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Everyone at high risk of developing coronary heart disease and all those who have been diagnosed as having the disease should have access to a multifactorial risk assessment and be offered an appropriate treatment plan.

Patients at high risk of coronary heart disease are defined as those with a 10 year coronary heart disease risk of > 30%[i,ii].

i. National Assembly for Wales. Chapter 5: The implementation of Standard 2. In *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, 2001
http://www.wales.nhs.uk/Publications/coronary-heart-disease-e.pdf [accessed 22.12.03]

ii. Department of Health. Chapter 2. Preventing coronary heart disease in high risk patients. In *National Service Framework for Coronary Heart Disease*. London: Department of Health, March 2000
http://www.doh.gov.uk/nsf/coronary.htm [accessed 22.12.03]

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…all those included on primary care CHD management systems will have been offered a Multifactorial Risk Assessment and an appropriate treatment plan. [key action 9]

Which instruments have been validated for multifactorial risk assessment?

…each Primary Care Team must develop an opportunistic screening programme for CHD risk factors amongst the practice population… [key action 6]

Which are the best screening aids?

The *statements* | The *evidence*

2.1 Risk assessment in primary care

2.1a. The **Framingham risk model** for the prediction of CHD mortality rates provides a reasonable rank ordering of risk for white individuals[i,ii]. However, prediction of absolute risk is less accurate[i,iii] and currently recommended risk scoring methods derived from the Framingham study significantly overestimate the absolute coronary risk assigned to men in the United Kingdom[iii]. Following a simple adjustment (dividing the final score for 10 year predictions by 1.47) the predicted risk became close to the observed rate at all levels of risk[iii].

i. Liao Y, McGee DL, Cooper RS. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts. *American Heart Journal* 1999; **137(5)**: 837-45
(Type IV evidence – systematic review and meta-analysis of data from 1,846 men and 2,323 women 35 to 69 years of age free of coronary heart disease at the fourth examination from the Framingham Study; 2,753 men and 3,858 women from the First National Health and Nutrition Examination Survey (NHANES) and 2,655 men and 3,050 women from the second NHANES.

ii. Yudkin JS, Chaturvedi N. Developing risk stratification charts for diabetic and nondiabetic subjects. *Diabetes.Medicine* 1999; **16(3)**: 219-27
(Type IV evidence – validation of risk coefficients derived from the Framingham Study by comparison with the Dundee Risk Disk and PROCAM studies)

iii. Brindle P, Emberson J, Lampe F *et al*. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *British Medical Journal* 2003; **327**: 1267-1272
http://bmj.bmjjournals.com/cgi/content/full/327/7426/1267 [accessed 22.12.03]
(Type IV evidence – prospective cohort study in 24 towns in the UK of 6,643 men aged 40-59 years and free from cardiovascular disease at entry)

The *statements*

The *evidence*

2.1b. **Routine calculation** of the risk of coronary heart disease is hampered by poor availability of data on risk factors. General practitioners and practice nurses were able to evaluate the risk of coronary heart disease from patients' records with only moderate accuracy[i]. *Data about risk factors need to be collected systematically in general practice*[i].

i. McManus RJ, Mant J, Meulendijks CFM *et al*; on behalf of the Midlands Research Practice Consortium. Comparison of estimates and calculation of coronary heart disease by doctors and nurses using different calculation tools in general practice; cross sectional study. *British Medical Journal* 2002; **324**: 459-64 and online correspondence. **http://bmj.bmjjournals.com/cgi/content/full/324/7335/459** [accessed 22.12.03]

(Type IV evidence – subjective estimates by 18 general practitioners and 18 practice nurses in central England of the risk of coronary heart disease using four methods of risk calculation based on a random sample of patients' records. Results were compared with a reference standard calculated from the Framingham equation. Tools used were: The Sheffield table, the New Zealand hypertension guideline risk table, the joint European Societies' recommendations on prevention of coronary heart disease and the joint British Societies' recommendations on the prevention of coronary heart disease in clinical practice)

2.1c. Of three risk assessment methods, **nurses** are more likely to interpret correctly the New Zealand guidelines and joint British chart, and both general practitioners and nurses find these two methods easier to use and prefer them to the Sheffield table. 33/37 doctors and 22/35 nurses scored at least 10 of 12 case histories correctly when using the Sheffield table; corresponding numbers for the New Zealand guidelines were 37 and 33 respectively and for the joint British chart 36 and 34 respectively. There were no significant differences between the three scores for doctors, whereas accuracy among nurses was significantly poorer ($P<0.001$) with the Sheffield table than with each of the other two guidelines. Only 6 doctors and 6/34 nurses gave the Sheffield table a high preference rating (4 or 5). More doctors and nurses gave high preference scores for the New Zealand guidelines (26 doctors and 25 nurses) and for the joint British chart (23 and 25) ($p<0.001$ for the Sheffield table compared with each of the other two guidelines for both doctors and nurses). Similar results were found for ease of use[i].

i. Isles CG, Ritchie LD, Murchie P, Norrie J. Risk assessment in primary prevention of coronary heart disease: randomised comparison of three scoring methods. *British Medical Journal* 2000; **320**: 690-691 **http://bmj.bmjjournals.com/cgi/content/full/320/7236/690** [accessed 22.12.03]

(Type II evidence – a randomised controlled trial of 37 general practices – 37 doctors and 35 nurses)

2 HIGH-RISK AND CHD-DIAGNOSED

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2.1d. **Software programmes** are available to assist with the prevention and management of coronary heart disease[i,ii,iii].

The **Clinical Decision Support System (SDSS)** is now widely used in primary care in Scotland[i].

Data from the Framingham Heart Study and risk-appraisal models were used to develop a Coronary Heart Disease (CHD) **Risk Factor Calculator** for early identification of high-risk individuals[ii].

The PRECARD(R) **computer program** was developed using a new coronary risk score (the Copenhagen Risk Score) for myocardial infarction and a model for calculating the effect of intervention. Two Danish population studies (n = 11 765) with 10 years of follow up were used to establish the risk score[iii].

The *evidence*

i. 5. Information technology and the development and use of databases. In *Coronary Heart Disease and Stroke Strategy for Scotland*. Scottish Executive, 2002 **http://www.scotland.gov.uk/library5/health/chds-09.asp** [accessed 22.12.03]

ii. Day D. Population-based screening with the Coronary Heart Disease Risk Factor Calculator. *Advances in Therapy* 2001; **18(1)**: 21-32

iii. Thomsen T, Davidsen M, Ibsen H, Jorgensen T, Jensen G, Borch-Johnsen K. A new method for CHD prediction and prevention based on regional risk scores and randomized clinical trials; PRECARD(R) and the Copenhagen risk score. *Journal of Cardiovascular Risk* 2001; **8(5)**: 291-297

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Recognition of…familial hypercholesterolaemia is particularly important. At present the proportion of patients with early CHD identified as being due to familial hypercholesterolaemia is low, and even fewer of their healthy relatives at high risk of developing CHD are detected and offered treatment. There is a need for carefully constructed and monitored Research & Development pilot programmes based in primary and secondary care, which can give information in both the feasibility of systematic detection of familial hypercholesterolaemia and also on the benefits and possible harmful effects of testing healthy relatives…

A specialised service needs to be provided for (patients) including LDL Apheresis for the very few who need it. [paragraph 5.1]

Screening for familial hypercholesterolaemia?

Interventions to target those at high risk?

The *statements* | The *evidence*

Familial hypercholesterolaemia

2.2 Screening for familial hypercholesterolaemia

2.2a. **Tracing and screening** family members of people with familial hypercholesterolaemia appears to be cost effective from modelling exercises[i,ii].

A study using a simulated population from England & Wales suggested that **tracing of family members** was the most cost effective strategy (£3,097 per life year gained) as 2.6 individuals needed to be screened to identify one case at a cost of £133 per case detected. **Universal population screening** was least cost effective (£13,029 per life year gained) as 1,365 individuals needed to be screened at a cost of £9,754 per case detected[ii]. However, **population screening of 16 year olds** is as cost effective as family tracing[i,ii] assuming that such screening is acceptable and that at least 55% of those invited for screening attend[i].

i. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. *Health Technology Assessment* 2000; **4(29)** **http://www.hta.nhsweb.nhs.uk/fullmono/mon429.pdf** [accessed 22.12.03]

(Type IV evidence – systematic review of 39 quantitative and qualitative studies, 16 including primary data, using a constructed model to investigate the relative cost and effectiveness of various forms of population screening (universal or opportunistic) and case-finding screening (screening relatives of known FH cases))

ii. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *British Medical Journal* 2002; **324(7349)**: 1303-1308 **http://bmj.bmjjournals.com/cgi/content/full/324/7349/1303** [accessed 22.12.03]

(Type IV evidence – cost-effectiveness analysis of a simulated population aged 16-54 years in England and Wales)

2.2b. In the Netherlands, **targeted family screening with DNA analysis** proved to be highly effective in identifying patients with hypercholesterolaemia. In the first five years of the programme, 5,442 relatives of 237 people with familial hypercholesterolaemia were screened; 2,039 individuals were identified as hererozygous by LDL-receptor gene mutation analysis. At the time of examination, 667 of these adults (39%) received some form of lipid-lowering treatment. One year later, this percentage had increased to 93%[i].

i. Umans-Eckenhausen MAW, Defesche JC, Sijbrands EJG, Schreerder RLJM, Kastelein JJP. Review of the first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* 2001; **357(9251)**: 165-168

(Type IV evidence – longitudinal study of the effects of the screening programme in the Netherlands from 1994-1999)

The *statements*

The *evidence*

Interventions for familial hypercholesterolaemia

2.2c. No conclusions can be made about the effectiveness of the **cholesterol-lowering diet**, or any of the other dietary interventions suggested for familial hypercholesterolaemia (FH), due to the lack of adequate data. *A large, parallel, randomised controlled trial is needed to investigate the effectiveness of the cholesterol-lowering diet and other dietary interventions for FH.* Until further evidence is available current dietary treatment of FH should continue to be observed and monitored with care[i].

i. Poustie VJ, Rutherford P. Dietary treatment for familial hypercholesterolaemia (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 28 February 2001)
http://www.update-software.com/abstracts/ab001918.htm [accessed 22.12.03]
(Type I evidence – systematic review of 5 randomised, controlled cross-over trials including a total of 60 patients (22 children with familial hypercholesterolaemia) between 1-3 months duration)

2.2d. The addition of **statins to diet therapy** in children > 10 years of age may be effective when diet therapy alone has failed to obtain the recommended maximum LDL-C concentration of 130 mg/dL. *The use of statins during childhood and adolescence is generally safe, but large, long-term studies should be performed before statins are routinely prescribed to children with elevated cholesterol or lipoprotein concentrations*[i].

See also Statement 2.2c and Section 2.5

i. Duplaga BA. Treatment of childhood hypercholesterolemia with HMG-CoA reductase inhibitors. *Annals of Pharmacotherapy* 1999; **33(11)**: 1224-7.
(Type V evidence – narrative overview based on a Medline literature search (1966-1999) for English language studies)

Guidelines for the screening and treatment of familial hypercholesterolaemia

2.2e. The Joint British recommendations on prevention of coronary heart disease in clinical practice include recommendations on screening of **hypercholesterolaemia in childhood** and the management of **familial hypercholesterolaemia**[i].

i. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* 1998; **80(suppl.2)**; S1- S29)
(Evidence based guidelines. These guidelines are currently being updated)
Summary published as:
British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *British Medical Journal* 2000; 320: 705-708
http://bmj.bmjjournals.com/cgi/content/full/320/7236/705
Correction on:
http://bmj.bmjjournals.com/cgi/content/full/323/7316/780/a [accessed on 22.12.03]

The *statements*

The *evidence*

2.2f. Guidelines and algorithms are available on **lipid screening** in children and adolescents[i].
Caveat: The search strategy and selection criteria for including studies are not stated.

i. Institute of Clinical Systems Improvement. *Lipid Screening in Children and Adolescents*. Bloomington: Institute of Clinical Systems Improvement, July 2002
http://www.icsi.org/index.asp [accessed 22.12.03]
(Type V evidence – expert guidelines)

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Diabetes and hypertension are particularly prevalent in people of South East Asian and African origin; therefore, targeted and specific plans need to be developed for these ethnic minority groups in Wales. [paragraph 2.9]
Evidence to support recommendation?
How to best target these ethnic minorities?

The *statements*

The *evidence*

2.3 Risk assessment and treatment in minority population groups

2.3a. Estimates of **South Asians'** excess risk of coronary heart disease (CHD) are imprecise. South Asians are a heterogeneous group yet most studies report on Bangladeshis, Indians and Pakistanis combined. Indians probably have less CHD than Bangladeshis and Pakistanis. *Cohort studies on CHD in South Asians are needed and these should be designed so that data can be combined for future systematic reviews*[i].
Caveat: A single author review with well-reported methods although study designs unclear and incidence studies were not found

i. Bhopal, R. What is the risk of coronary heart disease in South Asians? A review of UK research. *Journal of Public Health Medicine* 2000; **22(3)**: 375-85
(Type IV evidence – systematic review of 19 observational (surveys, observational studies and data analysis) studies. Literature search to 1998)

2.3b. A **reduced sodium** intake is a broadly effective, nonpharmacologic therapy that can lower blood pressure and control hypertension in older individuals (see statement 2.10j). In African Americans, the relative hazard ratio was 0.56 (p = .005); results were similar in other subgroups[i].
Caveat: There is no clinical trial evidence that low-sodium diets decrease morbidity and mortality. However, two cohort studies showed a substantive direct relation between sodium intake and cardiovascular disease, at least in overweight people[ii].

i. Appel JL, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Archives of Internal Medicine* 2001; **161(5)**: 685-93
(Type II evidence - a randomised controlled trial of 681 patients with hypertension, aged 60 to 80 years with a mean follow-up of 27.8 months. Reviewed in:

ii. Anonymous. Reduced sodium intake lowered blood pressure and need for antihypertensive medication. *ACP Journal Club* 2001; **135(2)**: 61)

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2.3c. In a small study **simvastatin** was effective and well tolerated at doses of 20, 40, and 80 mg/d in **Asian patients** with coronary heart disease. Titration enabled the majority to achieve target LDL-C levels of ≤ 100 mg/dL. Overall, 104 (78.2%) patients treated with simvastatin achieved LDL-C levels <=100 mg/dL at week 14, and 125 (94.0%) achieved this target at some point during the study[i].

Simvastatin was well tolerated across the dose range. Only 14 (10.5%) had adverse experiences that were possibly, probably, or definitely related to study drug; none of these experiences were considered serious[i].

See also Sections 2.5-2.8

2.3d. **Pharmacologic hypertension treatment** lowers the relative and absolute risk of cardiovascular morbidity and mortality in **African American** women of all ages[i].

Hypertension treatment in African American women (mean age 52 years) reduced the risk of fatal and nonfatal cerebrovascular events by 53% (95% CI 29-69%, 5 year NNT 39), fatal and nonfatal cardiovascular events by 45% (95% CI 18-63%, 5 year NNT 21), fatal and nonfatal coronary events by 33% (95% CI 6-52%, 5 year NNT 48), and all cause mortality by 34% (95% CI 14-49%, 5 year NNT 32)[i].

A Cochrane review is underway to evaluate the short- and long-term effect of single drug treatment versus placebo for hypertension in people of **sub-Saharan Africa** or of sub-Saharan African descent[ii].

See also Sections 2.9-2.12

The *evidence*

i. Chung N, Cho S-Y, Choi D-H *et al*. STATT: A titrate-to-goal study of simvastatin in Asian patients with coronary heart disease. *Clinical Therapeutics* 2001;**23(6)**: 858-870

(Type IV evidence - a multicenter, open-label, uncontrolled, 14-week study of 133 (93 men, 40 women;mean age 59.5 years) Asian patients with coronary heart disease and serum low-density lipoprotein cholesterol (LDL-C) levels of 115-180 mg/dL and triglyceride levels of <=400 mg/dL)

i. Quan A, Kerlikowske D, Gueyffier F, Boissel JP; INDANA investigators. Pharmacotherapy for hypertension in women of different races (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 3 December 1999) **http://www.update-software.com/abstracts/ab002146.htm** [accessed 22.12.03]

(Type I evidence - systematic review of 11 randomised controlled trials of 23,000 women (30-98 years of age, white or African American) with essential hypertension. The following literature sources were searched for published, English-language papers: MEDLINE (1966-1998), reference lists from review articles & consultation with experts)

Also published as: Quan A, Kerlikowske D, Gueyffier F, Boissel JP, INDANA investigators. Efficacy of treating hypertension in women. *Journal of General Internal Medicine* 1999; **14**: 718-729

ii. Brewster L, Kleijnen J, van Montfrans G. Pharmacotherapy for hypertension in people of sub-Saharan Africa or of sub-Saharan African descent. 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*

2.3e. Among patients deemed appropriate for coronary artery bypass grafting, **South Asian** patients are **less likely** than white patients to receive it. This difference is not explained by physician bias. There was no difference between south Asian and white patients in the proportions deemed appropriate for revascularisation (72% (361) v 68% (2,022)) or in the proportions for whom the physician's intended management was revascularisation (39% (196) v 41% (1,218)).

Among patients appropriate for revascularisation, age adjusted rates of coronary angioplasty (hazard ratio 0.69, 95% CI 0.47-1.00, P=0.058) and coronary artery bypass grafting (0.74, 0.58-0.91, P=0.007) were lower in south Asian than in white patients. These differences were smaller but still present after adjustment for socioeconomic status and after restriction of analysis to those patients for whom the intended management was revascularisation. There were no differences in mortality and non-fatal myocardial infarction between south Asian and white patients (1.07, 0.78-1.47)[i].

The *evidence*

i. Feder G, Crook AM, Magee P, Banerjee S, Timmis AD, Hemingway H. Ethnic differences in invasive management of coronary disease: Prospective cohort study of patients undergoing angiography. *British Medical Journal* 2002; **324(7336)**: 511-516 **http://bmj.bmjjournals.com/cgi/content/full/324/7336/511** [accessed 22.12.03]

(Type IV evidence - prospective cohort study of 502 South Asian and 2,974 white patients undergoing coronary angiography in the Appropriateness of Coronary Revascularisation Study (ACRE) with two and a half years follow-up. Appropriateness of revascularisation rated by nine experts with no knowledge of ethnicity of the patient)

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All patients diagnosed with CHD, and all people identified as being of high risk of developing it, will be provided with: [parargraph 1.9]

- information on how the risks of either developing CHD or worsening the CHD they already have can be minimised or reduced.

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]

By 2006/7, local health groups and district general hospitals in partnership will have established resource centres which will provide a locally accessible and acceptable source of advice to patients. These centres will where appropriate develop to provide a base for other services for those with CHD and their families. [key action 7]

Patient information support schemes/strategies?

The *statements* | The *evidence*

2.4 Patient information

2.4a. **Health promotion programmes** for patients at risk of coronary heart disease can be valuable but the effects wear off with time[i,ii].

Brief behavioural counselling of adults by practice nurses led to improvements in healthy behaviour. Favourable differences were recorded in the intervention group for dietary fat intake, regular exercise, and cigarettes smoked per day at 4 and 12 months. Systolic blood pressure was reduced to a greater extent in the intervention group at 4 but not at 12 months. No differences were found between groups in changes in total serum cholesterol concentration, weight, body mass index, diastolic pressure, or smoking cessation. *More extended counselling to help patients sustain and build on behaviour changes may be required before differences in biological risk factors emerge*[i].

Three years after the end of a **personalised health promotion programme** based in primary care for patients with angina most of the benefits identified at the end of two years had worn off. The results suggest that prolonged provision of health promotion for patients may be desirable[ii].

i. Steptoe A, Doherty S, Rink E, Kerry S, Kendrick T, Hilton S. Behavioural counselling in general practice for the promotion of healthy behaviour among adults at increased risk of coronary heart disease: randomised trial. *British Medical Journal* 1999; **319(7215)**: 943-7 **http://bmj.bmjjournals.com/cgi/content/full/319/7215/943** [accessed 22.12.03]

(Type II evidence – One year cluster randomised controlled trial of 20 general practices (883 participants with a mean age of 46.7 years) with the presence of one or more modifiable risk factors: regular cigarette smoking, high serum cholesterol concentration (6.5-9.0 mmol/l), and high body mass index (25-35) combined with low physical activity)

ii. Cupples ME, McKnight A. Five year follow up of patients at high cardiovascular risk who took part in randomised controlled trail of health promotion. *British Medical Journal* 1999; **319**: 687-688 **http://bmj.bmjjournals.com/cgi/content/full/319/7211/687** [accessed 22.12.03]

(Type II evidence – randomised controlled trial in 18 general practices in Belfast of patients aged under 75 with angina who were assigned to usual NHS care and personal health promotion from a trained nurse every four months for two years or usual NHS care alone)

2.4b. **Patient decision aids** improve knowledge and realistic expectations, enhance active participation in decision making, lower decisional conflict, decrease the proportion of people remaining undecided, and improve agreement between values and choice. The effects on persistence with chosen therapies and cost-effectiveness require further evaluation[i].

i. O'Connor AM, Stacey D, Entwistle V *et al*. Decision aids for people facing health treatment or screening decisions (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 18 October 2002) **http://www.update-software.com/abstracts/ab001431.htm** [accessed 22.12.03]

(Type I evidence-systematic review, literature search to August 2002, and meta-analysis of 35 randomised controlled trials of which two examined ischemic heart disease)

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For each patient on the chronic disease management system, the following are the aims, based on best evidence at time of publication, which need to be updated over time in light of the research: [key action 9]

- Avoiding B.P. consistently more than 140/85 (in diabetes <130/80) *see Section 2.9*
- Cholesterol <5 mmol/l; or a reduction by 2 mmol/L *see Section 2.5*
- LDL cholesterol <3 mmol/L *see Section 2.5*
- A fasting blood sugar should be recorded to exclude diabetes
- On dispersible aspirin 75 mg, clopidogrel or warfarin *see Statements 2.15d-2.15e*
- On beta-blockers/ACE inhibitors (unless contra indicated) after a myocardial infarction *see Chapter Three*
- Enrolled in a smoking cessation programme if applicable see Chapter One *Sections 1.23-1.26*
- A record of the body mass index (BMI)
- An individual nutrition programme overseen by a State Registered Dietician *see Section 2.6, especially statement 2.6b and Chapter One Sections 1.27-1.29*
- An exercise programme see *Section 2.11 and Chapter One Sections 1.30-1.31*
- Advice about alcohol intake *see statement 2.10f and Chapter One Section 1.10*
- Regular review

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For each patient on the chronic disease management system, the following are the aims, which need to be updated over time in light of the research: [key action 9]

- Cholesterol <5 mmol/l; or a reduction by 2 mmol/L
- LDL cholesterol <3 mmol/L

Greater use of statins to achieve these levels should be considered.

