Ipswich and East Suffolk
Clinical Commissioning Group

New Medicine Report	**Clopidogrel for Acute Coronary Syndrome Classification GREEN** **(Adopted by the CCG until review and further notice)**
Document Status	Following submission to Suffolk Drug & Therapeutics Committee
Date of Last Revision	15th May 2003
Approved Name	Clopidogrel
Trade Name	Plavix™
Manufacturer	Sanofi~Synthelabo
Legal Status	POM
Indication	Prevention of atherothrombotic events in patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) in combination with aspirin
Dosage	Loading dose 300mg Then 75mg daily with aspirin The optimal duration of treatment has not been formally established. Clinical trial data [CURE study] supports use up to 12 months and the maximum benefit was seen at 3 months
Cost	£35.31 for 28 tablets
Possible Number of Suffolk Patients	1480
Number Needed to Treat	See Tables but about 45 at 9 month mean period of treatment
Number Needed to Harm	See Tables but about 100 at 9 month mean period of treatment for a major bleed or 30 for any bleed
Treatment Alternatives	Current treatments – NB this is an additional arm of treatment
Future Alternatives	Not known
Possible Future Indications	Not known

NHS

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Reviewer's Comments

Clopidogrel has recently been licensed for the prevention of atherothrombotic events in patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) in combination with aspirin.

The NNT is about 45, the NNH for the complication of an induced serious bleed is 100 and that for any induced bleed is 30. Thus for every two people receiving benefit from this product in this licensed indication one person will receive some harm due to a serious bleed and two further people will receive some harm due to a bleed.

The limited evidence available suggests that the benefit occurs within the first three months although the CURE study was carried out over a mean of 9 months. Given the associated risks of treatment it is imperative that the patient is treated for the optimum time whilst balancing the risks and benefits.

At present it is not clear where the use of clopidogrel and glycoprotein IIb/IIIa fits in the clinical pathway.

Some Drug & Therapeutic Committees have recommended that it should only be prescribed for 3 months and that the whole supply should be provided to the patient on discharge. This would go against the current expectation that hospitals will supply a 28-day discharge supply and also against the development of 28 day prescribing in general practice.

It is suggested that a consultant should initiate the treatment after discussion with the patient of the benefit and risks of treatment. It should be prescribed as part of a package of care as laid out in the NSF for coronary care. If responsibility for treatment is handed over to the patient's GP then the consultant must state the length of course they wish the patient to be prescribed.

Evidence Reviewed

Paper, Review, Abstract etc.	Level of evidence
Trial Investigators Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-Segment elevation. N Eng J Med 2001;345:494-502 Known as the CURE study	I
Mehta SR, Yusuf S, Peters RJG, et al Effects of pre-treatment with clopidogrel and aspirin followed by long term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study Lancet 2001;358:527-533	I
Bertrand ME, Simoons ML, Fox KAA, et al Management of acute coronary syndromes in patients presenting *without* persistent ST-segment elevation Eur Heart J 2002;23:1809-1840	III
MTRAC VS02/17 Clopidogrel in ACS	III
Bedfordshire PCT JPC Bulletin 63 Clopidogrel in ACS	III
Anon Clopidogrel and acute coronary syndrome DTB2002;40:41-2	III

Level of evidence adapted from "Quick and Clean" : authorative health technology assessment for local health care contracting Andrew Stevens, Duncan Collin-Jones & John Gabbay Health Trends Vol 27 No 2 1995

Review

Acute coronary syndrome (ACS) has a major impact on the cost of healthcare and leads to a large number of hospital episodes. Despite treatment the rates of mortality, myocardial infarction and readmission remain high.

The use of an ECG following a period of acute chest pain though to be of cardiac origin allows the differentiation of patients into two groups, each of which requires different treatment.

ST-segment elevation signifies complete occlusion of a major coronary artery and immediate reperfusion therapy is normally indicated. Such patients account for about 42% of those presenting with pain.

A further 51% have either ST-segment changes but without persistent ST–segment elevation or a normal ECG.

The remaining 7% have no definite characterisation.

Other tests are necessary to ensure the correct diagnosis.

The aim of treatment for those with non-ST-segment elevation is to control pain and prevent progression to myocardial infarction and subsequent death.

The recommended treatment strategy in acute coronary syndromes devised by the European Society of Cardiology Guidelines is shown in Appendix A.

Long term management of patients following ACS is set out in the NSF for coronary heart disease. The interventions recommended include smoking cessation, treatment with aspirin, betablockers, statins, ACE inhibitors and assessment of modifiable risks such as diet and exercise. The British Cardiac Society Guidelines also suggest that patients should be referred for cardiac rehabilitation.

