Health Evidence Bulletins Wales

Cardiovascular Diseases

December 1998

Gwent Health Authority
Team Leader: Dr David Fone

Protocol Enhancement Project
Sir Herbert Duthie Library
University of Wales College of Medicine
Heath Park
Cardif CF4 4XN

Project Director: Dr Nicholas Phin
Director of Public Health
Dyfed Powys Health Authority

A project supported by the Wales Office of Research & Development for Health & Social Care

NHS CYMRU WALES

Dr David Fone, (Team Leader) Consultant in Public Health Medicine, Gwent Health Authority

Appraisal Team:
Dr Sarah Aitken,
Locum Consultant in Public Health Medicine, Gwent Health Authority
Dr Mariella Borg,
Specialist Registrar in Public Health Medicine, Gwent Health Authority
Dr Jane Layzell,
Lecturer in Public Health Medicine, University of Wales College of Medicine
Dr Stephen Osika,
Lecturer in Public Health Medicine, University of Wales College of Medicine
Dr Mark Temple,
Senior Registrar in Public Health Medicine, Gwent Health Authority
Ms Fiona Wood,
Tutorial Fellow, School of Social and Administrative Studies, Cardiff University

Members of the Internal Review Group:
Mr R Blackett,
Consultant Surgeon, Nevill Hall Hospital
Dr E Coyle,
Director of Public Health, Gwent Health Authority
Dr A Davies,
Consultant Cardiologist, Nevill Hall Hospital
Dr P Donnelly,
Director of Public Health, Iechyd Morgannwg Health
Dr S Hutchison,
Consultant Cardiologist, Nevill Hall Hospital
Dr P Khanna, Consultant Physician (Care of the Elderly), Nevill Hall Hospital
Dr R Kirk, Consultant Paediatric Cardiologist, University Hospital of Wales
Dr C Price, General Practitioner, Cwmbran
Dr D Robinson,
Consultant Radiologist, Nevill Hall Hospital
Professor R Walker, Director of Pharmaceutical Public Health, Gwent Health Authority/Professor of Pharmacy Practice, Cardiff University

Project Director:
Dr Nicholas Phin, Director of Public Health, Dyfed Powys Health Authority

Information Manager:
Dr Alison Weightman Duthie Library, University of Wales College of Medicine, Cardiff
Information Assistant:
Mrs Mala Mann Duthie Library, University of Wales College of Medicine, Cardiff

Members of the External Review Group:
Dr M R Cowie,
Senior Lecturer, Cardiology Research Group, University of Aberdeen
Dr G J Green,
Consultant Physician and Cardiologist, Ysbyty Glan Clwyd, Rhyl
Professor G C Kaye,
Consultant Cardiologist, Castle Hill Hospital, Cottingham

Other bulletins in the series address the following subjects:

- cancers
- healthy environments
- healthy living
- injury prevention
- learning disabilities
- maternal and early child health
- mental health
- oral health
- pain, discomfort and palliative care
- physical disability and discomfort
- respiratory diseases

The format of this bulletin was devised by Dr C Riley and Mrs J Barker of the Clinical Effectiveness Support Unit, Llandough and Dr AL Weightman of the Duthie Library, University of Wales College of Medicine, Cardiff

The Protocol Enhancement Project is funded by the Wales Office of Research and Development for Health and Social Care

This bulletin should be cited as: Health Evidence Bulletins. Health Evidence Bulletins - Wales: Cardiovascular Diseases
Cardiff: Welsh Office 1998
ISBN 0 7504 2283 1

CONTENTS

Date of completion of this document

30.9.98

CARDIOVASCULAR DISEASES BULLETIN

Introduction

The original *Protocols for Investment in Health Gain* were written in the early 1990s to suggest areas where the introduction, or more widespread use, of certain practices could lead to worthwhile improvements in health for the people of Wales. The documents also highlighted current practices which were of questionable value. This revision has been prepared by reviewing the earlier *Protocol for Investment in Health Gain: Cardiovascular Diseases*[1] to provide some clear, updated statements with a precise indication of the strength of the evidence and its sources for each statement; and to introduce new statements covering subjects of important current interest.

The statements represent a methodical summary of the evidence in this area found through a formal literature search across a wide range of sources[2]. The evidence has been critically appraised using internationally accepted methods[2], compiled into this technical document under the direction of a public health physician, and reviewed by a multidisciplinary team who are directly involved in patient care[3]. In addition to this document, the information will be available electronically, via the NHS Cymruweb (http://cymruweb.wales.nhs.uk/pep) and the Internet (http://www.uwcm.ac.uk/pep). Information on the methodology adopted (including a copy of the documentation), the formats in which the document is issued and details of other publications in the series, are available on request[4].

The convention used in this document to indicate the type of **evidence** is [5]:

'Type I evidence' - at least one good systematic review (including at least one randomised controlled trial).
'Type II evidence' - at least one good randomised controlled trial
'Type III evidence' - well designed interventional studies without randomisation
'Type IV evidence' - well designed observational studies
'Type V evidence' - expert opinion; influential reports and studies

Many health issues do not lend themselves to investigation by randomised controlled trial. By valuing evidence from these trials more highly than observational studies there is a danger that interventions with limited effectiveness might be judged to be more worthy than those based on observation. Similarly, those observational studies which clearly prove effectiveness (and make a randomised trial unethical) might be undervalued. Randomised controlled trials are a valuable form of evidence and, when available, they are included. If not, high quality evidence has been sought within the other categories. Information assigned as Type V evidence may include expert opinion and narrative review of randomised controlled trials for clinical guideline development, important reports or recommendations which should rightly be highly regarded.

The health gain notation (used to indicate the potential **benefit** to health) is [6]:

'beneficial' - effectiveness clearly demonstrated (1)
'likely to be beneficial' - effectiveness not so firmly established (2)
'trade-off between beneficial and adverse effects' - effects weighed according to individual circumstances (3)
'unknown'- insufficient/inadequate for recommendation(4)
'unlikely to be beneficial' - ineffectiveness is not as clearly demonstrated as for 6 (5)
'likely to be ineffective or harmful' - ineffectiveness or harm clearly demonstrated (6)

It should be stressed that these gradings, while aiming to be impartial, represent only the best advice of the professionals involved in preparing the Bulletin. Although the statements are deliberately brief, statistically significant quantitative information has been provided where possible. This is usually given as *Number Needed to Treat* (NNT), *Odds Ratio, Relative Risk or Proportional or Absolute % Risk Difference*, together with 95% confidence intervals, as per the original source of the information[7]. Issues of cost-effectiveness or cost-benefit are considered where evidence is available.

In keeping with the original Protocols, these revised documents are designed to assist Health Authorities in developing local strategies and in commissioning high quality health care. It is anticipated, however, that they will be of value to all health professionals in keeping abreast of the huge and increasing body of medical literature and can provide an agenda for future action in a wide variety of settings. It should be stressed that the publications will act as a supplement to, not a substitute for, clinical skills and experience. We anticipate that some of the conclusions reached will be controversial. Every effort has been made to include the best evidence within a subject area. Readers who are aware of any important studies that have been overlooked are encouraged to contact the project team[4].

Diseases of the heart and circulation are the major cause of morbidity and mortality in Wales and the United Kingdom, with coronary heart disease still the single largest cause of death in Wales[8]. The cardiovascular diseases included in this bulletin are coronary heart disease, heart failure, congenital heart disease, stroke and transient ischaemic attack (TIA), peripheral vascular disease and aortic aneurysm, varicose veins, leg ulcers and deep vein thrombosis, and the common arrhythmias.

There is a wealth of literature on the multifactorial and largely preventable risk factors for cardiovascular disease, mainly from large prospective cohort studies. They are reviewed in the chapter on primary prevention which cites some of the main historical studies to illustrate the most important population-based associations and reviews the evidence for the effectiveness of interventions in the primary prevention of cardiovascular disease. Lifestyle factor interventions to reduce cardiovascular risk at the level of the individual are reviewed in the *Healthy Living* Bulletin[9].

As in the original Protocol[1], coronary heart disease is reviewed in sections of stable and unstable angina, and myocardial infarction. These are defined clinical entities and allow a more thorough assessment of the sub-groups of patients to whom the evidence is applicable, but inevitably some overlap across the sections will occur. Up-dated evidence for the common arrhythmias is reviewed in the most appropriate chapter.

New and increasingly complex diagnostic, therapeutic and technological interventions have generated a wealth of new evidence from randomised controlled trials since the original Protocol[1] was published. Much of this new evidence relates to technical details of invasive management of patients. This bulletin focuses on the evidence of effectiveness of established interventions and in comparing new interventions, technologies and therapies to those established in clinical practice. Wherever possible, evidence from systematic reviews and meta-analyses has been cited. Many of these have been undertaken by the Cochrane Collaboration and published in the Cochrane Database of Systematic Reviews or critically appraised in the Database of Reviews of Effectiveness (DARE) in the *Cochrane Library*[10]. Where a DARE report is available from the current edition of Cochrane Library, this is referenced together with the original journal article.

Where systematic reviews have not been undertaken, evidence from individual randomised controlled trials has been cited. In the absence of Type I or II evidence, when necessary, well designed and conducted non-randomised trials, observational studies and expert opinion have been cited. The literature searches were complete to 30 September 1998 and The Cochrane Library 1998 Issue 4. With new systematic reviews, meta-analyses and randomised controlled trials published each month, some statements in this bulletin will soon become out of date. It is intended that the electronic version posted on the web will be regularly updated.

The statements made in this bulletin present a graded summary of the best available evidence of effectiveness across the spectrum of cardiovascular disease.
The statements are intended to act as *signposts* to further sources of evidence, not as guidelines for clinical management of patients. To place the evidence in the clinical context, evidence-based clinical guidelines have been cited.
It is hoped that this bulletin will facilitate *evidence-based practice*, which involves "integrating individual clinical expertise with the best available external clinical evidence from systematic research"[11].

Dr David Fone, Team Leader. December 1998.

1 Welsh Health Planning Forum. Protocol for Investment in Health Gain - Cardiovascular Diseases. Cardiff: Welsh Office NHS Directorate, May 1991.

2 Barker J, Weightman AL, Lancaster J. Project for the Enhancement of the Welsh Protocols for Investment in Health Gain: Project Methodology 2. Cardiff: Duthie Library UWCM, 1997

3 See inside front cover

4 Contact: Protocol Enhancement Project Office, Duthie Library, UWCM, Heath Park, Cardiff CF4 4XN.

5 This table is adapted from the *Bandolier* system (derived from the work at McMaster University, Canada) using the NHS Centre for Reviews and Dissemination criteria for a systematic review. See p.18 in ref.2 or http://www.jr2.ox.ac.uk/Bandolier/band6/b6-5.html and the Database of Abstracts of Reviews of Effectiveness (DARE) in the *Cochrane Library*.

6 This Notation is modified from the tables used in Enkin M, Keirse MJNC, Renfrew M and Neilson J. A guide to effective care in pregnancy and childbirth. 2nd ed. Oxford: Oxford University Press, 1995 pp. 389-90.

7 Number Needed to Treat (NNT) = The number of patients to be treated to prevent the outcome of interest.

Odds Ratio: If equal to 1, the effects of the intervention are no different from control. If the OR is greater (or less) than 1, then the effects of the intervention are more (or less) than control. Note that the effect being measured may be adverse or desirable.

Relative risk: Defined as the ratio of the incidence of the outcome in the exposed or intervention group to the incidence in the control group. Other comments as per odds ratio.

95% confidence interval: The range of values within which we can be 95% certain that the true population value lies.

8 Office for National Statistics. 1996 Mortality Statistics: Cause. England and Wales. Series DH2 No.23. London: HMSO, 1998.

9 *Healthy Living* Health Evidence Bulletin - due for publication 1999.

10 Available on CD-ROM and floppy disc from Update Software, PO Box 696, Oxford OX2 7YX.

11 Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine. Edinburgh: Churchill Livingstone, 1997.

This initiative is funded by the Wales Office of Research and Development for Health and Social Care.

Date of completion of this document

30.9.98

1 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

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

The *statements*

The *evidence*

1.1 Smoking

1.1a **Cigarette smoking** is associated with a two to three-fold increase in coronary heart disease[i] (CHD) and peripheral vascular disease[ii] risk in the whole adult population. The risk rises with the number of cigarettes smoked per day. In 1990, smoking accounted for 28% of male and 26% of female all-cause vascular deaths aged 35 to 69[iii]. Smoking is associated with a doubling of the relative risk of ischaemic stroke[iv].
Health gain notation - 6 *"harmful"*)

i. Dawber TR. *The Framingham Study.* The *Epidemiology of atherosclerotic disease.* Cambridge, MA: Havard University Press, 1980
(Type IV evidence - summary of results from prospective cohort study of 5127 persons with 24 year follow-up)

ii. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *Journal of the American Geriatric Society* 1985;**33**:13-18
(Type IV evidence - prospective cohort study of 5209 subjects with 26 year follow-up)

iii. Peto R, Lopez AC, Boreham J, Thun M, Heath C. *Mortality from smoking in developed countries 1950-2000*. Oxford: Oxford University Press (Oxford Medical Publications), 1994
(Type IV evidence - summary of indirect estimates of mortality from National Vital Statistics)

iv. Marmot MG, Poulter NR. Primary prevention of stroke. *Lancet* 1992;**339**:344-47
(Type IV evidence - summary of observational studies)

1.1b In **non-smokers,** self-reported exposure levels to **environmental tobacco smoke** ("passive smoking") and serum cotinine levels are associated with diagnosed ischaemic heart disease[i]. The best estimate of the reversible (cause and effect) component of the association is a relative risk of 1.23; 95% CI: 1.14, 1.33[ii, iii].
(Health gain notation - 6 *"harmful"*)

i. Tunstall-Pedoe H, Brown CA, Woodward M, Tavendale R. Passive smoking by self report and serum cotinine and the prevalence of respiratory and coronary heart disease in the Scottish heart study. *Journal of Epidemiology and Community Health* 1995;**49**:139-43
(Type IV evidence - cross-sectional survey of 786 men and 1492 women aged 40-59 years who reported never having smoked)

ii. Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *British Medical Journal* 1997;**315**:973-80
(Type IV evidence - systematic review and meta-analysis of 19 observational studies)

iii. Poswillo D, Chairman. Department of Health, Department of Health and Social Services, Northern Ireland, The Scottish Office Department of Health, Welsh Office. *Report of the Scientific Committee on Tobacco and Health*. London: The Stationery Office, 1998
(Type V evidence - expert opinion)

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

The *statements*

The *evidence*

1.2 Air pollution

1.2a Air pollution is associated with cardio-respiratory morbidity and mortality[i].
(Health gain notation - 6 "*harmful*")

i. See *Healthy Environments* bulletin in this series

1.3 Cholesterol

1.3a. The relationship between **serum cholesterol** and CHD mortality is continuous and curvilinear. The strength of this relationship is greatest in younger people: a 10% reduction in serum cholesterol is associated at five year follow-up with a 54% reduction in the incidence of CHD at 40 years, 27% at 60 years and a 19% reduction at 80 years[i].
(Health gain notation - 1 "*beneficial*")

i. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal* 1994;**308**:367-72
(Type II evidence - review of randomised controlled trials and prospective cohort studies)

1.3b. **Pravastatin** therapy in men aged 45 to 64, with no history of myocardial infarction (MI), a non-fasting plasma cholesterol ≥6.5 mmol/l and a **trial entry fasting LDL cholesterol of between 4.5 to 6.0 mmol/l**, significantly reduced the risk of non-fatal MI or death from definite CHD by 31% (95% CI: 17%, 43%; p<0.001), with non-significant reductions in the risk of death from any cause of 22% (95% CI: 0%, 40%; p=0.051) and fatal or non-fatal stroke of 11% (95% CI: -33%, 40%; p=0.57)[i]. Reductions in the risk of non-fatal MI and CHD death were seen in all subgroups of patients, including classification by cholesterol level and smoking status[i].
A further analysis[ii] of a systematic review and meta-analysis of three primary prevention trials[iii] found **to prevent** one combined endpoint of death from any cause, non-fatal MI or non-fatal stroke, 35 people (95% CI: 24, 63) with elevated lipids (defined above)[i] have to be treated with a statin for 4.6 years[ii].
(Health gain notation - 1 "*beneficial*")

Caveat: Five percent of subjects in the WOSCOP primary prevention trial[i] had a history of stable angina.

i. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group (WOSCOP). Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *New England Journal of Medicine* 1995;**333**:1301-7
(Type II evidence - randomised controlled trial of 6595 men aged 45 to 64 with mean plasma cholesterol of 7.0 mmol/l randomised to pravastatin 40 mg daily or placebo, mean 4.9 year follow-up)

ii. Statins. *Bandolier* 1997, Number 47. Volume 5 Issue 1 http://www.jr2.ox.ac.uk/bandolier/band47/b47-2.html
(Type I evidence - NNT calculations using data from three randomised controlled primary prevention trials (reference iii) involving 7961 patients, mean 4.6 year follow-up)

iii. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomised trials. *Journal of the American Medical Association* 1997;**278**:313-21. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of three randomised controlled primary prevention trials involving 7961 patients, mean 4.6 year follow-up)

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

The *statements*

1.3c. **Lovastatin** therapy 20-40mg in men aged 45 to 73 and women aged 55 to 73 with a **trial entry total cholesterol of 4.65 to 6.82mmol/l**, average LDL-C, below average HDL-C and no clinically evident atherosclerotic cardiovascular disease, significantly reduced the incidence of a first acute major coronary event (primary endpoint defined as fatal or non-fatal MI, unstable angina, or sudden cardiac death): relative risk 0.63; 95% CI: 0.50, 0.79; p<0.001[i]. Significant reductions in the secondary endpoints of revascularisation (relative risk 0.67; 95% CI: 0.52, 0.85; p=0.001), unstable angina (relative risk 0.68; 95% CI: 0.49, 0.95; p=0.02), and fatal or non-fatal MI (relative risk 0.60; 95% CI: 0.43, 0.83; p=0.002). There were no statistical differences in treatment effects between the sexes.
(Health gain notation - 1 *"beneficial"*)

Caveat: High drop-out rates (29% lovastatin, 37% placebo). Placebo group subjects were more likely to be withdrawn from study as a result of developing CHD or starting cholesterol lowering medication.

The *evidence*

i. Downs JR, Clearfield M, Weis S, et al. Women with average cholesterol levels. Results of AFCAPS/TexCAPS. *Journal of the American Medical Association* 1998;**279**:1615-22
(Type II evidence - randomised controlled trial of 5608 men aged 45 to 73 and 997 women aged 55 to 73 with entry total cholesterol of 4.65 to 6.82mmol/l randomised to lovastatin 20 mg daily or placebo, mean 5.2 year follow-up)

1.3d. **Cost-effectiveness** studies suggest that statins should only be used in primary prevention of MI in high risk patients after using other more cost-effective interventions, including aspirin, smoking cessation, dietary change and exercise, and antihypertensive therapy[i].
(Health gain notation - 3 *"balance of risk and cost-benefit"*)

i. Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care Bulletin*. Volume 4 Number 1. University of York: NHS Centre for Reviews and Dissemination, 1998
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type II evidence - systematic literature review of cost-effectiveness studies based on randomised controlled trial data)

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

The *statements* | The *evidence*

1.4 Hypertension

1.4a. Hypertension is a major risk factor for stroke[i] and CHD[ii]; 40% of strokes are attributable to a systolic blood pressure of >140mmHg[i]. Drug therapy to reduce blood pressure reduces the risk of mortality from stroke (odds ratio 0.60; 95% CI: 0.46, 0.79), equivalent to eight deaths prevented /1000 patients treated over five years (95% CI: 2, 13) and mortality from CHD (odds ratio 0.74; 95% CI: 0.64, 0.86), equivalent to eight deaths prevented /1000 patients treated over five years (95% CI: 4, 13)[iii]. Benefits apply to all ages but the five year absolute morbidity and mortality benefits are greater for older age-groups, particularly aged 60-80 years[iii,iv].
(Health gain notation - 1 "*beneficial*")

i. Marmot MG. Primary prevention of stroke. *Lancet* 1992;**339**:344-47
(Type IV evidence - narrative summary of observational studies)

ii. Dawber TR. *The Framingham Study. The epidemiology of atherosclerotic disease.* Cambridge, MA: Havard University Press, 1980
(Type IV evidence - summary of results from prospective cohort study of 5127 persons with 24 year follow-up)

iii. Mulrow C, Lau J, Cornell J, Brand M. Antihypertensive drug therapy in the elderly. Cochrane Review [updated 1 December 1997]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 21,908 hypertensive patients aged 60 and over in 15 trials evaluating the effects of drug treatment on morbidity and mortality outcomes)

iv. Lievre M, Leizorovicz A. Treatment of high blood pressure in patients aged over 60 years: lessons from randomised clinical trials. *Cardiology in the Elderly* 1995;3:217-22. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 12,483 patients aged over 60 years in five randomised controlled trials and 24,230 patients in 11 randomised controlled trials)

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

The *statements*

1.4b. 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/24hrs 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, 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].
(Health gain potential - 1 "*beneficial*")

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.