Cholesterol lowering interventions (and for those at high risk)?

2 HIGH-RISK AND CHD-DIAGNOSED

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2.5 Cholesterol lowering interventions

2.5a. Reduction in LDL-C associated with **statin drug treatment** decreases the risk of coronary heart disease and all-cause mortality[i,ii].

A systematic review published in 1999 found that, overall, statin drug treatment reduced the risk of major coronary events by 31% (95% CI, 26-36%) and all-cause mortality by 21% (14-28%). The risk reduction in major coronary events was similar between women (29%; 95% CI 13-42%) and men (31%; 26-35%) and between persons aged at least 65 years (32%; 23-39%) and persons younger than 65 years (31%;24-36%)[i]. A more recent systematic review found that statins can lower LDL cholesterol concentration by an average of 1.8 mmol/l and reduces the risk of ischaemic heart disease events by about 60% and stroke by 17%[ii].

i. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease. A meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 1999; **282(24)**: 2340-2346.

(Type I evidence – systematic review and meta-analysis, literature search to 1998, of five randomised controlled trials including 30,817 participants (mean age 59 years) with a mean duration of 5.4 treatment years and a mean follow-up of 5.4 years)

ii. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *British Medical Journal* 2003; **326**: 1423 **http://bmj.bmjjournals.com/cgi/reprint/326/7404/1423**

[accessed 22.12.03]

(Type I evidence – systematic review, literature search to 2001, of 164 short term randomised placebo controlled trials of six statins; 58 RCTs of cholesterol lowering by any means and IHD events; and nine cohort studies and the same 58 trials on stroke)

2.5b. **Statins** are indicated in preference to other antilipidemic agents[i,ii]. In a meta-analysis of 26 randomised controlled trials total mortality only decreased with statins: Odds ratio, OR=0.76 (95% CI 0.68-0.86). Other agents had no effect on total mortality: Fibrates OR=1.08 (95% CI 0.97-1.21), nicotinic acid together with acipimox OR=0.94 (95% CI 0.81-1.09), resins OR=0.86 (95% CI 0.66-1.11). Trials with probucol were not found[i].

In another systematic review, of the cholesterol-lowering interventions, only statins showed a large and statistically significant reduction in mortality from coronary heart disease (risk ratio, 0.66; 95% CI 0.54-0.79) and from all causes (risk ratio, 0.75;95% CI 0.65-0.86). For both all-cause and cardiovascular mortality, the difference between statins and the combined estimate of the other classes of agents was unlikely to be due to chance ($p<0.02$ for both comparisons)[ii].

i. Sterno A. Comparison of different groups of cholesterol lowering drugs and total mortality: A meta-analysis. *Medical Science Monitor* 1999; **5(4)**: 786-793

(Type I evidence – systematic review and meta-analysis, literature search to 1997, of 26 randomised controlled trials with 1-10 follow-up years)

ii. Bucher HC, Griffith LE, Guyatt GH. Systematic review on the risk and benefit of different cholesterol-lowering interventions. *Arteriosclerosis Thrombosis and Vascular Biology* 1999; **19(2)**: 1887-195

(Type I evidence – systematic review and meta-analysis, literature search to 1996, of 59 randomised controlled trials pooled into 7 pharmacological categories of cholesterol-lowering and dietary interventions with 173,160 participants)

The *statements*

The *evidence*

2.5c. Lipid-lowering therapy generally should be **more aggressively** applied to patients with **diabetes** and/or at the time of coronary heart disease (CHD) diagnosis. Further studies are needed to address the effects of lipid modification in primary prevention of CHD in populations other than middle-aged men and to study markers of lipid metabolism other than LDL-C[i].

i. Ansell BJ, Watson KE, Fogelmann AM. An evidence based assessment of the NCEP adult treatment panel guidelines. National cholesterol education programme. *Journal of the American Medical Association* 1999; 282(21): 2051-7

(Type I evidence – systematic review, literature search to 1999, of 37 clinical trials)

2.5d. The absolute safety of **statins** has **not** been demonstrated for patients at **low risk** of CHD[i,ii] although the AFCAPS/TexCAPS trial of lovastatin found a benefit in patients with average total and LDL-cholesterol and below average HDL-cholesterol[iii].

Treatment with lipid lowering drugs lasting five to seven years reduces coronary heart disease events but not all cause mortality in people with **no known cardiovascular disease**. In a meta-analysis of four randomised controlled trials drug treatment reduced the odds of a coronary heart disease event by 30% (summary odds ratio 0.70, 95% CI 0.62-0.79) but not the odds of all cause mortality (0.94, 0.81-1.09). When statin drugs were considered alone, no substantial differences in results were found[i].

The results of another review suggested that statin use could be associated with an increase in mortality of 1% in 10 years. This would be sufficiently large to negate statin's beneficial effect in patients with a coronary heart disease event risk of less than 13% over 10 years. Patients' absolute risk of CHD should be calculated before starting statin treatment for primary prevention. *Extensions of such treatment to low risk patients should await further evidence of safety*[ii].

A two-month UK government consultation commenced in November 2003 on the reclassification of simvastatin from prescription only to pharmacy (over the counter) medicine[iv].

i. Pignone M, Phillips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomised trials. *British Medical Journal*, 2000; **321(7267)**: 983-986
http://bmj.bmjjournals.com/cgi/content/full/321/7267/983 [accessed 22.12.03]

(Type I evidence – systematic review and meta-analysis, literature search to 1999, of four randomised controlled trials with 21,087 subjects (mean age years 48-58) and study duration of 5-7 years)

ii. Jackson PR, Wallis EJ, Haq IU, Ramsay LE. Statins for primary prevention: at what coronary risk is safety assured? *British Journal of Clinical Pharmacology* 2001; **52(4)**: 439-446

(Type I evidence-systematic review, Medline only and literature date not specified, of five placebo controlled clinical trials. The analysis was performed using the Grover risk function to establish a balance between possible harm and proven benefit)

iii. Downs JR, Clearfield M, Weis S *et al*. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *Journal of the American Medical Association* 1998; **279(20)**: 1615-22

(Type II evidence – randomised controlled trial of 5,608 men and 997 women with average total cholesterol and LDL-cholesterol and below-average HDL-cholesterol, and without clinically evident cardiovascular disease, randomised to lovastatin or placebo)

iv. Anon. Statin set to become next big POM-to-P switch: is this good news for patients? *The Pharmaceutical Journal* 2003; **271**: 705
www.pharmj.com/pdf/news/pj_20031122_statin.pdf
[accessed 22.12.03]

(News feature)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.5e. The understanding of the **pharmacologic effects of statins** has led to the realization that the benefits of these agents extend beyond simply lowering cholesterol. These properties include beneficial effects on vessel endothelial tissue; decreased low-density lipoprotein oxidation and inflammation; ability to stabilize atherosclerotic plaques and perhaps promote regression; proliferative effects on smooth-muscle growths, possibly strengthening atherosclerotic plaques; antithrombotic effects by inhibiting platelet aggregation and stimulation of

fibrinolytic factors; and improvement of blood viscosity and flow. With these actions, statins may benefit the situation of long-term atherosclerotic plaque formation and the setting of acute coronary syndrome. *Further large-scale studies, however, are needed to determine the clinical importance and validity of these postulated beneficial effects of statins*[i].

The *evidence*

i. Sotiriou CG, Cheng JW. Beneficial effects of statins in coronary artery disease-beyond lowering cholesterol. *Annals of Pharmacotherapy* 2000; **34(12)**: 1432-1439

(Type V evidence – expert review based on a literature search of Medline only to May 2000)

Statins in older moderately hypercholesterolemic, hypertensive patients

2.5f. **Pravastatin** did not reduce either all-cause mortality or coronary heart disease significantly when compared to usual care in **older participants with well-controlled hypertension and moderately elevated LDL-C**. The relative risk for CHD events in the pravastatin versus usual care group was 0.91 (95% CI 0.79-1.04, p=0.16) with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care[i].

The authors suggested that the results may be due to a modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention[i]

i. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *Journal of the American Medical Association* 2002; **288(23)**: 2998-3007

(Type II evidence – randomised controlled trial, mean follow-up of 4.8 years, in a non blinded subset of participants from the ALLHAT trial: 10,355 ambulatory persons aged 55 years or older with LDL-C of 120-189 mg/dL (100-129 mg/dL if known CHD) and triglycerides lower than 250 mg/dL. Mean age was 66 years, 49% were women, 38% black & 23% Hispanic. 14% had a history of CHD and 35% had type 2 diabetes)

The *statements*

The *evidence*

Statins and myopathy

2.5g. The incidence of **myopathy** associated with statin therapy is dose related and is increased when statins are used in combination with agents that interact. Clinicians should be alert to the potential for drug-drug interactions to minimise the risk of myopathy during long-term statin therapy[i].

i. Ballantyne CM, Corsini A, Davidson MH *et al*. Risk for myopathy with statin therapy in high-risk patients. *Archives of Internal Medicine* 2003; **163(5)**: 553-564
(Type V evidence – expert review)

Comparative studies of statins

2.5h. In a short-term study, **atorvastatin** treatment resulted in significantly greater reductions from baseline in LDL cholesterol than **simvastatin** in both comparator groups: atorvastatin 10 mg (37.1%) versus simvastatin 20 mg (35.4%; p=0.0097), and atorvastatin 80 mg (53.4%) versus simvastatin 80 mg (46.7%, p<0.0001). All treatments were well tolerated and all groups has a significantly decreased LD cholesterol/HDL cholesterol ratio from baseline (all p<0.0001)[i].
Caveat: There were some baseline differences.

In another study **atorvastatin** 10 mg was more effective than **simvastatin** 20 mg and significantly more effective than simvastatin 10 mg for reducing LDL cholesterol levels. The mean percent change in LDL cholesterol for atorvastatin 10 mg (-37.0%) was greater than and not equivalent to simvastatin 20 mg (-33.8%). In the secondary analysis, which compared the efficacy of atorvastatin 10 mg with that of simvastatin 10 mg, the mean decrease in LDL cholesterol was significantly greater (p<.001) for atorvastatin 10 mg than for simvastatin 10 mg (-37.0% vs. –28.9%)[ii].

See also 2.7c.

i. Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R; on behalf of the CHALLENGE Study Investigators. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease. *American Journal of Cardiology* 2002; **89**: 667-671
(Type II evidence – six-week randomised controlled trial of 1732 patients with hypercholesterolemia and triglycerides ≤ 6.8 mmol/L assigned to atorvastatin 10 mg, simvastatin 20 mg, atorvastatin 80 mg or simvastatin 80 mg. Compliance was >91% for all groups)

ii. Farnier M, Portal J-J, Maigret P. Efficacy of Atorvastatin compared with simvastatin in patients with hypercholesterolemia. *Journal of Cardiovascular Pharmacology & Therapeutics* 2000; **5(1)**: 27-32
(Type II evidence – randomised controlled trial of 272 (109 receiving atorvastatin 10 mg, 109 receiving simvastatin 20mg and 54 receiving simvastatin 10 mg) hypercholesterolic (uncontrolled by dietary intervention) patients, 18-70 years of age)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.5i. More patients with primary hypercholesterolemia and coronary heart disease or multiple risk factors for coronary heart disease reached LDL-C goals with **simvastatin** treatment and required less titration than those who received **fluvastatin**.

At the end of the study 60.8% of patients in the simvastatin group (10 mg) had reached target LDL-C goals compared with 35.1% in the fluvastatin group (20 mg, p<0.001). The proportion of patients requiring titration was higher in the fluvastatin group (87.1% versus 64.1%, p=0.001). The incidence of adverse events was similar between groups[i].

Caveat: The study was funded by, and one of the authors was employed by, Merck, Sharpe and Dohme but the study was double-blind.

The *evidence*

i. van Dam MJ, Penn HJAM, den Hartog FR *et al*. for the MUST Study Group. A comparison of the efficacy and tolerability of titrate-to-goal regimens of simvastatin and fluvastatin: A randomised, double-blind study in adult patients at moderate to high risk for cardiovascular disease. *Clinical Therapeutics* 2001; **23(3)**: 467-478

(Type II evidence – 18-week randomised controlled trial of 478 patients with type IIa or IIb primary hypercholesterolemia, LDL-C levels <6 mmol/L and triglyceride levels <4.5 mmol/L. Patients were randomised to simvastatin 10 mg once daily or fluvastatin 20 mg once daily. At 6- and 12-week titration visits, the dosage in patients who had not reached LDL-C goals could be increased to simvastatin 20 mg and then 40 mg once daily, or to fluvastatin 40 mg once daily or 40 mg twice daily. An intention to treat analysis was used)

Recent single statin studies (published from 2000-2003)

Pravastatin

2.5j. Treatment with **pravastatin** over 5 years reduces all-cause mortality and coronary mortality in patients with and those without a history of coronary heart disease. The size of the benefit was related principally to the baseline risk. Active treatment was associated with a reduction in coronary mortality (24%, 95%CI 14-33%). Larger reductions in absolute risk were estimated in those with prior coronary heart disease than in those without[i].

i. Simes J, Furberg CD, Braunwald E *et al*. Effects of pravastatin on mortality in patients with and without coronary heart disease across a broad range of cholesterol levels The Prospective Pravastatin Pooling project. *European Heart Journal* 2002; **23**: 207-15

(Type I evidence - systematic review and meta-analysis, where data from 3 large randomized trials with pravastatin 40 mg daily were analysed according to a prespecified published protocol, including 19,768 patients and 106,131 person years. All analyses were on an intention-to-treat basis)

2.5k. Long-term reduction of serum cholesterol with **pravastatin** has no adverse effect on **psychological well-being**. During follow-up there was no significant treatment effect on measures of anxiety or depression, anger expression, impulsiveness, excessive alcohol consumption or adverse life events[i].
Caveat: The study population did not include young people and those at highest risk of suicide or accidental death. In addition, some subgroups were small. Although unlikely, this study does not exclude a treatment effect for all potentially at-risk treatment groups.

i. Stewart RA, Sharples KJ, North FM, Menkes DB, Baker J, Simes J; for the LIPID Study Investigators. Long-term assessment of psychological well-being in a randomized placebo-controlled trail of cholesterol reduction with pravastatin. *Archives of Internal Medicine* 2000; **160(20)**: 3144-3152

(Type II evidence - randomised controlled trial of 1,130 participants with stable coronary artery disease in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study. Of those that returned the baseline questionnaire (93%), 90% completed the six-month and one year questionnaires and 88% completed the two-year questionnaire. An intention-to-treat analysis was carried out)

The *statements*

The *evidence*

Atorvastatin

2.5l. Formal publication is awaited of the REVERSAL trial, the results of which suggested that **intensive lipid lowering** with 80mg/d atorvastatin halted the progression of atherosclerosis whereas the moderate lipid-lowering regime of 40mg/d pravastatin was associated with continued artherosclerosis progression[i].

i. Anon. REVERSAL : Atorvastatin 80 mg halts atheroma progression, pravastatin 40 mg does not. **http://www.clevelandclinic.org/heartcenter/pub/news/archive/2003/reversal11_13.asp** [accessed 20.01.04]
(Web-based report from the American Heart Association Scientific Session, 13 November 2004)

2.5m. A trial is underway to assess both morphological and functional cardiovascular effects of **atorvastatin**[i].

i. Hagenaars T, Gussenhoven EJ, Poldermans D, van Urk H, van der Lugt A. Rational and design for the SARIS trial: Effect of statin on atherosclerosis and vascular remodelling assessed with intravascular sonography. *Cardiovascular Drugs and Therapy* 2001; **15**: 339-343
(Ongoing randomised controlled trial)

Simvastatin

2.5n. Adding **simvastatin** to existing treatments safely produces substantial additional benefits for a wide range of high-risk patients, irrespective of their initial cholesterol concentrations. The reduction for any major vascular event after five years was 24% (95% CI 19-28%, p<0.0001) and the reduction was highly significant from year two onwards[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 vitamin E as well as statin use (see statement 2.15b)

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 simvastatin (40 mg/d; average compliance 85%) or matching placebo (average non-study statin use: 17%). Previous myocardial infarction was reported by 41% of those randomised. Follow-up was 96% and an intention to treat analysis was used)

Ezetimibe

2.5o. Based on the data currently available, it appears that **ezetimibe** has a potential role in the treatment of primary hypercholesterolemia; however further data are needed to determine its long-term tolerability and efficacy. The potential roles for ezetimibe include its concurrent use with a statin to further enhance the lowering of LDL-C. Other possible roles for ezetimibe include its concurrent use with a statin to permit a lowering of statin dosage to avoid statin-related complications or its use as monotherapy to treat hypercholesterolemia when statin use cannot be tolerated or is contraindicated. Outcome data demonstrating that cardiovascular morbidity and/or mortality are reduced by ezetimibe therapy have yet to be generated[i].

i. Mauro VF, Tuckerman CE. Ezetimibe for management of hypercholesterolemia. *Annals of Pharmacotherapy* 2003; **37(6)**: 839-848
(Type I evidence – systematic review, Medline only to 2002)

2 HIGH-RISK AND CHD-DIAGNOSED

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Statins and fracture rate

2.5p. The results of a large observational study, and the secondary analysis of a randomised controlled trial, suggest that the use of **statins** at dosages prescribed in clinical practice is **not** associated with a reduction in the risk of **fracture**[i,ii]. It is suggested that the lower hip fracture rates previously reported among statin users may be explained by the residual confounding effect of obesity[i].

i. van Staa T-P, Wegman S, de Fries F, Leufkens B, Cooper C. Use of statins and risk of fractures. *Journal of the American Medical Association* 2001; **285(14)**: 1850-1855

(Type IV evidence – case-control study of data from the UK General Practice Research Database. Cases were 81,880 fracture patients, aged 50 or older, paired with 81,880 age-, sex- and practice-matched controls)

2.6 Dietary and lifestyle interventions for cholesterol reduction

2.6a. A systematic review of 27 randomised controlled trials to reduce or **modify dietary fat or cholesterol** suggest a small but potentially important reduction in cardiovascular risk in trials longer than two years. There was no significant effect on total mortality (rate ratio 0.98, 95% CI 0.86-1.12), a trend towards protection from cardiovascular mortality (0.91, 0.77-1.07) and significant protection from cardiovascular events (0.84, 0.72-0.99). Trials where participants were involved for more than two-years showed significant reductions in the rate of cardiovascular events and a suggestion of protection from total mortality. The degree of protection from cardiovascular events appeared similar in high and low risk groups, but was statistically significant only in the former. Lifestyle advice to all those at high risk of cardiovascular disease (especially where statins are unavailable or rationed), and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and partial replacements by unsaturates[i].

i. Hooper L, Summerbell CD, Higgins JPT *et al*. Reduced or modified dietary fat for preventing cardiovascular disease (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 30 May 2001)

http://www.update-software.com/abstracts/ab002137.htm [accessed 22.12.03]

(Type I evidence – systematic review and meta-analysis, literature search to 1998 plus other trials known to experts in the field through to May 1999, of 27 randomised controlled trials comprising 40 distinct intervention arms including participants > 18 years at low, moderate and high risk of cardiovascular disease)

The *statements*

The *evidence*

2.6b. Participants receiving advice from **dietitians** experienced a greater reduction in blood cholesterol than those receiving advice only from **doctors** (-0.25 mmol/L (95% CI -0.37 to -0.12 mmol/L))[i].

There was no statistically significant difference in change in blood cholesterol between dietitians and **self-help resources** (-0.10 mmol/L (95% CI -0.22 to 0.03 mmol/L)). There was no evidence that dietitians provided better outcomes than nurses[i].

Caveat: The results should be interpreted with caution as the studies were not of good quality and the analysis was based on a limited number of trials. *More evidence is required to assess whether change can be maintained in the longer term.*

i. Thompson RL, Summerbell CD, Hooper L *et al.* Dietary advice given by a dietitian versus other health professional or self-help resources to reduce blood cholesterol (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 30 October 2000)
http://www.update-software.com/abstracts/ab001366.htm [accessed 22.12.03]

(Type I evidence – systematic review of 11 randomised controlled trials comprising 12 comparisons of participants > 18 years with/without existing cardiovascular disease or previous MI. Literature search to 1998, Medline & Cochrane Library to early 1999)

2.6c. The **DASH diet** is likely to reduce coronary heart disease risk. Relative to the control diet, the DASH diet resulted in lower total (-0.35 mmol/L), LDL (-0.28 mmol/L) and HDL (-0.09 mmol/L) cholesterol concentrations (all $p<0.0001$) without significant effects on triacylglycerol. The fruit and vegetable diet produced few significant lipid changes. *The possible opposing effect on coronary heart disease risk of HDL cholesterol reduction needs further study*[i].

i. Obarzanek E, Sacks FM, Vollmer WM *et al*. on behalf of the DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Clinical Nutrition* 2001; **74(1)**: 80-89

(Type II evidence – 8 week randomized controlled trial of 436 participants of the DASH trial – mean age 44.6 years, 60% African American, baseline total cholesterol ≤ 6.7 mmol/L (≤ 260 mg/dL). A diet increased in fruit, vegetables, and low-fat dairy products and reduced in saturated fat, total fat, and cholesterol during which time subjects remained weight stable (the DASH diet) was compared with a control diet and a diet increased in fruit and vegetables)

2.6d. **Orlistat** as an adjunct to dietary intervention promotes weight loss and reduces LDL-C beyond the effect of weight loss in overweight or obese patients with concomitant hypercholesterolemia. Orlistat-treated patients lost significantly more weight than placebo recipients (–6.8% versus –3.8%, $p<0.001$). Moreover, more patients in the orlistat group achieved clinically meaningful weight loss of ≥ 5% (64% vs 39%) or ≥ 10% (23% vs 13%) at week 24[i].

i. Muls E, Kolanowski J, Scheen A, Van Gaal L; for the ObelHyx Study Group. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomised, double-blind, placebo-controlled, multicentre study. *International Journal of Obesity* 2001; **25(11)**: 1713-1721

(Type II evidence – 24-week randomised controlled trial of 294 obese hypercholesterolemic patients submitted to a hypocaloric diet and randomly assigned to either orlistat 120 mg or placebo three times daily)

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2.6e. **Fish consumption** is **not** associated with reduced coronary heart disease mortality in **low-risk** populations[i].