The CURE study (supported by Sanofi-Synthelabo and Bristol-Myers Squibb) reports a randomised, double-blind, placebo controlled trial comparing clopidogrel with placebo in patients with acute coronary syndrome without ST-segment elevation who had been hospitalised within 24 hours of the onset of the symptoms and showed either ECG changes or elevation in the serum level of cardiac enzymes or markers.

Patients with contraindications to antithrombotic or antiplatelet therapy, those at high risk of bleeding or severe heart failure, those taking oral anticoagulants and those who had undergone coronary revascularisation in the previous three months or had received intravenous glycoprotein IIb/IIIa receptor inhibitors in the previous three days were excluded.

Patients (n = 12,562) were randomised to treatment receiving either a loading dose of 300mg of clopidogrel and then 75mg daily (n = 6259) or matched placebo (n = 6303) for 3 to 12 months (mean duration 9 months). Aspirin 75mg to 325mg daily was either started or continued. The major outcomes are shown in Table 1.

Table 1
To show the incidence of the major CURE study outcomes

Outcome	Treatment arm	Placebo arm	Relative risk (95% CI)	P Value	NNT at mean of 9 months
	N = 6,259	N = 6,303			
	No (%)				
First primary outcome	582 (9.3)	719 (11.4)	0.80 (0.72 – 0.90)	<0.001	47
Second primary outcome	1,035 (16.5)	1,187 (18.8)	0.86 (0.79 – 0.94)	<0.001	44

First primary outcome is non-fatal MI, stroke or death from cardiovascular causes
Second primary outcome as above or refractory ischaemia

It should be noted that the major driver of these outcomes is a reduction in the number of patients suffering from a MI.

It has been noted that following the initial recruitment the entry criteria were altered and most of the subsequent participants were at a higher risk of progressing to MI or death than the normal hospital population with ACS without ST-elevation.

The paper from Mehta reports a sub analysis of the CURE data for the 21% of patients who also underwent percutaneous coronary intervention (PCI) reported under the title PCI-CURE. The primary outcome measure was the composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI. Cardiovascular death or myocardial infarction from the time of PCI to the scheduled end of the trial was also assessed. The major outcomes are shown in Table 2.

Table 2
To show the incidence of the major PCI-CURE study outcomes

Outcome	Treatment arm	Placebo arm	Relative risk (95% CI)	P Value	NNT at mean of 9 months
	N = 1,313	N = 1,345			
	No (%)				
Primary outcome within 30 days of PCI	59 (4.5)	86 (6.4)	0.70 (0.50 – 0.97)	0.03	53
Outcome from 30 days to end of trial	240 (18.3)	292 (21.7)	0.83 (0.70 – 0.99)	0.03	29

It has been noted that NICE guidance states that there is clear evidence for the use of glycoprotein IIb/IIIa inhibitor in patients undergoing PCI. In the CURE

study only about 24% of patients were given these drugs. There is no evidence of how clopidogrel compares with glycoprotein IIb/IIIa inhibitor therapy.

Adverse Effects etc.

For full information please refer to the published SPC.

The CURE study showed that the major adverse effect was unwanted bleeding. Table 3 shows the incidence of this complication.

Table 3
To show the incidence of bleeds during treatment

Variable	Treatment arm	Placebo arm	Relative risk (95% CI)	P Value	NNH at mean of 9 months
	N = 6259	N = 6303			
	No (%)				
Major bleed	231 (3.7)	169 (2.7)	1.38 (1.13 - 1.67)	0.001	100
Requiring ≥ 2 units of blood	177 (2.8)	137 (2.2)	1.30 (1.04 - 1.62)	0.02	167
Life threatening	135 (2.2)	112 (1.8)	1.21 (0.95 - 1.56)	0.13	250
Non life threatening	96 (1.5)	57 (0.9)	1.70 (1.22 - 2.35)	0.002	167
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75 - 2.56)	<0.001	37
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48 - 1.94)	<0.001	29

Health Economics

The cost of treatment for the expected numbers of patients who may benefit from the addition of clopidogrel to their therapy for ACS is shown in Table 4. The cost is calculated for a period of 9 periods of 28 days and ignores the initial loading dose cost.