The *evidence*

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
(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. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1131 hypertensive subjects in 28 randomised controlled trials and 2374 normotensive subjects in 28 randomised controlled trials)

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

The *statements*

1.4c. **Oral potassium supplements** significantly reduce systolic blood pressure (pooled estimate of effect = -3.11mmHg, 95% CI: -1.91, -4.31) and diastolic blood pressure (-1.97mmHg, 95% CI: -0.52, -3.42), particularly in patients with high sodium intake[i]. **Calcium supplementation** has also been shown to significantly reduce systolic blood pressure (pooled estimate of effect = –1.27mmHg; 95% CI: -0.29, -0.92)[ii].
(Health gain potential - 2 *"likely to be beneficial"*)

Caveat: No studies with mortality outcomes have been identified.

The *evidence*

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. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1560 hypertensive and 1005 non-hypertensive subjects in 33 trials of potassium supplementation of median 75mmol per day with maximum three year follow-up)

ii. Bucher H, Cook RJ, Guyatt GH, et al. Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomised controlled trials. *Journal of the American Medical Association* 1996;**275**:1016-22. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 2412 hypertensive and non-hypertensive subjects in 33 trials of calcium supplementation)

1.4d. Evidence-based guidelines for the management of **essential hypertension** are available[i,ii] and due to be updated in 1999[i].
(Health gain notation - 1 *"beneficial"*)

i. *Management guidelines in essential hypertension: modified recommendations based on the report by the second working party of the British Hypertension Society*. British Hypertension Society: London, 1997
(Type V evidence - expert opinion)

ii. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Archives of Internal Medicine* 1997;**157**:2413-46 http://www.nhlbi.nih.gov/nhlbi/cardio/hbp/prof/jncintro.htm
(Type V evidence - expert opinion)

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

The *statements*

The *evidence*

1.5 Diabetes

1.5a. **Diabetes** is a major risk factor for CHD, ischaemic stroke and peripheral vascular disease[i]: evidence-based guidelines for the management of diabetic cardiovascular disease are available[i]. **Intensive glycaemic control** in non-insulin dependent diabetes has not been shown to be associated with reduced all-cause or cardiovascular disease mortality[ii].
(Health gain notation - 4 "*unknown*")

Caveat: UKPDS[ii] was unlikely to answer whether intensive glycaemic control influences macrovascular disease due to the use of aggregate endpoints.

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Diabetic Cardiovascular Disease.* Edinburgh: Royal College of Physicians,1997 http://www.show.scot.nhs.uk/sign/pdf/sign19.pdf [Adobe Acrobat reader required]
(Type V evidence - expert opinion)

ii. Intensive blood-glucose control with sulponylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:837-53
(Type II evidence - randomised controlled trial of 3867 newly diagnosed patients with type 2 diabetes, median age 54 years, randomised to conventional or intensive therapy with 10 year follow-up)

1.5b. There is significant benefit from treatment of **hypertension** in the **primary prevention** of cardiovascular mortality in **diabetic** subjects (odds ratio 0.64; 95% CI: 0.50, 0.82)[i]. **Secondary prevention** trials show a reduction of all-cause mortality: short-term follow-up of less than one year odds ratio 0.64; 95% CI: 0.50, 0.83; long-term odds ratio 0.82; 95% CI: 0.69, 0.99[i]. In the UKPDS trial, tight blood pressure control (mean BP 144/82) with a beta-blocker or ACE inhibitor was associated in a 34% reduction (p=0.019) in risk of the combined endpoint of myocardial infarction, sudden death, stroke and peripheral vascular disease[ii].
(Health gain notation - 1 "*beneficial*")

Caveat: Data are taken from the hypertension trials with defined diabetic sub-groups[i]. Lack of information in these trials on cardiovascular outcomes reduced the power of the meta-analysis to detect possible benefits of the interventions.

i. Fuller J, Stevens LK, Chaturvedi N, Holloway JF. Anti-hypertensive therapy in diabetes mellitus. Cochrane Database of Systematic Reviews. *The Cochrane Library,* Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1355 diabetic patients in two primary prevention trials and 3922 diabetic patients in seven long-term and five short-term secondary prevention trials)

ii. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study (UKPDS) Group. *British Medical Journal* 1998;**317**:703-13
(Type II evidence - randomised controlled trial of 1148 hypertensive patients with type 2 diabetes (mean age 56, mean entry BP 160/94) comparing the effect of intensive blood pressure control with moderate control, median follow-up 8.4 years)

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

The *statements*

The *evidence*

1.6 Physical activity

1.6a. **Physical activity** is independently associated with a two-fold reduction in the relative risk of CHD[i,ii] and stroke[iii], with a protective effect similar to not smoking, not being hypertensive or not being hypercholesterolaemic.
(Health gain notation - 1 *"beneficial"*)

i. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *American Journal of Epidemiology* 1990;**132**:612-28
(Type IV evidence - systematic review and meta-analysis of 27 prospective cohort studies)

ii. Shaper AG, Wannamethee G. Physical activity and ischaemic heart disease in middle-aged British men. *British Heart Journal* 1991;**66**:384-94
(Type IV evidence - prospective cohort study of 7735 men aged 40-59 years with eight year follow-up)

iii. Wannamethee G, Shaper AG. Physical activity and stroke in British middle aged men. *British Medical Journal* 1992;**304**:597-601
(Type IV evidence - prospective cohort study of 7735 men aged 40-59 years with nine year follow-up)

1.7 Obesity

1.7a Obesity (body mass index (BMI) >25) is associated with an increase in cardiac and stroke mortality, particularly at follow-up of ten years or more[i-iii].
(Health gain notation - 6 *"harmful"*)

i. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26 year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;**67**:968-77
(Type IV evidence - prospective cohort study of 5209 males and females aged 28-62 years with 26 year follow-up)

ii. Jarrett RJ, Shipley MJ, Rose G. Weight and mortality in the Whitehall study. *British Medical Journal* 1982;**285**:535-37
(Type IV evidence - prospective cohort study of 18,393 males aged 40 to 64 at ten year follow-up)

iii. Imeson JD, Haines AP, Meade TW. Skinfold thickness, body mass index and ischaemic heart disease. *Journal of Epidemiology and Community Health* 1989;**43**:223-27
(Type IV evidence - prospective occupational cohort study of 1511 males aged 40-64 years with six year follow-up)

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

The *statements*

1.7b Patients with **central obesity** are at higher risk of MI, angina or stroke death than those of similar BMI with peripheral fat distribution[i-iii].
(Health gain notation - 6 *"harmful"*)

The *evidence*

i. Ducimetiere P, Richard J, Cambien F. The pattern of subcutaneous fat distribution in middle aged men and the risk of coronary heart disease: the Paris Prospective Study. *International Journal of Obesity* 1986;**10**:229-40
(Type IV evidence - prospective cohort study of 6718 men aged 42 to 53 with six year follow-up)

ii. Lapidus L, Benbgtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *British Medical Journal* 1984;**289**:1257-61
(Type IV evidence - prospective cohort study of 1462 women aged 38 to 60 years with 12 year follow-up)

iii. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, and risk of cardiovascular disease and death: 13 year follow-up of participants in the study of men born in 1913. *British Medical Journal* 1984;**288**:1401-4
(Type IV evidence - well designed prospective cohort study of 792 men aged 54 years with 13 year follow-up)

1.7c. **Weight loss** has beneficial effects on cardiovascular risk factors - blood pressure, plasma lipids and insulin resistance[i,ii].
(Health gain notation - 1 *"beneficial"*)

i. Noppa H. Body weight change in relation to incidence of ischaemic heart disease and change in risk factors for ischaemic heart disease. *American Journal of Epidemiology* 1980;**111**:693-704
(Type IV evidence - prospective cohort study of 1302 women aged 38-60 years with six year follow-up)

ii. Hubert HB, Eaker ED, Garrison RJ, Castelli WP. Life-style correlates of risk factor change in young adults: an eight-year study of coronary heart disease risk factors in the Framingham offspring. *American Journal of Epidemiology* 1987;**125**:812-31
(Type IV evidence - prospective cohort study of 794 persons aged 20-29 years with eight year follow-up)

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

The *statements*

1.8 Alcohol consumption

1.8a. Observational studies in both men and women consistently show a strong J-shaped dose-effect relationship between **alcohol consumption and incidence of CHD**[i-iv] **and ischaemic stroke**[v]; consumption of one or two drinks per day is associated with a risk reduction of 30% - 50%, compared to abstinence. (Number needed to treat (NNT) to prevent one ischaemic heart disease event in six years = 24; 95% CI: 13, 169)[iv,vi].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*).

1.8b Both **acute and chronic heavy alcohol consumption** of over four drinks per day is associated with increased blood pressure[i] and an increased risk of stroke, especially cerebral haemorrhage[ii]. Heavy consumption of alcohol is associated with **cardiomyopathy**[iii].
(Health gain notation - 6 *"harmful"*)

The *evidence*

i. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption of coronary disease in men. *Lancet* 1991;**338**:464-68
(Type IV evidence - prospective cohort study of 44,000 men aged 40-75 with two year follow-up)

ii. Klatsky AL, Armstrong MA, Friedman GD. Alcohol and Mortality. *Annals of Internal Medicine* 1992;**117**:646-54
(Type IV evidence - well designed prospective cohort study of 128,934 adults with seven year follow-up)

iii. Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. *New England Journal of Medicine* 1995;**332**:1245-50
(Type IV evidence - prospective cohort study of 85,709 women aged 34-59 years with 12 year follow-up)

iv. Hein HO, Suadicani P, Gyntelberg F. Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow up in the Copenhagen male study. *British Medical Journal* 1996;**312**:736-41
(Type IV evidence - prospective cohort study of 2826 men aged 53-74 years with six year follow-up)

v. Camargo CA. Moderate alcohol consumption and stroke: the epidemiologic evidence. *Stroke* 1989;**20**:1611-26
(Type IV evidence - narrative review of 62 observational studies)

vi. Evidence-based drinking. *Bandolier* 1996, Number 27. Volume 3 Issue 5
http://www.jr2.ox.ac.uk/bandolier/band27/b27-9.html
(Type IV evidence - NNT calculations using data from reference (iv) - prospective cohort study of 2826 men aged 53-74 years with six year follow-up)

i. Klatsky AL. Blood pressure and alcohol consumption. In: Bulpitt CJ, ed. *Epidemiology of hypertension*. Amsterdam: Elsevier, 1985: 159-74. (Birkenhager WH, Reid JL, eds. Handbook of hypertension, Vol 6)
(Type IV evidence - summary of observational evidence)

ii. Camargo CA. Moderate alcohol consumption and stroke: the epidemiologic evidence. *Stroke* 1989;**20**:1611-26
(Type IV evidence - narrative review of 62 observational studies)

iii. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscle. *New England Journal of Medicine* 1989;**320**:409-15
(Type III evidence - non-randomised cross-sectional comparison of 50 alcoholic men, mean age 38.5 years, with healthy controls)

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

The *statements*	The *evidence*
1.8c The **balance of risk and benefit** is against a population strategy of increased alcohol consumption to reduce the risk of coronary heart disease[i]. (Health gain notation - 5 "unlikely to be beneficial")	**i.** Marmot M, Brunner E. Alcohol and cardiovascular disease: the status of the U-shaped curve. *British Medical Journal* 1991;**303**:565-68 (Type IV evidence - review of observational studies)

1.9 Antiplatelet therapy

1.9a. **Antiplatelet therapy** in low risk "primary prevention" patients for five years is associated with a small but significant reduction in non-fatal MI of 5 (SD 2) per 1000 patients treated (% odds reduction 29%, SD 8%; p<0.0005, NNT=200) and a non-significant reduction in MI, stroke or vascular death. A small, non-significant increase was found for non-fatal stroke, and a marginally significant excess of haemorrhagic fatal or non-fatal stroke[i]. (Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)	**i.** Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994; **308**: 81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 28,000 low risk patients in five trials of antiplatelet therapy)

1.10 Atrial fibrillation

1.10a. **Atrial fibrillation** is a major risk factor for stroke, associated with a five-fold excess in age-adjusted incidence[i]. **Anticoagulation** in patients with non-rheumatic atrial fibrillation is effective in the **primary prevention of ischaemic stroke** - relative risk reduction 68% (NNT 31/1000, p<0.001) with a significant increase in the risk of major haemorrhage of 3/1000[ii]. Patients with atrial fibrillation aged under 65 years were at very low risk of stroke even when not treated[ii]. (Health gain notation - 1 *"beneficial"*)	**i.** Wolf PA, Abbott R, Kannel W. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;**22**:983-88 (Type IV evidence - prospective cohort study of 5070 participants with 34 year follow-up)
	ii. Atrial Fibrillation Investigators. Risk factors for stroke and efficiency of antithrombotic therapy in atrial fibrillation analysis of pooled data from five randomised controlled trials. *Archives of Internal Medicine* 1994;**154**:1449-57 (Type I evidence - meta-analysis of 1889 patient-years receiving warfarin and 1802 control)

Caveat: Primary prevention trials included six percent of patients with a previous TIA or stroke. Generalisability of the results is limited by entry into the trials of a small proportion of eligible patients and only 20% of patients were aged over 75 years.

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

The *statements*

1.10b. There is evidence that **aspirin alone** in patients with non-rheumatic atrial fibrillation is effective in the **primary prevention** of stroke. Two trials have shown a reduction of 15-20 strokes per 1000 patients treated per year[i,ii]. One study found a non-significant 16% relative risk reduction with 75mg aspirin[i] and the second study found a significant 42% (95% CI: 9%, 63%; p=0.02) reduction with 325mg aspirin daily[ii]. An overview of these primary prevention trials found a non-significant risk reduction of 31% (95% CI: -12%, 58%)[iii].

An extended overview which included a third **secondary prevention** trial found a borderline significant risk reduction of 21%; 95% CI: 0%, 38%; p=0.05[iv,v] for aspirin alone and a significant risk reduction of 49%, p<0.001[iv,v], associated with a greater risk of major haemorrhage (2.8% vs. 0.9% per year) for anticoagulation with **warfarin** compared to aspirin. Further trials comparing warfarin, low-dose warfarin, warfarin plus aspirin and aspirin alone are in progress.

(Health gain notation - 1 *"beneficial"*)

The *evidence*

i. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989;**i**:175-79
(Type II evidence - randomised controlled trial of 1007 patients aged >18 years (median age 74 years) with chronic atrial fibrillation, two year follow-up)

ii. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study: final results. *Circulation* 1991;**84**:527-39
(Type II evidence - randomised controlled trial of 1330 patients with constant or intermittent atrial fibrillation with one year follow-up)

iii. 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. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1792 patients with non-rheumatic atrial fibrillation in two primary prevention trials of aspirin vs. placebo)

iv. Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from three randomised trials. *Archives of Internal Medicine* 1997;**157**:1237-40
(Type I evidence - meta-analysis of 3852 patient-years, mean age 70 years)

v. Albers GW. Atrial fibrillation and stroke. Three new studies, three remaining questions. *Archives of Internal Medicine* 1994;**154**:1443-48
(Type II evidence - review of randomised controlled trials)

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

The *statements*	The *evidence*
1.10c. Evidence-based guidelines for the management of patients with **atrial fibrillation** are available[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Prystowsky EN, Benson WD Jr, Fuster V, et al. Management of patients with atrial fibrillation: a statement for healthcare professionals from the subcommittee on electrocardiography and electrophysiology, American Heart Association. *Circulation* 1996;**93**:1262-77 http://www.americanheart.org/Scientific/statements/1996/039602.html (Type V evidence - expert opinion)
1.10d. Evidence-based guidelines for the **investigation and management of valvular heart disease** are available[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Prendergast BD, Banning AP, Hall RJC. *Valvular heart disease: recommendations for investigation and management. Guidelines produced by a working group of the British Cardiac Society and the research unit of the Royal College of Physicians.* London: Royal College of Physicians, 1996 http://www.cardiac.org.uk/ (Type V evidence - expert opinion)

1.11 Multifactorial clinical guidelines

1.11a. UK multi-factorial evidence-based guidelines for the **prevention of coronary heart disease** are due for publication in 1999[i]. Updated Joint European guidelines are now available[ii]. (Health gain notation - 1 *"beneficial"*)	**i.** British Cardiac Society, British Hypertension Society, British Hyperlipidaemia Association http://www.cardiac.org.uk (Type V evidence - expert opinion) **ii.** Wood D, De Backer G, le Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. *European Heart Journal* 1998;**19**:1434-1503 http://www.escardio.org/guidelines/98prevention.pdf [Adobe Acrobat reader required] (Type V evidence - expert opinion)

Date of completion of this document

30.9.98

2 STABLE ANGINA

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

The *statements*

The *evidence*

2.1 Clinical guidelines

2.1a. Stable angina is characterised by exertional chest pain relieved by rest, resulting from the partial obstruction of a coronary artery by atheroma. Angina is more common in men and with increasing age. Overall it is estimated that over a one year period around 1% of the population present with symptoms of angina to their GP and of these around 10% will subsequently have a non-fatal or fatal myocardial infarction[i]. Clinical guidelines and audit standards for the **investigation and management of stable angina** are available from the British Cardiac Society and Royal College of Physicians[ii], and the European Society of Cardiology[iii].
(Health gain notation - 1 *"beneficial"*)

i. Management of Stable Angina. *Effective Health Care Bulletin.* Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type II evidence - review of randomised controlled trials)

ii. de Bono DP, Hopkins A, for a working party of the joint audit committee of the British Cardiac Society and the Royal College of Physicians of London. *The investigation and management of stable angina.* British Cardiac Society, 1996.
http://www.cardiac.org.uk/
(Type V evidence - expert opinion)

iii. Julian DG, Bertrand ME, Hjalmarsson A, et al. Management of stable angina pectoris. *European Heart Journal* 1997;**18**:394-413
http://www.escardio.org/guidelines/97management.pdf [Adobe Acrobat reader required]
(Type V evidence - expert opinion)

2.2 ECG and exercise testing

2.2a. 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].
(Health gain notation - 2 *"likely to be beneficial"*)

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 9801 patients)

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

The *statements*

The *evidence*

2.2b. **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].
(Health gain notation - 2 *"likely to be beneficial"*)

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 IV evidence - case series of 2842 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 4083 patients referred for cardiac catheterisation from the CASS clinical trial registry followed-up for three years)

2.2c **Exercise ECG** is of limited usefulness in the diagnosis of patients with a **low pre-test probability of coronary heart disease** (CHD)[i-iv], particularly in women[iii,iv] in whom the specificity and positive predictive value of exercise ECG are significantly lower than in men (71% vs. 93%, p<0.001 and 76% vs. 95%, p<0.001, respectively)[iii].
(Health gain notation - 5 *"unlikely to be beneficial"*)

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)

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

The *statements*	The *evidence*
2.2d. Evidence-based guidelines for **exercise testing** are available[i]. (Health gain notation - 1 "*beneficial*")	**i.** Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on exercise testing). *Circulation* 1997;**96**:345-54 http://www.americanheart.org/Scientific/statements/1997/079702.html (Type V evidence - expert opinion)
2.3 Myocardial perfusion imaging	
2.3a. Radionuclide 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[i,ii], particularly in patients unable to exercise. (Health gain notation - 1 "*beneficial*")	**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)
2.3b. Evidence-based guidelines for the use of **cardiac radionucleide imaging** are available[i]. (Health gain notation - 1 "*beneficial*")	**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. *Circulation* 1995;**91**:1278-303 http://www.americanheart.org/Scientific/statements/1995/049501.html (Type V evidence - expert opinion)

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

The *statements*	The *evidence*

2.4 Drug therapy

2.4a. There is no randomised controlled trial evidence for major differences between the main classes of **drug treatment** (beta-blockers, nitrates and calcium channel blockers) in the effectiveness of relief of **symptomatic angina**, or that combination therapy is more effective than monotherapy[i].
(Health gain notation - 1 *"beneficial"*)

i. Management of Stable Angina. *Effective Health Care Bulletin* Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997 http://www.york.ac.uk/inst/crd/ehcb.htm
(Type II evidence - review of randomised controlled trials)

2.4b. There is evidence to suggest that **bisoprolol** is more effective than nifedipine for complete cessation of **transient asymptomatic ischaemic episodes**[i] (number needed to treat NNT=3; 95% CI: 2, 4), for 20mg daily bisoprolol compared to 40mg twice daily slow release nifedipine) and more effective than isosorbide dinitrate for **cessation of exercise induced angina** (NNT 5.0; 95% CI: 2.8, 21.0) for 20mg daily bisoprolol compared to 20mg isosorbide dinitrate three times a day[ii]. Benefits were sustained at one year follow-up[iii].
(Health gain notation - 2 *"likely to be beneficial"*)

i. von Arnim T, for the TIBBS Investigators. Medical treatment to reduce total ischaemic burden bisoprolol study (TIBBS), a multicentre trial comparing bisoprolol and nifedipine. *Journal of the American College of Cardiology* 1995;**25**:231-38
(Type II evidence - review of randomised controlled trial of 330 patients with stable angina, positive exercise test and transient ischaemia during Holter monitoring and eight week follow-up)

ii. Angina. *Bandolier* 1997, Number 40. Volume 4 Issue 6 http://www.jr2.ox.ac.uk/bandolier/band40/b40-3.html
(Type II evidence - NNT calculations using data from reference (i) and review of randomised controlled trials)

iii. von Arnim T, for the TIBBS Investigators. Prognostic significance of transient ischaemic episodes: response to treatment shows improved prognosis. *Journal of the American College of Cardiology* 1996;**28**:20-24
(Type II evidence - review of randomised controlled trial of 330 patients with stable angina, positive exercise test and transient ischaemia during Holter monitoring and one year follow-up)

