic review (Medline only searched from 1993-1997 plus personal contact). Five major trials of statins were identified. Data from these and from another 18 RCTs were included in the analysis)

3.22f. Post-hoc analysis of the results of cholesterol lowering trials have produced diverging indications as to what is the **optimal goal of cholesterol lowering**. Analysis of the 4S indicates that aggressive treatment aiming at LDL-cholesterol levels lower than the current recommendations of expert panels in the United States and in Europe may yield additional benefit. This strategy finds some support in epidemiological studies and in a study with angiographic end points. Analysis of two trials using pravastatin contradict this and conclude that there is little or no additional benefit of reducing LDL-cholesterol below 125 mg/dL (3.2 mmol/L). *Future studies need to address this question properly*[i].

i.   Pedersen TR. Statin trials and goals of cholesterol-lowering therapy after AMI. *American Heart Journal* 2000; **138(2, part 2)**: S177-S182

(Type V evidence – expert overview of the Scandinavian Simvastatin Survival Study, the Cholesterol and Recurrent Events Study, and the Long-Term Intervention with Pravastatin in Ischemic Disease Study)

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3.22g. Recent studies with angiographic and clinical end-points have provided evidence for a beneficial effect of some **fibric acid derivatives** in the secondary prevention of atherosclerosis[i].

Gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with coronary disease whose primary lipid abnormality was a low HDL cholesterol level. The relative risk reduction in nonfatal myocardial infarction or death from coronary causes was 22% (95% CI 7-35%, p=0.006)[ii].

Benzafibrate was safe and effective at elevating HDL-C levels and lowering triglycerides. An overall trend in a reduction of the incidence of primary end points (fatal or nonfatal myocardial infarction or sudden death) was observed. A statistically significant 39.5% (p=0.02) reduction in the primary end point in patients with high baseline triglycerides ($\geq$ 200 mg/dL) requires further confirmation[iii].

i.   Krakoff J, Vela SB, Brinton EA. The role of fibric acid derivatives in the secondary prevention of coronary heart disease. *Current Cardiology Reports* 2000; **2(5)**: 452-458
(Type V evidence – expert review of the literature)

ii.   Rubins HB, Robins SJ, Collins D *et al;* for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *New England Journal of Medicine* 1999; **341**: 410-418
(Type II evidence – double-blind randomised controlled trial comparing gemfibrozil (1,200 mg per day) with placebo in 2,531 men with coronary heart disease, an HDL cholesterol level of 40 mg per decilitre (1.0 mmol per liter) or less, and an LDL cholesterol level of 140 mg per decilitre (3.6 mmol per liter) or less. The median follow up was 5.1 years. The VA-HIT trial)

iii.   The BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000; **102**: 21-27
(Type II evidence – 6.2 year randomised controlled double-blind trial of 3,090 patients with a previous myocardial infarction or stable angina, total cholesterol of 180-250 mg/dL, HDL-C $\leq$ 45 mg/dL, triglycerides $\leq$ 300 mg/dL, and low-density lipoprotein cholesterol $\leq$ 180 mg/dL were randomised to receive either 400 mg bezafibrate per day or placebo)

3.22h. A study is underway to examine the effect of additional **reductions in cholesterol and homocystene** on outcomes in coronary heart disease[i].

i.   Second Heart Protection Study (HPS-2): the effects on CHD of standard v. larger blood cholesterol reductions with HMG CoA reductase inhibitor therapy and of blood homocysteine reduction with folinic acid vitamin B12 therapy (SEARCH). NRR N0235097204 end date. 2004/2005 (12,000 patients)

3.22i. A study is underway to examine the effect of **statin** treatment on acute coronary syndrome patients randomised to enoxaparin or unfractionated heparin and aspirin[i].

i.   Early treatment with simvastatin 40 mg daily for 30 days, followed by simvastatin 80 mg daily thereafter in tirofiban-treated acute coronary syndrome patients randomised to receive enoxaparin or unfractionated heparin in conjunction with aspirin. NRR N0059096407. End date 2003. (4,426 patients)

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3.22j. Clinical trial evidence supports treating **hyperlipidemia** in elderly persons for secondary prevention of coronary heart disease. Evidence from four secondary prevention trials demonstrated that major coronary heart disease risk decreased by 25% to 30% in elderly subjects treated for 5 years. Unanswered questions include cholesterol treatment for primary prevention in the elderly, gender effect, and benefit of treatment in persons older than 70[i].

i. Hall KM, Luepker RV. Is hypercholesterolemia a risk factor and should it be treated in the elderly? *American Journal of Health Promotion* 2000;**14(6)**:347-56.

