
Monograph:
Sutton, J., Tomlinson, J. and Calvert, N. (2000) Long term use of oral antiplatelet therapy for the prevention of stroke and other serious vascular events. Other. Guidance Note for Purchasers (00/05). Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield , Sheffield. ISSN 1900752158

October 2000

LONG–TERM USE OF ORAL ANTIPLATELET THERAPY FOR THE PREVENTION OF STROKE AND OTHER SERIOUS VASCULAR EVENTS

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GUIDANCE NOTE FOR PURCHASERS 00/05

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 10 October 2000 at which this Guidance Note for Purchasers (in a draft form) was considered.

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AUTHORS: Sutton J, Tomlinson J, Calvert N. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 2000. Guidance Note for Purchasers: 00/05.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee made a number of recommendations and amendments to the report's conclusions. Once these amendments had been taken into account in the report, the Committee supported the conclusions outlined by the authors.

ACKNOWLEDGEMENTS

The authors would like to acknowledge gratefully the help and advice of the following people: Professor P Bath (Professor of Stroke Medicine, Nottingham City Hospital), Ms V Chapman (Trent Drug Information Service), Ms J Charles (Pharmaceutical Advisor, Leicestershire Health Authority), Mr P Golightly (Director, Trent Drug Information Services), Professor J Hampton (Professor of Cardiology, University of Nottingham), Dr R Henderson (Consultant Cardiologist, Nottingham City Hospital), Dr M Muthiah (Respiratory Physician, Bassetlaw District General Hospital), Dr T Robinson (Consultant in Stroke Medicine, Leicester General Hospital), Mr D Spence (Pharmaceutical Advisor, Leicestershire Health Authority), Dr W Sunman (Consultant Physician, Nottingham City Hospital), Dr G Venables (Consultant Neurologist, Royal Hallamshire Hospital, Sheffield) and Professor R Wilcox (Professor of Cardiovascular Medicine, University of Nottingham).

Grateful acknowledgements are also due to Suzy Paisley (Information Resources, ScHARR) for her help with literature searching and obtaining articles; also to Pat Holmes, Mike Jacobs, Danny Hind and Gill Rooney for their invaluable help in the editing, formatting and proof-reading of this document.

EXPIRY DATE

The normal 'product life' for these Guidance Notes is about three years. The reader should be aware of ongoing trials for drugs discussed in this paper (e.g. ESPRIT for dipyridamole), the results of which may have bearing on the analyses and conclusions presented in this Guidance Note.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking HSR;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor M Clarke (Leicester); and
Professor H Williams (Nottingham).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterTASC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The University of Birmingham Department of Public Health and Epidemiology and the Centre for Research and Dissemination, University of York.

Professor R L Akehurst

Chairman, Trent Working Group on Acute Purchasing

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SUMMARY

Evidence for the effectiveness, cost-effectiveness, and safety of currently available oral antiplatelet agents (aspirin (ASA), dipyridamole, clopidogrel, and ticlopidine) for the prevention of stroke and other serious vascular events in patients at high vascular risk is presented. Atherosclerosis of the arterial walls is the underlying aetiology common to all the conditions under review, that is, transient ischaemic attack (TIA), ischaemic stroke (IS), coronary heart disease (CHD), and peripheral arterial disease (PAD). Calculating the overall prevalence of atherosclerotic disease in the population is hard to establish, as many of those affected are asymptomatic. However, it is estimated that the prevalence of symptomatic disease in the Trent Region lies between 127,000 and 185,000. In an average health district of 500,000 residents it is estimated that 12,400-18,000 people are affected.

For those who can tolerate it, the evidence that ASA should remain the first line treatment for the prevention of stroke and other serious vascular events is strong. Until facilities for testing ASA dose-responsiveness are more widely available, present evidence indicates the dose of 75mg daily to optimise the secondary prevention of stroke and serious vascular events, whilst minimising the risk of gastrointestinal (GI) side-effects. Although ASA is effective and inexpensive, intolerance is the main reason for considering second line therapy. The precise level of ASA sensitivity/intolerance is unknown although GI intolerance ranges from 2-20% (dose-related). Options for the reduction of intolerance include lowering dosage, prescribing enteric-coated (EC) ASA, or co-prescribing acid-suppressant therapy. The effectiveness of ASA for GI intolerance for the latter option is unknown, since all the trial evidence is for non-steroidal anti-inflammatory drugs (NSAIDs). Routine acid-suppressant therapy is not indicated for patients taking aspirin and, if this therapy is given to patients with gastric side-effects from aspirin, then it should be discontinued if there is no improvement in symptoms.

Dipyridamole may be considered for IS and TIA patients unable to tolerate ASA, however, the main pharmacological mechanisms of dipyridamole are not fully understood. The ESPS-2 study suggests that dipyridamole and ASA have similar efficacy, and that when prescribed in combination, there is an additive effect. The view of clinicians on the validity of the ESPS-2 study, however, remains divided. The Royal College of Physicians' (RCP) Guidelines on Stroke recommend combined low dose ASA and modified release dipyridamole for first line therapy, and dipyridamole for second line therapy. These RCP guidelines are not applicable to other types of symptomatic atherosclerotic disease covered by this report.