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

The *statements*

The *evidence*

2.5 Secondary prevention

2.5a. Antiplatelet therapy in patients with stable angina reduces myocardial infarction (MI), stroke or vascular death (odds reduction 33%, SD 9%, p<0.0005). Most patients in the trials received aspirin - where comparison between regimens and antiplatelet agents were possible no significant differences were noted[i].
(Health gain notation - 1 *"beneficial"*)

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and sub-group meta-analysis of 3000 patients with stable angina in seven trials of antiplatelet therapy)

2.5b 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].
(Health gain notation - 6 *"harmful"*)

i. Hasdai D, Garratt KN, Grill DE, Lerman A, Holmes DR Jr. Effect of smoking status on the long-yerm outcome after successful percutaneous coronary revascularisation. *New England Journal of Medicine* 1997;**336**:755-61
(Type IV evidence - prospective cohort study of 5450 patients (mean age 64 years, 74% men) with 16 year follow-up)

2.5c. Smoking cessation reduces mortality in patients with CHD with no diminution of effect with increasing age. The excess risks of coronary artery death, MI and atherosclerosis return to non-smoking levels within 10-20 years[i,ii].
(Health gain notation - 1 *"beneficial"*)

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 yearsí 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)

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

The *statements*

The *evidence*

2.6 Coronary revascularisation

2.6a. Coronary Artery Bypass Grafting (CABG) is more effective at relieving symptoms of angina and improving quality of life indicators over five years than medical therapy, with less advantage by ten years follow-up[i].
(Health gain notation - 2 *"likely to be beneficial"*)

i. Rogers WJ, Coggin, CJ, Gersh BJ, et al. Ten year follow-up of quality of life in patients randomised to receive medical therapy or coronary artery bypass graft surgery. *Circulation* 1990;**82**:1647-58
(Type II evidence - randomised controlled trial of 780 patients with ten year follow-up)

2.6b. 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].
(Health gain notation - 1 *"beneficial"*)

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

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)

2.6c. Percutaneous Transluminal Coronary Angioplasty (PTCA) is more effective in relieving symptoms of angina than medical treatment[i,ii] (64% vs. 46% angina free at six-month follow-up, p<0.01)[i]; the advantages are greatest in patients with more severe angina[ii] and single vessel disease[iii]. PTCA has not been shown to improve survival[ii]; death or non-fatal MI was significantly more frequent with PTCA at median 2.7 years follow-up (6.3% vs. 3.3%, absolute risk difference 3%; 95% CI: 0.4%, 5.7%; p=0.02), but not deaths alone (2% vs. 1%, p=0.32)[ii]. At three year follow-up PTCA confers little benefit over medical treatment due to high rate of stenosis[ii,iii].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

Caveat: *Further trials comparing PTCA vs. medical therapy in patients with double vessel disease are required.*

i. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs, ACME Investigators. *New England Journal of Medicine* 1992;**326**:10-16
(Type II evidence - randomised controlled trial of 212 patients with significant stenosis in at least one coronary artery randomised to PTCA or medical therapy)

ii. RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet* 1997;**350**:461-68
(Type II evidence - randomised controlled trial of 1018 patients with stable angina, unstable angina or previous MI and significant stenosis in at least one coronary artery randomised to PTCA or medical therapy)

iii. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single-vessel coronary artery disease in a Veterans Affairs Cooperative randomised trial. Veterans Affairs ACME Investigators. *Journal of the American College of Cardiology* 1997;**29**:1505-11
(Type II evidence - randomised controlled pilot trial of 328 male patients with single or double vessel disease and stable angina randomised to PTCA or medical therapy)

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

The *statements*

The *evidence*

2.6d. **CABG is more effective** at relieving symptoms of angina than PTCA at three year follow-up (odds ratio 1.47; 95% CI: 1.32, 1.87; p<0.000) with no difference in mortality (3.7% vs. 3.9%) or combined risk of death or non-fatal MI (10.1% vs. 9.8%). CABG patients were less likely to undergo either a subsequent CABG (1% vs. 19.7%, odds ratio 0.04; 95% CI: 0.02, 0.07; p<0.000) or subsequent PTCA (6% vs. 22.9%, odds ratio 0.21; 95% CI: 0.16, 0.27; p<0.000)[i].
(Health gain notation - 1 *"beneficial"*)

Caveat: Stringent entry criteria may limit generalisability to the wider population of patients requiring revascularisation.

i. Sim I, Gupta M, McDonald K, Bourassa MG, Hlatky MA. A meta-analysis of randomised trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. *American Journal of Cardiology* 1995;**76**:1025-29. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 2943 patients in five randomised controlled trials)

2.6e. No recent **cost-effectiveness** analyses comparing either CABG or PTCA to medical therapy are available. *Further research in this area is recommended*[i].
(Health gain notation - 4 *"unknown"*)

i. Management of Stable Angina. *Effective Health Care Bulletin*. Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type I evidence - systematic literature search)

2.6f. **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].
(Health gain notation - 4 *"unknown"*)

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)

2.6g. **PTCA** is appropriately used for **palliation** in patients with **less severe disease**, inadequately controlled on medical treatment. There is little evidence that this will improve survival[i].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

i. Management of Stable Angina. *Effective Health Care Bulletin*. Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type I evidence - systematic review)

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

The *statements*	The *evidence*
2.6h. 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%, 40/1000 patients treated). The odds of reocclusion for CABG and PTCA combined was reduced at six-months by 41% (SD 6), p<0.0001[i]. (Health gain notation -1 *"beneficial"*)	**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. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 5323 patients in 20 CABG trials and 833 patients in three PTCA trials)
2.6i. 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]. (Health gain notation - 1 *"beneficial"*)	**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)
2.6j. Calcium antagonists[i] and fish oils (omega-3 fatty acids)[ii] may reduce restenosis rates following PTCA. (Health gain notation - 4 *"unknown"*) **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. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 2. Oxford: Update Software, 1998 (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)

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

The *statements*

2.6k. **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[i].
(Health gain notation - 2 *"likely to be beneficial"*)

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.

The *evidence*

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(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)

2.6l. There is increasingly valid evidence that **PTCA with elective stenting** is more effective than standard angioplasty in reducing the need for subsequent revascularisation, or in reducing angina, stroke, MI or mortality at up to one year follow-up[i,ii]. Event-free survival (death, MI or revascularisation) at six months 12.8% vs. 19.3%, relative risk 0.67; 95% CI: 0.48, 0.92; p=0.013[ii]. There is no evidence that stents are cost-effective: the additional cost per quality adjusted life year is around £250,000[i]. **Antiplatelet therapy** reduces the incidence of cardiac events and haemorrhagic and vascular complications at 30 days post-stenting compared to anticoagulation[iii]. 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)[iv].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Methodological flaws including non-blinded outcome assessment or analysis not based on intention to treat and narrow inclusion criteria and operator skill dependence limits the validity[v] and generalisability[i] of the early published trials.

i. Chase D, Best L, Milne R. *Development & Evaluation Committee Report (DEC) No. 87. Stents for Coronary Artery Disease*. The Wessex Institute for Health Research & Development, 1998.
http://www.epi.bris.ac.uk/rd/publicat/dec/index.htm
(Type I evidence - systematic review of five randomised controlled trials)

ii. Serruys PW, van Hout B, Bonnier H, et al, for the Benestent Study Group. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673-81
(Type II evidence - randomised controlled trial of 827 patients with stable or unstable angina)

iii. Schomig A, Neumann F, Kastrati A, et al. A randomised comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. *New England Journal of Medicine* 1997;**334**:1084-89
(Type II evidence - randomised controlled trial of 517 patients undergoing coronary artery stenting with mix of acute and chronic coronary syndromes)

iv. 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 2399 patients with stable or unstable angina)

v. Management of Stable Angina. *Effective Health Care Bulletin*. Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997.
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type II evidence - summary review of randomised controlled trials)

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

The *statements*

2.6m. There is currently 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].
(Health gain notation - 4 *"unknown"*)

Caveat: DCA remains a rarely used technique. *Further evaluation in trials to compare DCA with PTCA and stenting is required.*

The *evidence*

i. Management of Stable Angina. *Effective Health Care Bulletin.* Volume 3 Number 5. University of York: NHS Centre for Reviews and Dissemination, 1997 http://www.york.ac.uk/inst/crd/ehcb.htm
(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)

Date of completion of this document

30.9.98

3 UNSTABLE ANGINA

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

The *statements*

The *evidence*

3.1 Clinical guidelines

3.1a. The clinical syndrome of **unstable angina** includes patients within a spectrum ranging from stable angina through to myocardial infarction (MI). Patients present with symptoms of angina at rest (usually more than 20 minutes), new onset of exertional angina with marked limitation of ordinary physical activity, or recent (<2 months) increase in the severity of angina. The risk of death or complications in patients with unstable angina is lower than in patients with MI but higher than with stable angina. Around 5% to 10% of patients with unstable angina progress to MI, of which in 1% the outcome will be fatal[i]. **Evidence-based guidelines** for the diagnosis and management of unstable angina are available[i].
(Health gain notation - 1 *"beneficial"*)

i. Braunwald E, Mark DB, Jones RH, et al. *Unstable Angina: Diagnosis and Management. Clinical Practice Guideline Number 10 (amended)* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic/
(Type V evidence - expert opinion)

3.2 Thrombolytic therapy

3.2a **There is no evidence that thrombolytic therapy** is of benefit in patients without acute ST-segment elevation or left bundle branch block on 12-lead ECG, and is associated with a non-significant 1.7% (95% CI: -2.4%, 5.8%) increased risk of acute myocardial infarction (MI)[i].
(Health gain notation - 5 *"unlikely to be beneficial"*)

i. Braunwald E, Mark DB, Jones RH, et al. *Unstable Angina: Diagnosis and Management. Clinical Practice Guideline Number 10 (amended)* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic/
(Type I evidence - systematic review and AHCPR meta-analysis of eight trials)

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

The *statements*

The *evidence*

3.3 Antiplatelet and anticoagulant therapy

3.3a. Antiplatelet therapy is likely to reduce the odds of MI, stroke or vascular death in patients with unstable angina 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[i].
(Health gain notation - 2 *"likely to be beneficial"*)

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

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994; **308**: 81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 4000 patients in seven trials of antiplatelet therapy in patients with unstable angina)

3.3b. Intravenous heparin during the acute phase of unstable angina significantly reduces the risk of MI (fatal or non-fatal) at mean follow-up of 5.7 days compared to aspirin (0.8% of heparin patients vs. 3.7% of aspirin patients, p = 0.035: absolute risk difference 2.9%; 95% CI: 0.3%, 5.6%)[i].
(Health gain notation - 1 *"beneficial"*)

i. Theroux P, Waters D, Qiu S, et al Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993;**88**:2045-48
(Type II evidence - randomised controlled trial of 484 patients with unstable angina randomised to 325mg aspirin twice daily or dose-adjusted heparin)

3.3c. There is some evidence that **combination therapy of oral aspirin and intravenous heparin** in the initial management of unstable angina may reduce the incidence of MI and death compared to aspirin alone both during treatment (odds ratio 0.67; 95% CI: 0.44, 1.02; p=0.06) and at 12 week follow-up (odds ratio ratio 0.82; 95% CI: 0.56, 1.20; p=NS)[i].
(Health gain notation - 4 *"unknown"*)

Caveat: It is not clear that all relevant studies were included, and follow-up was short. *A large randomised controlled trial with long-term follow-up is necessary.*

i. Oler A, Whooley MA, Oler J, Grady D. Adding aspirin to heparin reduces the incidence of myocardial infarction and death in patients with unstable angina. *Journal of the American Medical Association* 1996;**276**:811-15. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1353 patients in six randomised controlled trials comparing combination therapy of aspirin and heparin to aspirin alone)

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

The *statements*

3.3d. In view of the evidence for the efficacy of heparin and aspirin as monotherapy, in the absence of contra-indications it is recommended that all patients with unstable angina should be treated with both **heparin in the acute phase** and **long-term aspirin**[i].
(Health gain notation - 1 *"beneficial"*)

The *evidence*

i. Braunwald E, Mark DB, Jones RH et al. *Unstable Angina: Diagnosis and Management. Clinical Practice Guideline Number 10 (amended)* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic/
(Type V evidence - expert opinion)

3.3e. There is accumulating evidence that antithrombotic therapy with **low-molecular weight heparins** in combination with aspirin is at least as effective[i] or more effective[ii - iv] as unfractionated heparin and aspirin in reducing the incidence at up to four month follow-up of ischaemic events (death, new infarct or recurrent angina) or revascularisation in patients with unstable angina. **Enoxaparin** is associated with an excess risk of both minor[ii] and major haemorrhage at catheterisation sites[iii].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

Caveat: *Further assessment of relative effectiveness, cost-effectiveness and safety is required.*

i. Klein W, Buchwald A, Hillis S, et al. Comparison of low-molecular weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary disease. Fragmin in Unstable Coronary Artery Disease Study (FRIC). *Circulation* 1997;**96**:61-68
(Type II evidence - randomised controlled trial of 1482 patients with unstable angina randomised to a maximum of 45 days of 7500 IU dalteparin daily or continuous dose-adjusted heparin)

ii. Cohen M, Demers C, Gurfinkel E, et al, for the ESSENCE study group. A comparison of low-molecular weight heparin with unfractionated heparin for unstable coronary disease. *New England Journal of Medicine* 1997;**337**:447-52
(Type II evidence - randomised controlled trial of 3171 patients with unstable angina randomised to a maximum of 8 days 1mg/kg body weight of sub-cutaneous enoxaparin twice daily or continuous dose-adjusted heparin)

iii. The Thrombolysis in Myocardial Infarction (TIMI) IIA Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI IIA. *Journal of the American College of Cardiology* 1997;**29**:474-82
(Type II evidence - randomised controlled trial of 630 patients with unstable angina randomised to 1.25mg/kg or 1.0mg/kg body weight enoxaparin for 14 days)

iv. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular weight heparin during instability in coronary artery disease. *Lancet* 1996;**347**:561-68
(Type II evidence - randomised controlled trial of 1506 patients with unstable angina randomised to a maximum of 45 days of 7500 IU dalteparin daily or placebo)

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

The *statements*

3.3f. Abciximab therapy in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) with severe unstable angina or evolving MI[i] or refractory unstable angina[ii] or stable angina[iii] is associated with reduced occurrence of death, non-fatal MI or re-intervention at 30 days compared to placebo (11.3% vs. 15.9%, p=0.012)[ii]. Major bleeding was more frequent with abciximab[i,ii] (3.8% vs. 1.9%, p=0.04)[ii]. There was no difference in death, MI or repeat intervention between abciximab and placebo in one trial at six-month follow-up[ii]: another trial found no significant difference in major bleeding and a small advantage in the cumulative incidence of death, MI or repeat revascularisation in the abciximab group[iii].
(Health gain notation - 4 *"unknown"*)

Caveat: *Further trials of clinical and cost-effectiveness are required.* Evidence that other glycoprotein IIb/IIIa inhibitors (tirofiban, eptifibatide and lamifiban) are also effective is accumulating, and trials are in progress to clarify the benefits in patients undergoing stenting or as an adjunct to thrombolytic therapy or primary angioplasty[iv].

The *evidence*

i. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *New England Journal of Medicine* 1994;**330**:956-61
(Type II evidence - randomised controlled trial of 2099 patients with severe unstable angina or evolving MI randomised to abciximab or placebo pre-PTCA)

ii. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;**349**:1429-35
(Type II evidence - randomised controlled trial of 1265 patients with refractory unstable angina randomised to abciximab or placebo pre-PTCA)

iii. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularisation. *New England Journal of Medicine* 1997;**336**:1689-96
(Type II evidence - randomised controlled trial of 2792 patients with stable angina randomised to abciximab with standard dose or low dose heparin, or placebo pre-PTCA)

iv. Adgey AAJ. An overview of the results of clinical trials with glycoprotein IIb/IIIa inhibitors. *European Heart Journal* 1998;**19** (suppl D):D10-21
(Type II evidence - narrative overview of randomised controlled trials)

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

The *statements*

The *evidence*

3.4 Coronary revascularisation

3.4a. **"High risk" patients with unstable angina** - failure to stabilise with medical treatment, recurrent ischaemia, congestive heart failure or left ventricular (LV) dysfunction - are at increased risk of MI or cardiac death and should be considered for prompt revascularisation[i].
(Health gain notation - 2 *"likely to be beneficial"*)

3.4b. Patients found at **catheterisation** to have significant **left main disease** (>50% stenosis) or significant (>70%) **three-vessel disease** with depressed LV function (ejection fraction <0.50) should be referred promptly for **coronary artery bypass grafting**[i].
(Health gain notation - 1 *"beneficial"*)

3.4c. Patients with **two-vessel disease**, with proximal severe subtotal stenosis (>95%) of the left anterior descending coronary artery and depressed LV function should be referred promptly for revascularisation[i].
(Health gain notation - 2 *"likely to be beneficial"*)

i. Braunwald E, Mark DB, Jones RH et al. *Unstable Angina: Diagnosis and Management. Clinical Practice Guideline Number 10 (amended)* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic
(Type II evidence - narrative review of randomised controlled trials)

3.4d. An **Early Invasive Strategy** of routine cardiac catheterisation of all patients without contra-indications does not achieve significantly different outcomes at 42 days of death, non-fatal MI or positive six-week exercise test compared to an **Early Conservative Strategy** of selective catheterisation of high risk patients (prior revascularisation, reduced LV function, recurrent ischaemia or ventricular arrhythmia) 15.5% vs. 17.7%; p =0.26[i].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

i. TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-q wave myocardial infarction. *Circulation* 1994; **89**:1545-56
(Type II evidence - 1473 patients randomised to early invasive or early conservative catheterisation strategy)

3.4e. A USA cost-effectiveness analysis based on the TIMI III data suggests the costs of **Early Invasive Strategy** are similar to the **Early Conservative Strategy**; either strategy is acceptable from the economic viewpoint[i].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

i. Conti CR. Unstable angina: cost of conservative and invasive strategies using TIMI 3B as a model. *Clinical Cardiology* 1995; **18**:187-88
(Type II evidence - analysis of 1995 USA health care costs based on results of trial of 1473 patients randomised to early invasive or early conservative catheterisation strategy)

Date of completion of this document

30.9.98

4 MYOCARDIAL INFARCTION

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

The *statements*

The *evidence*

4.1 Clinical guidelines

4.1a. Acute myocardial infarction characteristically presents with an acute onset of severe chest pain at rest[i]. Clinical guidelines and audit standards for the **management of acute myocardial infarction** are available from the British Cardiac Society[i], the American Heart Association[ii] and European Society of Cardiology[iii].
(Health gain notation - 1 "*beneficial*")

i. de Bono DP, Hopkins A, for a working party of the joint audit committee of the British Cardiac Society and the Royal College of Physicians of London. *The management of acute myocardial infarction.* British Cardiac Society, 1996. http://www.cardiac.org.uk/
(Type V evidence - expert opinion)

ii. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on management of acute myocardial infarction). *Circulation* 1996;**94**:2341-50 http://www.americanheart.org/Scientific/statements/1996/acmi-toc.htm
(Type V evidence - expert opinion)

iii. Julian DG, Boissel JP, de Bono DP, et al. Acute Myocardial Infarction: pre-hospital and in-hospital management. *European Heart Journal* 1996;**17**:43-63. http://www.escardio.org/knowledge/guidelines/Management_of_AMI.htm (login required, but registration is free).
Click "Previous versions" - recent version (2002). (Type V evidence - expert opinion)

4.2 Out of hospital cardiac arrest

4.2a. Bystander cardio-pulmonary resuscitation (CPR) is associated with improved survival to discharge from hospital to home (2.9% vs. 0.8%, odds ratio for survival 3.7; 95% CI: 1.7, 8.8; p<0.001). CPR judged to be performed effectively has greater benefit (survival 4.6% vs. 2.0%, odds ratio for CPR effectively compared to ineffectively performed 3.9; 95% CI: 1.1, 14.0; p<0.04)[i].
(Health gain notation - 1 "*beneficial*")

i. Gallagher E, Lombardi G, Gennis P. Effectiveness of bystander cardiopulmonary resuscitation and survival following out-of hospital cardiac arrest. *Journal of the American Medical Association* 1995;**274**:1922-25
(Type IV evidence - prospective cohort of 2071 consecutive arrests, 662 receiving CPR, over a six-month period in New York)

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

The *statements*

4.2b. **Defibrillation** and Basic Life Support (BLS) of patients **with out-of-hospital cardiac arrest** is associated with a 9.2% increase in survival compared to BLS and no defibrillation[i] (odds ratio 0.92; 95% CI: 0.88, 0.96; p=0.0003)[ii].
(Health gain notation - 1 "*beneficial*")

Caveat: Meta-analysis based on USA case series, limited by exclusion of unpublished studies and the complexity of confounding variables.