Table 4
To show the possible patient numbers in Suffolk who may benefit from the addition of clopidogrel to their therapy for ACS

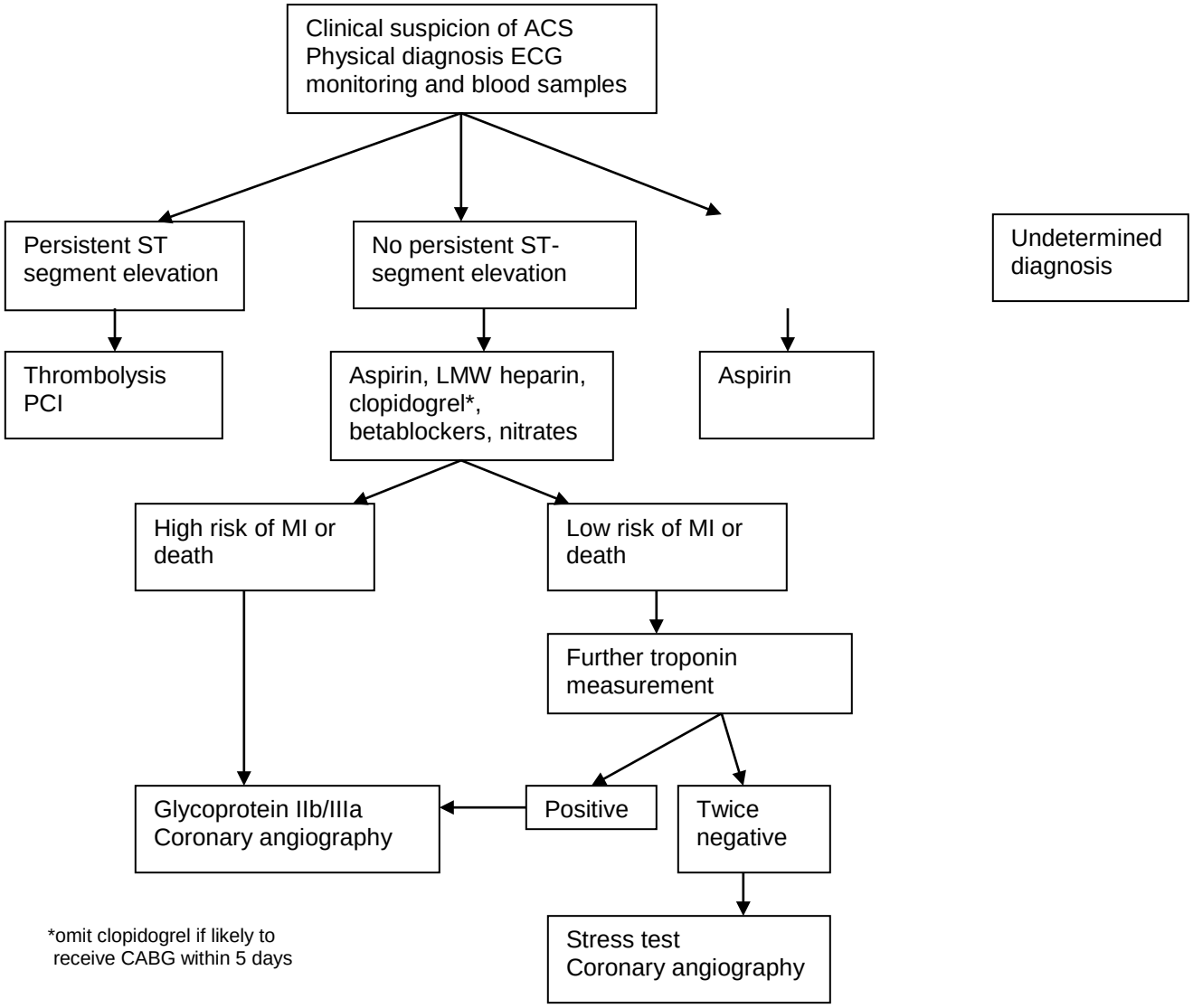
PCT	Population	Expected number of patients at 226/100,000	Expected cost at £35.31 per 28 days for 9 periods
Central	96,000	220	69,914
Ipswich	143,000	320	101,693
Suffolk Coastal	99,000	220	69,914
Suffolk West	203,000	500	146,183
Waveney	114,000	260	82,625
Total for Suffolk	655.000	1,480	470,329
Total for East Commissioning	338,000	760	241,520

Given an NNT of 45 the cost of one patient receiving benefit over the 9 periods of 28 days is about £14,300 and the cost of an adjusted quality of life year assuming that full quality of life is obtained following treatment is about £20,660 (based on 13 periods of 28 days).

It should be noted that for every two patients with benefit three patients have some level of harm and the cost of treating this has not been calculated. However it will undoubtedly increase the cost of treatment per QALY.

Appendix A

Recommended strategy in acute coronary syndrome



From European Society of Cardiology Guidelines