LIST OF ABBREVIATIONS

ASA	Acetylsalicylic Acid (Aspirin)
ADP	Adenosine 5'-disphosphate
CAST	Chinese Acute Stroke Trial
CE	Cost-effectiveness
CEA	Cost-effectiveness Analysis
CHD	Coronary Heart Disease
CI	Confidence Interval
CUA	Cost Utility Analysis
DKK	Danish Krona
DP	Dipyridamole
DU	Duodenal Ulcer
EC-ASA	Enteric-coated ASA
FB	Belgian Francs
GI	Gastrointestinal
GU	Gastric Ulcer
H_2A	H_2-antagonists
HCHS	Hospital and Community Health Services
IS	Ischaemic Stroke
IST	International Acute Stroke Trial
MI	Myocardial Infarction
MRD	Modified Release Dipyridamole
NNT	Number Needed to Treat
NSAID	Non-Steroidal Anti-inflammatory Drug
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PPI	Proton Pump Inhibitor
QALY	Quality Adjusted Life Years
RR	Relative Risk
RRR	Relative Risk Reduction
SFLY	Stroke-Free Life Year
TASS	Ticlopidine Aspirin Stroke Study
TIA	Transient Ischaemic Attack
TTP	Thrombotic Thrombocytopenic Purpura

2. BACKGROUND

2.1 UNDERLYING DISEASE FOR WHICH ANTIPLATELET THERAPY IS APPROPRIATE

2.1.1 Aetiology

Antiplatelet therapy is a useful means of preventing acute thrombo-embolic artery occlusions in patients at increased vascular risk.[1] However, cardiovascular disease can present in a variety of ways. This report focuses on IS, MI, and PAD and the evidence for their prevention by antiplatelet therapy.

The underlying aetiology is common to all these conditions. That is, atherosclerotic plaques on the arterial walls may break off and become the site for the development of a thrombus. This would further narrow the artery. The symptoms vary, depending on the part of the vascular system affected. Thus, stroke, MI or PAD can result and those at risk of one are likely to be at risk of the others.[2]

2.1.2 Epidemiology

The prevalence of cardiovascular disease is hard to establish, as symptomatic disease is just the tip of the iceberg and the extent of asymptomatic disease is uncertain. However, the symptomatic conditions provide an estimate of those in need of the health services. Table 1 summarises the prevalence of symptomatic disease in the community. No studies were found on the prevalence of people who have had TIA. However, the incidence is reported to be 0.42 per 1,000 population per year.[3] Within the Trent Region this would be 2,150 TIA events annually and, in a health district of 500,000 population, 210 annually.

Calculating the overall prevalence of atherosclerotic disease from the figures in Table 1 could provide an inaccurate estimate of the numbers of people involved for the following reasons. TIA prevalence is excluded. Due to the overlap of IS, CHD and PAD within individuals, there would be double (or triple) counting of an unknown proportion of the atherosclerotic population. People with asymptomatic atherosclerotic disease are excluded, but may benefit from intervention with antiplatelet therapy.

b) Morbidity

In addition to preventable mortality, a large proportion of patients who have had a major vascular event suffer from long-term morbidity and disability as a result. They also have an increased risk of further major vascular events. 'Saving Lives: Our Healthier Nation'[8] reports that:

- CHD is an important cause of disability – one in 20 people reporting serious disability identifies CHD as a cause.
- Stroke is the second most important cause of expenditure on community health and social care for adults – accounting for over 7% of such expenditure.

PAD causes pain and disability from intermittent claudication. Ultimately, lower limb amputation may be required which would result in further disability and even greater input from the disability services.

2.1.4 Oral Antiplatelet Therapies for Discussion

The oral antiplatelet therapies for the prevention of serious vascular events being considered here include ASA, which is an age-old remedy for many ills with proven efficacy for its antiplatelet effect, DP, and newer thienopyridine derivatives.[9,10] DP has been used alone or in combination with ASA. The thienopyridine derivatives are more recent and include ticlopidine and clopidogrel. These drugs act in different ways to inhibit platelet aggregation. They will be discussed further in the following sections.