The *evidence*

i. Watts DD. Defibrillation by basic emergency medical technicians: effect on survival. *Annals of Emergency Medicine* 1995;**26**:635-39. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type IV evidence - systematic review and meta-analysis of 1827 patients in seven prospective case series)

ii. Auble TE, Menegazzi JJ, Paris PM. Effect of out-of-hospital defibrillation by basic life support providers on cardiac arrest mortality: a meta-analysis. *Annals of Emergency Medicine* 1995;**25**:642-48. In: Database of Reviews of Effectiveness. The Cochrane Library, Issue 4. Oxford: Update Software, 1998
(Type IV evidence - systematic review and meta-analysis of 4017 patients in ten case series)

4.2c. Compared to Basic Life Support (BLS) & defibrillation, a two-tier system including **Advanced Life Support** (ALS) for out-of-hospital cardiac arrest is associated with increased survival (ALS survival to discharge 10.5% vs. BLS & defibrillation 5.2%). A one-minute decrease in the mean response time of ALS was associated with an absolute increase in survival of 0.7%[i].
(Health gain notation - 1 "*beneficial*")

Caveat: Meta-analysis based on USA case services in limited geographical areas. *Further studies are required to examine the effectiveness of out-of-hospital life support systems.*

i. Nichol G, Detsky AS, Stiell IG, OíRourke K, Wells G, Laupacis A. Effectiveness of emergency medical services for victims of out-of-hospital cardiac arrest: a meta-analysis. *Annals of Emergency Medicine* 1996;**27**:700-10. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type IV evidence - systematic review and meta-analysis of 23,313 cardiac arrests in 36 case series)

4.2d. Evidence-based guidelines for the **pre-hospital management** of acute myocardial infarction (MI) are available[i].
(Health gain notation - 1 "*beneficial*")

i. Arntz H, Bossaert L, Carli P, et al. The pre-hospital management of acute heart attacks. Recommendations of a Task Force of the European Society of Cardiology and the European Resuscitation Council. *European Heart Journal* 1998;**19**:1140-64
http://www.escardio.org/knowledge/guidelines/Pre-Hospital_Management_of_Acute_Heart_attacks.htm .
(login required, but registration is free) (Type V evidence - expert opinion)

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

The *statements*

The *evidence*

4.3 Thrombolytic therapy

4.3a. **Thrombolytic therapy** improves survival in acute MI, with greatest benefit in patients treated **within one hour of symptom onset**[i]: proportional mortality reduction at 35 days 48%; 95% CI: 31%, 61%; and significantly higher in patients treated within two hours, 44% (32%, 53%) than in those treated later, 20% (15%, 25%). Pre-hospital thrombolysis is associated with significantly reduced risk of cardiac death[ii,iii]. Survival benefits apply to all age-groups and cost-effectiveness has been demonstrated in the elderly[iv]. **Overall benefits** of thrombolytic therapy are 65 (95% CI: 38, 93) lives saved per 1000 treated patients at 0-1 hours following symptom onset, 37 (20, 55), 26 (14, 37), 29 (19, 40) and 18 (7, 29) in the 1-2, 2-3, 3-6 and 6-12 hour intervals, respectively. No benefit was found for thrombolysis at 12-24 hours, 9 (-5, 22)[i].
(Health gain notation - 1 "*beneficial*")

Caveat: Thrombolytic therapy is associated with several major adverse effects[v]: five extra deaths/1000 patients treated and four extra strokes (two fatal)/1000 on day of randomisation, and 7/1000 excess of major non-cerebral bleeds (requiring transfusion or life-threatening) at 35 days.

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

ii. Rawles J. Magnitude of benefit from earlier thrombolytic treatment in acute myocardial infarction: new evidence from Grampian Region Early Anistreplase Trial. (GREAT). *British Medical Journal* 1996;**312**:212-26
(Type II evidence - randomised controlled trial of 311 patients (mean age 63 years, 70% men) with suspected acute MI randomised to anistreplase or placebo at home within four hours of symptom onset)

iii. The European Myocardial Infarction Project (EMIP) Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. *New England Journal of Medicine* 1993;**329**:383-89.
(Type II evidence - randomised controlled trial of 2750 patients with suspected acute MI home within six hours of symptom onset randomised to anistreplase prehospital with placebo in hospital, or placebo prehospital followed by anistreplase in hospital)

iv. Krumholtz HM, Pastemak RC, Weinstein MC, et al. Cost effectiveness of thrombolytic therapy with streptokinase in elderly patients with suspected acute myocardial infarction. *New England Journal of Medicine* 1992; **327**:7-13
(Type IV evidence - decision analytical model based on randomised controlled trial data)

v. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311-22
(Type I evidence - systematic review and meta-analysis of nine trials randomising >1000 patients with suspected acute MI to fibrinolytic therapy or control)

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

The *statements*

The *evidence*

4.3b. Immediate percutaneous transluminal coronary angioplasty (PTCA) is more effective than thrombolytic therapy in acute MI: odds ratio of death at 30 days 0.66; 95% CI: 0.46, 0.94; p=0.02[i]. No convincing reduction in mortality in patients receiving both thrombolysis and PTCA compared to thrombolysis alone has been demonstated[ii].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Studies were performed in hospitals with the experience and facilities to provide primary PTCA. *Further trials evaluating longer-term outcomes, operator experience, time to treatment and optimal thrombolytic regimes are required.*

i. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *Journal of the American Medical Association* 1997;**278**:2093-98. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 2606 patients in ten trials comparing primary PTCA vs. thrombolysis)

ii. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomised clinical trials. *Circulation* 1995;**91(2)**:476-85
(Type I evidence - systematic review and meta-analysis of seven trials evaluating primary PTCA and 16 trials evaluating PTCA following thrombolysis)

4.4 Drug therapy

4.4a. Treatment of patients with suspected or definite **acute MI** with **antiplatelet therapy** is associated with reduced MI, stroke and vascular mortality at one month (% odds reduction 29% (SD 4%), risk reduction 38/1000 patients, p<0.000, NNT=26) and a significant reduction in non-fatal MI (% odds reduction 54%, SD 8%, 12/1000; p<0.000, NNT=83) and non-fatal stroke (% odds reduction 40%, SD 17%, 2/1000; p<0.02, NNT=50)[i]. Benefits of aspirin therapy are independent of, and additive to, thrombolytic therapy[ii] and early survival benefits are maintained for at least ten years[iii].
(Health gain notation - 1 *"beneficial"*)

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and sub-group meta-analysis of 20,000 patients in nine trials of antiplatelet therapy in patients with acute MI)

ii. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**:349-60
(Type II evidence - randomised controlled trial)

iii. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *British Medical Journal* 1998;**316**:1337-43
(Type II evidence - randomised controlled trial)

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

The *statements*

4.4b. Early or late post-MI therapy with **beta-blockers** reduces one year mortality[i,ii] (odds ratio 0.81; 95% CI: 0.75, 0.87, p<0.0001)[ii]. High risk patients (previous MI or angina) receive greater benefit than low risk[i].
(Health gain notation - 1 *"beneficial"*)

Caveat: Trial data mainly pre-dates the thrombolytic era

The *evidence*

i. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomised trials in post infarction patients. *European Heart Journal* 1988;**9**:8-16
(Type I evidence - systematic review and meta-analysis of 13,679 patients in nine trials)

ii. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomised controlled trials. *Journal of the American Medical Association* 1993;**270**:1589-95
(Type I evidence - systematic review and meta-analysis of 53,268 patients in 55 trials)

4.4c. **Heparin** therapy without aspirin reduces ten day mortality by 25% (95% CI: 10%, 38%; p=0.002) representing 35 (SD11) fewer deaths/1000. There is little benefit from the addition of heparin therapy to aspirin: reduction in ten day mortality 6% (95% CI: 0%, 10%; p=0.03) representing 5 fewer deaths/1000. Both regimes are associated with adverse effects of excess major bleeds of between 3 and 13/1000, p<0.000[i].
(Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)

Caveat: Outcome measures were poorly defined and not assessed blind to treatment group in the primary studies.

i. Collins R, Mac Mahon S, Flather M, et al. Clinical effects of anticoagulant therapy in suspected therapy in suspected acute myocardial infarction: a systematic overview of randomised trials. *British Medical Journal* 1996;**313**:652-59. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 5000 patients in 21 trials without routine use of aspirin and 68,000 patients in six trials with routine use of aspirin that assessed the addition of iv or sc heparin)

4.4d. **Hirudin** has not been shown to be more effective than **heparin** as adjunctive therapy to thrombolysis in preventing unsatisfactory outcome at 30 days (death, recurrent infarction, congestive failure or cardiogenic shock) in patients with acute MI, with no difference in the rate of major haemorrhage[i,ii].
(Health gain notation - 4 *"unknown"*)

Caveat: *Further trials to assess the most effective dose and duration of hirudin therapy are required.*

i. Antman E, for the TIMI 9B Investigators. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B Trial. *Circulation* 1996;**94(5)**:911-21
(Type II evidence - randomised controlled trial of 3002 patients with unstable angina or acute MI randomised to heparin or hirudin together with thrombolytic therapy)

ii. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *New England Journal of Medicine* 1996;**335**:775-82
(Type II evidence - randomised controlled trial of 12,142 patients with unstable angina or acute MI randomised to 72 hours therapy with heparin or hirudin following treatment with aspirin and thrombolytic therapy)

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

The *statements*

4.4e The most robust evidence available suggests that **magnesium sulphate following thrombolysis** in acute MI is not associated with a reduction in mortality at short-term (five week) follow-up[i].
(Health gain notation - 5 *"unlikely to be beneficial"*)

4.4f. An overview of early trials suggests **amiodarone** reduces the risk of arrhythmic cardiac death post-MI (odds ratio 0.71; 95% CI: 0.51, 0.97; p=0.03)[i]. Patients at high risk of arrhythmic death are likely to benefit[ii,iii].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Poor validity of some primary studies in the meta-analysis[i]. Due to serious adverse effects of amiodarone, use is reserved for patients at high risk of arrhythmic death.

4.4g. Angiotensinogen converting enzyme (ACE) inhibitor therapy started early in acute MI is associated with a one-month odds reduction in mortality of 7%; 95% CI: 2%, 11%; p=<0.004, equivalent to 5 (SD 2) fewer deaths/1000 treated. Survival benefit seems to persist for at least one year[i].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: ACE inhibitors have significant adverse effects of hypotension and renal dysfunction.

The *evidence*

i. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669-85
(Type I evidence - meta-analysis of nine small trials, and two larger trials: one randomising 2316 patients with acute MI to iv magnesium sulphate or placebo and ISIS-4, a randomised controlled trial of 58,050 patients in a 2x2x2 factorial design comparing captopril, mononitrate and iv magnesium sulphate with placebo)

i. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomised controlled trials. *Journal of the American Medical Association* 1993;**270**:1589-95
(Type I evidence - systematic review and meta-analysis of 1557 patients in eight trials, 191 patients in heart failure in three trials and 1366 patients within one month post-MI)

ii. Julian DG, Camm AJ, Frangin G, et al, for the European Myocardial Infarct Amiodarone Trial Investigators. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after myocardial infarction: EMIAT. *Lancet* 1997;**349**:667-74
(Type II evidence - randomised controlled trial of 1486 patients with acute MI and ejection fraction <40% randomised to amiodarone or placebo with median 21 month follow-up)

iii. Cairns JA, Connolly SJ, Roberts R, Gent M, for the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations. CAMIAT. *Lancet* 1997;**349**:675-82
(Type II evidence - randomised controlled trial of 1202 patients with acute MI and frequent ventricular premature depolarisations randomised to amiodarone or placebo with two year follow-up)

i. ACE inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction. *Circulation* 1998;**97**:2202-12
(Type I evidence - systematic review and meta-analysis of 98,496 patients in four randomised controlled trials ACE inhibitor treatment in acute phase MI)

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

The *statements*

4.4h. Oral mononitrate therapy started early in acute MI is not associated with a significant reduction in five-week mortality[i]. Meta-analysis of trials of oral and iv nitrates found a non-significant 3% odds reduction in short-term mortality[i].
(Health gain notation - 4 *"unknown"*)

Caveat: There was significant heterogeneity between the trials - effectiveness of nitrates remains unproven.

4.4i **Nifedipine** therapy may be associated with an increased risk in total mortality in patients with coronary heart disease (CHD); overall risk ratio 1.16; 95% CI: 1.01, 1.33. The risk increases with increasing doses so that only daily doses of 80mg or more are associated with excess mortality: risk ratio 2.83; 95% CI: 1.35, 5.93[i].
(Health gain notation - 6 *"likely to be harmful"*)

Caveat: The validity of the primary studies was not assessed and the search strategy not stated. *Further larger trials comparing with other therapies such as beta-blockers are necessary for more robust clinical implications to be drawn.*

The *evidence*

i. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;**345**:669-85
(Type I evidence - randomised controlled trial of 58,050 patients in a 2x2x2 factorial design comparing captopril, mononitrate and iv magnesium sulphate with placebo, and meta-analysis of 23 randomised controlled trials of oral and iv nitrates in early MI)

i. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;**92**:1326-31. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 8354 patients in 16 trials of secondary prevention with nifedipine: 12 MI, three unstable and one stable angina)

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

The *statements*

The *evidence*

4.5 Implantable cardioverter defibrillators and pacemakers

4.5a. There is preliminary evidence that **implantable cardioverter defibrillators** may prove an efficacious[i - iii] and cost-effective[ii] treatment for malignant ventricular tachyarrhythmias: % relative reduction in total mortality 39% (95% CI: 19%, 59%) at one year, 27% (6%, 48%) at two years and 31% (10%, 52%) at three years[iii]. No benefit was found in a trial of prophylactic implantation of defibrillators in patients undergoing elective coronary artery bypass surgery[iv].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Restrictive entry criteria to these trials limit the generalisability of the findings. Further trials are in progress to ascertain the precise sub-groups of high risk patients likely to benefit[v] and *further evidence of cost-effectiveness is required*.

i. Moss AJ, Hall J, Cannom DS, et al, for the Multicenter Automatic Defibrillator Implantation Trial (MADIT) Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *New England Journal of Medicine* 1996;**335**:1933-40
(Type II evidence - randomised controlled trial of 196 high-risk patients aged 25 to 80 years with CHD and asymptomatic unsustained ventricular tachycardia, randomised to antiarrhythmic therapy or defibrillator)

ii. Wever EFD, Hauer RNW, Schrijvers G, et al. Cost-effectiveness of implantable defibrillator as first-choice therapy versus electrophysiologically guided, tiered strategy in post-infarct sudden death survivors. A randomised study. *Circulation* 1996;**93**:489-96
(Type II evidence - randomised controlled trial of 60 cardiac arrest survivors randomised to antiarrhythmic therapy or defibrillator)

iii. The antiarrhythmics versus implantable defibrillators (AVID) investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *New England Journal of Medicine* 1997;**337**:1576-83
(Type II evidence - randomised controlled trial of 1016 ventricular arrhythmia survivors randomised to antiarrhythmic therapy or defibrillator with three year follow-up)

iv. Bigger JT, for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary artery bypass graft surgery. *New England Journal of Medicine* 1997;**337**:1569-75
(Type II evidence - randomised controlled trial of 900 patients undergoing elective CABG randomised to defibrillator or control with four year follow-up)

v. Connolly SJ. Implantable cardioverter defibrillators - for whom? *Lancet* 1998;**352**:338-39
(Type V evidence - expert opinion)

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

The *statements*	The *evidence*
4.5b. Guidelines for the management of arrhythmias with **cardiac pacemakers** and **implantable cardioverter defibrillators** are available[i]. (Health gain notation - 1 "*beneficial*")	**i.** Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on pacemaker implementation). *Journal of the American College of Cardiology* 1998;**31**:1175-1209 http://www.americanheart.org/Scientific/statements/1998/049802.html (Type V evidence - expert opinion)
4.6 Secondary prevention	
4.6a. CHD and total mortality risk is proportional to net **reduction in total cholesterol** (10% reduction in total cholesterol associated with an expected 15% risk reduction in CHD and 11% total mortality)[i]. (Health gain notation - 1 "*beneficial*")	**i.** Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit - impact of statin trials. *Circulation* 1998;**97**:946-52 (Type I evidence - systematic review and meta-analysis of 38 observational primary and secondary prevention studies and randomised controlled trials of lipid lowering agents including eight statin trials)
4.6b. Simvastatin therapy in men and post-menopausal women aged 35 to 70 years, with a history of **MI** more than six months previously and/or stable angina, and a **trial entry total cholesterol of 5.5 to 8.0 mmol/l** and serum triglyceride (2.5 mmol/l) reduced the risk of death from any cause (primary endpoint) by 30% (95% CI: 15%, 42%; p=0.0003), from CHD by 42% (95% CI: 27%, 54%), of a major coronary event (secondary endpoint - CHD death, non-fatal MI or resuscitated cardiac arrest) by 34% (95% CI: 25%, 41%; p<0.00001), and revascularisation (one of four tertiary endpoints) by 37% (95% CI: 26%, 46%; p<0.00001). Post-hoc analysis found a reduction in fatal or non-fatal stroke of 30% (95% CI: 4%, 48%; p=0.024)[i]. No interactions between therapy, gender or age were found; benefits apply to both males and females aged under or over 60 years. (Health gain notation - 1 "*beneficial*") **Caveat:** The many exclusion criteria used in this study, including unstable angina, MI in previous six months, planned revascularisation, arrhythmia, heart failure and previous stroke, limits the generalisability of the results. In addition only 37% of subjects were taking aspirin.	**i.** Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383-89 (Type II evidence - randomised controlled secondary prevention trial of 3617 men and 827 post-menopausal women aged 35-70 with stable angina or previous MI (79%), randomised to double blind treatment with simvastatin 20-40mg or placebo, median 5.4 year follow-up)

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

The *statements*

4.6c. **Pravastatin** therapy in men and post-menopausal women aged 21-75 years, with a history of **MI** in the last three to 20 months, a **trial entry total cholesterol < 6.2 mmol/l**, LDL cholesterol of 3.0 to 4.5 mmol/l, and fasting triglyceride <4.0 mmol/l, reduced the overall risk of the study primary endpoint of non-fatal MI or death from CHD by 24% (95% CI: 9%, 36%; p=0.003). The risk reduction of a major coronary event (primary endpoint or revascularisation) was minus 3% (95% CI: -38%, 23%) for those with an LDL cholesterol <3.2 mmol/l, 26% (95% CI: 13%, 38%) with an LDL cholesterol 3.2 to 3.9 mg/dl, and 35% (95% CI: 17%, 50%) with an LDL cholesterol >3.9 to 4.5 mmol/l. These effects were not substantially altered by factors such as age, smoking status co-morbidity or previous revascularisation[i]. Risk reduction for **stroke** was 31% (95% CI: 3%, 52%; p=0.03).
(Health gain notation - 1 "*beneficial*")

Caveat: Patients with poorly controlled diabetes or symptomatic congestive heart failure (ejection fraction <25%) were excluded from the trial; the results may not be generalisable to these sub-groups.