However, fish consumption at 40-60 g daily **is** associated with markedly reduced coronary heart disease mortality in **high-risk** populations. The underlying biochemical mechanism is not known and causal inference is premature[i].

The *evidence*

i. Marckmann P, Gronbaek M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *European Journal of Clinical Nutrition* 1999; **53(8)**: 585-90

(Type I evidence – systematic review of 11 prospective cohort studies based on individual records of fish or n-3 polyunsaturated fatty acid consumption and coronary heart disease death. Literature search to January 1998)

2.7 Cost-effectiveness of cholesterol lowering therapies

Cost-effectiveness of statin therapy

2.7a. Two reviews concluded that the **cost effectiveness** of cholesterol lowering in general practice **deteriorates** when all relevant costs are taken into account and when efficacy is corrected for community effectiveness[i] and that statins should only be used in primary prevention of myocardial infarction in high risk patients after using other more cost-effective interventions, including aspirin, smoking cessation, dietary change and exercise, and antihypertensive therapy[ii].

NB Simvastatin is already off patent and pravastatin will be off patent later in 2004, leading to large reductions in cost.

i. Van der Weijden T, Knottnerus JA, Ament AJH, Stoffers HEJ, Grol RPT. Economic evaluation of cholesterol-related interventions in general practice. An appraisal of the evidence. *Journal of Epidemiology and Community Health* 1998;**52(9)**:586-94

(Type IV evidence – systematic review and economic evaluation, literature search date unclear, of 39 analyses (4 cost-utility and 35 cost-effectiveness) with an evaluation timespan ranging from four months to lifetime intervention)

ii. NHS Centre for Reviews and Dissemination. Cholesterol Replacement and Coronary Heart Disease: Screening and Treatment. *Effective Health Care* **4(1)**. University of York: NHS Centre for Reviews and Dissemination, 1998 **http://www.york.ac.uk/inst/crd/ehcb.htm**

[accessed 22.12.03]

(Type IV evidence - systematic literature review of cost-effectiveness studies based on randomised controlled trial data)

2.7b. When the risk levels of patients were considered **statin treatment** for secondary prevention, and for primary prevention at a CHD event risk of 3.0% per year, was as **cost effective** as many treatments in wide use. Primary prevention at lower CHD event risks (<3.0% per year) was less cost effective and unlikely to be affordable at current prices and levels of health service funding. The costs per life year gained according to annual CHD event risk were: for a risk level of 4.5%, £5,100; 3.0%, £8,200; 2.0%, £10,700;and 1.5%, £12,500. As the cost of statins falls, primary prevention at lower risk levels becomes more cost effective. However, the large volume of treatment needed will remain a major problem[i].

i. Pickin DM, McCabe CJ, Ramsay LE *et al*. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. *Heart* 2000; **82(3)**: 325-32

(Type IV evidence – a cost-effectiveness analysis, cohort life table method of data using outcome trials, to estimate the cost effectiveness of statin treatment in preventing coronary heart disease (CHD) and to examine the effect of the CHD risk level targeted and the cost of statins on the cost effectiveness of treatment)

The *statements*

The *evidence*

2.7c. Across Europe there was a significant reduction in the cost of maintaining patients at their appropriate LDL-C levels with **simvastatin** versus **atorvastatin**. In this study, there was no significant difference between groups in the percentage of patients reaching their LDL-C goal over the study period (80% for simvastatin-treated patients vs 89% for atorvastatin-treated patients, P = 0.135). However, the cost of maintaining a similar percentage of patients at their appropriate LDL-C levels was significantly lower in the simvastatin group compared with the atorvastatin group in 13 of the 17 countries assessed. In the remaining 4 countries, there was a cost advantage for simvastatin, but it did not reach statistical significance[i].

See also 2.5h.

i. Attanasio E, Russo P, Allen SE. Cost-minimization analysis of simvastatin versus atorvastatin for maintenance therapy in patients with coronary or peripheral vascular disease. *Clinical Therapeutics* 2001; **23(2)**: 276-283

(Type IV evidence – cost-effectiveness analysis of the maintenance costs of treatment with simvastatin versus that of treatment atorvastatin in a European context)

2.8 Guidelines for hyperlipidaemia screening and management

2.8a. **Guidelines** for the **screening and management of hyperlipidaemia** are available[i,ii,iii].

i. Scottish Intercollegiate Guidelines Network (SIGN). *Lipids and the primary prevention of coronary heart disease*. Edinburgh: Scottish Intercollegiate Guidelines Network, 1999

http://www.show.scot.nhs.uk/sign/pdf/sign40.pdf

[accessed 22.12.03]

(Evidence based guidelines; Literature search to 1997)

ii. Fodor JG, Frohlich JJ, Genest JG, McPherson PR, for the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the Management and treatment of dyslipidemia. *Canadian Medical Association Journal* 2000; 162(10): 1441-7

(Evidence based guidelines; No details provided of methods for literature searching or selection of papers)

iii. American Association of Clinical Endocrinologists. The American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of dyslipidemia and prevention of atherogenesis. *Endocrine Practice* 2000; **6(2)**: 164-213

(Evidence based guidelines; No details provided of methods for literature searching or selection of papers)

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2.8b. Guidelines and algorithms are available on **lipid screening** and management in adults [i,ii].
Caveat: The search strategies and selection criteria for including studies are not stated.

The *evidence*

i. Institute of Clinical Systems Improvement. *Lipid Screening in Adults*. Bloomington:Institute of Clinical Systems Improvement, December 2002
http://www.icsi.org/index.asp [accessed 22.12.03]
(Type V evidence – expert guidelines)

ii. Institute of Clinical Systems Improvement. *Lipid Management in Adults*. Minnesota:Institute of Clinical Systems Improvement, July 2002
http://www.icsi.org/index.asp [accessed 22.12.03]
(Type V evidence – expert guidelines)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001
For each patient on the chronic disease management system, the following are the aims, which need to be updated over time in light of the research: [key action 9]

- Avoiding B.P. consistently more than 140/85 (in diabetes <130/80)

What is the evidence concerning interventions to lower blood pressure?

The *statements*

2.9 Hypertension

2.9a. Intensive lowering of blood pressure in patients with **hypertension** was associated with a low rate of cardiovascular events. Additional therapy with **aspirin** significantly reduced major cardiovascular events with the greatest benefit seen in all myocardial infarction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg; the lowest risk of cardiovascular mortality occurred at 86.5 mm Hg. Further reduction below these blood pressures was safe[i].

In patients with **diabetes mellitus** the addition of aspirin reduced major cardiovascular events by 15% (p=0.03) and all myocardial infarction by 36% (p=0.002), with no effect on stroke. There were seven fatal bleeds in the aspirin group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two groups, respectively (p<0.001)[i].

The *evidence*

i. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; **351(9118)**: 1755-62
(Type II evidence – randomised controlled trial of 18,790 patients, from 26 countries, aged 50-80 years (mean 61.5 years) with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg (mean 105 mm Hg. Patients were randomised to the calcium antagonist felodipine (5mg/day) and additional hypertensive therapy as required, and 75 mg/day aspirin or placebo. Average time of follow-up, 3.8 years)

The *statements*

The *evidence*

2.9b. **Pharmacologic hypertension treatment** lowers the relative and absolute risk of cardiovascular morbidity and mortality in older women. In women aged 55 years or older (90% white), hypertension treatment results in a 38% risk reduction in fatal and nonfatal cerebrovascular events (95% confidence interval (CI) 27-47%, 5 year NNT 78), a 25% reduction in fatal and nonfatal cardiovascular events (95% CI 17-33%, 5 year NNT 58), and a 17% reduction in cardiovascular mortality (95% CI 3-29%, 5 year NNT 282). In women aged 30 to 54 years (79% white), hypertension treatment results in a 41% risk reduction in fatal and nonfatal cerebrovascular events (95% CI 8-63%, 5 year NNT 264), and a 27% risk reduction in fatal and nonfatal cardiovascular events (95% CI 4-44%, 5 year NNT 259)[i].

Decisions for treatment of hypertension in younger white women should be influenced by the individual patient's absolute risk of cardiovascular disease[i].

i. Quan A, Kerlikowske D, Gueyffier F, Boissel JP, INDANA investigators.
Pharmacotherapy for hypertension in women of different races (Cochrane Review). In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 3 December 1999)
http://www.update-software.com/abstracts/ab002146.htm [accessed 22.12.03]

(Type I evidence - systematic review of 11 randomised controlled trials of 23,000 women (30-98 years of age, white or African American) with essential hypertension. The following literature sources were searched for published, English-language papers: MEDLINE (1966-1998), reference lists from review articles & consultation with experts)

Also published as: Quan A, Kerlikowske D, Gueyffier F, Boissel JP, INDANA investigators. Efficacy of treating hypertension in women. *Journal of General Internal Medicine* 1999; **14**: 718-729

2.9c. **Combination low dose drug treatment** increases efficacy and reduces adverse effects. From the average blood pressure in people who have strokes (150/90 mm Hg) three drugs at half standard dose are estimated to lower blood pressure by 20 mm Hg systolic and 11 mm Hg diastolic and thereby reduce the risk of stroke by 63% and ischaemic heart disease events by 46% at age 60-69[i].

i. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *British Medical Journal* 2003; **326**: 1427-1434
http://bmj.bmjjournals.com/cgi/reprint/326/7404/1427
[accessed 22.12.03]

(Type I evidence – systematic review, literature search to 2000 (and to 2001 for angiotensin II receptor antagonists), of 354 randomised double-blind placebo controlled trials 50 of which (119 comparisons) tested the effects of drugs of two different categories separately or in combination)

2.9d. **Tight control of blood pressure** in hypertensive patients with **type 2 diabetes** substantially reduced the cost of complications, increased the interval without complications and survival, and had a cost effectiveness ratio that compared favourably with many accepted healthcare programmes. Based on use of resources in standard clinical practice, incremental cost per extra year free from end points amounted to £1,049 (costs and effects discounted at 6% per year) and £434 (costs discounted at 6% per year and effects not discounted). The incremental cost per life year gained was £720 (costs and effects discounted at 6% per year) and £291 (costs discounted at 6% per year and effects not discounted)[i].

i. UK Prospective Diabetes Study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *British Medical Journal* 1998; **317(7160)**: 720-726
http://bmj.bmjjournals.com/cgi/content/full/317/7160/720 [accessed 22.12.03]

(Type IV evidence – cost-effectiveness analysis incorporating within trial analysis and estimation of impact on life expectancy through use of the within trial hazards of reaching a defined clinical end point. Use of resources driven by trial protocol and use of resources in standard clinical practice were both considered)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

The *evidence*

2.9e. A **registry** of major ongoing or planned randomised trials (with more than 1000 patient-years of follow-up for each randomised group) of blood-pressure-lowering agents has been established[i].

i. World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomised trials of blood-pressure-lowering treatments. *Journal of Hypertension* 1998; **16(2)**: 127-37

2.9f. Among patients with non-malignant hypertension enrolled in randomised trials, treated patients did not have a lower risk of **renal dysfunction**. Overall, treated patients had lower blood pressure and fewer cardiovascular events. Patients randomised to antihypertensive therapy (or more intensive therapy) did not have a significant reduction in their risk of developing renal dysfunction (relative risk = 0.97; 95% CI 0.78-1.21; P = 0.77)[i].

A Cochrane review is in progress to assess the effect of antihypertensive treatment for protecting **kidney function** in hypertensive adults[ii].

i. Hsu CY. Does treatment of non-malignant hypertension reduce the incidence of renal dysfunction? A meta-analysis of 10 randomised, controlled trials. *Journal of Human Hypertension* 2001; **15(2)**: 99-106

(Type I evidence – systematic review and meta-analysis of 10 randomised controlled trials involving 26,521 individuals and 114,000 person-years. Literature search to 1998. All excluded subjects with advanced baseline renal disease. Definition of renal dysfunction outcome varied among trials but within each trial was applied similarly to both treatment and control groups. Drug treatment consisted mostly of diuretics and adrenergic blockers)

ii. Laville M, Gueyffier F. Antihypertensive treatment for protecting kidney function in hypertensive adults. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Systematic review and meta-analysis of major clinical trials, in progress)

2.9g. A review of the use of **complementary medicine** in the treatment of hypertension is available[i].

i. Lewith G. Hypertension. *The CompMed Bulletin* 2000; **2(7)**:1-2

(Type V evidence – expert opinion based on a review of systematic reviews and randomised controlled trials)

The *statements*

The *evidence*

Diuretics for hypertension treatment

2.9h. **Thiazide-type diuretics** are superior in preventing one or more major forms of cardiovascular disease and are less expensive than calcium channel blockers or ACE-inhibitors[i]. They should be preferred for first-step antihypertensive therapy[i,ii].

In ALLHAT, the primary outcome (combined fatal CHD or non-fatal myocardial infarction) and all-cause mortality did not differ between groups. Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, P =.03) and lisinopril (2 mm Hg, P<.001) groups compared with chlorthalidone, and 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, P<.001). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI 1.02-1.30); and HF (8.7% vs 7.7%; RR, 1.19; 95% CI 1.07-1.31)[i].

i. The ALLHAT Officers and coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of the American Medical Association* 2002; **288(23)**: 2981-2997

(Type II evidence – randomised controlled trial of 33,357 participants aged 55 years or older with hypertension and at least one other coronary heart disease risk factor. Participants were randomly assigned to receive chlorthalidone, 12.5-25 mg/d (n=15,225) amlodipine, 2.5-10 mg/d (n=9048) or lisinopril, 10-40 mg/d (n=9054). Mean follow-up 4.9 years)

ii. Wright JM, Lee C-H, Chambers CK. Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug? *Canadian Medical Association Journal* 1999; **161(1)**: 25-32

(Type I evidence – systematic review, literature search to 1997, of 50,853 hypertensive (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 90 mm Hg) patients > 21 years old in 23 randomised controlled trials.

Reviewed in:
Review: Low-dose thiazides are the most effective first-line drugs for hypertension. *ACP Journal Club* 2000;**132**: 1)

2.9i. Cochrane reviews are underway to look at the blood pressure lowering efficacy of **thiazide** diuretics[i] and a **comparison of pharmacological interventions**[ii] for hypertension. The thiazide review will determine the blood pressure lowering efficacy and adverse effects of each of the thiazide diuretics[i].

i. Musini VM, Wright JM, Bassett KL, Jauca CD. Blood pressure lowering efficacy of thiazide diuretics for primary hypertension. 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)

ii. Wright JM, Musini VM, Lee CH, Chambers GK. Comparison of pharmacological interventions for hypertension. 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*

Beta-blockers for hypertension treatment *See also statement 2.9r*

2.9j. The **INternational VErapamil SR/trandolapril STudy (INVEST)** study to examine therapies for patients with coexisting hypertension and coronary artery disease is currently underway. Treatment strategies include verapamil SR and atenolol with and without trandolapril and/or hydrochlororthiazide. Final follow-up visits took place in December 2002[i].

i. Erdine S, Handberg EM, Kolb B.Characteristics of patients with coronary artery disease and hypertension: A report from INVEST. *Clinical Cardiology* 2001;**24(11 SUPPL)**:V6-V8)

(Ongoing multicentre randomised controlled trial including 22,599 patients with coexisting hypertension and coronary artery disease from around the world. This trial had not yet been published in September 2003)

2.9k. For patients with **hypertension** and **left ventricular hypertrophy, losartan** (an angiotensin II receptor antagonist) prevents more cardiovascular morbidity and death than **atenolol** (a beta-blocker) for a similar reduction in blood pressure and is better tolerated. Blood pressure fell by 30.2/16.6 (SD 18.5/10.1) and 29.1/16.8 mm Hg (19.2/10.1) in the losartan and atenolol groups respectively. The primary composite endpoint (cardiovascular mortality, stroke and myocardial infarction) for losartan was 23.8 per 1,000 patient years and 27.9 per 1,000 patients years for atenolol (relative risk 0.87, 95% CI 0.77-0.98, p=0.021). The discontinuation in losartan versus atenolol groups for all adverse events was significantly less common (p<0.0001). New onset diabetes was less frequent with losartan[i].

For the subset of patients with **isolated systolic hypertension** and left ventricular hypertrophy the data also suggested that losartan is superior to atenolol for treatment. The primary composite endpoint (see above) was reduced by 25% with losartan compared with atenolol (relative risk, 0.75 95% CI 0.56-1.01)[ii].

See Chapter 4, statement 4.6l

A Cochrane review is underway to quantify the effects of **beta adrenergic blocking agents** on morbidity and mortality in adults with hypertension[iii].

i. Dahlöf B, Devereux RB, Kjeldsen SE *et al*; for the LIFE study group. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995-1003

(Type II evidence – double-blind, randomised, parallel-group trial in 9,193 participants aged 55-80 years with essential hypertension and left ventricular hypertrophy to compare losartan- with atenolol-based antihypertensive treatment with at least four year follow-up. An intention to treat analysis was used)

ii. Kjeldson SE, Dahlöf B, Devereux RB *et al*; for the LIFE study group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. *Journal of the American Medical Association* 2002; **288**: 1491-1498

(Type II evidence – analysis of 1,326 men and women from the above trial with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy)

iii. Volmink J, Bradley H, Maroney R, Mbewu A, Opie L. Betablockers for hypertension. 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*

Vasodilators for hypertension treatment

■ ACE inhibitors ■ Calcium antagonists/Calcium channel blockers ■ Angiotensin II receptor antagonists

2.9l. Strong evidence of benefits of **ACE inhibitors** in the reduction of high blood pressure is provided by overviews of placebo-controlled trials[i,ii].

Placebo-controlled trials of ACE inhibitors revealed reductions in stroke (30%, 95% CI 15-43%), CHD (20%, 95% CI 11-28%) and major cardiovascular events (21%, 95% CI 14-27%) in one review[i] and the risk of the major clinical outcomes (death, myocardial infarction, stroke, hospital admission for congestive heart failure, or revascularisation) by 22% (p<0.0001) in a more recent review[ii].

In a recent trial among patients with stable coronary heart disease without apparent heart failure, **perindopril** can significantly improve outcome. 603 (10%) placebo and 488 (8%) perindopril patients experienced the primary endpoint, which yields a 20% relative risk reduction (95% CI 9-29, p=0.0003) with perindopril. These benefits were consistent in all predefined subgroups and secondary endpoints. Perindopril was well tolerated[iii]

i. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet 2000*; **355(9246)**: 1955-64

(Type I evidence – systematic review, literature search date unknown, of 15 randomised controlled trials of 74,696 patients (4 placebo-controlled trials of ACE inhibitors of 12,124 patients mostly with CHD;2 placebo-controlled trials of calcium antagonists of 5,520 patients mostly with hypertension; 3 trials comparing blood-pressure-lowering strategies of different intensity of 20,408 hypertensive patients; 8 trials comparing different antihypertensive regimens of 37,872 patients with hypertension)

ii. 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)

iii. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362**: 782-788

(Type II evidence – randomised, double-blind, controlled trial of 12,236 patients in patients with proven stable coronary heart disease but with no evidence of heart failure. 12,218 patients were randomly assigned perindopril 8 mg once daily or matching placebo. The mean follow-up was 4.2 years and the mean age of patients was 60 years (SD 9). The primary endpoint was cardiovascular death, myocardial infarction, or cardiac arrest)

2.9m. 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].

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)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.9n. There is conflicting evidence concerning the benefits of **calcium antagonists**[i,ii].

The Blood Pressure Lowering Trialists' review found that placebo-controlled trials of calcium antagonists showed reduction in stroke (39%, 95% CI 15-56) and major cardiovascular events (28%, 95% CI 13-41)[i].

In contrast, another review found that calcium antagonists were inferior to other types of antihypertensive drugs as first-line agents in reducing the risks of several major complications of hypertension. Calcium antagonists and other drugs achieved similar control of both systolic and diastolic blood pressure. Compared with patients assigned diuretics, beta-blockers, angiotensin-converting-enzyme inhibitors, or clonidine (n=15,044), those assigned calcium antagonists (n=12,699) had a significantly higher risk of acute myocardial infarction (odds ratio, OR 1.26 [95% CI 1.11-1.43], p=0.0003), congestive heart failure (p=0.005), and major cardiovascular events (p=0.018). The treatment differences were within the play of chance for the outcomes of stroke (0.90 [0.80-1.02], p=0.10) and all-cause mortality (1.03 [0.94-1.13], p=0.54)[ii].

Caveats: The meta-analysis had limited power to precisely assess stroke and cardiac outcomes because few large, long-term trials exist that directly compare the effects of different antihypertensive agents. The trials were also heterogeneous and had other limitations.

Both sets of authors concluded that the situation will become clearer as the results from more large trials that directly compare antihypertensive agents become available[i,ii].

The *evidence*

i. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; **355(9246)**: 1955-64

(Type I evidence – systematic review, literature search date unknown, of 15 randomised controlled trials of 74,696 patients (4 placebo-controlled trials of ACE inhibitors of 12,124 patients mostly with CHD; 2 placebo-controlled trials of calcium antagonists of 5,520 patients mostly with hypertension; 3 trials comparing blood-pressure-lowering strategies of different intensity of 20,408 hypertensive patients; 8 trials comparing different antihypertensive regimens of 37,872 patients with hypertension)

ii. Pahor M, Psaty BM, Alderman MH *et al*. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356(9246)**: 1949-54

(Type I evidence – systematic review and meta-analysis of 9 randomised controlled trials including 27,743 participants with approximately 120,000 person-years of follow-up. Literature search to 2000.