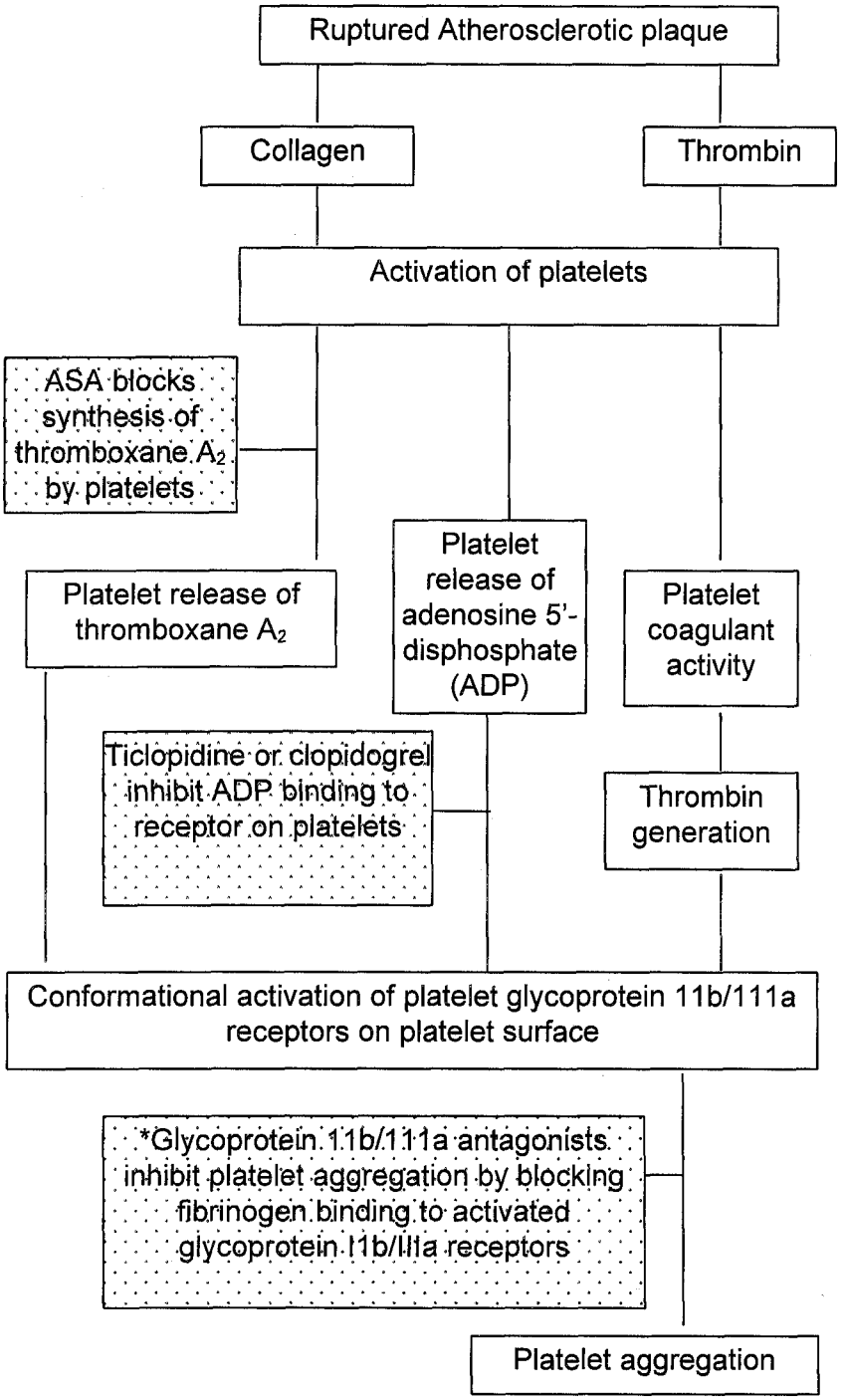
There are other oral agents in development, which include lotrafiban, heparin oral-Emisphere, LDP 01, Cilostazol and dipyridamole extended release/aspirin. These are not included because the relevant research is not yet available.

Table 2 presents the treatment costs of current oral antiplatelet agents.

2.2 DRUG INTERVENTIONS

Figure 1 illustrates the sites of action of different platelet inhibitors. Source given below.

Figure 1 Sites of Action of Different Platelet Inhibitors



(Source: Hirsch and Weitz 1999[11])

*These agents are normally intravenous and are not included in this report. DP is not included in this diagram, as, although its antiplatelet mechanisms are understood, their relative importance has not been fully determined. It is based on the ability to modify various aspects of platelet function, such as the inhibition of platelet adhesion and aggregation. It also lengthens platelet survival time.

3. EFFECTIVENESS

3.1 METHODS FOR REVIEWING EFFECTIVENESS

The original Medline searching strategy undertaken for this paper is presented in the Appendix. Similar searches using Science Citation Index and Cochrane databases were also undertaken. Because the number of clinical papers identified by these searches was not of a manageable size, a more restricted search for clinical papers, where the 'publication type' was restricted to 'clinical trial' was used.

3.2 RESULTS

3.2.1 Quantity and Quality of Research Available

Approximately 40 publications were selected for review following the literature search. Of these, 11 papers met the aim of this report (see Section 1). Of these, 11 were selected for further analysis. Four of the 11 were original studies and seven were reviews. The details of the papers are summarised in Tables 4 and 5 respectively. The review articles identified were of variable quality and often did not indicate specific inclusion or exclusion criteria. The review by Hankey et al.[25] (Cochrane systematic review) is a high quality review which identifies four original publications, one comparing ASA with Clopidogrel (the CAPRIE study), and three comparing ASA with ticlopidine. The meta-analysis results of this review are given in Table 6.

Table 4 continued

Author & Year	Type, Size, Setting of Study	Purpose, Aim of Study	Intervention	Results	Comments
CAPRIE Steering Committee 1996.[2]	Randomised blinded trial of 19,185 patients (6,431 with IS, 6,302 MI, 6,452 PAD), aged 21 years or over with symptomatic atherosclerosis – 1992-1995, 384 centres in USA, Europe & Australia	Comparison of the long-term safety and tolerability of clopidogrel and ASA.	Clopidogrel 75mg daily, ASA 325mg daily – minimum of 1 year and maximum of 3 years.	Clopidogrel patients had annual risk of 5.32% of IS, MI and vascular death compared with 5.83% with ASA. No differences in safety. Reported adverse reactions judged to be *severe* included: Adverse events – Clopidogrel – ASA Skin Rash – 0.26% – 0.1% Diarrhoea – 0.23% – 0.11% Upper GI Discomfort – 0.97% – 1.22% Intracranial bleed – 0.33% – 0.47% GI Bleed – 0.52% – 0.72% Neutropenia – 0.1% – 0.17% Stroke patients – average event rate per year for clopidogrel was 7.15% and 7.71% for ASA (relative risk reduction (RRR) 7.3% range – 5.7-18.7) for MI 5.03% and 4.84% (relative risk increase 3.7% range 22.1- -12.0) and for PAD 3.71% and 4.86% (RRR 23.8% - range 8.9-36.2)	Study sponsored by Sanofi. Bristol–Myers–Squibb
JW Harbison et al., 1992.[28]	Ticlopidine Aspirin Stroke Study (TASS) Sub-group. Multicentre double blind randomised trial of 927 patients with recent minor completed stroke within 3 months of study entry.	To investigate: - First occurrence of non-fatal stroke, - Death, any cause, - First occurrence of fatal and non-fatal stroke	ASA 650mg x 2 daily Or Ticlopidine 250mg x 2 daily.	Ticlopidine more effective than ASA (RRR of 36%)	Consistent with overall TASS study – i.e. ticlopidine more effective than ASA for reducing risk of stroke in patients with completed minor stroke.