(Type I evidence – systematic review and meta-analysis, literature search to 2000, including five randomized, controlled clinical trials of all lipid intervention trials with elderly (n=8,500; 65-75 years of age) participants or subgroup analyses of the elderly)

3.22k. In a multi-center, randomised double-blind clinical controlled trial the long-term clinical benefit observed during extended follow-up in patients assigned to an **aggressive lowering of LDL cholesterol** (LDL-C) levels to <100 mg/dL is consistent with the angiographic findings of delayed atherosclerosis progression in grafts observed during the trial. A 30% reduction in revascularization procedures and 24% reduction in a composite clinical end point were observed in patients assigned to aggressive strategy compared with patients assigned to moderate strategy during 7.5 years of follow-up, p=0.0006 and 0.001, respectively. Reductions of 35% in deaths and 31% in deaths or myocardial infarctions with low-dose anticoagulation compared with placebo were also observed, P=0.008 and 0.003, respectively. The apparent long-term benefit of low-dose warfarin remains unexplained[i].

i. Knatterud GL, Rosenberg Y, Campeau L *et al*. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the Post Coronary Artery Bypass Graft Trial. *Circulation* 2000; **102(2)**: 157-165

(Type II evidence – follow-up analysis of a randomised controlled trial of two lipid lowering regimens and low-dose anticoagulation with a main trial and extended follow-up of approximately 7.5 years. Of 1,351 patients in the original trial 996 of 1,103 patients still alive (21-74 years of age who had undergone CABG 1-11 years previously) were interviewed. Information was obtained from a relative or physician for 107 patients)

Other treatments for secondary prevention
- **Beta blockers** ■ **Antiarrythmics** ■ **Anticoagulants** ■ **Calcium channel blocker (nifedipine)**
- **Chelation therapy** ■ **Calcium ion influx inhibitor (verapamil)** ■ **Brain natriuretic peptide**
- **Dietary advice** ■ **Antioxidant vitamins**

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3.23   Beta-blockers for secondary prevention

3.23a. The relative benefit of **beta-blockers** on mortality **after a myocardial infarction** is similar in the presence or absence of heart failure but the absolute benefit may be greater in the former. Overall treatment with a beta-blocker was associated with a 22.6% reduction in the odds of death (95% CI, 11%-32.3%). In the analysis that included heart failure as a factor, treatment with a beta-blocker was associated with a non-significant interaction with the presence of heart failure. However, because the group including heart failure patients were at higher risk, the absolute benefit of treatment with beta-blockers appeared greater in this group. *Current clinical practice has changed radically from the time when the majority of these trials were conducted (eg prior to the widespread use of ACE inhibitors). Further trial evidence would be desirable to confirm the value of beta-blockers for contemporary clinical practice, and to examine any variations in individual therapies within the beta-blocker class*[i].

i.   Houghton T, Freemantle N, Cleland JGF. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. *European Journal of Heart Failure* 2000; **2(3)**: 333-40.

(Type I evidence – systematic review and meta-analysis of 17 randomised controlled trials, without cross-over, with beta-blocker treatment lasting more than one month and with 50 or more patients)

3.23b. Compared with **high-dose beta-blocker therapy**, low-dose treatment is associated with a lower rate of hospital admission for heart failure and has a similar one year survival benefit for **older patients**. Compared with those not dispensed beta-blocker therapy, the adjusted risk ratio for mortality was lower for all three doses (low 0.40, 95% CI [0.34-0.70], standard 0.36 [0.34-0.47], high 0.43 [0.33-0.56])[i].
These findings support the need for a randomised controlled trial comparing doses in elderly patients.

i.   Rochon PA, Tu JV, Anderson GM *et al*. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet* 2000; **356(9230)**: 639-644

(Type IV evidence – cohort study of 13,623 patients aged 66 years or older discharged from hospital in Ontario, Canada (April 1993 – March 1995) with a diagnosis of myocardial infarction stratified to no beta-blocker or low, standard or high dose. Low-dose therapy was defined as a dose lower than that achievable with the smallest available tablet size; standard-dose as a dose achieved with available tablet sizes but less than the doses used in randomised controlled trials; high-dose as doses equal to of higher than doses used in RCTs)