The *evidence*

i. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events (CARE) Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New England Journal of Medicine* 1996;**335**:1001-09
(Type II evidence - randomised controlled secondary prevention trial of 3583 men and 576 post menopausal women aged 21-75 years, with previous MI, and total cholesterol levels <6.2mmol/l and LDL cholesterol 3.0 to 4.5 mmol/l, randomised to double blind treatment with pravastatin 40mg daily or placebo, median five year follow-up)

4.6d. A further analysis[i] of a systematic review and meta-analysis of ten secondary prevention trials[ii] found that to **prevent** one combined endpoint of death, non-fatal stroke or non-fatal myocardial infarction, 11 people (95% CI: 10, 13) with a history of MI and/or stable angina would have to be treated with a statin for 2.9 years.
(Health gain notation - 1 "*beneficial*")

i. Statins. *Bandolier* 1997, Number 47. Volume 5, Issue 1 http://www.jr2.ox.ac.uk/bandolier/band47/b47-2.html
(Type I evidence - NNT calculations using data from ten randomised controlled secondary prevention trials of 20,589 patients, mean 2.9 year follow-up)

ii. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomised trials. *Journal of the American Medical Association* 1997;**278**:313-21
(Type I evidence - systematic review and meta-analysis of ten randomised controlled secondary prevention trials of 20,589 patients, mean 2.9 year follow-up)

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

The *statements*	The *evidence*
4.6e. The evidence for the **cost-effectiveness** of simvastatin and pravastatin in the secondary prevention of MI is strong after other cost-effective interventions, including aspirin, smoking cessation, dietary change and exercise, and antihypertensive therapy have been implemented[i]. (Health gain notation - 3 *"balance of risk and cost-benefit"*) **Caveat:** The cost-effectiveness of statin therapy improves when treatment is targeted at high risk individuals. *Further research is needed to determine whether a previous MI or an elevated LDL cholesterol is the best risk factor to identify those patients likely to benefit most.*	**i.** Cholesterol and coronary heart disease: screening and treatment. *Effective Health Care Bulletin*. Volume 4 Number 1. University of York: NHS Centre for Reviews and Dissemination 1998 http://www.york.ac.uk/inst/crd/ehcb.htm (Type II evidence - systematic literature review of cost-effectiveness studies based on randomised controlled trial data)
4.6f. **Antiplatelet therapy** for patients with **previous MI** reduces MI, stroke and vascular mortality at 27 month follow-up (% odds reduction 25%, SD 4%; risk reduction 36/1000 patients, NNT=28) and significantly reduces non-fatal MI (% odds reduction 31%, SD 6%, 18/1000; p<0.000, NNT=56) and non-fatal stroke (% odds reduction 39%, SD 11%, 6/1000; p=0.0005, NNT=200)[i]. Most patients received aspirin - where comparison between regimens and antiplatelet agents were possible no significant differences were noted[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and sub-group meta-analysis of 20,000 patients in 11 trials of antiplatelet therapy in patients with previous MI)

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

The *statements*

4.6g. **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].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Significant benefit of clopidogrel was only found for the protocol specified primary outcome. No benefit was shown for clopidogrel over aspirin in the four protocol specified secondary outcomes, including vascular and all-cause mortality. 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 *evidence*

i. CAPRIE steering committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329-39
(Type II evidence - randomised controlled trial of 19,185 patients, mean 1.9 year follow-up)

4.6h. A Cochrane Review to determine the relative effectiveness and safety of **ticlopidine and clopidogrel** compared to aspirin in the secondary prevention of important vascular outcomes in patients at high risk (previous TIA, ischaemic stroke, MI and peripheral vascular disease) is due for publication in 1999[i].
(Health gain notation - 2 *"likely to be beneficial"*)

i. Hankey GJ, Dunbabin DW, Sudlow CLM. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin in the secondary prevention of stroke and other important vascular events among high risk patients. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis)

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

The *statements*	The *evidence*
4.6i. UK multi-factorial evidence-based guidelines for the **prevention of coronary heart disease** are due for publication in 1998[i]. Updated Joint European guidelines are now available[ii]. (Health gain notation - 1 "*beneficial*")	**i.** British Cardiac Society, British Hypertension Society, British Hyperlipidaemia Association http://www.cardiac.org.uk/ (Type V evidence - expert opinion) **ii.** Wood D, De Backer G, le Faergeman O, Graham I, Mancia G, Pyorala K. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. *European Heart Journal* 1998;**19**:1434-1503 http://www.escardio.org/knowlege/guidelines/CVD_Prevention_in_Clinical_Practice.htm (login required, but registration is free). (Type V evidence - expert opinion)

4.7 Cardiac rehabilitation

4.7a. Cardiac rehabilitation exercise training leads to improvement in exercise tolerance in patients with CHD and heart failure. Improvement occurs without significant cardiovascular complications or adverse outcomes[i]. (Health gain notation - 1 "*beneficial*")	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic/ (Type I evidence - systematic review of 46 randomised controlled trials, 25 non-randomised controlled trials and 43 observational studies)

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

The *statements*	The *evidence*
4.7b. **Cardiac rehabilitation exercise training** reduces symptoms of angina pectoris in patients with CHD and reduces symptoms of heart failure in patients with left ventricular systolic dysfunction[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic (Type I evidence - systematic review of 12 randomised controlled trials, seven non-randomised controlled trials and seven observational studies)
4.7c. **Improved lipid and lipoprotein levels** are achieved in patients with CHD who have undergone multifactorial cardiac rehabilitation[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic (Type I evidence - systematic review of 18 randomised controlled trials, six non-randomised controlled trials and 13 observational studies)

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

The *statements*	The *evidence*
4.7d. Cigarette smoking is reduced in patients who undergo multifactorial cardiac rehabilitation with well designed educational and behavioural components[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic (Type I evidence - systematic review of five randomised controlled trials, one non-randomised controlled trial and one observational study)
4.7e. Psychological and social functioning are enhanced through exercise training, particularly as a component of multifactorial cardiac rehabilitation[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic (Type I evidence - systematic review of nine randomised controlled trials, eight non-randomised controlled trials and two observational studies)
4.7f. Total and cardiovascular mortality are reduced in patients following MI who participate in cardiac rehabilitation exercise training as a component of multifactorial rehabilitation. Based on meta-analysis, at three year follow up, there is a 25% relative reduction in total mortality in patients undergoing rehabilitation including exercise training[i]. (Health gain notation - 1 *"beneficial"*) **Caveat:** Low risk patients were studied. Benefits are likely to apply to high risk patients, but caution in generalising the results is required.	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic (Type I evidence - two meta-analyses of 7063 patients in 21 randomised controlled trials)

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

The *statements*	The *evidence*
4.7g. Based on aggregate data from the USA (1980-1984), the very low rates of occurrence of MI (one non-fatal MI per 293,900 patient-hours with one cardiac mortality per 783,976 patient-hours) and few cardiovascular complications (one cardiac arrest per 111,996 patient-hours) associated with exercise training as part of **cardiac rehabilitation, suggest that cardiac rehabilitation exercise training is relatively safe**[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic/ (Type IV evidence - questionnaire survey of 167 randomly selected cardiac rehabilitation programmes in the USA covering 51,303 patients)
4.7h. **Post-MI exercise stress tests** are recommended for determining functional capacity before prescription of exercise intensity as a component of cardiac rehabilitation[i,ii]. (Health gain notation - 2 *"likely to be beneficial"*)	**i.** Thompson DR, Bowman GS, de Bono D P, Hopkins A. *Cardiac rehabilitation: guidelines and audit standards*. London: Royal College of Physicians of London, 1997 (Type V evidence - expert opinion) **ii.** American College of Sports Medicine. *Guidelines for exercise testing and prescription, 4th ed.* Philadelphia: Lea and Febiger, 1991 (Type V evidence - expert opinion)
4.7i. Guidelines and audit standards for **cardiac rehabilitation** in the UK are available[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Thompson DR, Bowman GS, de Bono D P, Hopkins A. *Cardiac rehabilitation: guidelines and audit standards*. London: Royal College of Physicians of London, 1997 (Type V evidence - expert opinion)

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

The *statements*	The *evidence*
4.7j. **Psychosocial interventions** in patients with CHD in cardiac rehabilitation schemes are associated with greater reductions in physiological distress, systolic blood pressure, heart rate, cholesterol level, a 41% reduction in mortality at two year follow-up (log-adjusted odds ratio for mortality in patients not receiving psychosocial interventions 1.70; 95% CI: 1.09, 2.99) and a 46% reduction in cardiac recurrence (log-adjusted odds ratio for mortality in patients not receiving psychosocial interventions 1.84; 95% CI: 1.12, 2.99)[i]. (Health gain notation - 2 *"likely to be beneficial"*) **Caveat:** Poor quality meta-analysis with limited literature search did not assess the validity of the primary studies. *Further research to identify the specific most effective types of psychosocial interventions is necessary.*	**i.** Linden W, Stossel C, Maurice J. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. *Archives of Internal Medicine* 1996; **156**:745-52. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 23 randomised controlled trials covering 3180 patients)
4.7k. There is no valid evidence that **patient education** in patients with CHD improves mortality, morbidity and lifestyle factors[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** Methodological problems include the validity of the primary studies, the diversity of interventions and follow-up, the imprecise inclusion criteria and systematic exclusion of studies in multiple sub-group analyses.	**i.** Mullen PD, Mains DA, Velez R. A meta-analysis of controlled trials of cardiac patient education. *Patient Education and Counselling* 1992;**19**:143-62. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 28 studies: 14 randomised controlled trials and 14 quasi-experimental studies)
4.7l. There has been **no comprehensive economic evaluation** of cardiac rehabilitation. The available economic evaluations, while limited in scope, suggest that there may be favourable economic outcomes[i]. (Health gain notation - 4 *"unknown"*)	**i.** Wenger NK, Froelicher ES, Smith LK, et al. *Cardiac Rehabilitation. Clinical Practice Guideline Number 17* AHCPR. Rockville MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, US Department of Health and Human Services, 1995. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 http://www.ahcpr.gov.clinic/ (Type II evidence - two randomised controlled trials and two non-randomised controlled studies)

Date of completion of this document

30.9.98

5 HEART FAILURE

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

The *statements*

The *evidence*

5.1 Clinical guidelines

5.1a. Heart failure is characterised by breathlessness, fatigue and fluid retention resulting from pump failure of the heart. It is a major public health problem, affecting around 1% of the general population and 10% of the elderly; 50% of patients die within a five year period[i]. **Evidence-based guidelines** are available for the evaluation and management of heart failure[i-iv].
(Health gain notation - 1 "*beneficial*")

i. Konstam M, Dracup K, Baker D, et al. *Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic dysfunction. Clinical Practice Guideline Number 11* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994
http://www.ahcpr.gov/clinic/
(Type V evidence - expert opinion and review of randomised controlled trials, non-randomised and observational studies)

ii. Williams JF Jr, Bristow MR, Fowler MB, et al. ACC/AHA guidelines for the evaluation and management of heart failure: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on evaluation and management of heart failure). *Circulation* 1995;**92**:2764-84
http://www.americanheart.org/Scientific/statements/1995/21955555.html
(Type V evidence - expert opinion)

iii. Cleland JGF, Erdmann E, Ferrari R, et al. Guidelines for the diagnosis of heart failure. *European Heart Journal* 1995;**16**:741-51
(Type V evidence - expert opinion)

iv. Remme WJ. The treatment of heart failure. *European Heart Journal* 1997;**18**:736-53
(Type V evidence - expert opinion)

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

The *statements*

The *evidence*

5.2 Echocardiography

5.2a. Echocardiography to assess left-ventricular performance and valve structure and function is a critical step in the evaluation and management of patients with suspected or clinically evident heart failure[i]. **Guidelines** for the clinical application of echocardiography are available[ii].
(Health gain notation - 1 "*beneficial*")

i. Konstam M, Dracup K, Baker D, et al. *Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic dysfunction. Clinical Practice Guideline Number 11* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994
http://www.ahcpr.gov/clinic/
(Type V evidence - expert opinion and review of randomised controlled trials, non-randomised and observational studies)

ii. 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). *Journal of the American College of Cardiology* 1997;**29**:862-79
http://www.americanheart.org/Scientific/statements/1997/039703toc.html
(Type V evidence - expert opinion)

5.3 Immunisation

5.3a. Influenza and pneumococcal immunisation are effective in patients with heart failure[i].
(Health gain notation - 1 "*beneficial*")

i. See *Respiratory Diseases* bulletin in this series.

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

The *statements*

The *evidence*

5.4 Drug therapy

5.4a. Angiotensin converting enzyme (ACE) inhibitors reduce mortality and morbidity in patients with chronic heart failure. However this benefit may be limited to patients with relatively poor left ventricular ejection fraction.
A consistent effect among a broad range of patients and different ACE inhibitors is seen.
The largest reductions with treatment are observed in the first 90 days[i].
(Health gain notation - 1 *"beneficial"*)

i. Garg R, Yusuf S. Overview of randomised trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *Journal of the American Medical Association* 1995;**273**:1450-56. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 7105 patients in 32 trials comparing ACE inhibitors with placebo)

5.4b. Early **economic analyses** suggest **ACE inhibitors** are cost-effective therapy. The balance between overall savings and costs depends on the proportion of patients whose treatment is initiated by the general practitioner[i].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: *Further up-to-date analyses are required*[ii].

i. ACE Inhibitors in the treatment of chronic heart failure: Effective and cost-effective. *Bandolier* 1994, Number 8. Volume 1 Issue 8
http://www.jr2.ox.ac.uk/bandolier/band8/b8-1.html
(Type II evidence - economic analyses based on data from randomised controlled trials)

ii. Garg R, Yusuf S. Overview of randomised trials of angiotensin converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *Journal of the American Medical Association* 1995;**273**:1450-56. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 7105 patients in 32 trials comparing ACE inhibitors with placebo)

5.4c. ACE inhibitors can usually be started safely in **primary care** following exclusion of high risk patients requiring hospitalisation[i].
(Health gain notation - 1 *"beneficial"*)

i. Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. *British Medical Journal* 1994;**308**:321-28
(Type V evidence - expert opinion)

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

The *statements*	The *evidence*
5.4d. There is some evidence that **losartan** 50mg/day, an angiotensin II receptor blocker, may be more effective than captopril 50mg tds in reducing mortality at 48 week follow-up from congestive cardiac failure (all-cause mortality risk reduction 46%; 95% CI: 5%, 69%; p=0.035)[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** Unexpected finding from a protocol specified secondary endpoint. *Further large trials are necessary to confirm these findings and investigate the possibility of a class effect.*	**i.** Pitt B, Segal R, Martinez FA, et al, on behalf of ELITE Study Investigators. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;**349**:747-52 (Type II evidence - randomised controlled trial of 722 patients aged over 65 with ejection fraction <40%)
5.4e. **Diuretics** are an effective symptomatic treatment for acute and chronic heart failure. Their impact on mortality has not been evaluated[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. *British Medical Journal* 1994;**308**:321-28 (Type V evidence - expert opinion)
5.4f. **Cardioversion** (chemical or electrical) is the preferred management for patients in **atrial fibrillation** with left-atrial diameters of <50mm and less than a one year history, following anticoagulation and digitilisation to control the heart rate[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Konstam M, Dracup K, Baker D, et al. Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic dysfunction. Clinical Practice Guideline Number 11 AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic/ (Type V evidence - expert opinion and review of randomised controlled trials, non-randomised and observational studies)
5.4g. **Digoxin** therapy for patients with heart failure in sinus rhythm is associated with fewer hospital admissions than placebo (26.8% vs. 34.7%, risk ratio 0.72; 95% CI: 0.66, 0.79; p<0.001), a borderline reduced risk of death from worsening heart failure (11.6% vs. 13.2%, risk ratio 0.88; 95% CI: 0.77, 1.01; p=0.06) but no difference in overall mortality (34.8% vs. 35.1%, risk ratio 0.99; 95% CI: 0.91, 1.07; p=0.80)[i]. (Health gain notation - 2 *"likely to be beneficial"*)	**i.** The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heat failure. *New England Journal of Medicine* 1997;**336**:525-33 (Type II evidence - randomised controlled trial of 6800 patients in sinus rhythm with ejection fractions <0.45 randomised to digoxin or placebo in addition to diuretics and ACE inhibitors)

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

The *statements*

The *evidence*

5.4h **Ibopamine**, a positively inotropic dopamine agonist, is associated with ventricular arrhythmias and excess mortality[i].
(Health gain notation - 6 *"harmful"*)

i. Hampton JR, van Veldhuisen DJ, Kleber FX, et al, for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997;**349**:971-77
(Type II evidence - randomised controlled trial of 1906 patients with advanced heart failure randomised to ibopamine or placebo)

5.4i. **Beta-blocker** therapy provides symptomatic benefit in patients with heart failure[i], and there is evidence for a reduction in all-cause mortality; odds ratio 0.69; 95% CI: 0.54, 0.89; p=0.0035[ii]. Sub-group analyses found a beneficial effect of lower mortality only in patients receiving vasodilator beta blockers compared to patients not treated with a beta blocker.
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Methodological issues limit the validity of the meta-analysis[ii]. Cause-specific mortality was not available from primary studies due to small size, un-specified primary mortality outcomes and short duration (mean 13 months) of follow-up. Criteria for the selection or assessment of the relevance and validity of the primary studies were not specified. *Large scale, long-term randomised controlled mortality trials are required to determine more reliably the size of effects of treatment on survival and the sub-groups of patients with heart failure likely to benefit.*

i. Cleland JG, Bristow MR, Erdmann E, Remme WJ, Swedberg K, Waagstein F. Beta-blocking agents in heart failure. Should they be used and how? *European Heart Journal* 1996;**17**:1629-39
(Type II evidence - narrative review of randomised controlled trials)

ii. Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure: a systematic overview of randomised controlled trials. *European Heart Journal* 1997;**18**:560-65. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 3141 patients in 24 randomised controlled trials)

5.4j. **Phosphodiesterase inhibitors** are associated with a non-significant increased mortality at minimum follow-up of three months in patients with chronic heart failure. Analysis of studies excluding vesnarinone found a significant increase in mortality of 41% (95% CI: 11%, 79%)[i].
(Health gain notation - 6 *"likely to be harmful"*)

i. Nony P, Boissel JP, Lievre M, et al. Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients: a meta-analysis. *European Journal of Clinical Pharmocology* 1994;**46**:191-96. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review of 2732 patients in 13 randomised controlled trials)

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

The *statements*	The *evidence*
5.4k. There is no good evidence for or against the effectiveness of **anticoagulation** in preventing stroke, arterial or pulmonary embolus in patients with heart failure in sinus rhythm without a history of thrombus or emboli[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** No clinical trials were located. Evidence from seven small studies of benefits conflicts with no evidence of benefits in two larger studies. Full anticoagulation was found to increase the risk of major bleeding.	**i.** Baker DW, Wright RF. Management of heart failure IV: anticoagulation for patients with heart failure due to left ventricular systolic dysfunction. *Journal of the American Medical Association* 1994;**272**:1614-18. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type IV evidence - narrative review of nine observational studies examining effectiveness of anticoagulation; five studies examined risk of major bleeding associated with anticoagulation)
5.5 Surgical management	
5.5a. Coronary artery bypass grafting improves survival and functional outcome (improvement in ejection fraction) in males with moderate to severe heart failure and concomitant limiting angina with a likely mortality reduction of between 30% and 50%. There is insufficient evidence of benefit for women, for men without angina, or of benefit from angioplasty[i]. (Health gain notation - 2 *"likely to be beneficial"*) **Caveat:** Conclusions based on the three highest quality primary studies, one showing no difference and one compromised by un-adjusted baseline differences. The mortality reduction may differ from the 30% to 50% reported.	**i.** Baker DW, Jones RJ, Hodges J, Massie B M, Konstam MA, Rose EA. Management of heart failure III: the role of revascularisation in the treatment of patients with moderate or severe left ventricular systolic dysfunction. *Journal of the American Medical Association* 1994;**272**:1528-34. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type IV evidence - narrative review of 2691 patients (80% male) with moderate to severe left ventricular dysfunction in eight cohort studies of CABG vs. medical treatment)
5.5b. Cardiac transplantation should be considered in patients severely limited by heart failure despite aggressive medical therapy in whom revascularisation is unlikely to be beneficial[i]. (Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)	**i.** Konstam M, Dracup K, Baker D, et al. *Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic dysfunction. Clinical Practice Guideline Number 11* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1994 http://www.ahcpr.gov/clinic/ (Type V evidence - expert opinion)
5.5c. There is currently insufficient evidence that **cardiomyoplasty** is an effective treatment for patients with advanced heart failure[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** Cardiomyoplasty is potentially a lower cost alternative to cardiac transplantation: few patients have been studied world wide.	**i.** Cowley D. Cardiomyoplasty. Canberra: Australian Institute of Health and Welfare 1992. In: Health Technology Assessment: author abstracts. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type V evidence - expert opinion)

Date of completion of this document

30.9.98

6 CONGENITAL HEART DISEASE

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

The *statements*

The *evidence*

6.1 Echocardiography

6.1a. Extended mid-trimester fetal echocardiography has greater sensitivity than four chamber view alone in the pre-natal diagnosis of major cardiac defects in a low risk population (78% vs. 48%)[i]. In a large case-series, the extended fetal heart examination identified 18/21 major abnormalities (sensitivity 86%, specificity 99.9%)[i]. Echocardiography for structural abnormalities correlates well with post-natal diagnosis[ii,iii].
(Health gain notation 1 *"beneficial"*)

i. Achiron R, Glaser J, Gelernter I, Hegesh J, Yagel S. Extended fetal echocardiographic examination for detecting cardiac malformations in low risk pregnancies. *British Medical Journal* 1992;**304**:671-74
(Type IV evidence - comparison of extended fetal echocardiography with standard four chamber view in 5400 fetuses in low risk pregnancies between 18 and 24 weeks gestation)

ii. Allan LD, Chita SK, Sharland GK, Fagg NL, Anderson RH, Crawford DC. The accuracy of fetal echocardiography in the diagnosis of congenital heart disease. *International Journal of Cardiology* 1989;**25**:279-88
(Type IV evidence - retrospective comparison of echocardiography and post-mortem findings in 41 cases with major cardiac malformation)

iii. Oberhoffer R, Cook AC, Lang D, et al. Correlation between echocardiographic and morphological investigations of lesions of the tricuspid valve diagnosed during fetal life. *British Heart Journal* 1992;**68**:580-85.
(Type IV evidence, - retrospective comparison of echocardiography and post-mortem findings in 19 cases with severe tricuspid valve malformation)

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

The *statements*	The *evidence*
6.1b. Echocardiography is the definitive diagnostic method for the recognition and assessment of congenital and acquired heart disease in the paediatric population[i]. (Health gain notation 1 "*beneficial*")	**i.** *XV Echocardiography in the Paediatric Patient.* In: 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 the clinical application of echocardiography). *Journal of the American College of Cardiology* 1997;**29**:862-79 http://www.americanheart.org/Scientific/statements/1997/039703xec.html (Type V evidence - expert opinion)
6.2 Clinical guidelines	
6.2a. Evidence-based guidelines for the evaluation and management of congenital heart disease are available[i]. (Health gain notation 1 "*beneficial*")	**i.** Driscoll D, Allen HD, Atkins DL, et al. Guidelines for evaluation and management of common congenital cardiac problems in infants, children and adolescents. A statement for healthcare professionals from the committee on congenital cardiac defects of the council on cardiovascular disease in the young, American Heart Association. *Circulation* 1994;**90**:2180-88 http://www.americanheart.org/Scientific/statements/1994/109402.html (Type V evidence expert opinion)
6.2b. Evidence-based recommendations for the management of the **adult with congenital heart disease** are available[i]. (Health gain notation 1 "*beneficial*")	**i.** Connelly MS, Webb GD, Somerville J, et al, for the Canadian Consensus Conference on Adult Congenital Heart Disease 1996. *Canadian Journal of Cardiology* 1998;**14**:395-452 http://www.cachnet.org/consens.htm (Type V evidence - expert opinion)