Table 5 continued

Author & Year	Type, Size, Setting of Study	Purpose, Aim of Study	Intervention	Results	Comments
SM Davis et al., 1998.[30]	Review article – 26 papers.	To highlight importance of antiplatelet therapy in stroke prevention.	Not applicable.	Ticlopidine offered as second line therapy due to mild statistical benefit over ASA, increased risk of serious adverse events (e.g. 1% reversible neutropenia rate), need for blood monitoring and cost. Clopidogrel should replace ticlopidine as second line therapy, due to lack of serious adverse effects and comparable efficacy, but will not replace ASA as first line therapy due to modest superiority and higher cost. Would not use DP due to lack of evidence in all studies except ESPS-2. ESPS –2 – challenged for violation of ethics and fraud. Dosage of ASA and DP different from other studies. Study may be biased in favour of DP due to low ASA dosage used.	Review includes many papers, but authors were asked to focus on CAPRIE and ESPS-2.
Canadian Co-ordinating office for HTA 1999.[31]	Review article – 17 publications.	Compares efficiency and cost of clopidogrel to ASA/ticlopidine /DP/ sulfinpyrazone for patients with TIA, stroke, unstable angina, MI and PAD.	Not Applicable.	ASA should remain first line therapy. Both clopidogrel and ticlopidine are more expensive than ASA without significant advantage as first line therapy. CAPRIE study - only significant difference in RRR for clopidogrel versus ASA was for PAD (i.e. not stroke or MI). Side-effects: - Dyspepsia (18% ASA, 15% clopidogrel) - GI Bleed (3% ASA, 2% clopidogrel).	No explicit inclusion/ exclusion criteria.

Table 6 Summary of Meta-analysis Results (Hankey 1999)[25]

High Vascular Risk Patients	ASA %	Thienopyridines %	Odds Ratio (OR)	95% Confidence interval (CI)	Comments
1. Serious Vascular Events					
Stroke, MI, vascular death	13	12	0.91	0.84 – 0.98	11 events avoided per 1,000 treated over 2 years
Strokes of all types	6.4	5.7	0.88	0.79 – 0.98	7 events avoided per 1,000 treated over 2 years
IS or stroke of unknown type	6.1	5.5	0.90	0.81 – 1.01	Non-significant
Haemorrhagic stroke	4.0	3.3	0.82	0.53 – 1.27	Non-significant
MI	3.9	3.4	0.88	0.76 – 1.01	Non-significant
Vascular/unknown cause of death during follow up	4.8	4.5	0.93	0.82 – 1.06	Non-significant
Death from any cause	6.8	6.5	0.95	0.85 – 1.05	Non-significant
Extra – cranial haemorrhage site including GI	8.86	8.84	1.0	0.91 – 1.09	Non-significant
GI haemorrhage	2.5	1.8	0.71	0.59 – 0.86	
Neutropenia	0.8	2.3	2.7	1.5 – 4.8	Ticlopidine only. Clopidogrel similar to ASA
Severe Thrombocytopenia	0.10	0.19	1.77	0.84 – 3.71	Clopidogrel only. No data for ticlopidine
Skin rash	4.6 5.5	6.0 11.8	1.3 2.2	1.2 – 1.5 1.7 – 2.9	- Clopidogrel - Ticlopidine
Diarrhoea	3.4 9.9	4.5 20.4	1.3 2.3	1.2 – 1.6 1.9 – 2.8	- Clopidogrel - Ticlopidine
Indigestion/nausea/vomiting	17.1	14.8	0.84	0.78 – 0.90	
2. TIA or IS Patients					
Serious vascular events	18.3	16.8	0.90	0.81 – 1.00	Borderline significance 14 events avoided per 1,000 treated over 2 years
Stroke of all types	12	10.4	0.86	0.75 – 0.97	16 events avoided per 1,000 treated over 2 years
IS/stroke of unknown type	11.5	10.2	0.87	0.77 – 0.99	
Haemorrhagic stroke	0.7	0.6	0.87	0.52 – 1.44	No difference
Other outcomes	-	-	-	-	Similar to those given for all high risk patients

(n = 22,656 – TIA or IS = 9,840, MI = 6,302, PAD = 6,514)

- It has not been studied in people with a previous history of ASA sensitivity.
- It is not known, therefore, if clopidogrel works in ASA-sensitive people and if those who are ASA-sensitive are also more likely to be clopidogrel-sensitive.
- Its overall efficacy (all cause mortality) is no better than ASA.
- The proportion of patients who discontinue treatment, due to adverse events, is equal to that of ASA (Table 7).

3.3.2 Aspirin and Dipyridamole

The ESPS-2 study[26] suggests that:

- DP 400mg daily and ASA 50mg daily have similar efficacies.