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3.23c. A Markov model suggests that increased use of **beta-blockers** would lead to impressive gains in health and be potentially cost saving (cost per QALY gained = $4,500 at year 2000 rates)[i].

i. Phillips KA, Shlipak MG, Coxson P *et al.* Health and economic benefits of increased beta-blocker use following myocardial infarction. *Journal of the American Medical Association* 2000; **284(21)**: 2748-2754

(Type IV evidence – cost-utility analysis based on a Markov model and US figures to estimate the epidemiological impact and cost-effectiveness of increased beta-blocker use from current (44%) to target levels (92%, ie all except those with absolute contraindications) among myocardial infarction survivors aged 35 to 84 years)

3.23d. A large multicentre study is underway to compare once daily **beta-blocker** versus heart rate lowering **calcium channel blocker** therapy in the reduction of one-year non fatal reinfarction and cardiovascular death[i].

i. Goodman S, Hill C, Bata I *et al.* PROTECT (Prospective Outcomes in the Thrombolytic Era Cardizem CD Trial): A randomized double-blind clinical trial of diltiazem versus atenolol in secondary prophylaxis post non-Q-wave myocardial infarction. *Canadian Journal of Cardiology* 1996; **12(11)**: 1183-1190

(Type II evidence – randomised controlled trial of >7,500 men and women (aged 21+) with enzyme confirmed non-Q-wave MI and without significant left ventricular systolic dysfunction will be recruited over two years. Once daily beta-blocker therapy (oral atenolol, 50-200 mg/day) will be compared to once daily calcium channel blocker (oral diltiazem, 120-360 mg/day) with follow-up for up to three years. Ongoing)

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3.24 Antiarrythmics for secondary prevention.
See also antiarrythmic therapies (section 4.7) and implantable cardioverter defibrillators (statements 4.17g – 4.17m) in Chapter Four: Heart Failure.

3.24a. Amiodarone may lead to modest reductions in the risk of arrhythmic cardiac death post-MI (odds ratio 0.79; 95% CI 0.60-1.04)[i].

Patients at high risk of arrhythmic death are likely to benefit[ii,iii,iv].

Prophylactic **amiodarone** reduces the rate of arrhythmic/sudden death in high-risk patients with recent myocardial infarction or congestive heart failure and this effect results in an overall reduction of 13% in total mortality (odds ratio=0.87, 95% CI 0.78-0.99, p=0.30). There was no difference in treatment effect between post-MI and heart failure studies. The excess (amiodarone minus control) risk of pulmonary toxicity was 1% per year[ii].
Caveat: No details of the literature review were provided

i. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. *Circulation* 1997; **96**: 2823-2829 Reviewed as: Amiodarone reduces all-cause mortality in patients at risk for sudden cardiac death. ACP Journal Club 1998;v129:3-Aug

(Type I evidence – systematic review of 15 randomised controlled trials and 5,864 patients in total. The literature search was completed in March 1997)

ii. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6,500 patients in randomised trials. *Lancet* 1997; **350**: 1417-1424

(Type I evidence – systematic review and meta-analysis of eight randomised controlled trials post-myocardial infarction and five randomised controlled trials of patients with heart failure (6,553 patients in all).

iii. Julian DG, Camm AJ, Frangin G *et al;* for the European Myocardial Infarct Amiodarone Trial Investigators. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after myocardial infarction: EMIAT. Lancet 1997;349:667-74

(Type II evidence - randomised controlled trial of 1,486 patients with acute MI and ejection fraction <40% randomised to amiodarone or placebo with median 21 month follow-up)

iv. Cairns JA, Connolly SJ, Roberts R, Gent M; for the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations. CAMIAT. *Lancet* 1997;**349**:675-82

(Type II evidence - randomised controlled trial of 1,202 patients with acute MI and frequent ventricular premature depolarisations randomised to amiodarone or placebo with two year follow-up)

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3.25 Anticoagulants for secondary prevention

3.25a. Among patients with coronary artery disease, high intensity and moderate intensity **oral anticoagulants (OA)** are effective in reducing myocardial infarction and stroke but increase the risk of bleeding. In the presence of aspirin, low intensity OA does not appear to be superior to aspirin alone, while moderate to high intensity OA and aspirin versus aspirin alone appears to be promising and the bleeding risk is modest. *This requires confirmation from ongoing trials*[i].