Date of completion of this document

30.9.98

7 STROKE

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

The *statements*

The *evidence*

7.1 Diagnostic imaging

7.1a. **Stroke** is characterised by an acute onset of neurological deficit lasting more than 24 hours, resulting from cerebral infarction or haemorrhage. Neurological symptoms from a Transient Ischaemic Attack (TIA) resolve completely within 24 hours[i]. **CT brain scanning** to confirm or exclude cerebral haemorrhage is part of the routine assessment of all patients who present with the acute onset of a focal neurological deficit (preferably within 48 hours and no later than seven days)[i-iii].
(Health gain notation - 1 *"beneficial"*)

7.1b. **MRI scanning** enables a positive diagnosis in the early stages of stroke to be made - of benefit if an effective early intervention in defined categories of stroke becomes available. MRI is currently most effectively used for assessment of stroke if thrombosis of dural sinus, deep vein or cortical vein is suspected, and for the positive diagnosis of thrombotic infarction[i,iii].
(Health gain notation - 2 *"likely to be beneficial"*)

7.1c. Practice guidelines including the use of **imaging** in transient ischaemic attack and acute stroke are available[i].
(Health gain notation - 1 *"beneficial"*)

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke I: Assessment, Investigation, Immediate Management and Secondary Prevention.* Edinburgh: Royal College of Physicians, 1997
http://www.show.scot.nhs.uk/sign/pdf/sign13.pdf
[Adobe Acrobat reader required]
(Type V evidence - expert opinion)

ii. Stroke. Towards better management: summary and recommendations of a report by the Royal College of Physicians. *Journal of the Royal College of Physicians* 1990;**24**:15-19
(Type V evidence expert - opinion)

iii. Culebras A, Kase C, Masdeu JC, et al. Practice guidelines for the use of imaging in transient ischaemic attack and acute stroke: a report of the stroke council, American Heart Association. *Stroke* 1997;**28**:1480-97
http://www.americanheart.org/Scientific/statements/1997/079705.html
(Type V evidence expert - opinion)

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

The *statements*

The *evidence*

7.2 Organisation of care and rehabilitation

7.2a. Full **medical assessment** should be undertaken and **multidisciplinary assessment** considered for all acute stroke patients to define the nature of the event, the need for investigation, further management, and the need for rehabilitation[i]: evidence-based guidelines are available.
(Health gain notation – 1 *"beneficial"*)

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke I: Assessment, Investigation, Immediate Management and Secondary Prevention.* Edinburgh: Royal College of Physicians, 1997
http://www.show.scot.nhs.uk/sign/pdf/sign13.pdf
[Adobe Acrobat reader required]
(Type V evidence – expert opinion)

7.2b. Stroke patients who receive **organised inpatient (stroke unit) care** are more likely to be alive, independent, and living at home a year after stroke than those receiving conventional care (odds ratio for death 0.81; 95% CI: 0.68, 0.96; p<0.05 and odds ratio for the combined outcome of death or requiring institutional care 0.75; 95% CI: 0.65, 0.87; p<0.0001)[i].
(Health gain notation – 2 *"likely to be beneficial"*)

Caveat: Subjective assessment of what constitutes a stroke unit limits the generalisability of the findings, particularly with respect to the relative effects of the differences in specific management in different models of the "stroke units" identified. *Further research and cost-benefit assessments are required.*

i. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care after stroke. Cochrane Review [updated 17 March 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 18 trials including 3249 patients with median 12 month follow-up)

7.2c. There is some evidence that **formal rehabilitation after stroke** is effective in prolonging short term survival[i] but not long term survival and function (long term survival odds ratio 1.20; 99% CI: 0.84, 1.55)[ii]. Rehabilitation is best provided by well organised multi-disciplinary teams[i].
There is some evidence to suggest that **remedial therapy services** (speech, occupational and physiotherapy) should be provided in hospital and in the community[i].
(Health gain notation – 2 *"likely to be beneficial"*)

Caveat: There are few well designed and reliable randomised controlled trials that assess the effectiveness of rehabilitation after stroke. *Further good quality research is required.*

i. Freemantal N, Pollock C, Sheldon TA, et al. Stroke Rehabilitation. *Effective Health Care Bulletin.* Number 2. Leeds: School of Public Health, University of Leeds, 1992
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type II evidence – narrative summary review of randomised and non-randomised trials)

ii. Evans RL, Connis RT, Hendricks RD et al. Multisciplinary rehabilitation versus medical care: a meta-analysis. *Social Science and Medicine* 1995;**40(12)**:1699-1706
(Type I evidence – systematic review and meta-analysis of 2183 patients in 11 studies)

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

The *statements*

7.2d. Evidence-based clinical guidelines for management of **dysphagia**[i] and **post-stroke rehabilitation** are available[ii,iii].
(Health gain notation – 1 *"beneficial"*)

The *evidence*

i. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke III: Identification and Management of Dysphagia*. Edinburgh: Royal College of Physicians, 1997
http://www.show.scot.nhs.uk/sign/html/html20.htm
(Type V evidence – expert opinion)

ii. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke IV: Rehabilitation, Prevention and Management of Complications, and Discharge Planning*. Edinburgh: Royal College of Physicians, 1998
http://www.show.scot.nhs.uk/sign/html/html24.htm
(Type V evidence – expert opinion)

iii. Gresham GE, Duncan PW, Stason WB, et al. *Post-stroke rehabilitation. Clinical Practice Guideline Number 16* AHCPR. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung and Blood Institute, Public Health Service, U.S. Department of Health and Human Services, 1995
http://www.ahcpr.gov/clinic/
(Type V evidence – expert opinion)

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

The *statements*

The *evidence*

7.3 Drug therapy

7.3a. There is evidence to suggest **antiplatelet therapy** with aspirin in the **acute phase of ischaemic stroke** produces a small net benefit of 9 (SD 3) fewer deaths or non-fatal strokes per 1000 in the first few weeks (p=0.001) and 13 (SD 5) fewer dead or dependent per 1000 at follow-up of several months (p<0.01)[i]. Comparisons of **heparin anticoagulant therapy vs. aspirin** are inconclusive[ii], however management with low-dose heparin (5000 IU) and aspirin in combination may be more effective than aspirin or heparin alone, and is more appropriate for patients in atrial fibrillation or with cardio-embolic stroke[ii].
(Health gain notation – 3 *"trade-off between beneficial and adverse effects"*)

Caveat: The IST trial[ii] was neither double blinded nor placebo controlled and anticoagulation monitoring was not systematic. CT scan was not an entry criterion and hence the comparisons of heparin vs. aspirin were subject to bias. Updated Cochrane Collaboration systematic reviews to include CAST[i] and IST[ii] in the meta-analyses are awaited[iii,iv]. *Further trials to address the questions of benefit from antiplatelet and anticoagulant therapy (including standard and low-molecular weight heparins), singly or in combination, in precisely defined sub-groups of patients with acute ischaemic stroke are required.*

i. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. *Lancet* 1997;**349**:1641-49
(Type II evidence – randomised controlled trial of 21,106 patients within 48 hours of suspected ischaemic stroke treated with 160mg/day aspirin for up to four weeks)

i. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *Lancet* 1997;**349**:1569-81
(Type II evidence – randomised controlled trial of 19,435 patients within 48 hours of suspected ischaemic stroke in factorial design of 300mg/day aspirin, 5000 or 12,500 IU heparin twice daily for up to two weeks)

iii. Counsell C, Sandercock P. Antiplatelet therapy compared to control in acute presumed ischaemic stroke. Cochrane Review [Updated 19 August 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 501 patients in five trials with six month follow-up plus narrative summary of references i and ii)

iv. Counsell C, Sandercock P. Anticoagulant therapy compared to control in patients with acute presumed ischaemic stroke. Cochrane Review [Updated 22 April 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 1599 patients in 15 trials)

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

The *statements*

7.3b. There is no evidence that **thrombolytic therapy** in the acute phase of ischaemic stroke reduces mortality, morbidity or the risk of clinically important complications such as pulmonary embolism (excess mortality within the first two weeks – odds ratio 1.99; 95% CI: 1.56, 2.53 and during follow-up odds ratio 1.36; 95% CI: 1.14, 1.62). Despite the excess mortality, there was a trend in favour of thrombolytic therapy in the combined outcome of death or dependency at the end of follow-up (odds ratio 0.75; 95% CI: 0.63, 0.88)[i]. There are currently too few data to draw any reliable conclusions on the whether lower doses of different thrombolytic agents by different routes of administration are safer or more effective than higher doses[ii].
(Health gain notation – 4 *"unknown"*)

Caveat: *Further trials are required, in which comparisons of thrombolytic therapy, antiplatelet and anticoagulant (standard and low-molecular weight heparins) therapy are made, and the sub-group of stroke patients most likely to benefit are assessed.*

The *evidence*

i. Wardlaw JM, Yamaguchi T, del Zoppo G. Thrombolytic therapy versus control in acute ischaemic stroke. Cochrane Review [Updated 12 August 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 3435 patients with CT/MRI proven acute ischaemic stroke in 12 trials)

ii. Liu M, Wardlaw J. Thrombolysis in acute ischaemic stroke: direct randomised comparisons of different doses, routes of administration and agents. Cochrane Review [updated 13 April 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of seven trials including 725 patients)

7.3c. There is some evidence for the effectiveness of the methylxanthines **pentoxifylline and propentofylline** in the routine management of acute ischaemic stroke (non-significant reduction of odds of early death – odds ratio 0.64; 95% CI: 0.41, 1.02). No data on outcomes such as quality of life or stroke recurrence are available[i].
(Health gain notation – 4 *"unknown"*)

Caveat: Primary trials randomised or quasi-randomised are too small and of insufficient quality to draw firm conclusions. *A large randomised controlled trial to assess the efficacy and safety of pentoxifylline is required.*

i. Bath PMW, Bath SJ, Asplund K. Pentoxifylline, propentofylline and pentifylline in acute ischaemic stroke. Cochrane Review [Updated 11 June 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 793 patients in five trials)

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

The *statements*

7.3d. Current evidence suggests **theophylline and aminophylline** are not effective therapy in the management of acute ischaemic stroke (early case fatality or neurological deterioration was non-significantly reduced by 13%)[i].
(Health gain notation – 4 *"unknown"*)

Caveat: Insufficient patients have been studied.
A large randomised controlled trial to assess the efficacy and safety of theophylline or analogues would be required although the present results do not suggest theophylline is likely to be very effective[i].

7.3e Current evidence suggests **haemodilution** is not an effective treatment for acute ischaemic stroke (odds ratio for dead/dependent/institutionalised 1.03; 95% CI: 0.87, 1.22). This conclusion concerns both hyper- and iso-volaemic haemodilution regimens and all types of haemodiluting agents used (dextran, hydroxyethyl starch and albumin)[i].
(Health gain notation – 6 *"likely to be ineffective"*)

7.3f. The balance of benefit and risk from the routine use of **vasoactive drugs** in acute stroke is unclear[i].
(Health gain notation – 4 *"unknown"*)

Caveat: Insufficient numbers of patients have been studied in trials to assess the effect of changing blood pressure on clinical outcomes in patients with acute stroke.

The *evidence*

i. Mohiuddin AA, Bath FJ, Bath PMW. Theophylline, aminophylline, caffeine and analogues in acute stroke. Cochrane Review [Updated 2 June 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 119 patients in two trials)

i. Asplund K, Israelsson K, Schampi I. Haemodilution in acute ischaemic stroke. Cochrane Review [Updated 9 July 1995]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 2756 patients in 15 trials)

i. Blood pressure in Acute Stroke Collaboration (BASC). Blood pressure management in acute stroke. Part I: assessment of trials designed to alter blood pressure. Cochrane Review [Updated 4 May 1997]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 133 patients in three trials)

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

The *statements*	The *evidence*
7.3g. There is little evidence for the effectiveness of **glycerol treatment** in acute ischaemic stroke. Short-term (two week) case fatality showed a 37% reduction in odds of death (95% CI: 9%, 64%) and a long-term death reduction of 18% (95% CI: 23%, 46%)[i]. (Health gain notation – 4 *"unknown"*) **Caveat:** Studies have too few patients to determine effects and in some methods of randomisation are unclear. *Attention also needs to be given to other outcomes such as quality of life and long term handicap as well as survival.*	**i.** a'Rogvi-Hansen B, Boysen G. Glycerol treatment in acute ischaemic stroke. Cochrane Review [Updated 10 February 1994]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 254 patients in eight trials)
7.3h. There is no evidence that **nimodipine** and other calcium antagonists are effective in improving independence (Barthel index 60 and over at six-months) in patients with **acute ischaemic stroke**[i]. (Health gain notation – 4 *"unknown"*)	**i.** Trust Study Group. Randomised, double-blind, placebo-controlled trial of minodipine in acute stroke. *Lancet* 1990; **336**:1205-09 (Type II evidence – randomised controlled trial of 1215 patients randomised to 120mg oral nimodipine daily or placebo)
7.3i. There is insufficient evidence that **prostacyclin** is effective in the management of acute ischaemic stroke (odds ratio for early death 0.63; 95% CI: 0.22, 1.85)[i]. (Health gain notation – 4 *"unknown"*) **Caveat:** Insufficient numbers of patients have been studied. *A large randomised controlled trial is required.*	**i.** Bath P, Bath F. Prostacyclin and analogues in acute ischaemic stroke. Cochrane Review [Updated 11 January 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 191 patients with presumed ischaemic stroke in five trials)

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

The *statements*	The *evidence*
7.3j. There is insufficient evidence to support the use of **fibrinogen depleting agents** in the treatment of acute ischaemic stroke[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** There have been too few patients and outcome events to draw any reliable conclusions from the present studies.	**i.** Liu M, Counsell C, Wardlaw J. Fibrinogen depleting agents in acute ischaemic stroke. Cochrane Review [Updated 1 November 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 182 patients in three trials)
7.3k. A Cochrane Review to determine the effectiveness and safety of preventing **venous thromboembolism** in patients with **cerebral haemorrhage** is due for publication in 1999[i]. (Health gain notation - 4 *"unknown"*)	**i.** Feigin VL, Rinkel GJE, Algra A, van Gijn J. Standard heparin, heparinoids, or low-molecular weight heparin in the treatment of patients with primary intracerebral haemorrage. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis)
7.3l. There is insufficient evidence to support the use of **corticosteroids** in the routine management of acute ischaemic stroke. Analysis of case fatality found an 8% increase in the odds of death (95% CI: 72% increase to 32% reduction)[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** *Further assessment of mega-dose corticosteroids in large infarcts with cerebral oedema required.*	**i.** Qizilbash N, Lewington SL, Lopez-Arrieta JM. Corticosteroids following acute presumed ischaemic stroke. Cochrane Review [Updated 10 January 1997]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 453 patients with definite or presumed ischaemic stroke in seven trials)
7.3m. A Cochrane Review to determine whether treatment with **mannitol** reduces short and long-term mortality and dependency following ischaemic stroke or cerebral parenchymal haemorrhage is due for publication in 1999[i]. (Health gain notation - 4 *"unknown"*)	**i.** Bereczki D, Liu M, do Prado GF, Fekete I. Mannitol in acute ischaemic stroke and cerebral parenchymal haemorrhage. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis)

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

The *statements*

The *evidence*

7.4 Secondary prevention

7.4a. Long-term **antiplatelet therapy** in patients with previous stroke/TIA is associated with reduced MI, stroke and vascular mortality at three year follow-up (% odds reduction 22% (SD 4), risk reduction 37 (SD 8)/1000 patients treated, p<0.000, NNT=26) and a significant reduction in non-fatal MI (% odds reduction 36% (SD 11), 9 (SD 3)/1000, p<0.000, NNT=100) and non-fatal stroke (% odds reduction 23% (SD 6), 20 (SD 6)/1000, p<0.000, NNT=50). Medium dose aspirin (75-325mg) is the most widely tested antiplatelet regimen and no other regimen appears to have a greater protective effect. Higher doses are associated with increased adverse events[i]. Other antiplatelet drugs, either alone or in combination with aspirin, have not been shown to be more effective than aspirin alone[i]. However more recent evidence suggests a **synergistic benefit of aspirin with dipyridamole** in the risk of stroke or death[ii,iii]; dipyridamole may be better tolerated than aspirin.
(Health gain notation - 1 *"beneficial"*)

i. Antiplatelet Trialist's Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal* 1994;**308**:81-106. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and sub-group meta-analysis of 11,707 patients with previous stroke/TIA in 18 trials of antiplatelet therapy)

ii. Lowenthal A, Buyse M. Secondary prevention of stroke: does dipyridamole add to aspirin? *Acta Neurologica Belgica* 1994;**94**:24-34. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 7666 patients in treatment groups and 3776 in placebo groups)

iii. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Journal of Neurological Science* 1996;**143**:1-13
(Type II evidence - randomised controlled secondary prevention trial of 6602 patients in a 2x2 factorial design involving 50 mg aspirin and 400mg dipyridamole daily)

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

The *statements*

7.4b. **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].
(Health gain notation - 2 *"likely to be beneficial"*)

Caveat: Significant benefit of clopidogrel was only found for the protocol specified primary outcome. No benefit was shown for clopidogrel over aspirin in the four protocol specified secondary outcomes, including vascular and all-cause mortality. 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 either alone or in combination with dipyridamole.*

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**:1329-39
(Type II evidence - randomised controlled trial of 19,185 patients, mean 1.9 year follow-up)

7.4c. A Cochrane Review to determine the relative effectiveness and safety of **ticlopidine and clopidogrel** compared to aspirin in the secondary prevention of stroke and other important vascular outcomes in patients at high risk (previous TIA, ischaemic stroke, MI and peripheral vascular disease) is due for publication in 1999[i].
(Health gain notation - 4 *"unknown"*)

i. Hankey GJ, Dunbabin DW, Sudlow CLM. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin in the secondary prevention of stroke and other important vascular events among high risk patients. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis)

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

The *statements*

The *evidence*

7.5 Anticoagulation

7.5a. **Anticoagulation** of patients with **non-rheumatic atrial fibrillation** within three months of a transient ischaemic attack or minor ischaemic stroke reduces the risk of serious vascular events at two year follow-up compared to control[i] (all major vascular events, odds ratio 0.55; 95% CI: 0.37, 0.82: recurrent stroke odds ratio 0.36; 95% CI: 0.22, 0.58), and compared to **aspirin**[ii] (all major vascular events, odds ratio 0.55; 95% CI: 0.36, 0.83: recurrent stroke odds ratio 0.36; 95% CI: 0.22, 0.59). Anticoagulation is associated with a higher risk of major bleeding complications (odds ratio 4.65; 95% CI: 1.66, 12.99)[i].
(Health gain notation - 1 *"beneficial"*)

i. Koudstaal P. Secondary prevention following stroke or transient ischaemic attack in patients with non-rheumatic atrial fibrillation: anticoagulant versus control. Cochrane Review [Updated 14 February 1995]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type II evidence - systematic review of two randomised controlled trials randomising 1053 patients to open label anticoagulants or placebo)

ii. Koudstaal P. Secondary prevention following stroke or transient ischaemic attack in patients with non-rheumatic atrial fibrillation: anticoagulant versus antiplatelet therapy. Cochrane Review [Updated 15 February 1995]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type II evidence - systematic review of one randomised controlled trial randomising 455 patients to open label anticoagulants or 300mg aspirin)

7.5b. There is no clear evidence of benefit from **anticoagulation** of patients **not in atrial fibrillation** with acute non-embolic ischaemic stroke or transient ischaemic attack (odds ratio for death or dependency 0.83; 95% CI: 0.52, 1.34). Anticoagulation is associated with a higher risk of major bleeding complications (odds ratio for fatal intracranial haemorrhage 2.54; 95% CI: 1.19, 5.45; and fatal extracranial haemorrhage 4.87; 95% CI: 2.50, 9.49)[i].
(Health gain notation - 4 *"unknown"*)

Caveat: Poor methodological quality of old pre-1975 primary studies. *Further trials to assess the differential and combination effects of aspirin and anticoagulation in both the acute phase and secondary prevention of non-haemorrhagic stroke in patients not in atrial fibrillation are required.*

i. Liu M, Counsell C, Sandercock P. Anticoagulation versus no anticoagulation following non-embolic ischaemic stroke or TIA. Cochrane Review [Updated 10 September 1997]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 1214 patients in nine trials comparing at least one month anticoagulation with placebo)

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

The *statements*	The *evidence*
7.5c. Control of anticoagulation therapy can be satisfactorily achieved within General Practice, which offers the advantages of increased convenience and access for patients and continuity of care[i]. (Health gain notation - 2 *"likely to beneficial"*)	**i.** Anon. Anticoagulant therapy in General Practice.Welsh Medicines Resource Centre bulletin. Penarth: WeMeReC, 1997 (Type V evidence - expert opinion)