Reviewed in –

iii. Review: Calcium antagonists lead to a higher risk for MI, congestive heart failure and major cardiovascular events. *ACP Journal Club* 2001; **135(1)**: 7)

The *statements*

The *evidence*

2.9o. A trial is underway to compare the effects of the angiotensin II receptor antagonist **valsartan** with the calcium-antagonist **amlodipine** on the reduction of cardiac morbidity and mortality in high risk patients with essential hypertension[i].

ii. Kjeldsen SE, Juliau S, Brunner H *et al*; for the VALUE Trial Group. Characteristics of 15,134 hypertensive patients at high coronary risk. The VALUE trial. *Blood Pressure* 2001 ; **10(2)** : 83-91

(Ongoing randomised controlled trial of 15,314 patients aged 50 years or more and at particularly high risk for cardiac events)

Drug therapy for hypertension in older patients

2.9p. Drug treatment is justified in **older patients** with isolated systolic hypertension whose systolic blood pressure is 160 mm Hg or higher. Total mortality was reduced by 13% (95% CI 2-22%, p=0.02), cardiovascular mortality by 18%, (95% CI 4-29%, p=0.01,), all cardiovascular complications by 26% (95% CI 17-34%, p<0.0001), stroke by 30% (95% CI 18-41%, p<0.0001) and coronary events by 23% (95% CI 10-34%, p=0.001). Absolute benefit is larger in men, in patients aged 70 or more and in those with previous cardiovascular complications or wider pulse pressure. Treatment prevented stroke more effectively than coronary events. However the absence of a relation between coronary events and systolic blood pressure in untreated patients suggests that the coronary protection may have been underestimated[i].

i. Staessen JA, Gasowski J, Wang JG *et al*. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; **355(9207)**: 865-872

(Type II evidence – overview and meta-analysis of 15,693 patients (> 60 years old) in 8 randomised controlled trials followed up for 3.8 years (median). No evidence of a systematic search strategy. Trials looked at the effects of thiazide, calcium channel blocker, beta-blockers, plus other first line and add-on therapies)

2.9q. Meta-analysis of data suggested that **antihypertensive pharmacologic** treatment prevented 34% (95%CI 8-52%) of fatal and non-fatal strokes as a primary outcome in **very old people**. Rates of major cardiovascular events and heart failure were significantly decreased, by 22% and 39%, respectively. However, there was no treatment benefit for cardiovascular death, and a non-significant 6% (-5 to18%) relative excess of death from all causes. The inconclusive findings for mortality contrast with the benefit for non-fatal events. *Results of a large-scale specific trial are needed for definite conclusion that antihypertensive treatment is beneficial in very elderly hypertensive patients.* Meanwhile, an age threshold beyond which hypertension should not be treated cannot be justified[i].

i. Gueyffier F, Bulpitt C, Boissel J-P *et al*. for the Indiana Group. Antihypertensive drugs in very old people: A subgroup meta-analysis of randomised controlled trials. *Lancet* 1999;**353(9155)**:793-6.

(Type I evidence – systematic review and meta-analysis of 1,670 hypertensive patients (80-99 years) in 7 randomised controlled trials. Subgroup data was collected through direct contact with study investigators, the use of a literature review and the results of a systematic review by Mulrow and colleagues for the Cochrane Collaboration)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.9r. There is conflicting evidence for the use of **beta-blockers** in elderly patients with hypertension[i,ii].

One set of reviewers concluded that, in contrast to **diuretics**, which remain the standard first-line therapy, **beta-blockers**, until proven otherwise, should no longer be considered appropriate first-line therapy of uncomplicated hypertension in the **elderly** hypertensive patient[i].

Diuretic treatment reduced the odds for cerebrovascular events by 39% (OR, 0.61; 95%CI 0.51-0.72) and beta-blockers reduced the odds by 26% (OR, 0.75; 95% CI 0.57-0.98). The odds for CHD were reduced by 26% with diuretic treatment (OR, 0.74; 95% CI 0.64-0.85) while they were not reduced with beta-blockers (OR, 1.01; 95% CI 0.80-1.29). Diuretic treatment reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI 0.64-0.87) while beta-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI 0.78-1.23). Similarly, all-cause mortality was reduced only by diuretic treatment (OR, 0.86; 95% CI 0.77-0.96) and not by beta-blockers (OR, 1.05; 95% CI 0.88-1.25)[i].

An older review concluded that the benefits of treatment with **low dose diuretics** or **beta-blockers** are clear for persons in their **60s to 70s** with either diastolic or systolic hypertension. Differential treatment effects based on patient risk factors, pre-existing cardiovascular disease and competing co-morbidities could not be established from the published trial data[ii].

The *evidence*

i. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *Journal of the American Medical Association* 1998; **279**: 1903-1907

(Type I evidence - systematic review of 10 randomised controlled trials, literature review to 1998, of 16,164 elderly (60-79 years of age) hypertensive participants followed up for an average of approximately 5 years.

Reviewed in: Review: Diuretics are more efficacious than beta-blockers as first-line therapy for elderly patients with hypertension. *ACP Journal Club* 1998; **129**: 60)

ii. Mulrow C, Lau J, Cornell J, Brand M. Pharmacotherapy of hypertension in the elderly (Cochrane Review) In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 1 December 1997) **http://www.update-software.com/abstracts/ab000028.htm** [accessed 22.12.03]

(Type I evidence – systematic review of 15 randomised controlled trials including 21,908 elderly (60-97 years of age) hypertensive participants. The following literature sources were searched for English-language trials: MEDLINE (1966-1993 & updated 1994-1997), The Cochrane Library, two Japanese databases, WHO-ISH Collaboration register, Current Contents (Clinical Medicine). Bibliographic citations were reviewed and experts contacted)

2.9s. Antihypertensive treatment in **elderly** patients with **candesartan cilexetil** is well tolerated with a good safety profile and avoids the metabolic adverse effects of diuretic therapy[i].

No statistically significant difference in effect was found between the two treatments: At week 24, the adjusted mean changes in sitting diastolic blood pressure (24 hours post dose) were –12.0 mmg Hg (95% CI –10.4 to –13.6) in the candesartan cilexetil group and –11.4 mm Hg (-9.3 to –13.6) in the hydrocholorothiazide group. The profile of adverse effects was similar although hypokalaemia and hyperuricaemia were not found in patients treated with candesartan cilexetil but occurred in 8.1% and 6.5% respectively of patients treated with hydrochlorothiazide[i].

i. Neldam S, Forsén B; for the Multicentre Study Group. Antihypertensive treatment in elderly patients aged 75 years or over. *Drugs & Aging* 2001; **18(3)**: 225-232

(Type II evidence – 24-week double-blind randomised controlled trial of 185 patients ≥ 75 years with mean sitting diastolic blood pressure of 95 to 114 mm Hg assigned to candesartan cilexetil 8 mg/day or the diuretic hydrochlorothiazide (HCTZ) 12.5 mg/day. In both treatment groups the dosage could be doubled, according to blood pressure response, and subsequently reduced if poorly tolerated)

2.10 Dietary interventions for the management of hypertension

2.10a. **Sodium intake** is a determinant of population blood pressure: sensitivity to salt increases with age and higher initial blood pressure[i-iv]. A reduction of sodium intake of 100mmol/day is associated with a significant decrease in systolic blood pressure of 3.7mmHg (95% CI 2.35-5.05; p<0.001), but not diastolic blood pressure, 0.9mmHg (95% CI: -0.13 to 1.85; p=0.09)[iv]. This reduction is estimated to reduce the incidence of stroke by 39% and that of ischaemic heart disease by 30%[iii].

Caveat: The evidence for dietary sodium restriction in the younger normotensive population is not conclusive[iii,iv], and the validity of the meta-analysis is affected by publication bias and significant heterogeneity among trials in the effect of dietary sodium restriction on blood pressure.

i. Intersalt Co-operative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hours urinary sodium and potassium excretion. *British Medical Journal* 1988; **297**: 319-28

(Type IV evidence - cross-sectional study of 10,079 men and women aged 20-59 from 52 centres from 32 countries around the world)

ii. Elliott P, Stamler R, Nichols R *et al;* for the Intersalt Co-operative Research Group. Intersalt revisited: further analysis of 24 hour sodium excretion and blood pressure within and across populations. *British Medical Journal* 1996; **312**: 1249-53 **http://bmj.bmjjournals.com/cgi/content/full/312/7041/1249** [accessed 22.12.03]

(Type IV evidence - reanalysis of data from Intersalt)

iii. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I-Analysis of observational data among populations, II-Analysis of observational data within populations, III- Analysis of data from trials of salt reduction. *British Medical Journal* 1991; **302**: 811-24

(Type IV evidence - analysis of data from studies recording blood pressure and sodium intake in geographically defined populations: I - 47,000 subjects aged between 15 to 69 years from 24 communities, II - 14 population studies, III - 68 crossover trials and 10 randomised controlled trials of dietary salt reduction)

iv. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure. A meta-analysis of randomised controlled trials. *Journal of the American Medical Association* 1996; **275**: 1590-97.

(Type I evidence - systematic review and meta-analysis of 1,131 hypertensive subjects in 28 randomised controlled trials and 2,374 normotensive subjects in 28 randomised controlled trials)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.10b. The reduction of **sodium** levels to below the current recommendation of 100 mmol per day and the Dietary Approaches to Stop Hypertension (DASH) diet both lower blood pressure substantially, with greater effects in combination than singly. Reducing the sodium intake from the high to the intermediate level reduced the systolic blood pressure by 2.1 mm Hg ($p<0.001$) during the control diet and by 1.3 mm Hg ($p=0.03$) during the DASH diet. Reducing the sodium intake from the intermediate to the low level caused additional reductions of 4.6 mm Hg during the control diet ($p<0.001$) and 1.7 mm Hg during the DASH diet ($p<0.01$).

The effects of sodium were observed in participants with and in those without hypertension, black people and those of other races, and women and men. The DASH diet was associated with a significantly lower systolic blood pressure at each sodium level; and the difference was greater at high sodium levels than with low ones. As compared with the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mm Hg lower in participants without hypertension, and 11.5 mmHg lower in participants with hypertension[i].
Caveat: Since all food was provided for subjects the feasibility of such an intervention is difficult to assess although the study provides further argument for a reduction of sodium in the diet.

The *evidence*

i. Sacks FM, Svetkey LP, Vollmer WM *et al*; for the DASH Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *New England Journal of Medicine* 2001; **344**; 3-10

(Type II evidence – randomised controlled trial of 412 adults whose blood pressure exceeded 120/80 mm Hg, assigned to the DASH diet (rich in vegetables, fruits and low-fat dairy products) or a control diet typical of intake in the United States. Within the assigned diet, participants ate foods with high (150 mmol/day), intermediate (100 mmol/day) and low levels (50 mmol/day) of sodium for 30 consecutive days each, in random order. Outcomes were assessed blindly and an intention-to-treat analysis was carried out)

2.10c. Canadian recommendations for **salt intake** in hypertensive patients, particularly those over the age of 44 years, are that the intake of dietary sodium should be moderately restricted, to a target range of 90-130 mmol per day (3-7 g salt per day). The salt consumption of hypertensive patients should be determined by interview[i].

i. Campbell NRC, Burgess E, Choi BCK *et al*. Lifestyle modifications to prevent and control hypertension. *Canadian Medical Association Journal* 1999; **160(9Suppl)**: S1-S50

(Type V evidence – evidence based guidelines based on a systematic review of the evidence. The following literature sources were searched for each of the English-language interventions studied: MEDLINE (1966-1998), reference lists were scanned, experts were polled and the personal files of the authors were used to identify other studies. Studies were classified according to study design and graded according to level of evidence)

The *statements*

The *evidence*

2.10d. Oral potassium supplements reduce systolic and diastolic blood pressure, particularly in patients with high sodium intake[i].

One review found a pooled estimate of effect for systolic blood pressure of -3.11mmHg (95% CI -1.91 to -4.31) and for diastolic blood pressure (-1.97mmHg, 95% CI: -0.52, -3.42)I. In another analysis of the data, using a random-effects model, potassium supplementation was associated with a reduction in mean (95% confidence interval) systolic and diastolic blood pressures of -4.44 (range, -2.53 to -6.36) and -2.45 (range, -0.74 to -4.16) mm Hg, respectively[ii].

Authors concluded that oral potassium supplements should be included as a recommendation for prevention and treatment of hypertension, especially in those who are unable to reduce their intake of sodium[ii].

i. Whelton PK, He J, Cutler JA *et al*. Effects of oral potassium on blood pressure: meta-analysis of randomised controlled clinical trials. *Journal of the American Medical Association* 1997; **277**: 1624-32.

(Type I evidence - systematic review, literature search to 1995, and meta-analysis of 1,560 hypertensive and 1,005 non-hypertensive subjects in 33 trials of potassium supplementation of median 75mmol per day with maximum three year follow-up)

ii. Whelton PK, He J. Potassium in preventing and treating high blood pressure. *Seminars in Nephrology* 1999; **19(5)**: 494-99

(Type I evidence - systematic review, literature search to 1995, and meta-analysis of 33 randomised controlled trials of 2,609 (18 to 79 years of age) normotensive and hypertensive participants. Literature search was conducted for English-language trials published before 1995 – no details of literature search available)

2.10e. Dietary and non-dietary calcium supplementation can lead to a small reduction in systolic and diastolic blood pressure[i,ii]. Pooled analysis shows a reduction in systolic blood pressure of -1.44 mm Hg (95% CI -2.20 to -0.68; P < .001) and in diastolic blood pressure of -0.84 mm Hg (95% CI -1.44 to -0.24; P < .001). Although there was a trend toward larger effects with dietary interventions, none of the possible mediators of blood pressure reduction explained differences in treatment effect. The effect of supplemental calcium in the diet is at least as great as nondietary supplementation[i].

i. Griffith LE, Guyatt GH, Cook RJ, Bucher, HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure. An updated metaanalysis of randomised controlled trials. A*merican Journal of Hypertension* 1999; **12**: 84-92

(Type I evidence – systematic review, literature search to 1997, and meta-analysis of 3,538 non-pregnant normotensive or hypertensive patients in 42 randomised controlled trials receiving calcium supplementation (500-1,886 mg/day))

ii. Geleijnse JM, Grobbee DE. Calcium intake and blood pressure: an update. *Journal of Cardiovascular Risk* 2000; **7(1)**: 23-9.

(Type V evidence –expert opinion based on a review of the literature)

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For each patient on the chronic disease management system, the following are the aims, based on best evidence at time of publication, which need to be updated over time in light of the research: [key action 9]

- Advice about alcohol intake *see also Chapter One Section 1.10*

The *statements*

The *evidence*

Alcohol consumption and hypertension

2.10f. Over 60 population studies have reported associations between **alcohol consumption** and blood pressure; the relation was found to be generally linear, although several studies reported a threshold effect at about two to three standard drinks daily. Any adverse effect of up to two drinks daily on blood pressure was found to be either small or non-existent. A systematic review of 751 hypertensive patients found the data on the benefits of reducing alcohol among moderate to heavy drinkers (25-50 drinks/wk) to be inconclusive[i].

i. Murphy M, Foster C, Sudlow C *et al*. Primary prevention in *Clinical Evidence*. January 2003. London: BMJ Publishing Group, 2003. **http://www.clinicalevidence.com/** [accessed 22.12.03]
(Summary of quality appraised research evidence from a review of the literature completed in March 2002)

Weight reduction and hypertension

2.10g. The results of a systematic review suggested that **weight-reducing diets** in overweight hypertensive persons can affect modest weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decreases of roughly 3 mm Hg systolic and diastolic. Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications[i].

A more recent trial provided further support for this finding and suggested that intervention participants who lost at least 4.5 kg at 6 months and maintained this weight reduction for the next 30 months had the greatest reduction in blood pressure and a relative risk for hypertension of 0.35 (95% CI 0.20-0.59)[ii].

i. Mulrow CD, Chiquette E, Angel L *et al*. Dieting to reduce body weight for controlling hypertension in adults (Cochrane Review) In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 20 July 1998) **http://www.update-software.com/abstracts/ab000484.htm** [accessed 22.12.03]
(Type I evidence - systematic review, literature search to 1997, of 18 randomised controlled trials of 2,611 hypertensive patients (18-80 years of age))

ii. Stevens VJ, Obarzanek E, Cook NR *et al*. Long-term weight loss and changes in blood pressure: Results of the trials of hypertension prevention, phase II. *Annals of Internal Medicine* 2001; **134**: 1-11
(Type II evidence – three year randomised controlled trial of 1191 men and women aged 30-54 with nonmedicated diastolic blood pressure of 83 to 89 mm Hg and systolic blood pressure less than 140 mm hg and were 110% to 165% of their ideal body weight at baseline)

The *statements*

The *evidence*

2.10h. In **obese patients** whose hypertension is well controlled at the outset with an ACE inhibitor, with or without concomitant thiazide diuretic therapy, **sibutramine** safely and effectively achieves weight loss without compromising good blood pressure control. A total of 62 patients (42.8%) treated with sibutramine lost ≥ 5% of their body weight compared with six patients (8.3%) treated with placebo; 19 patients (13.1%) treated with sibutramine lost ≥ 10% of their body weight compared with two patients (2.8%) treated with placebo (LOCF; P ≤ 0.05 for both comparisons). Hypertension remained well controlled for the 52 weeks of the study with both sibutramine and placebo treatment[i].

i. McMahon FG, Weinstein SP, Rowe E *et al*. Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors. *Journal of Human Hypertension* 2002; **16(1)**: 5-11

(Type II evidence - 52-week, placebo-controlled, double-blind, randomised controlled study to investigate the effects of sibutramine 20 mg once daily or placebo on body weight in 220 obese (body mass index (BMI) 27-40 kg/m2), hypertensive patients)

Dietary interventions for the management of hypertension in older people (≥ 60 years old)

2.10i. A **chronic high salt diet** in **elderly patients** with essential hypertension is associated with an increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP)[i].

A chronic high salt diet significantly increased mean SBP and DBP by 5.58 mm Hg (95% CI 4.31-6.85) and 3.5 mm Hg (95% CI 2.62-4.38) respectively. There was a significant association between the level of NaCl intake and SBP (p=0.05) but not DBP (p=0.76). When trials were pooled separately, a chronic high NaCl diet increased SBP by 5.46 mm Hg (95% CI 3.56-7.36) and DBP by 2.63 mm Hg (95% CI 1.18-4.08) in trials including patients >60 years of age only, and increased SBP by 3.27 mm Hg (95% CI 1.23-5.31) and DBP by 2.69 mm Hg (95% CI 1.44-3.94) in trials including patients with mean age close to 60 years[i].

i. Alam S, Johnson AG. A meta-analysis of randomised controlled trials (RCT) among healthy normotensive and essential hypertensive elderly patients to determine the effect of high salt (NaCl) diet on blood pressure. *Journal of Human Hypertension* 1999; **13**: 367-374

(Type I evidence - systematic review, literature search to 1998, and meta-analysis of 11 randomised controlled trials of healthy normotensive and essential hypertensive elderly patients (5 of which included patients >60 years of age only and 6 included patients with a mean age close to 60 years. The definition of a chronic high NaCl diet varied in trials from 138-360 mmol/day)

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2.10j. A reduced sodium intake is a broadly effective, nonpharmacologic therapy that can lower blood pressure and control hypertension in older individuals. Prior to medication withdrawal, mean reductions in systolic and diastolic BPs from the reduced sodium intervention, net of control, were 4.3 mm Hg (P<.001) and 2.0 mm Hg (P =.001). The relative hazard ratio for any endpoint – defined as high blood pressure, resumption of antihypertensive medication, a cardiovascular clinical event - was 0.68, P<.001). In dose-response analyses, end points were progressively less frequent with greater sodium reduction (P for trend =.002)[i].
Caveat: There is no clinical trial evidence that low-sodium diets decrease morbidity and mortality. However, two cohort studies showed a substantive direct relation between sodium intake and cardiovascular disease, at least in overweight people[ii].

The *evidence*

i. Appel JL, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of **reduced sodium** intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Archives of Internal Medicine* 2001; **161(5)**: 685-93
(Type II evidence - a randomised controlled trial of 681 patients with hypertension, aged 60 to 80 years with a mean follow-up of 27.8 months. Reviewed in:

ii. Anonymous. Reduced sodium intake lowered blood pressure and need for antihypertensive medication. *ACP Journal Club* 2001; **135(2)**: 61)

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For each patient on the chronic disease management system, the following are the aims, based on best evidence at time of publication, which need to be updated over time in light of the research: [key action 9]

■ An exercise programme *see also Chapter One Sections 1.30-1.31*

The *statements*

2.11 Exercise for the management of hypertension

2.11a. Meta-analysis suggests that **aerobic exercise** causes small reductions in resting systolic and diastolic blood pressure in adults[i,ii,iii]. Statistically significant exercise-minus-control decreases were found for changes in resting systolic and diastolic blood pressure in both hypertensive and normotensive groups. Relative decreases were approximately 4% (systolic) and 5% (diastolic) in hypertensives, and 2% (systolic) and 1% (diastolic) in normotensives[i].
However, a need exists for additional, well-designed, studies among hypertensive adult women[ii].

The *evidence*

i. Kelley GA, Kelley KA, Vu Tran Z. Aerobic exercise and resting blood pressure: A meta-analytic review of randomised controlled trials. *Preventive Cardiology* 2001; **4(2)**: 73-80.
(Type I evidence – systematic review, literature search to December 1998, of 47 clinical trials representing a total of 72 effect sizes in 2543 subjects)

ii. Kelley GA, Kelley KS. Aerobic exercise and resting blood pressure in women A meta-analytic review of controlled clinical trials. *Journal of Women's Health & Gender-based Medicine* 1999; **8(6)**: 787-803
(Type I evidence - systematic review, literature search to January 1998, and meta-analysis of 1,029 patients in 21 randomised controlled trials)

iii. Fagard, RH. Exercise characteristics and the blood pressure response to dynamic physical training. *Medicine and Science in Sports and Exercise* 2001; **33(6)**: S484-S492.
(Type I evidence – systematic review, literature search to August 1998, of 44 randomised controlled trials and 2,674 subjects)

The *statements*

The *evidence*

2.11b. Canadian recommendations for regular **physical activity** in the treatment of **hypertension** in otherwise healthy adults are[i]:

- People with mild hypertension should engage in 50-60 minutes of moderate rhythmic exercise of the lower limbs, such as brisk walking or cycling, 3 or 4 times per week to reduce blood pressure
- Exercise should be prescribed as an adjunctive therapy for people who require pharmacologic therapy for hypertension, especially those who are not receiving beta-blockers.

i. Cléroux J, Feldman RD, Petrella RJ. 4. Recommendations on physical exercise training. *Canadian Medical Association Journal* 1999; **160(9 suppl.)**: S21-S28

(Type V evidence – expert advice based on a systematic review of the literature (Medline to 1997 plus reference list follow-up and personal contact))

2.11c. For hypertensive men aged 45-59 yrs, even without evidence of ischaemic heart disease, the dose response curve of exercise to benefit is **U shaped**[i].

i. Shaper AG, Wannamethe G, Walker M. Physical activity, hypertension and risk of heart attack in men without evidence of ischaemic heart disease. *Journal of Human Hypertension* 1994; **8**: 3-10.