The authors concluded that long-term use of OAs after MI can be recommended for the secondary prevention of MI in patients unable to tolerate daily aspirin, patients with persistent atrial fibrillation and patients with left ventricular thrombus. Preliminary results from the Combination Hemotherapy and Mortality Prevention (CHAMP) trial support this conclusion. Warfarin alone or in combination with aspirin at INR (international normalised ratio) values < 2 does not appear to be clinically effective in the secondary prevention of MI[i].

i. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *Journal of the American Medical Association* 1999; **282**: 2058-2067

(Type I evidence – systematic review and meta-analysis of 30 reports of 31 randomised controlled trials.

Reviewed in: Review: High- and moderate-dose oral anticoagulants reduce events in CAD but increase major bleeding and are no more effective than aspirin. *ACP Journal Club* 2000; **133(1)**: 8)

3.25b. **Warfarin (coumadin)** on top of aspirin following unstable angina or myocardial infarction is beneficial with an acceptable bleeding risk. Three deaths/reinfarctions are prevented at the cost of one major bleeding (relative risk 0.87, 95% CI 0.81-0.93)[i].
Caveat: Published as abstract only to date (November 2003).

i. Verheugt FW, Brouwer MA, van Els RF, Ezekowitz MD, Fiore L, Fuster V. A meta-analysis of risks versus benefit of oral anticoagulation on top of aspirin following unstable angina or myocardial infarction. [Abstract]. *Journal of the American College of Cardiologists* 2002; **39(5)**: 327A
(Abstract only. Meta-analysis of the ATACS, CARS, CHAMP, APRICOT-2 and ASPECT-2 trials, 15,044 patients)

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3.25c Oral direct thrombin inhibition with ximelagatran and aspirin is more effective than aspirin alone in preventing major cardiovascular events during 6 months of treatment in patients who have had a recent myocardial infarction.

Oral ximelagatran significantly reduced the risk for the primary endpoint compared with placebo from 16.3% (102 of 638) to 12.7% (154 of 1245) (hazard ratio 0.76, 95% CI 0.59-0.98, p=0.036) for the combined ximelagatran groups versus placebo. There was no indication of a dose response between the ximelagatran groups. Major bleeding events were rare, 1.8% (23 of 1245) and 0.9% (six of 638) (hazard ratio 1.97, 95% CI 0.80-4.84) in the combined ximelagatran and placebo groups respectively. No serious clinically adverse outcomes were judged as related to the investigational drug[i].

Ximelagatran is not (yet) licensed for use in the UK.

i. Wallentin L, Wilcox RG, Weaver WD *et al*. Oral ximelagatran for secondary prophylaxis after myocardial infarction: The ESTEEM randomised controlled trial. *Lancet* 2003; **362(9386)**: 789-797

(Type II evidence – randomised controlled trial of 1,883 patients with recent ST-elevation or non-ST-elevation myocardial infarction. Within 14 days after the index event participants were randomised in the proportions 1/1/1/1/2 to oral ximelagatran at doses of 24 mg, 36 mg, 48 mg, or 60 mg twice daily, or placebo, respectively for 6 months. All patients received aspirin 160 mg once daily)

3.26 Chelation therapy for secondary prevention

3.26a. Two randomised controlled trials looking at **chelation therapy** for coronary heart disease did not show a statistically significant difference in the primary outcome measures (exercise capacity). Review articles looking at this question were of variable quality and, in some cases, extremely polarised[i].

i. Connock M, Wilson J, Song F, Hyde C, Meads C. *Chelation Therapy for Intermittent Claudication and Coronary Heart Disease*. Report No. 33. University of Birmingham: Department of Public Health & Epidemiology, 2002

(Type I evidence – systematic review, literature search to July 2001. Two randomised controlled trials were found of chelation therapy for coronary heart disease and six reviews that attempted a critical analysis of primary data (five of which considered coronary heart disease) were also examined)

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3.27   Calcium channel blockers for secondary prevention