7.6 Carotid imaging

7.6a. Non-invasive imaging with **carotid duplex ultrasonography** is the first line investigation of carotid disease and can reliably select lesions appropriate for surgery only when critical stenosis of >70%[i] or >80%[ii] is present. Routine angiography is recommended for carotid stenosis of 50-70% when carotid endarterectomy is considered[i,ii]. The safety and effectiveness of performing carotid surgery on the basis of ultrasonography alone has not been formally demonstrated[iii]. (Health gain notation - 2 *"likely to be beneficial"*)	**i.** Eliasziw M, Rankin RN, Fox AJ, Haynes RB, Barnett HJM and the North American Symtomatic Carotid Endarterectomy Trial (NASCET) Group. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. *Stroke* 1995; **26(10)**:1747-52 (Type IV evidence - validation of ultrasonography findings against angiography performed on 1011 carotid bifurcations in the NASCET trial) **ii.** Chen JC, Salvian AJ, Taylor DC, Teal PA, Marotta TR, and Hsiang YN. Can duplex ultrasonography select appropriate patients for carotid endarterectomy? *European Journal of Vascular and Endovascular Surgery* **14 (6)**: 451-56 (Type IV evidence - prospective study of 145 carotid arteries in 102 patients comparing carotid duplex ultrasound with digital subtraction angiography) **iii.** Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke II: Management of Carotid Stenosis and Carotid Endarterectomy Assessment, Investigation, Immediate Management and Secondary Prevention.* Edinburgh: Royal College of Physicians, 1997 http://www.show.scot.nhs.uk/sign/pdf/sign14.pdf [Adobe Acrobat reader required] (Type V evidence - expert opinion)
7.6b. Magnetic resonance imaging (MRI) with contrast enhancement in combination with **duplex ultrasonography** has greater sensitivity and specificity than angiography in the assessment of **carotid stenosis**[i,ii]. (Health gain notation - 2 *"likely to be beneficial"*)	**i.** Young GR, Humphrey PRD, Shaw MDM, Nixon TE, Smith ETS. Comparison of magnetic resonance angiography, duplex ultrasound and digital subtraction angiography in assessment of extracranial internal carotid artery stenosis. *Journal of Neurology and Neurosurgical Psychiatry* 1994;**57**:1466-78 (Type III evidence - non-randomised prospective comparison study of 137 arteries in 70 patients) **ii.** Patel MR, Kuntz KM, Klufas RA, et al. Preoperative assessment of the carotid bifurcation. Can magnetic resonance angiography and duplex ultrasonography replace contrast arteriography? *Stroke* 1995;**26**:1753-58 (Type III evidence - non-randomised prospective comparison study of 176 carotid arteries in 88 patients)

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

The *statements*

The *evidence*

7.6c **Carotid bruits** have low sensitivity (36%), specificity (71%) and positive predictive value (68%) in the diagnosis of **carotid stenosis**[i].
(Health gain notation - 5 *"unlikely to be beneficial"*)

i. Davies KN. Do carotid bruits predict disease of the internal carotid arteries? *Postgraduate Medical Journal* 1994;**70**:433-35
(Type III evidence - non-randomised prospective study of 331 patients comparing clinical examination and duplex scanning)

7.7 Carotid endarterectomy

7.7a. Symptomatic patients with **severe carotid stenosis** (ECST 80% and over[i]) benefit from a reduced risk of stroke following **carotid endarterectomy**[i,ii]; three-year risk of any major stroke or death; surgery 14.9% vs. control 26.5%; overall difference 11.6%, p=0.001[i]. The downwards trend in benefit of surgery from 100% stenosis suggests patients with stenosis of between 70% and 80% may benefit depending on patient factors and the risk of surgery[i].
(Health gain notation - 1 *"beneficial"*)

7.7b **Carotid endarterectomy** has not been shown to be effective in patients with **mild or moderate carotid stenosis** (ECST<70%)[i].
(Health gain notation - 5 *"unlikely to be beneficial"*)

7.7c. **Carotid endarterectomy** for **asymptomatic carotid stenosis** of >60% is associated with a risk reduction for ipsilateral stroke or peri-operative stroke or death of 53% (95% CI: 22%, 72%)[iii]. Overall benefit is only achieved when perioperative morbidity and mortality is less than 3%. Because the incidence of stroke in these patients is small (three year incidence of all stoke<5%)[iv], carotid endarterectomy should only be performed in the context of randomised controlled trials[iii].
(Health gain notation - 4 *"unknown"*)

i. European Carotid Surgery Trialists'(ECST) Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379-87
(Type II evidence - randomised control trial of 3024 patients with mean 6.1 year follow-up)

ii. North American Symptomatic Carotid Enderterectomy Trial (NASCET) Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *New England Journal of Medicine* 1991;**325**:445-53
(Type II evidence - randomised controlled trial of 659 patients with >70% stenosis)

iii. Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for Asymptomatic Carotid Artery Stenosis. *Journal of the American Medical Association* 1995;**273**:1421-28
(Type II evidence - randomised controlled trial of 1659 patients with >60% stenosis receiving aspirin, median follow-up 2.7 years)

iv. Risk of stroke in the distribution of an asymptomatic carotid artery. *Lancet* 1995;**345**:209-12
(Type II evidence - 4.5 year mean follow-up of 2695 patients with >60% stenosis receiving aspirin randomised in the ECST trial)

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

The *statements*	The *evidence*
7.7d. There is insufficient data from randomised controlled trials to recommend the routine use of **local anaesthesia** for carotid endarterectomy[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** The non-randomised studies showed local anaesthesia was associated with significant reductions in the odds of stroke and death. *Large well designed randomised controlled trials are required.*	**i.** Tangkanakul C, Counsell C, Warlow C. Carotid endarterectomy performed under local anaesthetic compared to general anaesthetic. Cochrane Review [Updated 2 August 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review of 143 patients in three small trials and 17 non-randomised trials)
7.7e. A Cochrane Review of the risks and benefits of **carotid endarterectomy** in adult patients with ipsilateral symptomatic carotid stenosis is due for publication in 1999[i]. (Health gain notation - 4 *"unknown"*)	**i.** Cina CS, Clase CM, Haynes RB. Carotid endarterectomy in patients with symptomatic carotid stenosis. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis)
7.7f. Evidence-based guidelines for **carotid endarterectomy** are available[i,ii]. (Health gain notation - 1 *"beneficial"*)	**i.** Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke* 1998;**29**:554-62 http://www.americanheart.org/Scientific/statements/1998/029801.html (Type V evidence - expert opinion) **ii.** Scottish Intercollegiate Guidelines Network (SIGN). *Management of Patients with Stroke II: Management of Carotid Stenosis and Carotid Endarterectomy Assessment, Investigation, Immediate Management and Secondary Prevention.* Edinburgh: Royal College of Physicians, 1997 http://www.show.scot.nhs.uk/sign/pdf/sign14.pdf [Adobe Acrobat reader required] (Type V evidence - expert opinion)
7.7g. There is insufficient randomised controlled trial evidence to support the use of **routine shunting in carotid endarterectomy** (for death or stroke within 30 days, results show non-significant trends favouring shunting)[i]. (Health gain notation - 4 *"unknown"*) **Caveat:** Original trials were poorly randomised, with short duration of follow up and some important outcomes were not measured.	**i.** Counsell C, Salinas R, Naylor R, Warlow C. Routine or selective carotid artery shunting during carotid endarterectomy and the different methods of monitoring in selective shunting. Cochrane Review [Updated 8 December 1994]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence - systematic review and meta-analysis of 721 patients in three trials)

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

The *statements*

7.7h. There is insufficient evidence at present to support the use of **carotid patching** compared to primary closure during endarterectomy[i]. No evidence supports the use of one patch compared to another[ii].
(Health gain notation - 4 *"unknown"*)

Caveat: There were too few events in poor quality trials during the perioperative period to determine whether there were significant differences between the patch materials.

The *evidence*

i. Counsell C, Salinas R, Warlow C, Naylor R. Patch angioplasty compared to primary closure in carotid endarterectomy. Cochrane Review [Updated 17 May 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 882 operations in six trials)

ii. Counsell C, Warlow C, Naylor R. A comparison of different types of patch in carotid patch angioplasty. Cochrane Review [Updated 17 May 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 326 operations in three trials)

7.7i. There is no randomised controlled trial evidence to date to support a change in the routine clinical treatment of patients with carotid stenosis to **percutaneous transluminal angioplasty**, with or without stenting[i,ii].
(Health gain notation - 4 *"unknown"*)

Caveat: No completed randomised controlled trials identified. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is in progress[iii].

i. Crawley F, Brown MM. Percutaneous transluminal angioplasty and stenting for treatment of carotid artery stenosis. Cochrane Review [Updated 21 July 1997]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type III evidence - non-randomised studies)

ii. Bettmann MA, Katzen BT, Whisnant J, et al. Carotid stenting and angioplasty: a statement for healthcare professionals from the councils on cardiovascular radiology, stroke, cardio-thoracic and vascular surgery, epidemiology and prevention, and clinical cardiology, American Heart Association. *Circulation* 1998;**97**:121-23 http://www.americanheart.org/Scientific/statements/1998/019801.html
(Type V evidence - expert opinion)

iii. Sivaguru A, Venables GS, Beard JD, Gaines PA. European carotid angioplasty trial. *Journal of Endovascular Surgery* 1996;**3**:16-20
(Type II evidence - randomised controlled trial)

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

The *statements*

The *evidence*

7.8 Other surgical management of stroke

7.8a. **Surgery for intracerebral haematoma** has not been shown to be effective (odds ratio of craniotomy for death or dependence 1.99; 99% CI: 0.92, 4.31; and odds ratio for endoscopic evacuation 0.45; 99% CI: 0.15, 1.33)[i].
(Health gain notation - 4 "unknown")

Caveat: *The role of craniotomy and stereotactic surgery has not been adequately studied in randomised trials.*

i. Prasad K, Shrivastava A. Surgical treatment in patients with primary supratentorial intracerebral haemorrhage. Cochrane Review [Updated 11 November 1996]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 354 patients in four trials)

7.8b There is no evidence for the effectiveness of **extracranial-intracranial arterial anastomosis (EC/IC bypass)** in patients with transient ischaemic attack or stroke not amenable to carotid endarterectomy[i].
(Health gain notation - 5 *"unlikely to be beneficial"*)

i. Haynes RB, Mukherjee J, Sackett DL, Taylor DW, Barnett HJ, Peerless SJ, for the EC/IC Bypass Study Group. Functional status changes following medical or surgical treatment for cerebral ischaemia. Results of the extracranial-intracranial bypass study. *Journal of the American Medical Association* 1987;**257**:2043-46
(Type II evidence - randomised controlled trial of 1377 patients)

Date of completion of this document

30.9.98

8 AORTIC ANEURYSM AND PERIPHERAL VASCULAR DISEASE

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

The *statements*

The *evidence*

8.1 Abdominal aortic aneurysm

8.1a. Abdominal aortic aneurysm is present in about 5% of men and 2% of women aged over 65, and is usually asymptomatic unless rupture occurs, in around 6 per 1000 men aged over 65. The five year all-cause mortality is between 10% to 15%; in men over 65 ruptured aortic aneurysm accounts for 1% of all deaths[i]. The published evidence suggests that beyond abdominal palpation in those over 60 years old[ii], **screening for abdominal aortic aneurysms** is not a proven effective use of resources[i-iii].
(Health gain notation – 4 *"unknown"*)

Caveat: Screening in men aged 65 to 80 was associated with a significant reduction in deaths from ruptured aortic aneurysm[i]. All-cause mortality was not reduced as the incidence of ruptured aneurysm is low[i-iii]. *A much larger multi-centre trial is necessary.*

i. Scott RAP, Wilson NM, Ashton HA, Ray DN. Influence of screening of the incidence of ruptured abdominal aortic aneurysm: 5 year results of a randomised controlled study. *British Journal of Surgery* 1995;**82**:1066-70
(Type II evidence – randomised controlled trial of 15,775 men and women aged 65 to 80 years randomised to ultrasound screening or control with five year follow-up)

ii. Frame PS, Fryback DG, Patterson C. Screening for abdominal aortic aneurysm in men aged 60 to 80 years. A cost effective study. *Annals of Internal Medicine* 1993;**119**:411-16
(Type IV evidence – computer modelling cost-effectiveness study comparing physical examination with ultrasound in men aged 60 to 80 years)

iii. Abdominal Aortic Aneurysm. *Bandolier* 1996, Number 27. Volume 3 Issue 5
http://www.jr2.ox.ac.uk/bandolier/band27/b27-3.html
(Type II evidence – review of randomised controlled trial, reference i)

8.1b. A Cochrane Review of whether **beta-blockade** reduces the rate of **aortic dilatation** in abdominal aortic aneurysm is due for publication in 1999[i].
(Health gain notation – 4 *"unknown"*)

i. Powell JT, Quick C. Does beta-adrenergic blockade limit the rate of dilatation of the diseased aorta? Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review)

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

The *statements*

The *evidence*

8.1c. A Cochrane Review to assess whether there are significant differences in outcomes between different materials used as **aortic grafts** is due for publication in 1999[i].
(Health gain notation – 4 *"unknown"*)

i. Faris I, Quigley F. Graft materials used for abdominal aortic repair. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review)

8.2 Peripheral vascular disease

8.2a. Peripheral vascular disease results from atheromatous narrowing of the arteries to the legs. Symptoms may range from calf pain on exercise "intermittent claudication", to rest pain and gangrene. Intermittent claudication is the commonest symptom occuring in around up to 5% of men and 2.5% of women aged 60 or over. The five year mortality for men ranges from 5% to 17%, with coronary heart disease, stroke and ruptured aortic aneurysm as the leading causes of death[i,ii]. Evidence-based guidelines for the **diagnosis, medical and surgical treatment**[i] and **angioplasty**[ii] in the management of patients with peripheral vascular disease are available.
(Health gain notation – 1 *"beneficial"*)

i. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. American Heart Association. *Circulation* 1996;**94**:3026-49 http://www.americanheart.org/Scientific/statements/1996/1201.html
(Type V evidence – expert opinion)

ii. Pentecost MJ, Criqui MH, Dorros G, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels: a statement for health professionals from a special writing group of the councils on cardiovascular radiology, arteriosclerosis, cardio-thoracic and vascular surgery, clinical cardiology and epidemiology and prevention, the American Heart Association. *Circulation* 1994;**89**:511-31 http://www.americanheart.org/Scientific/statements/1994/019401.html
(Type V evidence – expert opinion)

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

The *statements*

The *evidence*

8.3 Medical management

8.3a. **Smoking cessation** improves the symptoms of intermittent claudication, and reduces the complications of peripheral vascular disease[i].
(Health gain notation – 1 *"beneficial"*)

i. Radack K, Wyderski RJ. Conservative management of intermittent claudication. *Annals of Internal Medicine* 1990;**113**:135-46
(Type IV evidence – review of observational studies of smoking cessation)

8.3b. The use of **lipid-lowering therapy** in peripheral vascular disease is of unproven benefit. The evidence suggests a trend towards reduced total mortality, lower total cholesterol and progression of underlying atheroma[i].
(Health gain notation – 4 *"unknown"*)

Caveat: Results should be interpreted with caution due to the variation in types of trials and small numbers of events. *Future trials of lipid lowering therapy with statins should include peripheral vascular disease outcomes.*

i. Leng GC, Price JF, Jepson RG. Lipid-lowering therapy in the treatment of lower limb atherosclerosis. Cochrane Review [Updated 14 August 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 700 patients in seven trials of diet and non-statin drug therapy)

8.3c. **Exercise** for patients with **intermittent claudication** improves maximal walking distance compared to control (pooled results from three trials odds ratio 6.51; 95% CI: 4.36, 8.66) with an overall improvement in walking ability of 150% (range 74% to 230%). Drug therapy with pentoxifylline may be of greater benefit in selected patients. Surgery may be more effective than exercise in the short-term but is associated with increased mortality and morbidity[i].
(Health gain notation – 1 *"beneficial"*)

Caveat: *A large trial with long-term follow-up is required to compare the effectiveness of different supervised and unsupervised exercise regimes and to compare exercise with pentoxifylline. Cost-benefit analyses are required.*

i. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. Cochrane Review [Updated 9 April 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis of 200 patients with intermittent claudication in nine trials of exercise vs. control or vs. medical or surgical therapy)

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

The *statements*	The *evidence*
8.3d. Cellular mechanisms of action suggest **pentoxifylline** may be an effective treatment in patients with peripheral vascular disease. A Cochrane Review is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Juni P, Fux C, Hertog MGL, Ernst E. Pentoxifylline for the treatment of intermittent claudication. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis)
8.3e. **Iloprost** may be effective in ulcer healing or relief of pain (rate difference 0.22, 95% CI: 0.12, 0.33) and in preventing amputation (rate difference –0.12, 95% CI: -0.21, -0.03) in patients with severe occlusive peripheral vascular disease, in whom surgery had failed or is impractical[i]. (Health gain notation – 4 *"unknown"*) **Caveat:** Criteria for assessment of validity of primary studies not stated. *Further assessment of cost-effectiveness is necessary in large randomised controlled trials.*	**i.** Loosemore TM, Chalmers TC, Dormandy JA. A meta-analysis of randomised placebo control trials in fontaine stage III and stage IV peripheral occlusive arterial disease. *International Angiology* 1994;**13**:133-42. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 705 patients with severe peripheral vascular disease in six trials of iloprost vs. placebo)
8.3f. A Cochrane Review of the effectiveness of **haemodilution** as a treatment for peripheral vascular disease is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Ernst E, Thompson J, Resch KL. Haemodilution for peripheral vascular disease. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
8.3g. A Cochrane Review to determine the efficacy of **antiplatelet agents**: aspirin, dipyridamole, indobufen, picotamide, suloctidil, sulphinpyrazone and ticlopidine on improving pain-free and total walking distance in patients with moderate intermittent claudication is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Saenz A, Ausejo M, Hood S, Barber G, Pham B, Moher D. Antiplatelet agents for intermittent claudication: aspirin, dipyridamole, indobufen, picotamide, suloctidil, sulphinpyrazone and ticlopidine. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis)

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

The *statements*	The *evidence*
8.3h. Evidence-based guidelines for **drug therapy** in peripheral vascular disease are available[i]. (Health gain notation – 1 *"beneficial"*)	**i.** Scottish Intercollegiate Guidelines Network (SIGN). *Drug therapy for peripheral vascular disease.* Edinburgh: Royal College of Physicians, 1998 http://www.show.scot.nhs.uk/sign/html/html27.htm (Type V evidence – expert opinion)
8.4 Surgical management	
8.4a. Three Cochrane Reviews to assess the comparative effectiveness of **surgery** and **thrombolysis** for acute limb ischaemia[i], different **fibrinolytic agents**[ii], and **optimal infusion techniques**[iii], are due for publication in 1999. (Health gain notation – 4 *"unknown"*)	**i.** Berridge DC, Kessel D. Surgery vs. thrombolysis for acute limb ischaemia. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review) **ii.** Berridge DC, Kessel D. Fibrinolytic agents for acute arterial occlusion. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review) **iii.** Berridge DC, Kessel D. Optimal infusion technique in peripheral arterial thrombolysis. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
8.4b. A Cochrane Review to determine the most effective **graft in femoro-popliteal bypass surgery** is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Mamode N, Scott RN. The best graft for femoro-popliteal bypass surgery. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
8.4c. Two Cochrane Reviews to determine the efficacy of **antiplatelet agents**[i] and **anticoagulants**[ii] in patients with lower limb atherosclerosis undergoing **femoro-popliteal and femoro-distal bypass grafting** are due for publication in 1999. (Health gain notation – 4 *"unknown"*)	**i.** Adam DJ, Stonebridge PA. Antiplatelet therapy after peripheral arterial bypass surgery. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review) **ii.** Adam DJ, Stonebridge PA. Anticoagulant therapy after peripheral arterial bypass surgery. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)

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

The *statements*

The *evidence*

8.4d. Angioplasty does not appear to be an effective treatment of mild or moderate intermittent claudication. In one trial, the angioplasty group were more likely to have a patent artery (odds ratio 5.5; 95% CI: 1.8, 17.0), but not a significantly better walking distance or quality of life. Ankle-brachial pressure indices were higher at six months in both trials, but in the second trial there were no significant differences in outcomes between the angioplasty and control groups at six year follow-up[i].
(Health gain notation – 4 *"unknown"*)

Caveat: Clinical heterogeneity and observer bias from lack of blinding require the results to be interpreted with caution. *Further well-designed large scale trials are required to draw firm conclusions on the cost-effectiveness of angioplasty for mild to moderate claudication.*

i. Fowkes FGR, Gillespie IN. Angioplasty (versus non-surgical management) for intermittent claudication. Cochrane Review [Updated 19 February 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review of two small trials of angioplasty vs. exercise programme and usual care in patients with peripheral vascular disease not warranting reconstructive surgery)

8.5 Secondary prevention

8.5a. Antiplatelet therapy is associated with a 43% (SD 8%) reduction at mean follow-up of 19 months in the odds of reocclusion following peripheral arterial grafting or angioplasty in patients with peripheral vascular disease (benefit 92 (SD 15) per 1000 patients treated, p<0.000). Most patients received aspirin – where comparison between regimens and antiplatelet agents were possible no significant differences were noted[i].
(Health gain notation – 1 *"beneficial"*)