(Type IV evidence – prospective study of 7,735 middle-aged men drawn from general practices in 24 British towns (The British Regional Heart Study). Analyses were restricted to 5,694 men with no evidence of pre-existing ischaemic heart disease or stroke at screening, in whom there were 311 major ischaemic heart disease events after 9.5 years follow-up)

2.12 Guidelines for the management of hypertension

2.12a. British evidence-based guidelines for the management of **essential hypertension** are available[i].

i. Ramsay LE, Williams B, Johnston GD *et al*. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *Journal of Human Hypertension* 1999; **13**: 569-592
Summary available: Ramsay LE, Williams B, Johnston GD *et al*. British Hypertension Society guidelines for hypertension management 1999: summary. *British Medical Journal* 1999; **319(7210)**: 630-5.
http://bmj.bmjjournals.com/cgi/content/full/319/7210/630 [accessed 22.12.03]

(Evidence based guidelines. No description of literature search strategy)

2.12b. Evidence-based Canadian recommendations for health care professionals on **lifestyle changes** to prevent and control hypertension in otherwise healthy adults (except pregnant women) are available[i]

i. Campbell NRC, Burgess E, Choi BCK. *et al*. Lifestyle modifications to prevent and control hypertension. *Canadian Medical Association Journal* 1999; **160(9Suppl)**: S1-S50

(Evidence based guidelines)

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2.12c. Evidence-based guidelines are available for **hypertension in older people** including special groups of older people: very old people, dementia, strokes and transient ischaemic attacks, renal disease, cardiovascular disease and diabetes mellitus[i].	**i.** Scottish Intercollegiate Guidelines Network (SIGN). *Hypertension in Older People*. Edinburgh: Royal College of Physicians, 2001 **http://www.show.scot.nhs.uk/sign/guidelines/fulltext/49/index.html** [accessed 22.12.03]
2.12d. Evidence-based Canadian recommendations for the **management of hypertension** are available[i].	**i.** McAlister FA, Levine M, Zarnke KB *et al*. The 2000 Canadian recommendations for the management of hypertension: part one – therapy. *Canadian Journal of Cardiology* 2001; **17(5)**: 543-559 (Evidence consensus guidelines: Literature search May 1998 to October 2000)
2.12e. A practice-oriented, evidence-based textbook for **primary care clinicians** on the management of hypertension is available[i].	**i.** Mulrow CD (ed). *Evidence-based Hypertension*. London: BMJ Books, 2001. (Summary of evidence from a systematic review - literature search completed June 2000)
2.12f. An **algorithm** for the diagnosis and management of hypertension is available[i]. **Caveat**: This algorithm is regularly revised on the basis of published literature and is piloted and amended after each revision. No details are given however of the searching, appraisal or summarising methods used.	**i.** Institute for Clinical Systems Improvement. Health care guideline: Hypertension diagnosis and treatment. Bloomington Minnesota: ISCI, January 2002 **http://www.icsi.org/knowledge/detail.asp?catID=29&itemID=173** [accessed 22.12.03] (Type V evidence – an algorithm for practice based on a literature review, regular testing & revision)
2.12g. Evidence based **guidelines** for the management of hypertension in **primary care** are currently being prepared. (Expected date of issue April 2004)[i].	**i.** National Institute for Clinical Excellence. Hypertension: hypertension in primary care. London: National Institute for Clinical Excellence (Evidence based guidelines - in progress)

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The development of a CHD management system by each Primary Care Team is an essential part of caring for patients with CHD in a consistent manner. Such a system will ensure that all patients and those at high risk (> 30% risk over 10 years) of developing the disease are offered appropriate ongoing care and the necessary support and information to make informed decisions. [paragraph 5.3]

By 2002/3 all those at high risk of and those with established CHD should be identified by the primary care team and included on a CHD management system. [key action 8]

What is the evidence concerning effective CHD management systems?

Primary Care Teams and LHGs should develop medicine management systems as part of their community pharmaceutical services, to provide ways of developing a partnership approach (for example concordance) with patients, many of whom will need complex medicine regimens, with the intention of increasing compliance with treatment. [key action 11]

What are the best collaborative medical management systems?

Interventions to improve medication compliance?

The *statements* | The *evidence*

2.13 Management in primary care

2.13a. **Computers** have a favourable effect on the uptake and follow up of patients in hypertension management. The effect of computers on physician knowledge, recording of information, and blood pressure control in patients is less conclusive and *further studies are required*[i].
Caveat: Cluster randomisation may have contributed to positive findings in 2 trials. Trials were diverse in nature and included multiple outcomes. This may have led to false positive conclusions with regard to the intervention effects due to the play of chance. Most of the computer systems and software used in the trails were outdated and unsophisticated.

i. Montgomery AA, Fahey T. A systematic review of the use of computers in the management of hypertension. *Journal of Epidemiology & Community Health* 1998; **52(8)**: 520-5
(Type I evidence – systematic review of 11,962 patients enrolled in seven randomised controlled trials. Literature search to 1997)

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2.13b. **Early telephone and postal reminders** did not improve prescribing of effective drugs for compliance with drug treatment or with recommended coronary risk-reducing behaviours[i,ii].
Neither early reminders nor baseline patient characteristics were significantly associated with reported pravastatin compliance rates, which were circa 79% overall. According to self-reports at six months, regimen compliance was associated with the adoption of other coronary risk-reducing behaviours[i].

The *evidence*

i. Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a National Registry: Results of the first Myocardial Infarction Risk Reduction Programme. *Clinical Therapeutics* 2001; **23(6)**: 970-980

(Type II evidence – randomised controlled trial comparing usual care (n=2,765) with an intervention involving postal and telephone reminders sent during the first two months of pravastatin treatment or usual care. Outcomes were through self-report and physician follow-up at three months. 34.7% of patients returned their six-month survey forms)

ii. Feder G, Griffiths C, Eldridge S, Spence M. Effect of postal prompts to patients and general practitioners on the quality of primary care after coronary event (POST): Randomised controlled trial. *British Medical Journal* 1999; **918**: 1522-1526 **http://bmj.bmjjournals.com/cgi/content/full/318/7197/1522** [accessed 22.12.03]

(Type II evidence - randomised controlled trial including 44 general practices (328 patients admitted to hospital for myocardial infarction or unstable angina) where postal prompts were sent to study participants 2 weeks and 3 months after discharge from hospital. The prompts contained recommendations for lowering the risk of another coronary event, including changes to lifestyle, drug treatment, and making an appointment to discuss these issues with the general practitioner or practice nurse)

2.13c. A Cochrane review is currently underway to evaluate interventions aimed at **improving adherence** with antihypertensive medication[i].

i. Schroeder K, Fahey T, Ebrahim S. Interventions used to improve the adherence with treatment in patients with high blood pressure in ambulatory settings (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)

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By 2002/3 LHGs and their local secondary providers must develop a patient pathway for the Assessment, Investigation, Treatment and Audit of the care of those presenting with suspected CHD and those with stable angina. This must include:- [key action 10]

- An agreed patient pathway for those with suspected CHD and those with stable angina;
- The establishment of an audit system of compliance with the pathway and the identification of the responsible person to undertake the audit;

…the completion of the necessary investigations including exercise testing and Angiography must not be more than three months for a patient with stable angina.

Which are the most reliable diagnostic and risk assessment methods for stable angina?

The *statements* | The *evidence*

2.14 Risk assessment in stable angina

Stress/exercise testing

2.14a. A 12 lead **electrocardiograph (ECG)** is a routine investigation for patients with suspected angina. A normal ECG does not exclude coronary artery disease; an abnormal ECG supports the clinical diagnosis and identifies patients with poorer prognosis[i,ii].

i. Norell M, Lythall D, Cochlan G *et al*. Limited value of the resting electrocardiogram in assessing patients with recent onset chest pain: lessons from a chest pain clinic. *British Heart Journal* 1992; **67**: 53-56
(Type IV evidence - case series of 250 patients referred with recent onset chest pain)

ii. Mirvis DM, El-Zeky F, Vander Zwaag R *et al*. Clinical and pathophysiologic correlates of ST-T wave abnormalities in coronary artery disease. *American Journal of Cardiology* 1990; **66**: 699-704
(Type IV evidence - cross-sectional analysis of clinical, ECG, haemodynamic and angiographic data from 9,801 patients)

2.14b. **Exercise ECG** is a low risk investigation (overall cardiac complication rate 0.8/10,000 tests, 95% CI 0.3-1.9)[i] and is effective in assessing prognosis in patients with coronary artery disease and identifying patients who would benefit from further investigation[ii,iii].

i. Gibbons L, Blair SN, Kohl HW, Cooper K. The safety of maximal exercise testing. *Circulation* 1980; **80**: 846-52
(Type IV evidence - case review of 71,914 maximal exercise tests conducted between 1971 and 1987)

ii. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Annals of Internal Medicine* 1987; **106**: 793-800
(Type V evidence – case series of 2,842 patients referred for exercise testing and cardiac catheterisation with a median follow-up of 10 years)

iii. Weiner DA, Ryan TJ, McCabe CH *et al*. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *Journal of the American College of Cardiology* 1984; **3(3)**: 772-79
(Type IV evidence - prospective cohort study of 4,083 patients referred for cardiac catheterisation from the CASS clinical trial registry followed-up for three years)

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2.14c. **Exercise ECG** is of limited usefulness in the diagnosis of patients with a **low pre-test probability of coronary heart disease** (CHD)[i,-iv].

The specificity and positive predictive value of exercise ECG in women was found to be significantly lower than in men (71% vs. 93%, p<0.001 and 76% vs. 95%, p<0.001, respectively)[iii].

However, a recent cohort study suggested that a strategy of discriminating true from false positive exercise tests is worthwhile in **women** but less successful in men. Independently of age, an exercise time of more than six minutes, a maximum heart rate of more than 150 beats/min, and an ST recovery time of less than one minute were the variables that best identified women at low risk. One to three of these variables identified between 11.8% and 41.2% of women as being at low risk, with a risk for prognostic disease of between 0-11.5%. The positive predictive value for the remaining women was improved from 47.8% up to 61.5%, and the number of normal angiograms was potentially reducible by between 21.1-54.9%. By the same criteria, men had higher risks for prognostic disease[v].

i. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *New England Journal of Medicine* 1979; **300**: 1350-58
(Type IV evidence - Bayesian analysis based on data from observational studies and post-mortem case series)

ii. Weiner DA, Ryan TJ, McCabe CH *et al*. Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the coronary artery surgery study (CASS). *New England Journal of Medicine* 1979; **301**: 230-35
(Type IV evidence - correlation of exercise test data with angiography in 2045 symptomatic patients from the CASS clinical trial registry)

iii. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *British Medical Journal* 1994; **308**: 883-86
(Type IV evidence - comparison of exercise test data with angiography in 202 women and 684 men referred with chest pain)

iv. Holdright DR, Fox KM. Characterisation and identification of women with angina pectoris. *European Heart Journal* 1996; **17**: 510-17
(Type IV evidence - summary review of clinical studies and case series)

v. Wong YK, Dawkins S, Grimes R, Smith F, Dawkins KD, Simpson IA. Improving the positive predictive value of exercise testing in women. *Heart* 2003; **89**: 1416-1421
(Type IV evidence – cohort study in the UK of 1,286 women and 1,801 men referred by primary care physicians to a rapid access chest clinic)

2.14d. Currently available exercise tests are only moderately sensitive and specific for the diagnosis of coronary artery disease in **women**. The **exercise ECG** had a weighted mean sensitivity, specificity, and a likelihood ratio (LR) of 0.61 (95% CI 0.54-0.68), 0.70 (0.64-0.75), (+) LR 2.25 (1.84-2.66), (-) LR 0.55 (0.47-0.62), respectively. The **exercise thallium** test had a weighted mean sensitivity, specificity, and LRs of 0.78 (0.72-0.83), 0.64 (0.51-0.77), (+) LR 2.87 (1.0 -4.96), (-) LR 0.36 (0.27-0.45). The **exercise echo** had a weighted mean sensitivity, specificity, and LRs of 0.86 (0.75-0.96), 0.79 (0.72-0.86), (+) LR 4.29 (2.93-5.65), (-) LR 0.18 (0.05-0.31). Thallium subset analysis revealed that studies using planar imaging were more specific than those using tomographic imaging[i].

i. Kwok Y, Kim C, Grady D, Segal M, Redbberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. *American Journal of Cardiology* 1999; **83(5)**: 660-6
(Type IV evidence - systematic review and meta-analysis including data from 21 studies. Some studies provided data on 2 tests. Overall, 19 studies presented data on an exercise ECG, 5 on exercise thallium and 3 on exercise echo. Literature search to 1995)

The *statements*

The *evidence*

2.14e. **Exercise ECHO** and **exercise SPECT** have similar sensitivities for the detection of coronary artery disease, but exercise ECHO has better specificity and, therefore, higher overall discriminatory capabilities as used in contemporary practice. In pooled data weighted by the sample size of each study, exercise ECHO had a sensitivity of 85% (95% CI, 83%-87%) with a specificity of 77% (95% CI, 74%-80%). Exercise SPECT yielded a similar sensitivity of 87% (95% CI, 86%-88%) but a lower specificity of 64% (95% CI, 60%-68%)[i].

Caveat: A critique of this publication has suggested that it contains serious flaws that limit its validity and generalizability. When the sample was stratified for sources of heterogeneity, it was found that there was no significant difference in diagnostic accuracy between the echocardiography and SPECT techniques used in current clinical practice[ii].

i. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *Journal of the American Medical Association* 1998; **280(10)**: 913-20

(Type I evidence - systematic review and meta-analysis of 44 studies (design unclear) including 2,456 patients (mean age 59 years) 66% male. Prevalence of coronary artery disease was 69% with past MI in 20%. Literature search 1990-1997)

ii. Kymes SM, Bruns DE, Shaw LJ, Gillespie KN, Fletcher JW. Anatomy of a meta-analysis: a critical review of "exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance". *Journal of Nuclear Cardiology* 2000; **7(6)**: 599-615

(Type I evidence – systematic review and meta-analysis. A critique of Fleischmann *et al.* was constructed obtaining the 44 articles used. These articles were reviewed and summarised with established techniques for meta-analysis)

2.14f. In the diagnosis of pharmacologic stress testing for coronary artery disease, the highest combination of sensitivity and specificity can be attained with **dobutamine echocardiography**. The sensitivity of dobutamine echocardiography, 80% (95% CI 77-83%) was similar to that of **dobutamine SPECT imaging**, but dobutamine echocardiography had a higher specificity, 84% (80-86%) than dobutamine SPECT[i].

Caveat: Many of the included studies were quite small.

i. Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic stress testing for coronary disease diagnosis: a meta-analysis. *American Heart Journal* 2001; **142(6)**: 934-944

(Type IV evidence – systematic review of diagnostic test studies, including published studies to June 1999; 44 studies using single photon emission computed tomography (SPECT) (3,737 subjects) and 66 studies using echocardiography (6,448 subjects) were examined)

2.14g. **Echocardiography, SPECT**, and **immediate angiography** are cost-effective diagnostic approaches. Test selection should reflect local variation in test accuracy. More sensitive tests increased QALYs more. Echocardiography improved health outcomes and reduced costs relative to stress testing and planar thallium imaging. The incremental cost-effectiveness ratio was $75,000/QALY for SPECT relative to echocardiography and was greater than $640,000 for PET relative to SPECT. Compared with SPECT, immediate angiography had an incremental cost-effectiveness ratio of $94,000/QALY. Qualitative findings varied little with age, sex, pretest probability of disease, or the test indeterminancy rate. Results varied most with sensitivity to severe coronary disease[i].

i. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Annals of Internal Medicine* 1999; **130(9)**: 719-28

(Type I evidence – meta-analysis of the accuracy of alternative diagnostic tests plus decision analysis to assess the health outcomes and costs of alternative diagnostic strategies for men and women 45, 55, and 65 years of age with a 25% to 75% pretest risk for coronary disease)

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2.14h. **Exercise** and **dipyridamole stress echocardiography** have comparable diagnostic accuracy for the non-invasive detection of coronary artery disease. Overall sensitivities for dipyridamole and exercise stress echocardiography were 72% (95% CI 66.9-76.0) versus 79% (74.8-83.1, p<0.05), respectively. Specificities were 92% (85.9-95.6) versus 82% (74.2-87.7, p<0.05) for dipyridamole and exercise, respectively[i].

2.14i. Direct diagnostic comparison of **stress echocardiography** and **perfusion scintigraphy** would appear to show that stress echocardiography (in particular when vasodilators are used) seems somewhat less sensitive to detecting and localising (mild) coronary artery disease, but seems the more specific test. For prognostic purposes, more related to severe forms of coronary artery disease, stress echocardiography and perfusion scintigraphy seem to have comparable strength[i].

2.14j. A randomised controlled trial is underway to decide whether **assessment of myocardial perfusion** (by TcMIBI or perfusion MRI or stress echocardiography) in comparison to routine investigation (exercise testing and angiography) can improve the identification of patients (with chronic stable angina and a positive stress exercise test) who will benefit from revascularisation[i].

2.14k. **Evidence-based guidelines** for the clinical application of **echocardiography**[i] and a clinical competence statement[ii] are available.

The *evidence*

i. Fonseca LD, Picano E. Comparison of dipyridamole and exercise stress echocardiography for detection of coronary artery disease a meta-analysis. *American Journal of Cardiology* 2001; **87(10)**: 1195-1198

(Type I evidence – systematic review and meta-analysis of 8 studies including 533 patients from 8 different institutions in 5 different countries. Literature search 1987-2000)

i. Geleijnse ML, Elhendy A. Can stress echocardiography compete with perfusion scintigraphy in the detection of coronary artery disease and cardiac risk assessment. *European Journal of Echocardiography* 2000; **1**: 12-21

(Type I evidence – systematic review and meta-analysis of 22 studies including 1,380 patients with and without angiographically defined coronary artery disease. Literature search date unknown)

i. The cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary heart disease. *National Research Register ID*: N0484099125
Start date. 01.07.2001 End date. 30.09.2004
Lead centre: Papworth and Addenbrooke's Hospitals, Cambridge

i. Cheitlin MD, Alpert JS, Armstrong WF *et al*. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation* 1997; **95(6)**: 1686-744 **http://circ.ahajournals.org/cgi/content/full/95/6/1686** [accessed 22.12.03]

(Type V evidence – expert consensus guidelines)

ii. Quiñones MA, Douglas PS, Salcedo EE *et al*. ACC/AHA clinical competence statement on echocardiography. *Journal of the American College of Cardiology* 2003; **41(4)**: 6887-708 **http://www.americanheart.org/downloadable/heart/1044978004593ja20038940p.pdf** [accessed 22.12.03]

(Type V evidence – expert consensus guidelines)

The *statements*

The *evidence*

2.14l. Guidelines for the use of **electrocardiography** in clinical practice are available[i,ii].

i. Crawford MH, Bernstein SJ, Green LA *et al*. ACC/AHA guidelines for ambulatory electrocardiography. *Journal of the American College of Cardiology* 1999; **34(3)**: 912-941
(Type V evidence – expert consensus guidelines)

ii. Kadish AH, Buxton AE, Mason JW *et al*. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography. Journal of the American *College of Cardiology* 2001; **38(7)**: 2093-3000
http://www.acc.org/clinical/competence/ECG/IV_ambulatory.htm [accessed 22.12.03]
(Type V evidence – expert consensus guidelines)

2.14m. Guidelines for **exercise testing** are available[i].

A protocol for cardiac physiologist managed exercise stress testing is available[ii].

i. Gibbons RJ, Balady GJ, Timothy Bricker J *et al*. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Journal of the American College of Cardiology* 2002; **40(8)**: 1531-40
http://www.acc.org/clinical/guidelines/exercise/exercise.pdf [accessed 22.12.03]
(Type V evidence – expert consensus guidelines)

ii. British Cardiac Society. *Protocol for Cardiac Physiologist Managed Exercise Stress Testing 2003*.
London: British Cardiac Society, 2003
www.bcs.com/doclibrary/bcs/tech_protocol_2003.pdf
[accessed 22.12.03]
(Type V evidence – expert opinion)

2.14n. **Performance recommendations** for the **cardiac sonographer** in the performance of contrast echocardiography are available[i].

i. Ehler D, Carney DK, Dempsey AL *et al*. Guidelines for cardiac sonographer education: recommendations of the American Society of Echocardiography Council on Cardiac Sonography. *Journal of the American Society of Echocardiography* 2001; **14(1)**: 77-84
(Type V evidence – expert consensus guidelines)

The *statements*

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Electron beam computed tomography

2.14o. The performance of Electron Beam Computed Tomography (EBCT) as a diagnostic test for obstructive coronary artery disease is reasonable. Pooled sensitivity for EBCT was 92.3% (95% CI, 90.7%-94.0%) and pooled specificity was 51.2% (95% CI, 47.5%-54.9%)[i].