3.27a. The results of a systematic review[i] and a subsequent large randomised controlled trial of **nifedipine**[ii] did not support an association with a late harmful effect on **long-term mortality**. In the trial, one year post-discharge mortality was 5.0% in the placebo group and 5.9% among patients receiving nifedipine (p=0.37). The five-year mortality risk ratio associated with randomisation to nifedipine over one year, adjusted for age, gender, post MI, angina, diabetes, hypertension, MI location and therapy was 1.00 (95% CI 0.81-1.22)[ii].
Caveat: The loss due to drop outs through adverse events is unclear and the results could support an increase as well as a reduction in mortality[iii].

i.   Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;**92**:1326-31.
(Type I evidence - systematic review and meta-analysis of 8,354 patients in 16 trials of secondary prevention with nifedipine (a calcium channel blocker): 12 MI, three unstable and one stable angina)

ii. Reicher-Reiss H, Behar VB, Mandelzweig L, Kaplinsky E, Goldbourt U; for the SPRINT Study Group. Long-term mortality follow-up of hospital survivors of a myocardial infarction randomized to nifedipine in the SPRINT Study. *Cardiovascular Drugs and Therapy* 1998; **12**: 171-176
(Type II evidence – randomised controlled trial of 2138 patients assigned to 30 mg/day nifedipine or placebo for a mean ten-month follow-up period)

iii. Harrell FE. The inappropriate use of hypothesis testing to infer safety of calcium channel blockers. *Cardiovascular Drugs and Therapy* 1998; **12**: 151-153

3.27b. In patients with myocardial infarction, the risks of both nonfatal reinfarction and the combined outcome of death or nonfatal MI were slightly reduced over the intermediate-term follow-up among patients treated with **verapamil** compared with controls. Based on over 4,000 years of patient observation patients with acute MI treated with verapamil had a decreased risk of nonfatal reinfarction compared with placebo (relative risk, RR=0.79, 95% CI 0.65-0.97; p=0.024). Verapamil had no significant effect on mortality compared with placebo. For the combined outcome of death or reinfarction, verapamil use was associated with a decreased risk compared with placebo (RR=0.82, 95% CI 0.70-0.97; p=0.016)[i].
Caveats: Results were only just significant and no sign of attempt to locate unpublished studies.

i.   Pepine CJ, Faich G, Makuch R. Verapamil use in patients with cardiovascular disease: An overview of randomized trials. *Clinical Cardiology* 1998; **21(9)**: 633-41.
(Type I evidence – systematic review of seven randomised controlled trials comparing verapamil with placebo or control therapy)

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3.27c **Diltiazem** did not reduce the cumulative occurrence of cardiac death, non-fatal reinfarction, or refractory ischaemia during a 6-month follow-up, but did reduce all composite endpoints of non-fatal cardiac events, especially the need for myocardial revascularisation (hazard ratio for the need for myocardial revascularisation alone = 0.61, 95% CI 0.39-0.96)[i].

Caveat: Only 2-3% of the patients had had a previous myocardial infarction and, thus, these results should not be extrapolated to all post infarction patients.

i. Boden WE, van Gilst WH, Scheldewaert RG *et al;* for the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT). *Lancet* 2000; **355(9217)**: 1751-1756

(Type II evidence – randomised double-blind controlled trial of 874 patients with acute myocardial infarction, but without congestive heart failure, who first received thrombolytic agents. Patients received either 300 mg oral diltiazem once daily, or placebo, initiated within 36-96 hours of infarct onset, and given for up to six months. Recruitment was initially restricted to patients not older than 70 years presenting with a first myocardial infarction; This was later amended to include patients up to 75 years and with previous infarction. Both groups received aspirin daily. An intention-to-treat analysis was used)

3.28 Brain natriuretic peptide for secondary prevention

3.28a **Brain natriuretic peptide** may be the superior prognosticators for risk stratification after myocardial infarction and is independent of left ventricular ejection fraction. Experimental trials suggest that the administration of exogenous natriuretic peptides or inhibitors of their catabolism to patients with ischaemic heart disease may be beneficial[i].

i. Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. *American Heart Journal* 1998; **135(5 Pt 1)**: 914-23.