There is, however, some dispute with respect to the use of DP in the literature. The Royal College of Physicians' *National Clinical Guidelines for Stroke*[13] do recommend, however, the use of a combination of low dose ASA and MRD for first line therapy, and DP for second line therapy for stroke prevention.

Other authors have questioned the ESPS-2 study[30] for violation of ethics (due to the study having a placebo arm when the use of ASA is beyond question) and fraud by one participating centre, although the latter was excluded from the final analysis. However, the ethics committees of participating centres gave their approval for the study, which was not withdrawn at any later stage of the research. In addition, the dose of ASA used in the study is different from that used in other studies and is not, therefore, directly comparable. ESPS-2[26] used ASA 25mg b.d. and MRD 200mg b.d. The argument is that this dose may have reduced the possible benefit of ASA, and biased the results in favour of DP. For these reasons, whilst the results should not be dismissed, they should be viewed with caution. However, the ongoing European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) of the co-formulation of ASA and DP versus ASA will provide further information.

3.3.3 Aspirin Intolerance: the Size of the Problem

If ASA intolerance is the main reason for considering second line therapy, it is important to determine how many patients fall into this category.

Table 7 Overall Safety Analysis – CAPRIE Study[2]

Adverse Events	Clopidogrel (n = 9599)	ASA (n = 9586)
Early permanent discontinuation of study due to adverse events (%)	11.94	11.92
GI Disorder (%)	3.21	4.02
Skin or Appendage Disorder (%)	1.52	0.76
Fatal adverse event during study drug treatment & 28 days after cessation (%).	4.15	4.39
Any GI bleed		
All	191 (1.99%)	255 (2.66%)
Severe	47 (0.49%)	68 (0.71%)
Hospitalised	71 (0.74%)	104 (1.08%)
Fatal	1 (0.01%)	2 (0.02%)
Any GI Adverse Symptoms		
All	27.14%	29.82%
Severe	2.98%	3.60%
Ulcer (Gastric, Peptic, Duodenal)	0.68%	1.15%

Table 8 Primary Reason for Premature Cessation of Study Medication (ESPS-2 Study)[26]

	Placebo	ASA	DP	DP-ASA	p-Value (Treatment Groups Overall Comparison)
Number of patients in each group	1,649	1,649	1,654	1,650	
Number of cessations	360	366	485	479	p<0.001
Reasons for cessation (medical)	275	290	385	398	p<0.001
Any adverse events ‡	127	141	249	262	p<0.001
Gastrointestinal event	60	61	102	116	p<0.001
Headache	39	31	132	133	p<0.001
Bleeding any site, any severity	5	20	3	21	p<0.001
Other medical reason	148	149	136	136	NS
Non-medical	81	72	95	79	NS
Unknown	4	4	5	2	-

‡ One patient may have had one or more adverse events.

A benefit of famotidine, as compared with placebo, in preventing both GU and DU in patients with arthritis who received NSAIDs for 24 weeks has also been published.[39] However, the dose required to produce only modest benefit was high (40mg given twice a day) making the costs of such treatment considerable. A recent review of the evidence by Wolfe et al.[40] concluded that the use of H_2-receptor antagonists for the prevention of NSAID-associated ulcers cannot be recommended.

b) Proton Pump Inhibitors

Omeprazole and lansoprazole are licensed for the prevention of NSAID-induced GU or DU.[41] One study in patients taking NSAIDs showed omeprazole to heal and prevent ulcers more effectively than did ranitidine over a six month period.[42] No studies were identified that have assessed specifically the efficacy of PPI prophylaxis in patients taking long-term low dose aspirin.

c) Other Acid Suppressant Therapy

Misoprostol is licensed for use in the prophylaxis of NSAID induced GU and DU, however, no studies on the efficacy of long-term low-dose ASA were found.

d) Comparison of Effectiveness between Different Acid Suppressant Treatments

Two RCTs compared omeprazole with misoprostol and placebo,[43] and omeprazole with ranitidine[42] in patients with established NSAID peptic ulcers and erosions. In one study, 61% of omeprazole patients remained in remission after six months, compared with 48% of misoprostol patients and 27% of placebo patients. In the second study, 72% of omeprazole patients and 59% of ranitidine were still in remission at six months.

In addition, a meta-analysis of trials compared misoprostol or H_2As in the prevention of NSAID-induced GI damage.[36]

- 200-800 micrograms of misoprostol significantly reduced the rate of GUs by 8% in long-term use, compared to placebo (Numbers needed to treat (NNT): 12.5).
- H_2As did *not* reduce the rate of GUs compared to placebo.
- Both drugs were comparable for DUs (NNT: misoprostol 29, H_2A 42).
- One short-term study of misoprostol 100 micrograms daily versus placebo in healthy volunteers taking 300mg ASA daily for four weeks[19] indicated that there was a significant reduction in gastric erosions in the misoprostol group.

4. ECONOMIC ANALYSIS

4.1 METHODS FOR ECONOMIC ANALYSIS

Papers containing economic and cost terms were filtered from the original literature search. Other papers were found as citation references in the course of researching this report. The search found a number of papers, which were either primarily reporting the results of economic evaluations, or made reference to the economic or costing implications of antiplatelet therapies.