Caveat: *The timing of commencement of therapy and duration of therapy should be investigated in further trials.*

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. In: Database of Reviews of Effectiveness. The Cochrane Library, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and sub-group meta-analysis of 3226 patients in 14 trials of antiplatelet therapy in patients with peripheral arterial disease)

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

The *statements*

8.5b. **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].
(Health gain notation – 2 *"likely to be beneficial"*)

Caveat: Significant benefit of clopidogrel was only found for the protocol specified primary outcome. No benefit was shown for clopidogrel over aspirin in the four protocol specified secondary outcomes, including vascular and all-cause mortality. 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 *evidence*

i. CAPRIE steering committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329-39
(Type II evidence – randomised controlled trial of 19,185 patients, mean 1.9 year follow-up)

8.5c. A Cochrane Review to determine the relative effectiveness and safety of **ticlopidine and clopidogrel** compared to aspirin in the secondary prevention of stroke and other important vascular outcomes in patients at high risk (previous TIA, ischaemic stroke, MI and peripheral vascular disease) is due for publication in 1999[i].
(Health gain notation – 4 *"unknown"*)

i. Hankey GJ, Dunbabin DW, Sudlow CLM. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin in the secondary prevention of stroke and other important vascular events among high risk patients. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence – systematic review and meta-analysis)

Date of completion of this document

30.9.98

9 VARICOSE VEINS AND LEG ULCERS

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

The *statements*

The *evidence*

9.1 Clinical assessment

9.1a. **Leg ulceration** is strongly associated with obesity, immobility, varicose veins and a history of deep vein thrombosis. Arterial disease is present (alone or with venous disease) in 20% of cases of leg ulceration. Careful assessment of patients to identify arterial and small vessel disease is essential to prevent damage from inappropriate use of compression treatments[i].
(Health gain notation – 1 *"beneficial"*)

i. Compression therapy for venous leg ulcers. *Effective Health Care Bulletin.* Volume 3 Number 4. University of York: NHS Centre for Reviews and Dissemination, 1997
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type IV evidence – review of observational evidence and case series)

9.1b. **Ankle: brachial pressure index** measured with a hand held Doppler ultrasound is better than manual palpation for excluding arterial disease, but is unreliable when carried out by inexperienced operators. Training of staff using ABPI can significantly improve reliability[i].
(Health gain notation – 3 *"trade-off between beneficial and adverse effects"*)

i. Compression therapy for venous leg ulcers. *Effective Health Care Bulletin.* Volume 3 Number 4. University of York: NHS Centre for Reviews and Dissemination, 1997
http://www.york.ac.uk/inst/crd/ehcb.htm
(Type IV evidence – review of observational evidece and case series)

9.1c. Early hospital **specialist vascular assessment** of leg ulcers, including duplex scanning of the arterial and venous systems, to determine the most appropriate early interventions and prevent chronic ulceration offers potential for clinical benefit and cost savings[i].
(Health gain notation – 2 *"likely to be beneficial"*)

i. Ruckley CV. Caring for patients with chronic leg ulcer. *British Medical Journal* 1998;**316**:407-8
(Type V evidence – expert opinion)

9.1d. Evidence-based guidelines for the care of patients with **chronic leg ulcer** are available[i].
(Health gain notation – 1 *"beneficial"*)

i. Scottish Intercollegiate Guidelines Network (SIGN). *The care of patients with chronic leg ulcer.* Edinburgh: Royal College of Physicians, 1998
http://www.show.scot.nhs.uk/sign/html/html26.htm
(Type V evidence – expert opinion)

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

The *statements*	The *evidence*
9.2 Medical management	
9.2a. Compression therapy using Unna's boot, 2-layer, 4-layer or short stretch bandages improves healing rates compared to treatments using no compression, and may be more cost-effective[i]. (Health gain notation – 2 *"likely to be beneficial"*) **Caveat:** Six small primary studies were poor quality trials with ill-defined inclusion/exclusion criteria and method of randomisation. None stated blinded outcome assessment and only one included intention to treat analysis.	**i.** Cullum N, Fletcher A, Nelson EA, Sheldon TA. Compression bandages and stockings in the treatment of venous leg ulcers. Cochrane Review [Updated 27 May 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type II evidence – review of randomised controlled trials)
9.2b. High compression 3-layer elastic bandaging is more effective in healing at three months than single layer low compression using elastocrepe (odds ratio 2.26; 95% CI: 1.4, 3.7)[i]. (Health gain notation – 2 *"likely to be beneficial"*) **Caveat:** Only three trials were included, two with blinded outcome assessment but intention to treat analysis was not stated.	**i.** Cullum N, Fletcher A, Nelson EA, Sheldon TA. Compression bandages and stockings in the treatment of venous leg ulcers. Cochrane Review [Updated 27 May 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 273 patients in three randomised controlled trials)
9.2c. Four layer high compression is more effective at healing ulcers by 24 weeks than single layer adhesive compression bandage. (odds ratio 2.2; 95% CI: 1.3, 3.5)[i]. (Health gain notation – 2 *"likely to be beneficial"*) **Caveat:** Primary studies include one large trial not stating baseline comparability and without blinded outcome assessment and two poor quality pooled trials with significant heterogeneity.	**i.** Cullum N, Fletcher A, Nelson EA, Sheldon TA. Compression bandages and stockings in the treatment of venous leg ulcers. Cochrane Review [Updated 27 May 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 254 patients in three randomised controlled trials)

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

The *statements*	The *evidence*
9.2d. Two small studies showed that at three and six month follow-up, more ulcers healed when **intermittent pneumatic compression** was used in addition to compression stockings or Unna's boot (pooled odds ratio = 10.0; 95% CI: 2.96, 33.8)[i]. (Health gain notation – 4 *"unknown"*) **Caveat:** Two poor quality trials were pooled. *Further studies are required.*	**i.** Cullum N, Fletcher A, Nelson EA, Sheldon TA. Compression bandages and stockings in the treatment of venous leg ulcers. Cochrane Review [Updated 27 May 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review and meta-analysis of 67 patients in two randomised controlled trials)
9.2e. **Recurrence rates** of healed ulcers at 3.5 years may be lower in patients using strong support from class 3 compression stockings than patients using class 2 (medium support) stockings (21% vs. 32%, p = 0.034); class 2 stockings were better tolerated[i]. (Health gain notation – 2 *"likely to be beneficial"*) **Caveat:** The trial does not state baseline comparability and outcome assessment was not blinded.	**i.** Harper D, Nelson E, Gibsom B, et al. A prospective randomised trial of class 2 and class 3 elastic compression in the prevention of venous ulceration. *Phlebology* 1995;**1**(suppl):872-73 (Type II evidence – randomised controlled trial of 300 patients with newly treated venous leg ulcers)
9.2f Neither **stanozolol** or **rutoside** reduce recurrence of leg ulcers compared to placebo in patients also receiving class 2 compression stockings[i]. (Health gain notation – 6 *"likely to be ineffective"*)	**i.** Compression therapy for venous leg ulcers. *Effective Health Care Bulletin*. Volume 3 Number 4. University of York: NHS Centre for Reviews and Dissemination 1997 http://www.york.ac.uk/inst/crd/ehcb.htm (Type II evidence – randomised controlled trials)

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

The *statements*	The *evidence*
9.2g. Care delivered in dedicated **leg ulcer clinics** by trained nurses following a treatment protocol involving 4-layer bandaging resulted in faster median healing times (20 vs. 43 weeks, p=0.03) than patients receiving usual treatments from their district nurse without 4-layer bandaging. During 12 month follow-up, clinic patients had a mean 5.9 extra ulcer-free weeks (95% CI: 1.2, 10.5). No difference in mean total NHS costs were found between the two groups[i]. (Health gain notation – 2 "likely to be beneficial") **Caveat:** Study does not provide information on the relative impact of extra clinic nurse training, compression bandaging or protocols for referral and treatment[ii]. Validity of the magnitude of effect unknown due to observational bias resulting from non-blinded outcome assessment.	**i.** Morrell CJ, Walters SJ, Dixon S, et al. Cost-effectiveness of community leg ulcer clinics: randomised controlled trial. *British Medical Journal* 1998;**316**:1487-91 (Type II evidence – randomised controlled trial of 233 ambulant patients randomised to clinic care or usual domiciliary district nurse care) **ii.** Compression therapy for venous leg ulcers. *Effective Health Care Bulletin.* Volume 3 Number 4. University of York: NHS Centre for Reviews and Dissemination 1997 http://www.york.ac.uk/inst/crd/ehcb.htm (Type II evidence – summary review of randomised controlled trials)
9.2h. There is no evidence that **oral zinc sulphate** is an effective treatment for promoting the healing of venous, arterial and sickle-cell leg ulcers. There is limited evidence of a beneficial effect in patients with low serum zinc and venous ulcer[i]. (Health gain notation – 4 *"unknown"*) **Caveat:** Included studies were of varying validity, settings and duration of follow-up. *A well-designed large randomised controlled trial is required to determine the serum zinc concentration below which zinc therapy is beneficial.*	**i.** Wilkinson E, Hawke C. Does oral zinc aid the healing of chronic leg ulcers? Cochrane Review [Updated 14 August 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review of six randomised controlled trials, median size 33 patients)
9.2i. A Cochrane Review to determine the relative effectiveness of **dressings** used in the treatment of venous leg ulcers is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Palfreyman SJ, Michaels JA, Lochiel R, Nelson EA. Use of dressings in the treatment of venous leg ulcers. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
9.2j. There is no evidence that **ultrasound** enhances cutaneous wound healing[i]. A Cochrane Review is due for publication in 1999[ii]. (Health gain notation – 4 *"unknown"*) **Caveat:** Poor quality review[i] - methodology not stated, limited literature review, inclusion/exclusion criteria not stated, outcomes not pre-defined.	**i.** Ernst E. Ultrasound for cutaneous wound healing. *Phlebology* 1995;**10**:2-4. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type II evidence – narrative review of five studies, including two randomised controlled trials) **ii.** Flemming K, Cullum NA, Nelson EA. Therapeutic ultrasound for venous leg ulcers. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)

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

The *statements*	The *evidence*
9.2k. Cochrane Reviews on the effectiveness of **laser therapy**[i] and **electrical stimulation**[ii] in the treatment of venous leg ulcers are due for publication in 1999. (Health gain notation – 4 *"unknown"*)	**i.** Flemming K, Cullum NA. Laser therapy for the treatment of venous leg ulcers. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review) **ii.** Flemming K, Cullum NA. Electrical stimulation for venous leg ulcers. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
9.2l. A Cochrane Review of reliable evaluations of **topical analgesics, anaesthetics and dressings** used to manage the pain of venous leg ulceration is due for publication in 1999[i]. (Health gain notation – 4 *"unknown"*)	**i.** Briggs M, Nelson EA. Local interventions for chronic pain in venous leg ulcers. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)
9.3 Surgical management	
9.3a. Surgical ligation of varicose veins has not been shown in randomised controlled trials to reduce recurrence rates of venous leg ulcers[i]. Saphenous ligation[ii] and subfascial endoscopic ligation[iii] have been shown in small case series to heal ulcers and prevent recurrence. A Cochrane Review to determine the effectiveness of **surgery** in the treatment of **deep venous incompetence** is due for publication in 1999[iv]. (Health gain notation – 4 *"unknown"*)	**i.** Compression therapy for venous leg ulcers. *Effective Health Care Bulletin*. Volume 3 Number 4. University of York: NHS Centre for Reviews and Dissemination 1997 http://www.york.ac.uk/inst/crd/ehcb.htm (Type II evidence – summary review of randomised controlled trials) **ii.** Darke SG, Penfold C. Venous ulceration and saphenous ligation. *European Journal of Vascular Surgery* 1992;**6(1)**:4-9 (Type IV evidence – case series of 213 patients) **iii.** Pierik EG, Wittens CH, van Urk H. Subfascial endoscopic ligation in the treatment of incompetent perforating veins. *European Journal of Vascular & Endovascular Surgery* 1995;**9(1)**:38-41 (Type IV evidence – case series of 38 patients) **iv.** Abidia A, Hardy SC. Surgical treatment of deep venous incompetence. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998 (Type I evidence – systematic review)

Date of completion of this document

30.9.98

10 DEEP VEIN THROMBOSIS

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

The *statements*

The *evidence*

10.1 Preventive therapy

10.1a. Prophylactic antiplatelet therapy for one to three weeks in high risk surgical and medical patients is associated with a 39% odds reduction of venous thrombosis (SD 5%), p<0.000; benefit 90/1000 patients treated and a 64% odds reduction of pulmonary embolism (SD 10%), p<0.000; benefit 17/1000 patients treated. There is limited evidence that the effects of antiplatelet therapy on pulmonary embolism are additive to heparin. Antiplatelet therapy is associated with a small increase in non-fatal haemorrhagic complications (0.7% vs. 0.4%, one-sided p=0.04)[i].
(Health gain notation - 1 *"beneficial"*)

i. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *British Medical Journal* 1994;**308**:235-46. In: Database of Reviews of Effectiveness. *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 5181 patients in 53 DVT trials and 9446 patients in 62 PE trials)

10.1b. There is evidence that **low molecular weight heparins** are at least as effective as standard heparin in prevention of deep vein thrombosis (DVT) and pulmonary embolus (PE) in perioperative patients[i-iii].
(Health gain notation - 1 *"beneficial"*)

i. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low molecular weight heparin versus standard heparin in general and orthopaedic surgery: a meta analysis. *Lancet* 1992;**340**:152-56
(Type I evidence - systematic review and meta-analysis of 6878 patients in 17 general surgery trials and 1294 patients in 6 orthopaedic surgery trials)

ii. Leyvraz PF, Bachmann F, Hoek J, et al. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *British Medical Journal* 1991;**303**:543-48
(Type II evidence - randomised controlled trial of 349 patients)

iii. Leizorovicz A, Haugh MC, Chapius FR, et al. Low molecular weight heparin in the prevention of perioperative thrombosis. *British Medical Journal* 1992;**305**:913-20
(Type I evidence - systematic review and meta-analysis of 2045 patients in 16 randomised controlled trials)

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

The *statements*	The *evidence*
10.1c. There is evidence that **graduated compression stockings** prevent post-operative DVT after moderate risk (non-orthopaedic) surgery (odds ratio 0.28; 95% CI: 0.23, 0.42; p<0.0001)[i]. (Health gain notation - 1 *"beneficial"*)	**i.** Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism: a meta-analysis. *Archives of Internal Medicine* 1994;**154**: 67-72 (Type I evidence - systematic review and meta-analysis of 1842 patients in 12 randomised controlled trials)
10.1d. **All hospital patients** who are at moderate or high risk of venous thromboembolism should receive specific prophylaxis[i,ii]. **Evidence-based guidelines** for the prophylaxis of venous thromboembolism are currently being updated[i] and due for publication in 1999. (Health gain notation - 1 *"beneficial"*)	**i.** Scottish Intercollegiate Guidelines Network (SIGN). *Prophylaxis of Venous Thromboembolism*. Edinburgh, Royal College of Physicians, 1995 (Type V evidence - expert opinion) **ii.** Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *British Medical Journal* 1992;**305**:567-74 (Type V evidence - expert opinion)
10.1e. **Thrombocytopenia** occurs in about 3% to 4% of patients given **prophylactic heparin**. The Committee on Safety of Medicines recommends that the platelet count is monitored in patients receiving heparin for more than five days, and that heparin is stopped immediately if thrombocytopenia occurs[i]. (Health gain notation - 3 *"trade-off between beneficial and adverse effects"*)	**i.** Scottish Intercollegiate Guidelines Network (SIGN). *Prophylaxis of Venous Thromboembolism*. Edinburgh: Royal College of Physicians, 1995 (Type V evidence - expert opinion)

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

The *statements*

The *evidence*

10.2 Diagnostic imaging

10.2a. Non-invasive **venous ultrasonography** is now the investigation of first choice in patients with suspected DVT[i]. **Compression venous ultrasonography** of the common femoral vein and the popliteal vein to the level of the trifurcation of the calf veins repeated at one week is an effective diagnostic investigation; after six months follow-up, the cumulative incidence of DVT or PE was 0.7% in patients with two normal scans[ii]. **Venography** should be reserved for patients with a high clinical probability of disease and a negative non-invasive test result[i]. **Evidence-based recommendations** for the non-invasive diagnosis of DVT have been published[iii].
(Health gain notation - 1 *"beneficial"*)

Caveat: Compression venous ultrasonography findings[ii] may not be generalisable to patients with previous DVT or pregnancy excluded from the study.

i. Wheeler HB, Hirsh J, Welss P, Anderson FA. Diagnostic tests for deep vein thrombosis. *Archives of Internal Medicine* 1994; **54**: 921-28
(Type IV evidence - narrative review of test characteristics of non-randomised studies and case series in patients with suspected thromboembolism)

ii. Cogo A, Lensing AWA, Koopman MMW, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *British Medical Journal* 1998;**316**:17-20
(Type IV evidence - case series of 1702 patients with clinically suspected DVT of common femoral vein in the groin and popliteal vein to the trifurcation of the calf veins, followed-up for six months after compression ultrasonography)

iii. Kearon C, Julian JA, Newman TE, Ginsberg JS, for the McMaster Diagnostic Imaging Practice Guidelines Initiative. Non-invasive diagnosis of deep venous thrombosis. *Annals of Internal Medicine* 1998;**128**:663-77
(Type I evidence - systematic review)

10.2b. The clinical utility of **D-dimer testing**, for the diagnostic evaluation of DVT has not been proven[i].
(Health gain notation - 4 *"unknown"*)

Caveat: Methodological problems in the primary studies, including wide variability in assay performance, heterogeneity among subjects and lack of criterion standard for diagnosis, results in a wide range of sensitivities and specificities for the test. *Further research is required before D-dimer testing is used as a diagnostic test for venous thromboembolism - the development of a highly specific test for the exclusion of DVT will have important clinical benefits.*

i. Becker D, Philbrick J, Bachhuber T, Humphries J. D-dimer testing and acute venous thromboembolism. *Archives of Internal Medicine* 1996;**156**:939-46
(Type II evidence - systematic review of 29 studies and 4205 patients)

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

The *statements*

The *evidence*

10.3 Drug therapy

10.3a. **Thrombophilia** should be considered in patients aged less than 40 years presenting with venous thromboembolism, recurrent venous thrombosis, venous thrombosis in an unusual site or with a family history[i].
(Health gain notation - 1 *"beneficial"*)

i. Anon. Management of patients with thrombophilia. *Drug & Therapeutics Bulletin* 1995;**33(1)**:6-8
(Type V evidence - expert opinion)

10.3b. **Low molecular weight heparin (LMW) preparations** are as effective and safer than adjusted doses of standard heparin for the treatment of venous thromboembolism. Odds ratio of recurrent venous thromboembolism for LMW heparin compared to adjusted dose standard heparin 0.75; 95% CI: 0.55, 1.01; for major haemorrhage during treatment 0.55; 95% CI: 0.34, 0.89; and mortality at long-term follow-up 0.74; 95% CI: 0.57, 0.98[i].
(Health gain notation - 1 *"beneficial"*)

Caveat: *Since the majority of patients had DVT, further trials of the efficacy and safety of LMW heparins in pulmonary embolism are required, together with trials comparing different LMW heparins*[i].

i. van den Belt AGM, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Review [Updated 14 January 1998]. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review and meta-analysis of 4354 patients (75% DVT and 25% PE) in 13 trials)

10.3c. A Cochrane Review to compare the effectiveness and safety of different **duration** of initial treatment with **standard** and **LMW heparin** is due for publication in 1999[i].
(Health gain notation - 4 *"unknown"*)

i. Castro AA, Clark OAC, Atallah AN, Burihan E. Duration of initial heparin treatment for deep-vein thrombosis. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 4. Oxford: Update Software, 1998
(Type I evidence - systematic review)

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

The *statements*

10.3d. Six months of **secondary prophylaxis** of deep vein thrombosis (DVT) or pulmonary embolus (PE) with **oral anticoagulants** following initial heparin therapy results in a lower recurrence rate over two years than treatment for six weeks, odds ratio 2.1; 95% CI: 1.4, 3.1[i].
(Health gain notation - 1 *"beneficial"*)

The *evidence*

i. Schulman S, Rhedin A, Lindmarker P, et al, for the Duration of Anticoagulation Trial Study Group. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *New England Journal of Medicine* 1995;**332**:1661-65
(Type II evidence - randomised controlled trial of 897 patients, 790 with DVT and 107 with PE with two year follow-up)

10.3e. Prophylactic **oral anticoagulation** for four years following a **second episode of venous thromboembolism** is associated with a lower rate of recurrence than treatment for six months: relative risk of recurrence in six month group 8.0; 95% CI: 2.5, 25.9, NNT 6 (4, 10), with no significant differences in the risk of major haemorrhage or mortality between the two groups[i].
(Health gain notation - 1 *"beneficial"*)

i. Schulman S, Granqvist S, Holmstrom M, et al, for the Duration of Anticoagulation Trial Study Group. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *New England Journal of Medicine* 1997;**336**:393-98
(Type II evidence - randomised controlled trial of 227 patients, over 95% with DVT, with four year follow-up)

INDEX