(Type V evidence – expert opinion based on a review of papers found through a MEDLINE search (1966 to 1997) supplemented with bibliographic references and texts)

3.29 Dietary advice for secondary prevention

3.29a **Dietetic practice** for people following myocardial infarction is out of line with current evidence. Almost half of UK departments (responding to a survey) correctly prioritised oily fish advice but frequently commented that they only see patients with raised lipids or weight[i].

i. Hooper L; on behalf of the UK Heart Health and Thoracic Dietitians Interest Group. Survey of UK dietetic departments; diet in secondary prevention of myocardial infarction. *Journal of Human Nutrition & Dietetics* 2001; **14(4)**: 307-318

(Type IV evidence – survey of UK chief dieticians (57% response rate – 138/224 questionnaires returned). Commentary provided by: Slevin K. Journal of Human Nutrition and Dietetics 2001; 14: 487-488)

Comprehensive systematic search to July 2002 plus selected update searches to December 2003 as advised by review groups

3 | ACUTE CORONARY SYNDROMES

The *statements*	The *evidence*

3.29b. The protective effect of a **Mediterranean dietary pattern** in maintained up to four years after a first infarction. In the Mediterranean diet group the composite outcomes of cardiac death and non-fatal myocardial infarction were reduced (14 events versus 44 in the prudent Western-type diet group, p=0.0001). Many traditional risk factors, such as high blood cholesterol and blood pressure, were shown to be independent and joint predictors of recurrence, indicating that the Mediterranean dietary pattern should be associated with other means aimed at reducing modifiable risk factors[i].
Caveat: The study took place between 1988 and 1992 and use of lipid lowering drugs varied considerably.

i. de Lorgeril M, Salen P, Martin J-L, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction. Final report of the Lyon Diet Heart Study. *Circulation* 1999; **99**: 779-785

(Type II evidence – 46 month randomised controlled trial of 425 patients post myocardial infarction aged <70 years)

3.30 Antioxidant vitamins for secondary prevention

3.30a. Antioxidant vitamins appeared to be safe among high-risk patients but there were no significant five year effects on vascular disease, cancer or other major outcomes[i].
Caveat: Only 65% of the patients included in the study had coronary heart disease.

The study design was a 2x2 format to examine the effect of statin as well as vitamin E use.

i. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7-22

(Type II evidence – Five year randomised controlled trial of 20,536 UK adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes allocated to antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily) or matching placebo. Follow-up was 96% and an intention to treat analysis was used)

3.31 Guidelines for the long-term management/secondary prevention of acute coronary syndromes

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3.31a. Guidelines for the prophylaxis/secondary prevention for patients who have experienced a myocardial infarction are available[i].

i. National Institute for Clinical Excellence. *Prophylaxis for Patients who have Experienced a Myocardial Infarction*. London: NICE, April 2001
http://www.nice.org.uk/Article.asp?a=10762 [accessed 22.12.03] Official review date: April 2003.
http://www.nice.org.uk/pdf/clinicalguidelinemiguidanceyorknewcastle.pdf [Adobe Acrobat reader required]

(Evidence based guidelines from a systematic review of the literature. A guideline from the North of England Evidence-based Guidelines Development Project)

This document is a supplement to, not a substitute for, professional skills and experience. Users are advised to consult the supporting evidence for a consideration of all the implications of a recommendation.

3 | ACUTE CORONARY SYNDROMES

The *statements*   The *evidence*

3.31b. Guidelines are available for the long-term management of unstable angina and non-Q-wave myocardial infarction but require updating[i,ii].

i. Mehta SR, Eikelboom JW, Yusuf S. Long-term management of unstable angina and non-Q-wave myocardial infarction. *European Heart Journal Supplements* 2000; **2(E)**: E6-E12
(Type V evidence - expert opinion)

ii. Smith SC, Blair SN, Bonow RO *et al*. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Journal of the American College of Cardiology* 2001; **38(5)**: 1581-1583
(Type V evidence – expert update (summary table) of the 1995 AHA/ACC guidelines. Also published as: Smith SC, Blair SN, Bonow RO *et al*. Scientific statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. *Circulation* 2001; **104(13)**: 1577-1579)

3.31c. A scientific statement from the American Heart Association on secondary prevention of coronary heart disease in the **elderly** is available[i].

i. Williams MA, Fleg JL, Ades P *et al*. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients ≥ 75 years of age). An American Heart Association Scientific Statement from the Council on clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation and Prevention. *Circulation* 2002; **105(14)**; 1735-1743
(Type V evidence – consensus guidelines)