Four of the papers (Chambers et al.,[44] Scott and Scott,[45] Oster et al.[46] and Kurz et al.[47] report original economic evaluations. Other papers found in the search frequently cite these papers. Two of the papers take a UK perspective (Chambers et al.[44] and Currie[48]), though the Currie paper is concerned with costing the burden of stroke rather than the economics of prevention. The papers by Alexandrov et al.[49] and Benesch et al.[50] are reviews investigating the prevention and treatment of stroke. The papers by Scott and Scott[45], Kurz et al.[47], and Chambers et al.[44] are all directed at the use of ASA and DP for the prevention of stroke in New Zealand, Belgium, and the UK respectively. The paper by Oster et al.[46] is a US-based analysis of ticlopidine and ASA, again for stroke prevention. A paper presented by Overell at the 8th European Stroke Conference in April 1999, has been published as an abstract in *Cerebrovascular Disease*[51].

Table 10 summarises details of the papers identified by the search.

Table 11 summarises the key original papers by disease and drug categories and shows that none of the identified papers addresses the economics of antiplatelets for MI or PAD. Consequently, most of the discussion in this section is directed at the economics of stroke prevention.

Table 11 Key Economics Papers Classified by Disease and Antiplatelet

	Dipyridamole	Clopidogrel	Ticlopidine
Primary prevention of stroke.			
Secondary prevention of stroke.	Chambers,[44] Scott,[45] Kurz[47]	Overell[51]	Oster[46]
MI	N/A		
PAD	N/A		

4.1.1 Estimation of Net Benefits

The benefits of treatment with antiplatelets include the avoidance of stroke and other neurological and vascular events, the avoidance of disability, and the prolongation of life. Disbenefits result as a consequence of adverse drug reactions, for example, GI bleeding with ASA, and neutropenia with ticlopidine. Many of the reported analyses have used either decision modelling or Markov models to estimate outcomes including numbers of avoided strokes, disabled life years avoided, life years, and quality adjusted life years (QALYs). Estimates of quality of life quoted in the published papers generally have poor empirical evidence to support them, and so there is considerable uncertainty around these estimates. The results of the various analyses are discussed in greater detail alongside the analysis of cost-effectiveness later in this chapter.

4.1.2 Estimation of Net Costs

The principal costs to the NHS of antiplatelet therapies are the drug costs themselves. Prescribing and monitoring have small cost implication from GP visits and blood tests. If the therapy lasts for a number of years, then the future drug costs should be discounted at an appropriate rate. The costs of antiplatelet formulations were presented in Table 2. This table highlights the relatively low cost of ASA compared to the newer antiplatelets. Depending on dosage, the annual cost of EC-ASA is about 3 times that of dispersible ASA. DP is between 12 and 30 times more expensive than dispersible ASA. Clopidogrel is nearly four times more expensive than DP, and ticlopidine is more than twice as expensive as clopidogrel. Ticlopidine is over 300 times more expensive than dispersible ASA 300mg. Ideally, the costs of treating adverse drug reactions should be included in an economic appraisal.

The scope for potential savings to the NHS comes from avoided hospital treatment for the conditions under review. At best, this might lead to actual resource savings, and should at least free up NHS beds, thereby reducing waiting times, and possibly preventing or delaying

The model in this Guidance Note is a simpler spreadsheet version of the model presented by Chambers et al.[44] Their model was developed to evaluate the cost-effectiveness of the co-formulation of ASA and DP for stroke prevention. The model is a Markov model in which transitional probabilities are allowed to vary by age and other factors. The estimates for these transitional probabilities are based primarily on the results of the ESPS-2 study. The costs and benefits of antiplatelets are modelled over a 25-year treatment period for a given cohort of patients using quarterly time periods. In this case the cohort is 1,000 30-day survivors of IS. The model in this Guidance Note uses the same assumptions as those used by Chambers et al.[44] with a few notable differences. The primary aim of the authors' modelling was to make only preliminary estimates and comparisons of the cost-effectiveness ratios for the drugs under review for secondary prevention of stroke. Having established that intolerance and side-effect assumptions had only a minor effect on the resulting cost-effectiveness ratios when compared with Chambers' estimates, we proceeded to make the following simplifying assumptions:

- Treatment is for life or for 25 years, whichever is the shorter;
- The disbenefits and costs of side-effects are not modelled;
- All patients are assumed to be tolerant of the drug prescribed.

Other key assumptions in the model include:

- The perspective is that of the UK health and social care sectors;
- The cohort of patients has a mean age of 70 years;
- 31% of the cohort are assumed disabled from the initial stroke;
- Only first recurrence of stroke is considered;
- Case fatality of recurrent stroke varies by therapy (reported in ESPS-2);
- Disablement of survivors of recurrent stroke does not vary by therapy and is assumed to be 35.6% of previously non-disabled patients. Further disablement can only occur as a result of a recurrent stroke;
- Rehabilitation and acute care costs of recurrent stroke are all assumed to take place in the same quarter in which the recurrent stroke occurs;
- Costs of care unrelated to modelled events are not included;
- Future costs are discounted at 6%; health benefits are not discounted.

The model structure is illustrated in the form of a decision tree in Figure 2.