Calcium scores calculated from **helical computed tomography** (CT) scans have been found to predict angiographically detected disease with a sensitivity of 87%-91%, a specificity of 52%-100%, a positive predictive value of 79%-89%, a negative predictive value of 59%-68%, and an accuracy of 84%-92%. There are no studies, to date, of the ability of the calcium score from helical CT to predict future coronary disease events. There has been considerably more research using electron beam computed tomography (EBCT). For the prediction of angiographically detected obstructive disease using a calcium score derived from an EBCT scan, sensitivity has ranged from 85%-97%, specificity from 31%-44%, positive predictive valued from 51%-72%, and negative predictive value from 70%-100%. In studies of EBCT detected coronary calcification as a predictor of future coronary artery disease, the calcium score has been found to be as good as, if not better than, conventional risk factors[ii].

i. Nallamothu BK, Saint S, Bielak L *et al*. Electron-beam computed tomography in the diagnosis of coronary artery disease: a meta-analysis. *Archives of Internal Medicine* 2001; **161(6)**: 833-8

(Type IV evidence –systematic review and meta-analysis of 9 diagnostic studies (mean number of subjects 119 with study samples ranging from 50 to 251) undergoing coronary angiography for evaluation of obstructive coronary artery disease. Literature search to 2000. Weighted pooled analysis and summary receiver operating characteristic (ROC) curve analysis were used to determine sensitivity and specificity rates. Results from 9 studies with 1,662 subjects were included.)

ii. Institute for Clinical Systems Improvement. Electron beam and helical computed tomography for coronary artery disease. Health Technology Assessment Report 34 (Revised). Bloomington: Institute for Clinical Systems Improvement, 2000

(Type IV evidence – systematic review. Literature search dates not reported)

Coronary angiography

2.14p. **Practice guidelines** for coronary angiography are available[i].

i. Scanlon PJ, Faxon DP, Audet A-M *et al*. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *Journal of the American College of Cardiology* 1999; **33(6)**: 1756-824

(Type V evidence – expert opinion. Also published in: Circulation 1999; (17): 2345-57)

The *statements*

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Magnetic resonance imaging

2.14q. Although a promising technique, *further technical advances are necessary* for clinical implementation of all major diagnostic capabilities of **cardiac magnetic resonance imaging**[i,ii].

i. Sinitsyn V. Magnetic resonance imaging in coronary heart disease. *European Journal of Radiology* 2001; **38(3):** 191-9 (Type V evidence – expert opinion)

ii. Li D, Deshpande V. Magnetic resonance imaging of coronary arteries. *Topics in Magnetic Resonance Imaging* 2001; **12(5)**: 337-348) (Type V evidence – expert opinion)

Stress myocardial perfusion imaging

2.14r. **Radionucleide myocardial perfusion imaging** with thallium-201 or technetium-99 based perfusion agents is a valuable adjunct to exercise ECG as a non-invasive method of assessment of patients, particularly in patients unable to exercise[i,ii].

i. Mayo Clinic Cardiovascular Working Group on Stress Testing. Cardiovascular stress testing: a description of the various types of stress tests and indications for their use. *Mayo Clinic Proceedings* 1996; **71**: 43-52 (Type IV evidence - summary review of clinical studies and case series)

ii. Brown KA. Prognostic value of cardiac imaging in patients with known or suspected coronary artery disease: comparison of myocardial perfusion imaging, stress electrocardiography, and positron emission tomography. *American Journal of Cardiology* 1995; **75**: 35-41 (Type IV evidence - summary review of observational clinical studies and case series)

2.14s. Evidence-based guidelines for the use of **cardiac radionucleide imaging** are available[i].

i. Ritchie JL, Bateman TM, Bonow RO *et al*. ACC/AHA guidelines for clinical use of cardiac radionucleide imaging: a report of the American Heart Association/American College of Cardiology task force on assessment of diagnostic and therapeutic cardiovascular procedures, committee on radionucleide imaging, developed in collaboration with the American Society of Nuclear Cardiology. *Journal of the American College of Cardiology* 1995; **25(2)**: 521-47 **http://www.americanheart.org/presenter.jhtml?identifier=1251** [accessed 22.12.03] (Type V evidence - expert opinion)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*	The *evidence*
2.14t. National Institute of Clinical Excellence guidance for **myocardial perfusion scintigraphy** diagnosis and management of cardiac disease are in preparation[i].	**i.** National Institute of Clinical Excellence. Coronary imaging myocardial perfusion scintigraph diagnosis and management of cardiac disease. (ongoing) **http://www.nice.org.uk/cat.asp?c=34137** [accessed 22.12.03]

New tools for risk assessment

2.14u. A number of **noninvasive imaging modalities** have the potential to measure and to monitor atherosclerosis in asymptomatic individuals and include exercise ECG testing, electron beam computed tomography, magnetic resonance coronary angiography, positron emission tomography, ankle-brachial index, and B-mode ultrasound. Novel serum markers, including C-reactive protein and homocysteine, have the ability to gauge risk in the individual patient[i].	**i.** Pearson TA. New tools for coronary risk assessment: what are their advantages and limitations? *Circulation* 2002; **105(7)**: 886-92 (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

For each patient on the chronic disease management system, the following are the aims, based on best evidence at time of publication, which need to be updated over time in light of the research: [key action 9]

- On dispersible aspirin 75 mg, clopidogrel or warfarin

By 2002/3 LHGs and their local secondary providers Must develop a patient pathway for the Assessment, Investigation, Treatment and Audit of the care of those presenting with suspected CHD and those with stable angina. [key action 10]

Which are the most appropriate treatments for stable angina?

2.15 Antiplatelets & anticoagulants for stable angina/coronary heart disease

2.15a. There is evidence or general agreement that **aspirin** is an effective treatment for stable angina[i,ii] at 75 mg daily[ii] in the absence of contraindications.

The net benefit of **aspirin** increases with increasing cardiovascular risk[iii,iv].

From one review, the authors concluded that, for 1000 patients with a 5% risk for coronary heart disease events over 5 years, aspirin would prevent 6-20 myocardial infarctions but would cause 0-2 haemorrhagic strokes and 2-4 major gastrointestinal bleeding events. For a risk factor of 1% over five years, aspirin would prevent 1-4 myocardial infarctions but would cause 0-2 haemorrhagic strokes and 2-4 major gastrointestinal bleeding events[iii].

In another study, the authors concluded that treatment for primary prevention is safe and worthwhile at coronary event risk ≥ 1.5% per year; safe but of limited value at coronary risk 1% per year; and unsafe at coronary event risk 0.5% per year. Advice on aspirin for primary prevention requires formal accurate estimation of absolute coronary event risk[iv].

At a coronary event risk of 1.5% per year the five year number needed to treat (NNT) was 44 to prevent a myocardial infarction and 77 to prevent a myocardial infarction net of any important bleeding complication. At coronary event risk 1% per year the NNT was 67 to prevent a myocardial infarction and 182 to prevent a myocardial infarction net of any important bleeding[iv].
Caveat: Hayden *et al.*[iii] found no significant heterogeneity in study results in terms of coronary heart disease. Sanmuganathan *et al.*[iv] found that end points for benefit were reasonably uniform among the trials but the analysis for myocardial infarction had to be forced through despite significant heterogeneity; a concern since the prevention of myocardial infarction was entirely responsible for the significant reduction in all cardiovascular events.

See also statement 3.25a.

i. Gibbons RJ, Chatterjee K, Daley J *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Management of Patients with Chronic Stable Angina*. ACC/AHA.ACP-ASIM, March 2000
http://www.americanheart.org/downloadable/heart/3377_pktangns.pdf [accessed 22.12.03]
(Evidence based guidelines)

ii. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Stable Angina*. Edinburgh: Royal College of Physicians, 2001
http://www.sign.ac.uk/guidelines/fulltext/51/
[accessed 22.12.03]
Quick reference guide:
http://www.sign.ac.uk/pdf/qrg51.pdf [accessed 22.12.03]
(Evidence based guidelines. This guideline will be reviewed in 2003)

iii. Hayden M, Pignone M, Phillips C and Murlow C Aspirin for primary prevention of cardiovascular events: a summary of evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2002; **136(2)**: 161-172
(Type I evidence – systematic review and meta-analysis of five randomised controlled trials including more than 50,000 patients and ranging from 3-7 years duration. Most participants were middle-aged although 4/5 trials included substantial numbers of patients 70-80 years of age. The trials included were: US (PHS), UK (BMD), TPT, TOP, PPP. Literature search to May 2001)
reviewed in: *Bandolier* February 2003
http://www.jr2.ox.ac.uk/bandolier/band108/b108-4.html
[accessed 22.12.03]

iv. Sanmuganathan P S, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001; **85**: 265-271
(Type I evidence – systematic review, Medline and reference list follow-up only from 1985, of four randomised controlled trials. The trials included were: US (PHS), UK (BMD), TPT, TOP. Reviewed in:
Review: Aspirin reduces the incidence of coronary artery disease in persons at risk. *ACP Journal Club* 2001; **135(3)**: 88)

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2.15b. In patients with cardiovascular risk but no history of cardiovascular disease, **aspirin** but not **vitamin E** prevented cardiovascular events. The trial was stopped early because evidence from 2 large trials indicated a benefit of aspirin in cardiovascular primary prevention that was borne out by the planned interim analysis in this trial. Patients who received aspirin had a significantly reduced risk for cardiovascular death (p=0.049) and total cardiovascular events (p=0.014), but the groups did not differ statistically for the main combined endpoint (cardiovascular death, non-fatal myocardial infarction & non-fatal stroke) or for any other outcome. Patients who received vitamin E had no reduction in risk for any outcomes except for the incidence of peripheral artery disease (0.7% v 1.3%, p=0.043)[i].

The *evidence*

i. Sherrard, H. Aspirin but not vitamin E prevented cardiovascular events in patients at risk... commentary on Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001; **13(357)**: 89-95

(Type II evidence – a 3.6 year unblinded, 2 x 2 factorial randomised controlled trial of 315 general practices and 15 hospital hypertension units (4,495 patients (mean age 64 y, 58% women) aged >/= 50 years who had >/= 1 major cardiovascular risk factor: age >/= 65 years, hypertension, hypercholesterolaemia, diabetes mellitus, obesity, and family history of myocardial infarction (MI) before 55 years of age in >/= 1 parent or sibling. Analysis was by intention to treat)

2.15c. **Long term aspirin therapy** is associated with a significant increase in the incidence of gastrointestinal haemorrhage. Gastrointestinal haemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (odds ratio 1.68, 95% CI 1.51-1.88); the number needed to harm was 106 (82-140) based on an average of 28 months' therapy. Meta-regression showed no relation between gastrointestinal haemorrhage and dose. For modified release formulations of aspirin the odds ratio was 1.93 (1.15-3.23)[i].

i. Derry S, Kong Loke Y. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta analysis. *British Medical Journal* 2000; **321**: 1183-1187 **http://bmj.bmjjournals.com/cgi/content/full/321/7270/1183** [accessed 22.12.03]

(Type I evidence – systematic review and meta-analysis, of 24 randomised controlled trials (almost 66,000 participants) comparing aspirin to placebo treatment for a minimum of one year. Trials were selected from the list of included studies in the 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, Antiplatelet Trialists' Collaboration (published up to 1993). Electronic literature search of Medline and Embase for 1990-1999)

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2.15d. When used for primary prevention in men at high risk **aspirin** reduced **non-fatal** ischaemic heart disease (IHD). **Warfarin** reduced all IHD chiefly because of an effect on fatal events. Combined treatment with warfarin and aspirin was more effective in the reduction of IHD than either agent on its own[i].

The main effect of warfarin was a reduction in all IHD of 21% (95% CI 4-35, p=0.02) chiefly due to a 39% reduction (15-57, p=0.003) in fatal events. The main effect of aspirin was a reduction in all IHD of 20% (1-35, p=0.04) almost entirely due to a 32% reduction (12-48, p=0.004) in non-fatal events. Combination therapy reduced all IHD by 34% (11-51, p=0.006) compared with placebo but increased haemorrhagic and fatal strokes. Ruptured aortic or dissecting aneurysms occurred in 15 of those who were or had been on warfarin compared with three of those who had not (p=0.01)[i].

The benefit of **low dose aspirin in primary prevention** for men at increased risk of coronary heart disease may occur mainly in those with lower systolic blood pressures, although it is not clear even in these men that the benefit outweighs the potential hazards[ii].

In the thrombosis prevention trial, the benefit, mainly for non-fatal events, was significantly greater the lower the blood pressure (interaction P=0.0015), the relative risk at pressures of < 130 mm Hg being 0.55 compared with 0.94 at pressures >145 mm Hg[ii].

i. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; **351**: 233-241

(Type II evidence – randomised controlled trial of 5,499 men, aged 45-69 years and at high risk of ischemic heart disease (in the top 20-25% of the risk score distribution), recruited from 108 general practices in the UK. Men were randomised to active warfarin (adjusted by increments until the international normalised ratio was about 1.5), controlled release aspirin (75 mg daily), placebo alone, or combination therapy in a double-blind factorial design. About 50% of subjects withdrew from the trial. It is unclear whether an intention-to-treat analysis was used)

ii. Meade TW, Brennan PJ; on behalf of the MRC General Practice Research Framework. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *British Medical Journal* 2000; **321**: 13-17 **http://bmj.bmjjournals.com/cgi/content/full/321/7252/13** [accessed 22.12.03]

(Type V evidence – expert advice based on a subgroup analysis of the thrombosis prevention trial – see above. An intention-to-treat analysis was used)

2.15e. American **evidence-based recommendations** are available for the use of **aspirin** in the primary prevention of cardiovascular events[i].

i. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Annals of Internal Medicine* 2002; **136(2)**: 157-60 **http://www.ahcpr.gov/clinic/3rduspstf/aspirin/aspnew.htm** [summary - accessed 22.12.03]

(Evidence based guidelines)

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Nitroglycerin for stable angina

2.15f. Sublingual nitroglycerin or **nitroglycerin** spray is effective for the immediate relief of angina[i,ii].

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of stable angina*. Edinburgh: Royal College of Physicians, 2001
http://www.sign.ac.uk/guidelines/fulltext/51/
OR **http://www.sign.ac.uk/pdf/sign51.pdf**
Quick reference guide:
http://www.sign.ac.uk/pdf/qrg51.pdf [accessed 22.12.03]
(Evidence based guidelines. Guideline due for review in 2003)

ii. Gibbons RJ, Chatterjee K, Daley J *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of patients with chronic stable angina. ACC/AHA.ACP-ASIM, March 2000
http://www.americanheart.org/downloadable/heart/3377_pktangns.pdf [accessed 22.12.03]
(Evidence based guidelines)

Beta-blockers for stable angina

2.15g. There is evidence or general agreement that the following treatments are effective for stable angina in the absence of contraindications[i,ii]:

- **Beta-blockers** as initial therapy in the absence of contraindications in patients with prior myocardial infarction
- **Calcium antagonists*** and/or long acting nitrates as initial therapy when beta-blockers are contraindicated
- Calcium antagonists* and /or long acting nitrates in combination with beta-blockers when initial treatment with beta blockers is not successful
- Calcium antagonists* and /or long acting nitrates as a substitute for beta-blockers if initial treatment with beta-blockers leads to unacceptable side effects

* Short-acting formulations of dihydropyridine calcium antagonists should be avoided.

i. Gibbons RJ, Chatterjee K, Daley J *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of patients with chronic stable angina. ACC/AHA.ACP-ASIM, March 2000
http://www.americanheart.org/downloadable/heart/3377_pktangns.pdf [accessed 22.12.03]
(Evidence based guidelines)

ii. Scottish Intercollegiate Guidelines Network (SIGN). *Management of stable angina*. Edinburgh: Royal College of Physicians, 2001
http://www.sign.ac.uk/guidelines/fulltext/51/
OR **http://www.sign.ac.uk/pdf/sign51.pdf**
Quick reference guide:
http://www.sign.ac.uk/pdf/qrg51.pdf
[accessed 22.12.03]
(Evidence based guidelines. This guideline will be reviewed in 2003)

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ACE-inhibitors for stable angina

2.15h. **ACE inhibitor** therapy is indicated for all patients with coronary artery disease who also have diabetes or left ventricular systolic dysfunction[i].

i. Gibbons RJ, Abrams J, Chatterjee K *et al*. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina – summary article. *Circulation* 2003; **107**: 149-
http://circ.ahajournals.org/cgi/content/full/107/1/149
[accessed 22.12.03]
(Evidence based guidelines)

Vasodilators for stable angina

2.15i. **Nicorandil** therapy in patients with stable angina and additional risk factors results in a significant improvement in outcome due to a reduction in major coronary events (hazard ratio for the treatment versus placebo group = 0.83, 95% CI 0.72-0.97, p=0.014)[i].

i. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002; **359(9314)**: 1269-1275
(Type II evidence – randomised controlled trial of 5,126 patients (male >45 years and women >55 years) with clearly established coronary heart disease or a positive exercise test with additional risk factors assigned to 20 mg nicorandil (a potassium channel activator) twice daily or identical placebo. The primary composite endpoint was coronary heart disease death, nonfatal myocardial infarction or unplanned hospital admission for cardiac chest pain. An intention to treat analysis was used)

2.16 Revascularisation versus medical intervention for stable angina/coronary heart disease

Many of the research findings in this section predate the widespread use of stents, particularly those that are drug eluting (see also Section 2.17)

2.16a. **Percutaneous Transluminal Coronary Angioplasty** (PTCA) is more effective in relieving symptoms of angina than medical treatment but at the cost of more coronary artery bypass grafting[i].

In patients treated with angioplasty compared with medical treatment the risk ratios were 0.70 (95% CI 0.50-0.98; heterogeneity P<0.001) for angina; 1.42 (0.90-2.25) for fatal and non-fatal myocardial infarction, 1.32 (0.65-2.70) for death, 1.59 (1.09-2.32) for coronary artery bypass graft, and 1.29 (0.71-3.36; heterogeneity P<0.001) for repeated angioplasty[i].

Trials have not included enough patients for informative estimates of the effect of angioplasty on myocardial infarction, death, or subsequent revascularisation, though trends so far do not favour angioplasty.

i. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *British Medical Journal* 2000; **321(7253)**: 73-7
http://bmj.bmjjournals.com/cgi/content/full/321/7253/73
[accessed 22.12.03]
(Type I evidence – systematic review and meta-analysis of 6 randomised controlled trials including 953 patients treated with angioplasty and 951 with medical treatment. Literature search 1979-1998)

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2.16b. **Coronary artery bypass** grafting (CABG) reduces total mortality at ten year follow-up compared to **medical** treatment (odds ratio 0.83; 95% CI 0.70-0.98). Survival benefit of CABG at ten years increases with severity of coronary artery disease: left main artery disease 19 months; 3 vessel disease 6 months; 1 or 2 vessel disease 2 months (p=0.02 for trend)[i].

Caveat: Inclusion criteria and assessment of validity of primary studies not stated.

Bilateral internal mammary artery grafts seem to give better survival rates than single grafts. The bilateral group had significantly better survival than the single group (hazard ratio for death 0.81; 95% CI 0.70-0.94)[ii]. *A randomised trial should be conducted* [ii].

i. Yusuf S, Zucker D, Peduzzi P *et al*. Effect of coronary artery bypass graft surgery on survival: overview of 10 year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; **344**: 563-70. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998

(Type I evidence - systematic review and meta-analysis of 2649 patients with stable angina or previous MI in seven trials)

ii. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001; **358(9285)**: 870-5

(Type IV evidence – systematic review of nine cohort studies. Seven studies yielded survival data for meta-analysis, and included 15,962 patients: 11,269 single and 4,693 bilateral IMA grafts. Literature search to 1999)

2.16c. **Recommendations** for the choice of PTCA or CABG in different groups of patients are available[i].

i. Gibbons RJ, Chatterjee K, Daley J *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of patients with chronic stable angina. ACC/AHA.ACP-ASIM, March 2000 **http://www.americanheart.org/downloadable/heart/3377_pktangns.pdf** [accessed 22.12.03]

(Evidence based guidelines)

2.16d. In low-risk patients with stable coronary artery disease, a small trial suggested that **aggressive lipid-lowering therapy** is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events. The incidence of ischemic events was 36% lower in the atorvastatin group over an 18-month period (p=0.048, which was statistically significant after adjustment for interim analyses). This reduction in events was due to a smaller number of angioplasty procedures, coronary-artery bypass operations, and hospitalisations for worsening angina. As compared with the patients who were treated with angioplasty and usual care, the patients who received atorvastatin had a significantly longer time to the first ischemic event (p=0.03)[i].

Caveat: The patient sample was at relatively low risk for ischaemic events, the sample size was small and stents were less used than in contemporary practice.

i. Pitt B, Waters D, Brown WV *et al*. for the Atorvastatin Versus Revascularization Treatment Investigators. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *The New England Journal of Medicine* 1999; **341**: 70-76

(Type II evidence – randomised controlled trial of 341 (164 patients receiving avorstatin and 177 patients to undergo angioplasty followed by usual care) patients with stable coronary artery disease, relatively normal left ventricular function, asymptomatic or mild-to-moderate angina, and a serum level of low-density lipoprotein (LDL) cholesterol of at least 115 mg per deciliter (3.0 mmol per liter) who were referred for percutaneous revascularisation with a mean age of 59+0.8 for the atorvastatin group and 58.+0.6 for the angioplasty group. An intention to treat analysis was used. Reviewed in:

Atorvastatin was at least as effective as PTCA for reducing ischemic events in patients with stable coronary artery disease. *ACP Journal Club* 2000; **132(1)**: 7)

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2.16e. Advances in the treatment of **chronic stable angina** have improved the outcome both for patients treated initially with surgery and for those treated initially with medical therapy. The improvements were of similar magnitude in both groups, so the fundamental conclusions of the bypass trials are unchanged. All subgroups experienced modest gains in survival with current therapies. At five years, the survival rate was 90% in the medical group (an absolute gain of 6%) and 94% in the surgical group (an absolute gain of 4%). Similar results were obtained for patients with triple-vessel disease. Among patients with a low ejection fraction, the 5-year survival rate was 85% for medical patients and 92% for surgical patients. Sensitivity analyses did not substantially affect the conclusions[i].

i. Kwok YS, Kim C, Heidenriech PA. Medical therapy or coronary artery bypass graft surgery for chronic stable angina: an update using decision analysis. *American Journal of Medicine* 2001; **111(2)**: 89-95

(Type IV evidence – cost-effectiveness analysis. A Markov decision analysis model was constructed to compare the 5-year and 10-year outcomes of a simulated trial of medical therapy versus bypass surgery for stable chronic angina)

2.16f. Patients aged **75 years or older** with angina **despite** standard drug therapy benefit more from **revascularisation** than from optimised medical therapy in terms of symptom relief and quality of life. After six months, angina severity decreased and measures of quality of life increased in both treatment groups; however, these improvements were significantly greater after revascularisation. Major adverse cardiac events occurred in 72 (49%) of patients in the medical group and 29 (19%) in the invasive group ($p<0.0001$). There was an increased risk of death early in follow-up for the invasive group but fewer hospital admissions for acute coronary syndrome or myocardial infarction later on[i].