Table 13 Other Transitional Probabilities (absolute risks)

Variable	Assumption (% per 3-month cycle)	Source
P(recurrent stroke without therapy)		
Years 1-2	4.88 to 1.53	ESPS-2
Years 3-24	1.25 to 2.52	OCSP
Non-stroke mortality prior to recurrent stroke (per 3 month cycle)		
year 1 (exc death before 30 days)	5.4 to 2	OCSP
Years 2-5	1.5	OCSP
Years 6-15 (age 75-84)	3.6	OCSP/OPCS
Years 16-25 (age 85+)	4.5	OCSP/OPCS
Mortality (all cause after recurrent stroke (per 3 month cycle)		
First year age 70-74	2.1	OCSP/OPCS
First year age 75-84	5.8	OCSP/OPCS
First year age 85+	12.9	OCSP/OPCS
Subsequent years age 0-74	2.7	OCSP/OPCS
Subsequent years age 75-84	4.6	OCSP/OPCS
Subsequent years age 85+	5.8	OCSP/OPCS

Source: Chambers et al.[44]

OCSP = Oxfordshire Community Stroke Project

The key outcome variables from the model are number of recurrent strokes, disability-free life years, stroke-free life years (SFLY), total life years gained, and net costs. The costs analysed are the costs of antiplatelet treatment, acute rehabilitation, and long-term care costs of stroke treatment. The rehabilitation and long-term care costs allow for disability where appropriate. Cost estimates used by Chambers et al.[44] have been adopted for these variables. An NHS and social care perspective is taken.

Having constructed the model, its outputs were validated against Chambers' results, and all cost variables then inflated to year 2000 prices. The inflated treatment cost estimates used in this model are presented in Table 14.

Table 14 Modelled Costs of Stroke Treatment

Variable	Cost Estimate (£)
Acute care of recurrent Stroke	3,270
Rehab. (disabled: modified Rankin 3-5)	801
Rehab. (not disabled: modified Rankin 0-2)	42
Long-term care (3-monthly disabled)	2,964
Long-term care (3-monthly non-disabled)	230

Source: Chambers et al.[44]

The key results of modelling the costs and benefits of treatment with ASA, DP, and their co-formulation are presented in Table 15.

effective than DP for ASA tolerant patients. The result is robust in that ESPS-2 used a relatively low dose of ASA, thereby possibly under-estimating its effects in the trial.

The model also estimates that the co-formulation has an incremental cost per avoided stroke of £2,437 compared to treatment with ASA alone. The incremental cost per life year gained for the co-formulation compared with ASA is estimated at £1,052. Chambers et al.[44] do not report costs per life year explicitly, although they do estimate a cost per QALY varying between £1,000 and £6,800 depending on a 25 or two year analysis. Their analysis assumed health-related quality of life values of 0.85 for non-disabled survivors and 0.39 for disabled survivors, although the evidence for these figures is poor.

The incremental cost-effectiveness analysis (CEA) reported above looks favourable for the co-formulation compared with ASA, however the following criticisms of the ESPS-2 and Chambers' results should be considered:

- Chambers et al.[44] admit that their results are sensitive to assumptions about background risk of recurrent stroke, the RRR of therapy on stroke, as well as the costs of acute and long-term stroke care. Treatment paths recommended by an expert panel and not from empirical evidence determined their cost estimates for stroke. Pollock[57] has reported lower costs for stroke than those deduced by the Chambers' panel experts.
- Chambers acknowledges that ESPS-2 used a relatively low dose of ASA, so that the RRR of stroke from ASA may be under-estimated in the trial and the models. A sensitivity analysis undertaken by Chambers et al.,[44] increasing the RRR of ASA from 18% to 23%, increased the incremental cost per avoided stroke for the co-formulation compared with ASA from £1,900 in the five year analysis to £4,700 (1996 sterling).
- A three-way sensitivity analysis presented by Chambers et al.,[44] using high costs of acute and long-term care and reducing the background risk of stroke by 20% from the base case, increases the cost per QALY gained (co-formulation versus ASA alone) to £10,500 from £2,900 in their five year analysis.
- Chambers acknowledges that in a previous study by Matchar et al.,[58] the co-formulation (ASA 700 to 1300mg/day and DP 150-300mg/day) was shown to be effective in reducing stroke in patients with a previous TIA when compared with no treatment, but not compared with ASA monotherapy. The sensitivity analysis presented by Chambers shows that using the lower 95% confidence interval value for RRR of the co-formulation increased the cost per stroke averted from £1,900 to £17,800. Using this assumption is not inappropriate if the Matchar results are accepted.

have been used to model the effectiveness of clopidogrel, though the relative risk (RR) of stroke has been lowered by 8.7% (that is, 25.2% RRR compared with no treatment). The three-monthly cost of antiplatelet treatment assumed to be £115.07 per patient.

The model indicates net costs of £28.0m for treating the 1,000 patient cohort for a maximum of 25 years. This figure is £2.3m more than treatment with ASA alone. The model also indicates that there would be 350 strokes and 7,151 life years for the cohort (5,542 SFLYs and 4,546 disability-free life years).

Comparing clopidogrel with no treatment, the incremental costs per stroke avoided and per life year saved are £23,760 and £11,884 respectively. Compared with ASA, the incremental costs of clopidogrel are £99,721 per stroke avoided and £34,856 per life year gained. These figures highlight the relatively high costs of clopidogrel compared with ASA.

A very simplistic approach to modelling clopidogrel has been taken. It could be argued that the absolute effects of clopidogrel have been under-estimated because the 8.7% RR adjustment was applied to the results of the ESPS-2 trial, which used a lower dose of ASA than that used in the CAPRIE study.[2] If this argument is accepted then the model will have under-estimated the cost-effectiveness of clopidogrel compared to no treatment. It should be borne in mind that the RRR of 8.7% recorded in the CAPRIE study[2] was a combined event risk reduction and not solely a stroke reduction effect.

Others might argue that the mortality benefits of clopidogrel have been over-estimated using this model. The CAPRIE study[2] indicated no statistically significant 'all mortality' benefits from clopidogrel compared with ASA. Although the modelled scenario assumes that the direct mortality risk for stroke patients taking clopidogrel is the same as that for ASA patients, clopidogrel patients gain some mortality benefits in the model because of an algorithm linking mortality to stroke incidence. Consequently, the model indicates fewer deaths for clopidogrel patients. Although this assumption does not affect the stroke avoidance cost-effectiveness estimates, the life year gain benefits of clopidogrel may have been over-estimated.

During the course of researching this report, a conference abstract by Overell et al.[51] reporting the results of a cost-effectiveness analysis of clopidogrel was found. Though it has not been possible to review the original conference paper, the abstract reports marginal

QALY ratio to be sensitive in the upward direction to the 'risk of stroke' assumption (95% CI of $18,000 to $306,000).

- The costs of added life years have been modelled, but were not weighted to allow for age. UK Hospital and Community Health Services (HCHS) per capita figures clearly indicate that costs of added life years increase significantly with age.
- Although it claims to incorporate a societal costing analysis, the paper provides no evidence of any direct or indirect patient costs.

Some of these assumptions bias the Oster et al.[46] analysis in favour of life prolonging treatments and, therefore, ticlopidine. Despite this, the authors argue that their analysis is biased against ticlopidine because of assumptions about the quality of life following stroke, and because the stroke incidence assumption used in the model is relatively low for the USA. This report's estimates for the cost-effectiveness of ticlopidine in stroke prevention are considerably higher than Oster's,[46] although well within the sensitivity analysis presented by them.

There appears to be a growing consensus in the UK that ticlopidine is not cost-effective for the prevention of stroke. The Drug and Therapeutics Committee for the Greater Glasgow Health Board Area, for example, has not added ticlopidine to its formulary because, in its view, as well as costing more than alternative therapies, it offers no advantages over other treatments.

4.3 HEALTH ECONOMICS CONCLUSIONS

The literature search conducted for this Guidance Note found only economic evaluations estimating the cost-effectiveness of antiplatelets for the secondary prevention of stroke. The economics of antiplatelets for the secondary prevention of MI and PAD were not reported and, therefore, are not evaluated in this report.

Based on the model presented by Chambers et al.,[44] a spreadsheet model has been built to enable preliminary estimates of the cost-effectiveness of antiplatelets in the secondary prevention of stroke to be derived and compared. The results of this modelling were validated using Chambers' model.

5. CONCLUSIONS

1. Dispersible ASA should remain the first line therapy for the secondary prevention of stroke and other serious vascular events, in patients at high vascular risk, except where it is not tolerated. There is no known advantage to using EC-ASA.

2. Further research is recommended in relation to the responsiveness of individuals to ASA, so that the dose may be adjusted to maximise efficacy and reduce side-effects. Until facilities for testing ASA dose-responsiveness are more widely available, present evidence indicates the dose of 75mg daily to optimise the secondary prevention of stroke and serious vascular events, whilst minimising the risk of GI side-effects.

3. ASA Failure / Intolerance.
   (a) Acid suppressant therapy is not indicated routinely for patients taking ASA. However, patients with a history of ulcer disease or GI bleed should be given a PPI, despite the evidence for its benefit being based on NSAIDs. If there is no improvement in GI symptoms, the acid-suppressant therapy should be discontinued.

   (b) MRD is licensed for use with TIA and IS patients only. MRD alone should be used as second line therapy for TIA and IS patients who are unable to tolerate ASA (as it is cheaper than clopidogrel).

   (c) As with MRD, the co-formulation of MRD and ASA is licensed for TIA and IS patients only. It cannot be advocated as first line therapy for these conditions at the present time. However, for TIA and IS patients who failed on ASA therapy alone, the co-formulation may be considered.

   (d) Clopidogrel should be considered as second line therapy for patients with MI and PAD who are unable to tolerate or have failed on ASA.

   (e) Clopidogrel should be considered as third line therapy for patients with TIA and IS for whom neither ASA nor MRD have been successful.

4. Ticlopidine should not be prescribed as an alternative to ASA for long-term therapy.

7. APPENDIX: MEDLINE LITERATURE SEARCH STRATEGY

Database: Medline <1966 to Present>

Search:

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1 ticlopidine/
2 ticlopidine.tw.
3 ticlopidine.rw.
4 55142 85 3.rn.
5 clopidogrel.tw.
6 clopidogrel.rw.
7 90055 48 4.rn.
8 or/1-7
9 economics/
10 exp "costs and cost analysis"/
11 economic value of life/
12 exp economics, hospital/
13 exp economics, medical/
14 economics, nursing/
15 economics, pharmaceutical/
16 exp models, economic/
17 exp "fees and charges"/
18 exp budgets/
19 ec.fs.
20 (cost or costs or costed or costly or costing$).tw.
21 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
22 or/9-21
23 clinical trial.pt.
24 meta$.pt.
25 review.pt.
26 exp review literature/
27 exp clinical trials/
28 meta-analysis/
29 exp guidelines/
30 health planning guidelines/
31 or/23-30
32 ASA/
33 (acetylsalicyclic adj acid).tw.
34 ASA.tw.
35 ASA.rw.
36 50 78 2.rn.
37 or/32-36
38 22 or 31
39 8 and 37 and 38
40 8 and 22 and 37
41 8 and 37 and 31
42 8 and 22 and 31 and 37
43 DP/
44 DP.tw.
45 DP.rw.
46 58-32-2.rn.
47 or/43-46
48 8 or 47
49 48 and 22 and 37
50 48 and 31 and 37
51 48 and 22 and 31 and 37
52 from 51 keep 1-10

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