Caveat: Baseline differences were similar other than for ACE inhibitor use which was higher in patients in the medical group.

i. The TIME Investigators. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *The Lancet* 2002; **358(9286)**: 951-957

(Type II evidence – randomised controlled trial of 305 patients, aged 75 or over, with chronic angina of at least Canadian Cardiac Society Class II despite at least two antianginal drugs. Patients were randomly assigned coronary angiography and revascularisation or optimised medical therapy. An intention to treat analysis was used)

The *statements*

The *evidence*

Equity of access to revascularisation

2.16g. The management and treatment of **older patients and women** with cardiac disease may be different from that of younger patients and men. Given the similarity of the indications for treatment and the lack of significant contraindications or comorbidities as a cause for these differences, one possible explanation is that these patients are being discriminated against principally because of their age and sex. Although clinical priority scores independently predicted access to catheterisation and CABG, large proportions of patients in high priority groups were not referred. The cost implications of redressing these inequities in service provision would be considerable[i].

Among patients deemed appropriate for coronary artery bypass grafting, **South Asian** patients are less likely than white patients to receive it. See statement 2.3e.

i. 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**: 680-686

(Type IV evidence - retrospective analysis of patients' medical case notes (n = 1,790), tracking each case back 12 months and forward 12 months from the patient's date of entry to the study. Patients (elective and emergency) with a cardiac ICD inpatient code at discharge or death, or who were referred to cardiology or care of the elderly unit over a 12 month period in 1996-7 (new episodes) were included)

The *statements* | The *evidence*

2.17 Comparisons of revascularisation techniques for stable angina/coronary heart disease

See also Section 3.12 for choice of revascularisation technique in acute coronary syndrome

2.17a. Guidance from NICE on the use of **coronary artery stents** are that:

- 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]

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 9,918 patients. Patients with myocardial infarction were excluded)

The *statements*

2.17b. 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].

In another study, the 6-month angiographic and 2-year clinical outcomes were better in patients who received **stents** than in those after **balloon angioplasty**. The difference in 2-year event-free survival rate was explained by a reduction in target lesion revascularization rate in the stent group The procedural success rate did not significantly differ between the stent and angioplasty groups (97.92% vs 97.45%, P = not significant). No stent thrombosis was found. The 6-month restenosis rate was lower in the stent group (18. 18% vs 24.87%, P = .055). At two years the target lesion revascularization rate was 17.19% in the stent group and 25.51% in the angioplasty group (P = .02, 33% reduction). No significant differences with regard to death and myocardial infarction were observed. Event-free survival rate at 6, 12, and 24 months was 86.77% vs 78.84%, 84.13% vs 76.70%, and 83.07% vs 73.54% for stent and angioplasty groups, respectively (P = .0172)[ii].

The *evidence*

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)

ii. Witkowski A, Ruzyllo W, Gil R *et al*. A randomized comparison of elective high-pressure stenting with balloon angioplasty: six-month angiographic and two-year clinical follow-up. On behalf of AS (Angioplasty or Stent) trial investigators. *American Heart Journal* 2000; **140(2)**: 264-71

(Type II evidence – randomised controlled trial comparing the 6-month angiographic restenosis rate and 2-year event-free survival rate in 400 patients randomly assigned to stent or angioplasty. Aspirin and ticlopidine were prescribed in both groups)

The *statements*

2.17c. There was no difference in rates of death, myocardial infarction, and cerebrovascular event at one year in patients with unstable angina and multivessel disease treated with either **stented angioplasty or bypass surgery** compared with patients with stable angina. The rate of repeat revascularisation of both unstable and stable angina was significantly higher in patients with stents ($p<0.01$). There was no significant difference in costs and cost-effectiveness at one year. Clinical outcomes, costs and cost-effectiveness analyses are also planned for 3 and 5 years post-intervention[i].
Caveat: Strict inclusion/exclusion criteria limit the generalisability of this study. There are some discrepancies between data presented in the abstract and in the text of this paper.

There were no statistically significant differences in the outcomes of bypass surgery or angioplasty and stenting in terms of death, stroke or myocardial infarction but there was a trend towards higher mortality with CABG. Among those who survived without stroke or myocardial infarction, 19.7% in the stent group underwent a second revascularisation, compared with 4.8% in the surgical group ($p<0.001$). In the diabetes sub-group, 82.3% of the surgical group and 56.3% of the stent group were free from any events after two years ($p<0.001$). For patients with diabetes, surgery clearly seems to be the preferable form of treatment[ii].
Caveats: The trial was carried out before glycoprotein IIb/IIIa receptor antagonists were in common use. Only a small proportion of treated patients were included in the trial (0-33% in an given week), limiting generalisability.

The *evidence*

i. de Feyter PJ, Serruys PW, Unger F *et al*. Bypass surgery versus stenting for the treatment of multivessel disease in patients with unstable angina compared with stable angina. *Circulation* 2002; **105(20)**: 2367-2372

(Type II evidence – randomised controlled trial of 755 patients with stable angina (and 450 patients with unstable angina) randomly assigned to coronary stenting or bypass surgery. The Arterial Revascularisation Therapies Study (ARTS) trial. All patients had multivessel disease considered equally treatable by either technique.

>75% male. All analyses were by intention to treat.

Direct medical costs per patient at one year were assessed in US $ using unit costs from the Netherlands (date not stated but circa 1999))

ii. Unger F, Serruys PW, Yacoub MH, Ilsley C *et al*. Revascularization in multivessel disease: Comparison between two-year outcomes of coronary bypass surgery and stenting. *Journal of Thoracic and Cardiovascular Surgery* 2003; **125(4)**: 809-820

(Type II evidence - Two year follow-up of the ARTS trial. 35% of the surgical and 37% of the stent group had unstable angina. 17.3% had diabetes)

The *statements*

The *evidence*

2.17d. The use of **coronary stents** has reduced the need for repeat revascularisation when compared with previous studies that used balloon angioplasty, though the rate remains significantly higher than in patients managed with CABG. The apparent reduction in mortality with CABG requires further investigation[i].

21% (n=101) of patients in the PCI group required additional revascularisation procedures compared with 6% (n=30) in the CABG group (hazard ratio 3.85, 95% CI 2.56-5.79, p<0.0001). The incidence of death or Q-wave myocardial infarction was similar in both groups (PCI 9% [n=46], CABG 10% [n=49]; hazard ratio 0.95, 95% CI 0.63-1.42, p=0.80). There were fewer deaths in the CABG group than in the PCI group (PCI 5% [n=22], CABG 2% [n=8]; hazard ratio 2.91, 95% CI 1.29-6.53, p=0.01)[i].

Caveats: Only 8% of patients received glycoprotein IIb/IIIa inhibitors at the index procedure. Trial centres only randomised 3-6% of patients undergoing revascularisation, limiting the generalisability of the results. No information was provided on the number of patients with stable or unstable angina although 70% of patients had severe angina or acute coronary syndrome as the presenting complaint.

i. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial.
Lancet 2002; **360(9338)**: 965-70, 2002

(Type II evidence – randomised controlled trial in 53 centres in Europe and Canada of symptomatic patients with multivessel coronary artery disease were randomised to CABG (n=500) or stent-assisted PCI (n=488). Median follow-up of two years)

2.17e. As measured one year after the procedure, **coronary stenting** for multivessel disease is less expensive than **bypass surgery** and offers the same degree of protection against death, stroke and myocardial infarction. The rate of event free survival at one year was 73.8% in the stent group and 87.8% in the bypass surgery group (p<0.001).

However, stenting is associated with a greater need for repeat revascularisation. Among patients who survived without a stroke or a myocardial infarction, 16.8% of those in the stenting group underwent a second revascularisation as compared with 3.5% of those in the surgery group. Overall, the net costs in favour of stenting (at Netherlands unit prices) were £2,973 per patient[i].

Caveat: The trial was initiated in April 1997 and the authors acknowledge that new surgical and medical techniques (eg minimally invasive surgery, glycoprotein IIb/IIIa inhibitors) may affect the applicability of these results to current practice.

i. Serruys PW, Unger F, Souse JE *et al;* for the Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *New England Journal of Medicine* 2001; **344(15)**: 1117-1124

(Type II evidence – randomised controlled trial of 1,205 patients assigned to stent implantation or bypass surgery. >40% of patients had a previous myocardial infarction. An intention-to-treat analysis was used)

The *statements*

The *evidence*

2.17f. A quality of life substudy of the Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI) randomised trial has shown that there is no general difference in health-related quality of life one year after **bypass surgery** or **angioplasty**; however, data presented are suggestive of a more favourable outcome in degree of perceived energy in the bypass group[i].

i. Wahrborg P. Quality of life after coronary angioplasty or bypass surgery. 1-year follow-up in the Coronary Angioplasty versus Bypass Revascularization investigation (CABRI) trial. *European Heart Journal* 1999; **20(9)**: 653-8

(Type II evidence – a quality of life substudy of the CABRI multinational, multicentre, randomised European trial of patients assigned to either PTCA or CABG. One hundred and fifty-four (14.6%) out of the 1054 main study patients participated. Perceived health status was assessed at baseline and 1 year after revascularization by means of The Nottingham Health Profile and a set of 12 other questions)

2.17g. In a high-risk group of patients with multivessel disease, **percutaneous transluminal coronary revascularisation** (PTCR) with **stent** implantation showed better survival and freedom from myocardial infarction than did conventional surgery[i].

Repeat revascularization procedures were higher in the PTCR group. During the first 30 days, PTCR patients had lower major adverse events (death, myocardial infarction, repeat revascularization procedures and stroke) compared with CABG patients (3.6% vs. 12.3%, p = 0.002). Death occurred in 0.9% of PTCR patients versus 5.7% in CABG patients, p < 0.013, and Q myocardial infarction (MI) occurred in 0.9% PTCR versus 5.7% of CABG patients, p < 0.013. 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 MI was also better in PTCR compared to CABG patients (97.7% vs. 93.4%, p < 0.017). Requirements for new revascularization procedures were higher in PTCR than in CABG patients (16.8% vs. 4.8%, p < 0.002)[i].

i. Rodriguez A, Bernardi V, Navia J *et al*. 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. ERACI II Investigators. *Journal of the American College of Cardiology* 2001; **37(1)**: 51-8

(Type II evidence – randomised-controlled trial of 2,759 patients with coronary artery disease (450 patients were randomly assigned to undergo either PTCR (225 patients) or CABG (225 patients). Both groups had similar clinical demographics: unstable angina in 92%; 38% were older than 65 years, and 23% had a history of peripheral vascular disease)

2.17h. An analysis of the results from two trials suggest that there is an advantage of CABG versus PTCA for **diabetic** but not for non-diabetic patients. It is limited to patients receiving an internal mammary artery (IMA) graft and is apparent earlier in insulin-treated patients[i].

i. Brooks RC, Detre KM. Clinical trials of revascularisation therapy in diabetics. *Current Opinion in Cardiology* 2000; **15**: 287-292

(Type V evidence – expert analysis of the Bypass Angioplasty Revascularization Investigation (BARI), Emory Angioplasty Versus Surgery Trial (EAST) and other clinical trials)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

The *evidence*

2.17i. A review of **coronary artery stents** including **drug eluting stents** is available[i] (see statement 3.12d for recommendations).

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 guidlines)

2.17j. **Stent thrombosis** occurred in <1.0% of patients undergoing stenting of native coronary artery lesions and receiving routine antiplatelet therapy with aspirin plus ticlopidine. Procedure-related variables of persistent dissection, total stent length, and final lumen diameter were significantly associated with the probability of stent thrombosis. *Continued efforts to eliminate this complication are warranted given the serious clinical consequences*[i,ii].

i. Cutlip DE, Baim DS, Kalon KL *et al*. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001; **103(15)**: 1967-71
(Type I evidence –systematic review and meta-analysis of 6 recently completed coronary stent trials and associated nonrandomized registries that enrolled 6,186 patients (6,219 treated vessels) treated with >/=1 coronary stent followed by antiplatelet therapy with aspirin and ticlopidine)

ii. Anonymous. Stents and thrombosis. Bandolier 2002;98(3) **http://www.jr2.ox.ac.uk/bandolier/band98/b98-3.html** [accessed 22.12.03]

2.17k. There is **no** evidence that **laser angioplasty, and rotational coronary atherectomy** are more effective than PTCA[i]. **Directional coronary atherectomy** (DCA) is associated with a lower six month restenosis rate than balloon angioplasty (31.4% vs. 39.8%, p=0.016), but with no difference in outcomes at one year[ii]. Catheter-based radiotherapy has been reported in one small trial to reduce restenosis at six months - further evaluation is required[i].
Caveat: DCA remains a rarely used technique.
Results from a small trial comparing primary stenting with optimal directional coronary artheretomy (DCA) at a single centre in Japan suggest that aggressive DCA may provide superior angiographic and clinical outcomes to primary stenting[iii] but a *large trial comparing compare DCA with PTCA and stenting is required*[ii].

i. Management of Stable Angina. *Effective Health Care;* **3(5)**. University of York: NHS Centre for Reviews and Dissemination, 1997 **http://www.york.ac.uk/inst/crd/ehc35warn.htm** [accessed 22.12.03]
(Type II evidence - summary review of randomised controlled trials)

ii. Baim DS, Cutlip DE, Sharma SK *et al;* for the BOAT Investigators. Final results of the balloon vs. optimal atherectomy trial. *Circulation* 1998; **97**: 322-31
(Type II evidence - randomised controlled trial of 989 patients with single coronary lesions, 40% with previous MI)

iii. Tsuchikane E, Sumiotsuji S, Awata N *et al*. Final results of the Stent Versus Directional Coronary Atherectomy Randomized Trial (START). *Journal of the American College of Cardiology* 1999; **34(4)**: 1050-1057
(Type II evidence – randomised controlled trial of patients with 122 lesions suitable for both Palmaz-Schatz stenting and DCA

The *statements*

The *evidence*

2.17l. A systematic review of studies published to 1999 suggested that the evidence currently available on **ultrasound-guided interventions** in coronary artery disease was too weak for there to be any reliable implications for clinical practice[i].

One more recent trial found that **intravascular ultrasound (IVUS) guided angioplasty** with provisional stenting appears to be feasible and safe. At the cost of a more complex procedure, it reduced the stent rate by half (cross over to stent was needed in 44% of patients), and had similar six-month angiographic IVUS and clinical outcome compared with stent implantation[ii].

Another recent trial found that angiographic and clinical outcome up to 12 months after **long stent placement** guided by IVUS was superior to guidance by angiography. At six months the mean lumen diameter was larger (p=0.042), restenosis rates were lower (23% in the IVUS and 45% of the angiography group, p=0.008) and end-points (death, myocardial infarction, and target lesion revascularisation) were reduced (12% versus 27%, p=0.026)[iii].

Caveat: Small single centre study using one type of stent only.

i. Berry E, Kelly S, Hutton J *et al*. Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness. *Health Technology Assessment* 2000; **4(35)**: 1-177
http://www.hta.nhsweb.nhs.uk/fullmono/mon435.pdf
[accessed 22.12.03]
(Type I evidence – systematic review, literature search to 1999, of one study of IVUS-guided angioplasty and 15 studies of IVUS-guided stenting, of which seven presented data on six-month outcomes)

ii. Schiele F, Meneveau N, Gilard M *et al*. Intravascular ultrasound-guided balloon angioplasty compared with stent. Immediate and 6-month results of the multicenter, randomized Balloon Equivalent to Stent Study (BEST). *Circulation* 2003; **107**: 545-551
(Type II evidence – randomised controlled trial of 254 patients randomised to IVUS-guided percutaneous transluminal coronary angioplasty (aggressive PTCA) or stenting)

iii. Oemrawsingh PV, Mintz GS, Schalij MJ *et al*. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenoses. Final results of a randomized comparison with angiographic guidance (TULIP Study). *Circulation* 2003; **107**: 62-67
(Type II evidence – randomised controlled trial of 144 patients with stenoses >20 mm in length and a reference diameter that permitted a stent diameter ≥ 3mm randomised to intravascular ultrasound or angiographic guidance)

The *statements*

The *evidence*

Cost-effectiveness of revascularisation techniques

2.17m. After 1 year of follow-up, **provisional angioplasty** was more expensive than **primary stenting** and without clinical benefit. The beneficial value of **stenting** is not limited to patients with a suboptimal result after balloon angioplasty. There was no significant difference in event-free survival at 1 year between primary stenting (86.6%) and provisional angioplasty (85.6%). Costs after one year were significantly higher for provisional angioplasty (EUR 6573 versus EUR 5885; P:=0.014). Results after the second randomization showed that stenting was also more effective after optimal balloon angioplasty (1-year event free survival, 93.5% versus 84.1%; p=0. 066)[i].

Caveat: Authors do not report the dates over which the effectiveness and resource use data were gathered. Patients included only had a single, relatively short lesion.

i. Serruys PW, de Bruyne B, Carlier S *et al*. Randomized comparison of primary stenting and provisional balloon angioplasty guided by flow velocity measurement. Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II Study Group. *Circulation* 2000; **102(24)**: 2930-7

(Type IV evidence – cost-effectiveness analysis of provisional angioplasty. Patients scheduled for single-vessel angioplasty were first randomized to receive primary stenting (97 patients) or balloon angioplasty guided by Doppler flow velocity and angiography (523 patients). Patients in the latter group were further randomized after optimization to either additional stenting or termination of the procedure to further investigate what is "optimal." An optimal result was defined as a flow reserve >2.5 and a diameter stenosis <36%. Bailout stenting was needed in 129 patients (25%) who were randomized to balloon angioplasty, and an optimal result was obtained in 184 of the 523 patients (35%).)

2.17n. With regard to **percutaneous transluminal coronary angioplasty (PTCA) cost data**, direct international comparisons are difficult since patient populations, methodological factors, and the timing and location of each study contributed to the differences observed between and within the studies reviewed. The increasing number of patients receiving PTCA emphasises the need for accurate cost data[i].

i. Lecomte P, McKenna M, Kennedy L, den Hartog M, Curry A, Rothman M. International review of the utilisation and cost of percutaneous transluminal coronary angioplasty. *Health Economics in Prevention & Care* 2001; **2(3)**: 118-127

(Type IV evidence – cost-effectiveness analysis to ascertain trends in the utilisation of percutaneous transluminal coronary angioplasty (PTCA) and to determine the availability of cost data)

2.17o. **Health service cost data** from the RITA trial suggests the average initial cost of PTCA is around 52% of a CABG, but after two years this increases to 80% because of the need for subsequent interventions. Longer-term follow-up is required to assess relative cost-effectiveness[i].

i. Sculpher MJ, Seed P, Henderson RA *et al*. Health service costs of coronary angioplasty and coronary artery bypass surgery: the randomised intervention treatment of angina (RITA) trial. *Lancet* 1994; **344**: 927-30

(Type IV evidence - UK health service costs for 1993-94 applied to randomised controlled trial data)

The *statements* | The *evidence*

2.18 Therapies before revascularisation for stable angina/coronary heart disease

2.18a. One study suggested that there is no benefit to be gained from a day of **pre-operative education** and that there is an associated increase in length of hospital stay[i,ii].

There were no significant differences between groups in the primary outcomes of anxiety (p=0.09) and pain (p=0.48), or in depression (p=0.62) and wellbeing ('worn out' p=0.11; 'tense and uptight' p=0.29) 6 months after operation. This was also the case 3 days after coronary artery surgery. There was a significant difference in the length of hospital stay with the experimental group having the longer stay (p=0.01). These findings contrast with much of the existing evidence[i].

Caveat: There were some baseline differences with more married people in the experimental group and this group was also admitted to hospital earlier on average.

i. Shuldham CM, Fleming S, Goodman H. The impact of pre-operative education on recovery following coronary artery bypass surgery. *European Heart Journal* 2002; **23(8)**: 666-674

(Type II evidence – six-month randomised controlled trial of 356 patients randomised to a day of education by members of the multidisciplinary team, prior to admission for surgery, or usual care. An intention to treat analysis was used)

ii. Shuldham C. Pre-operative education for the patient having coronary artery bypass surgery. *Patient Education & Counseling* 2001; **43(2)**: 129-137

(Type I evidence – systematic review of 10 studies examing pre-operative education and measuring post-operative outcomes. Literature search 1975-1995 followed by an update search)

2.18b. The waiting period for low risk patients awaiting elective procedures such as coronary artery bypass grafting (CABG) may be used to enhance in-hospital and early-phase recovery with a **multidimensional preoperative intervention including exercise training**. Patients who received the preoperative intervention spent one less day (95% CI 0.98-1.00) in the hospital overall (p=0.002) and less time in the intensive care unit (median 2.1 hours (95% CI –1.2 to 16 hours; p=0.001). During the waiting period, patients in the intervention group had a better quality of life than controls. Improved quality of life continued up to six months after surgery. Mortality rates did not differ[i].

Caveats: A single centre study that may limit generalisability. Findings were potentially confounded by the Hawthorne effect although all health workers with influence over the length of hospital stay were blinded to treatment assignment.

i. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized controlled trial. *Annals of Internal Medicine* 2000; **133(4)**: 253-262

(Type II evidence – eight-week randomised controlled trial of 249 patients on the waiting list for CABG whose surgeries were scheduled for a minimum of 10 weeks from the time of study recruitment. During the waiting period, the treatment group received exercise training twice per week, education and reinforcement, and monthly nurse-initiated telephone calls. After surgery, participation in a cardiac rehabilitation programme was offered to all patients)

The *statements*

2.18c. Stenting with **abciximab glycoprotein IIb/IIIa blockade** in addition to aspirin and ticlopidine reduces the 30 day incidence of death, MI or urgent revascularisation compared to stenting alone (10.8% vs. 5.3%, hazard ratio 0.48; 95% CI 0.33-0.69; p<0.001)[i].

For coronary revascularisation, **abciximab and stent implantation** confer complementary long-term clinical benefits[ii,iii]. The numbers needed to treat (95% CI) to avoid one death or myocardial infarction were 17 (12-32) for stent/abciximab versus stent/placebo and 28 (15-141) for angioplasty/abciximab versus stent/placebo. To avoid repeated target vessel revascularisation the NNT was 15 (10-30) for stent/abciximab versus angioplasty/abciximab[iii].

Among patients randomised to placebo, **ticlopidine** pre-treatment was associated with a significant decrease in the incidence of the composite end point of death, myocardial infarction or target vessel revascularisation (TVR) at one year (adjusted hazard ratio, 0.73, 95% CI 0.54-0.98, p=0.036) but did not significantly influence the risk of death or myocardial infarction in patients randomised to abciximab. Controlling for patient characteristics and for the propensity of being on ticlopidine, ticlopidine pre-treatment as an independent predictor of the need for TVR at one year (hazard ratio, 0.62, 95% CI 0.43-0.89; p=0.010) in both placebo- and abciximab-treated patients[iv]. **Caveat**: Ticlopidine pre-treatment was not controlled for or randomised and, thus, the baseline characteristics of patients varied.
Ticlopidine is not currently used in the UK.

The *evidence*

i. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of glycoprotein-IIb/IIIa blockade. *Lancet* 1998; **352**: 87-92

(Type II evidence - randomised controlled trial of 2,399 patients with stable or unstable angina)

ii. Lincoff AM, Califf RM, Moliterno DJ *et al*; for the Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. *New England Journal of Medicine* 1999; **341**: 319-327

(Type II evidence – six-month randomised controlled trial of 2,399 patients undergoing elective or urgent percutaneous coronary revascularisation but not undergoing intervention for acute myocardial infarction. Patients were randomised to stent implantation and placebo, stent implantation and abciximab or balloon angioplasty and abciximab. All patients were treated with aspirin. Reviewed in (and numbers needed to treat provided in:

iii. Abciximab and stenting reduced death, myocardial infarction, and repeated revascularization in coronary revascularization. *ACP Journal Club* 2000; **132(1)**: 5)

iv. Steinhubl SR, Ellis SG, Wolski K, Lincoff M, Topol EJ; for the EPISTENT Investigators. Ticlopidine pre-treatment before coronary stenting is associated with sustained decrease in adverse cardiac events. Data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial. *Circulation* 2001; **103(10)**: 1403-1409

(Type IV evidence – observational analysis of the effect of ticlopidine pre-treatment in patients enrolled in the above trial. 58% of patients were given ticlopidine before stenting at the discretion of the investigating physician)

The *statements*

The *evidence*

2.18d. In patients having coronary stenting, **abciximab** was more effective than **tirofiban** in preventing ischemic events. The primary end-point (death, nonfatal myocardial infarction or urgent target-vessel revascularisation at 30 days) occurred more frequently in the tirofiban group than in the abciximab group (hazard ratio = 1.26, 95% CI 1.01-1.57, p=0.038; number needed to harm = 64 (95% CI, 34-654)). There were no significant differences in the rates of major bleeding complications or transfusions, but tirofiban was associated with a lower rate of minor bleeding episodes and thrombocytopenia. At the time of the study (enrolment completed in August 2000) abciximab was more costly than tirofiban ($1,350 versus $350 for a 75 kg patient)[i].

i. Topol EJ, Moliterno DJ, Herrmann HC *et al*. for the TARGET Investigators. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *New England Journal of Medicine* 2001; **344(25)**: 1888-1894

(Type II evidence – randomised controlled trial of 4,809 patients assigned to tirofiban or abciximab before undergoing percutaneous coronary revascularisation with the intent to perform stenting. All patients received 250-500 mg aspirin before the procedure and, where possible, a loading dose of clopidogrel 300 mg. An intention-to-treat analysis was used. Reviewed in:

Abciximab was more effective than tirofiban in preventing ischemic events in patients having coronary stenting. *ACP Journal Club* 2002; **136(1)**: 5)

2.18e. Improvements of early clinical outcome with **abciximab** treatment and stenting justify the incremental cost of treatment in a community hospital setting. Use of abciximab in conjunction with balloon angioplasty or stenting and stenting alone was associated with significant reductions in incidence of major adverse cardiovascular events in hospital. Multivariate analysis indicated that use of abciximab and stenting were associated with significant independent effects on risk of an event. Lack of stenting but not use of abciximab was identified as a significant predictor of need for repeat revascularization procedures[i].

Caveat: Data were derived from a registry by retrospective analysis. Treatment strategy was at the discretion of the interventional cardiologist and was not randomized.

i. Lucore CL, Trask RV, Mishkel GJ *et al*. Impact of abciximab and coronary stenting on outcomes and costs of percutaneous coronary interventions in a community hospital. *Coronary Artery Disease* 2001; **12(2)**: 135-142

(Type IV evidence – cost-effectiveness analysis to assess costs and outcomes of coronary stenting and balloon angioplasty with and without adjunctive treatment with abciximab for 3,758 consecutive elective percutaneous coronary interventions at a single community center over a 2.5-year period between 1 January 1995 and 30 June 1997)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.18f. Intracoronary **dipyridamole** before **PTCA** reduces the incidence of abrupt vessel closure following PTCA for stable angina and acute coronary syndromes Intracoronary dipyridamole significantly reduced the incidence of abrupt vessel closure (odds ratio 0.42. 95% CI 0.22-0.79). While abrupt vessel closure occurred in 6.1% of interventions following conventional pretreatment, dipyridamole reduced the incidence to 2.5%. Restricting the analysis to balloon angioplasty, this reduction was observed in patients with stable angina (odds ratio 0.49, 95% CI 0.23-0.96) as well as in those with acute coronary syndromes (odds ratio 0.29, 95% CI 0.09-0.87). Reduction of secondary end points in the dipyridamole treated patients failed to reach significance in the PTCA group[i].

The *evidence*

i. Heintzen MP, Heidland UE, Klimek WJ *et al*. Intracoronary dipyridamole reduces the incidence of abrupt vessel closure following PTCA: a prospective randomised trial. *Heart* 2000; **83(5)**: 551-6

(Type II evidence - prospective randomised trial to investigate the effect of intracoronary dipyridamole on the incidence of abrupt vessel closure, myocardial infarction, necessity for bypass grafting, and death following percutaneous transluminal coronary angioplasty (PTCA). Patients were randomly allocated to receive either conventional pretreatment (heparin 15,000 IU and aspirin 500 mg intravenously) or additional intracoronary dipyridamole (0.5 mg/kg bodyweight). Dipyridamole was administered in 550 PTCA procedures (455 interventions in men, mean (SD) age 59.2 (8.4) years; 74 acute coronary syndromes), while conventional pretreatment was administered in 544 interventions (444 interventions in men 58.3 (7.9) years old; 81 acute coronary syndromes). In 53 interventions bail out stenting was performed for threatened abrupt vessel closure)

2.18g. A small study suggested that the intracoronary administration of the beta-blocker **propranolol** protected the myocardium during percutaneous coronary intervention, significantly reducing the incidence the myocardial infarction and improving short-term clinical outcomes. At 30 days the hazard ratio for placebo versus propranolol patients of the composite end-point of death, postprocedural MI, non-Q-wave MI after PCI hospitalisation, or urgent target-lesion revascularisation was 2.14 (95% CI 1.24-3.71, p=0.004). Further study is indicated[i].

i. Wang FW, Osman A, Otero J *et al*. Distal myocardial protection during percutaneous coronary intervention with an intracoronary beta-blocker. *Circulation* 2003; **107**: 2914-2919

(Type II evidence – randomised controlled trial of 150 patients undergoing PCI assigned to IC propranolol or placebo)

The *statements* | The *evidence*

2.19 Therapies after revascularisation for stable angina/coronary heart disease

2.19a. **Antiplatelet therapy** reduces re-occlusion rates in post-CABG patients compared to control (21% vs. 30%, benefit 90/1000 patients treated) and PTCA patients compared to control (4% vs. 8%, 40/1,000 patients treated). The odds of reocclusion for CABG and PTCA combined was reduced at six-months by 41% (SD 6, p<0.0001)[i].

Antiplatelet therapy is likely to reduce the odds of MI, stroke or vascular death in post-PTCA and post-CABG patients by around 25% at six to twelve month follow-up. Review of different doses of aspirin in long-term treatment suggests equal efficacy of daily doses 75mg to 324mg per day[ii].

Caveat: Based on a meta-analysis of antiplatelet therapy in 14 sub-categories of high-risk patients, including post-PTCA and post-CABG patients, which showed an odds reduction of 27% (SD 2%) for MI, stroke or vascular death without significant heterogeneity.

i. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *British Medical Journal* 1994; **308**: 159-68.
http://bmj.bmjjournals.com/cgi/content/full/308/6922/159 [accessed 22.12.03]
(Type I evidence - systematic review and meta-analysis of 5,323 patients in 20 CABG trials and 833 patients in three PTCA trials)

ii. 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 1332 patients in four trials of antiplatelet therapy in patients post-PTCA and 3075 in 19 trials post-CABG)

2.19b. Significant differences exist between clinical outcomes achieved by **abciximab** and those achieved by **eptifibatide** or **tirofiban** following PCI procedure. Neither abciximab (OR 0.69; 95% CI 0.4-1.9) nor eptifibatide or tirofiban treatment (OR 0.74; 95% CI 0.4-1.28) resulted in reductions in mortality. Only the abciximab-treated patients had reductions in myocardial infarction (4.3% vs 8.5%, OR 0.49; 95% CI 0.40-0.59). There was no effect of eptifibatide or tirofiban on myocardial infarction (OR 0.85; 95% CI 0.69-1.04)[i].

Urgent revascularization was reduced in both abciximab-treated (2.7% vs 6.2%, OR 0.42; 95% CI 0.34-0.53) and eptifibatide- and tirofiban-treated (4.2% vs 5.5%, OR 0.76; 95% CI 0.60-0.96) groups. Only abciximab-treated patients had increased major bleeding (5.8% vs 3.8%; OR 1.53; 95% CI 1.24-1.90). There was no effect of eptifibatide or tirofiban on major bleeding (5.0% vs 4.3%; OR 1.19; 95% CI 0.94-1.52)[i].

i. Brown DL, Fann CSJ, Chang CJ. Meta-analysis of effectiveness and safety of abciximab versus eptifibatide or tirofiban in percutaneous coronary intervention. *American Journal of Cardiology* 2001; **87(5)**: 537-41
(Type I evidence –systematic review and meta-analysis of 14,644 patients enrolled in 8 prospective, randomized, placebo-controlled clinical trials assessing treatment with a GP IIb/IIIa inhibitor to prevent ischemic complications of PCI. Literature search date not reported)

2 HIGH-RISK AND CHD-DIAGNOSED

The *statements*

2.19c. **Clopidogrel** may be more effective than aspirin in the secondary prevention of non-fatal ischaemic stroke, non-fatal MI, or vascular death (the CAPRIE composite primary outcome) in patients with recent ischaemic stroke, MI, or symptomatic peripheral vascular disease: 5.32% vs. 5.83%; relative risk reduction 8.7%; 95% CI 0.3-16.5; p=0.043. No benefit was found for the secondary outcomes of vascular death alone or death from any cause. No major differences in safety were shown[i].
Caveat: Sub-group analysis found significant heterogeneity between the three patient sub-groups, with significant benefit shown only in patients with previous history of peripheral vascular disease. *Further trials and evidence of greater cost-effectiveness is required before the use of clopidogrel is justified over aspirin*.

The results from a recent analysis suggested that, compared with aspirin, **clopidogrel** therapy results in a striking reduction in the elevated risk for recurrent ischemic events seen in patients with a **history of prior cardiac surgery**, along with a decreased risk of bleeding. In a multivariate model incorporating baseline clinical characteristics, clopidogrel therapy was independently associated with a decrease in vascular death, myocardial infarction, stroke, or rehospitalisation with a 32% relative risk reduction (95% CI, 15.8-43.8, p=0.0003)[ii].
Caveat: An on-treatment rather than an intention-to-treat analysis was used.

The *evidence*

i. CAPRIE steering committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348(9038): 1329-39

(Type II evidence – a randomised, blinded, international trial including 19,185 patients designed to assess the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of a composite outcome cluster of ischaemic stroke, myocardial infarction, or vascular death; their relative safety was also assessed. The population studied comprised subgroups of patients with atherosclerotic vascular disease manifested as either recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. Mean follow-up was 1.9 years)

ii. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001; **103(3)**: 363-368

(Type II evidence – sub-group analysis of a randomised controlled trial. The event rates were detemined for the 1,480 patients with a history of cardiac surgery assigned to clopidogrel or aspirin in a trial of 19,185 patients)

The *statements*

The *evidence*

2.19d. 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)

2.19e. **Lipid lowering therapy** reduces progression of atherosclerosis, risk of non-fatal MI, stroke or cardiac death and need for revascularisation compared to placebo in post-CABG patients[i].

Fluvastatin treatment in patients with **average cholesterol levels** after their first successful percutaneous coronary intervention significantly reduces the risk of major adverse cardiac events (MACE, comprising cardiac death, nonfatal myocardial infarction or reintervention procedure). The absolute reduction in MACE was 5.4% over four years; ie the number needed to treat was 19 (95% CI 11-82) for four years to prevent one fatal or nonfatal MACE[ii].
Caveat: There was a significant difference in diabetes incidence between groups at baseline (14.2% in the fluvastatin and 9.8% in the placebo group).

i. Azen SP, Mack WJ, Cashin-Hemphill L *et al*. Progression of coronary artery disease predicts clinical coronary events. Long-term follow-up from the cholesterol lowering atherosclerosis study. *Circulation* 1996; **93**: 34-41
(Type II evidence - randomised controlled trial of 162 non-smoking men aged 40-59 years with previous CABG randomised to colestipol/niacin plus diet or placebo plus diet followed-up for mean seven years)

ii. Serruys PWJC, de Feyter P, Macaya C *et al;* for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. A randomized controlled trial. *Journal of the American Medical Association* 2002 ; **287(24)**: 3215-3222
(Type II evidence – randomised controlled trial of 1,677 patients (aged 18-80 years), with stable or unstable angina or silent ischemia, following successful completion of their first percutaneous coronary intervention who had baseline total cholesterol levels between 3.5 and 7.0 mmol/L with fasting triglyceride levels < 4.5 mmol/L. Nearly 50% of the group had unstable angina. Subjects were randomised at hospital discharge to fluvastatin 80 mg/d or matching placebo for 3 to 4 years. An intention-to-treat analysis was used)

2.19f. **Calcium antagonists**[i] and **fish oils** (omega-3 fatty acids)[ii] may reduce restenosis rates following PTCA.
Caveat: Variation in clinically meaningful outcomes in primary studies[i]. *Further evaluations in large randomised controlled trials which address clinical outcomes are necessary to assess the potential benefits.*

i. Hillegass WB, Ohman EM, Leimberger JD, Califf RM. A meta-analysis of randomised trials of calcium antagonists to reduce restenosis after coronary angioplasty. *American Journal of Cardiology* 1994; **73**: 835-39.
(Type I evidence - systematic review and meta-analysis of 919 patients in five trials)

ii. Gapinski JP, Van Ruiswyk JV, Heudebert GR *et al*. Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. *Archives of Internal Medicine* 1993;**153**:1595-1601
(Type I evidence - systematic review and meta-analysis of 886 patients in seven trials)

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The *evidence*

2.19g. When controlling for age, comorbidity, and cardiac functional status, the results from a randomised-controlled trial of a **home recovery** trial showed positive effects on physical functioning in women and psychological distress, vigor and fatigue in men. Consistent with other studies, women had worse physical functioning and more symptom frequency than men. These findings indicate that the intervention is an effective method to prepare CABG patients for home recovery[i].

i. Moore SM, Dolansky MA. Randomized trial of a home recovery intervention following coronary artery bypass surgery. *Research in Nursing & Health* 2001; **24(2)**: 93-104

(Type II evidence – randomised-controlled trial of 180 patients (84 women and 96 men; mean age = 62 years) to test the effects of an early home recovery information intervention on physical functioning, psychological distress and symptom frequency 1 month following coronary artery bypass graft surgery. The Cardiac Home Information Program (CHIP) intervention consisted of a 15-min audiotaped message that describes the typical recovery experiences of CABG patients including particular emphasis on physical sensations they may experience and suggested behaviours for managing these experiences)

2.19h. **Coaching** may be an appropriate method to achieve lipid targets in the management of patients with coronary heart disease. At six months, the serum TC and LDL-C levels were significantly lower in the coaching intervention than the usual care group: mean TC (95%CI) 5.00 (4.82-5.17) mmol/L versus 5.54 (5.36-5.72) mmol/L (P <.0001); mean LDL-C (95%CI) 3.11 (2.94-3.29) mmol/L versus 3.57 (3.39-3.75) mmol/L (P <.0004), respectively. Coaching had no impact on TG or on HDL-C levels. Multivariate analysis showed that being coached (P <.001) had an effect of equal magnitude to being prescribed lipid-lowering drug therapy (P <.001)[i].

i. Vale MJ, Jelinek MV, Best JD, Santamaria JD. Coaching patients with coronary heart disease to achieve the target cholesterol: a method to bridge the gap between evidence-based medicine and the "real world"-randomized controlled trial. *Journal of Clinical Epidemiology* 2002; **55(3)**: 245-52

(Type II evidence – randomised controlled trial to test coaching as a technique to assist patients in achieving the target cholesterol level of <4.5 mmol/L. Patients with established CHD (n = 245) underwent a stratified randomization by cardiac procedure (coronary artery bypass graft surgery or percutaneous coronary intervention) to receive either the coaching intervention (n = 121) or usual medical care (n = 124)

2.19i. **Smoking** increases the risk of death (relative risk 1.76; 95% CI 1.37-2.26) and MI (relative risk 2.08; 95% CI 1.16-3.72) following PTCA[i].

i. Hasdai D, Garratt KN, Grill DE, Lerman A, Holmes DR Jr. Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularisation. *New England Journal of Medicine* 1997; **336**: 755-61

(Type IV evidence - prospective cohort study of 5,450 patients (mean age 64 years, 74% men) with 16 year follow-up)

2.19j. **Smoking cessation** reduces mortality in patients with CHD with no diminution of effect with increasing age[i]. The excess risks of coronary artery death, MI and atherosclerosis return to non-smoking levels within 10-20 years[ii].

i. Omenn GS, Anderson KW, Kronmal RA, Vlietstra RE. The temporal pattern of reduction of mortality risk after smoking cessation. *American Journal of Preventive Medicine* 1990; **6**: 251-57

(Type IV evidence - prospective cohort study of 21,112 men and women in the Coronary Artery Surgery Study (CASS))

ii. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. *British Medical Journal* 1976; **2**: 1525-36

(Type IV evidence - prospective cohort study of 34,440 male British doctors with 20 year follow-up)

The *statements* | The *evidence*

2.20 Guidelines for coronary revascularisation

2.20a. Practice guidelines are available for **coronary revascularisation**[i,ii,iii].

i. Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society. Coronary angioplasty: guidelines for good practice and training. *Heart* 2000; **83(2)**: 224-235
(Expert consensus guidelines)

ii. Eagle KA, Guyton RA, Davidoff R *et al*. ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 1999; **100(13)**: 1464-1480)
http://www.acc.org/clinical/guidelines/bypass/bypass.pdf [accessed 22.12.03]
(Expert consensus guidelines)

iii. Smith SC, Dove JT, Jacobs AK *et al*. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines). *Journal of the American College of Cardiology* 2001; **37(8)**: 2215-2238; 2239i-2239lxvi
http://www.americanheart.org/downloadable/heart/1012864103409perc_PDF.pdf [accessed 22.12.03]
Executive summary published in: *Circulation* 2001; **103(24)**: 3019-3041
http://circ.ahajournals.org/cgi/content/full/103/24/3019
[accessed 22.12.03]
(Expert consensus guidelines)

The *statements* | The *evidence*

2.21 Angina not controlled by medication or amenable to surgery

2.21a. A systematic review suggested short-term benefits from **transmyocardial laser revascularisation (TMR)** but no improvement in 12 month survival[i].
Caveat: A very limited search strategy was employed and there were no details of the critical appraisal techniques used. TMR is not currently recommended by the European Society for Cardiology. See statement 2.21b.

A more recent expert review of trials comparing **TMR** to maximum medical therapy demonstrated a significant benefit in relief of angina with TMR. The carbon dioxide laser provided a significant improvement in perfusion. The lack of documented improvement in perfusion with the Ho:YAG laser may be a reason that long-term results indicate a loss of angina relief in patients treated with Ho:YAG TMR. It may also play a significant role in the failure of the partial thickness treatment obtained with with Ho:YAG **percutaneous transmyocardial laser revascularisation (PMR)**[ii].

i. Wilson RJ, Slack R, Calvert N, Galinanes M, Gershlick AH. Transmyocardial laser revascularisation for angina not controlled by medication or amenable to surgery. Guidance Note for Purchasers 00/04. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 2000
(Type I evidence – systematic review, literature search date unknown, of four randomised controlled trials and four case-series)

ii. Horvath KA. Results of prospective randomized controlled trials of transmyocardial laser revascularization. *Heart Surgery Forum* 2002; **5(1)**: 33-39
(Type V evidence – expert review of randomised controlled trials; Only one trial included patients with unstable angina)

2.21b. The European Society for Cardiology Joint Study Group on the Treatment of Refractory Angina has proposed the following recommendations[i]:

- **Transcutaneous electrical stimulation, spinal cord stimulation**: These are comparatively well documented methods used in several centres with positive effects on symptoms and ischaemia and a favourable side-effect profile. The choice of method will largely depend on local resources
- **Left stellate ganglion blockade:** A theoretically promising method that needs further evaluation
- **Thoracic epidural anaesthesia, endoscopic thoracic sympathicotomy, tranmyocardial laser revascularisation, percutaneous laser revascularisation:** These therapies are less well documented and/or have unfavourable documentation with conflicting results.

Research in this field must also be encouraged[i].

i. Mannmeimer C, Camici P, Chester MR *et al*. The problem of chronic refractory angina. Report from the ESC Joint Study Group on the Treatment of Refractory Angina. *European Heart Journal* 2002; **23**: 355-370
(Type V evidence – expert guidance)

The *statements* | The *evidence*

2.22 Guidelines for the management of stable angina

2.22a. Evidence-based guidelines are available for the **management of stable angina**[i,ii,iii].

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of stable angina*. Edinburgh: Royal College of Physicians, 2001
http://www.sign.ac.uk/guidelines/fulltext/51/
OR **http://www.sign.ac.uk/pdf/sign51.pdf**
Quick reference guide:
http://www.sign.ac.uk/pdf/qrg51.pdf [accessed 22.12.03]
(Evidence based guidelines. Guideline due for review in 2003)

ii. Gibbons RJ, Chatterjee K, Daley J *et al*. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Management of patients with chronic stable angina. ACC/AHA.ACP-ASIM, March 2000
http://www.americanheart.org/downloadable/heart/3377_pktangns.pdf [accessed 22.12.03]
(Evidence based guidelines)

iii. Gibbons RJ, Abrams J, Chatterjee K *et al*. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina – summary article. *Circulation* 2003; **107**: 149
http://circ.ahajournals.org/cgi/content/full/107/1/149
[accessed 22.12.03]
(Evidence based guidelines)