MTA REPORT ADDENDUM 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)

ADDENDUM 2

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1 INTRODUCTION

The discussion prior to the first appraisal committee (AC) meeting for prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (Review of TA182) identified that further information (in particular key trial outcomes and costs) was required in order that the AC be fully informed about a key comparator in the decision problem: ticagrelor.

This addendum has been prepared by the Assessment Group (AG) to provide regulatory, cost and trial information relating to ticagrelor. The clinical data presented in this addendum is taken from the ERG report submitted for TA182.

2 TICAGRELOR LICENSING AND NICE GUIDANCE

Ticagrelor is licensed (in combination with aspirin) in Europe for the prevention of atherothrombotic events in adults with ACS including patients managed medically, with PCI or CABG.[1].

Ticagrelor was recommended by NICE in TA236[2] as a treatment option (in combination with low-dose aspirin) for up to 12 months in adults with ACS, including people with STEMI who are to be treated with PCI, people with NSTEMI or people with UA.

Ticagrelor is produced as 90mg tablets in packs of 56. The normal dose is one tablet twice daily. The current BNF[3] price of ticagrelor is £54.60 per pack, sufficient to last 28 days.

3 TICAGRELOR TRIAL INFORMATION

3.1 PLATO trial characteristics

The recommendations made in the NICE guidance TA236[2] were based on a single RCT known as the PLATO[4] trial. The PLATO[4] trial was an international, multicentre, double-blind, double-dummy phase III trial comparing ticagrelor plus aspirin with clopidogrel plus aspirin in 18,624 patients admitted to hospital with ACS with or without STEMI. It is important to note that patients were randomised to the trial irrespective of planned intervention and therefore the patient population included ACS patients who were to be medically managed as well as those who were to undergo PCI. The trial follow-up was for 12 months, however the AG notes that the trial protocol stipulated that once the requisite number of events (1780) had accrued, patients were required to leave the trial after their 6 month or 9 month visit. The key trial characteristics are described in Table 1.

Table 1 PLATO trial key characteristics

PLATO Trial design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
•RCT, Phase III, international, double blind, double dummy •43 countries including UK (18 centres, 281 patients) •18,624 patients admitted to hospital with ACS, with or without ST-segment elevation	• Ticagrelor (180mg loading dose, 90 mg twice daily thereafter) +ASA • Clopidogrel (300mg to 600mg loading dose, 75mg daily thereafter) +ASA <u>ASA dosing</u> Most patients received 75 to 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving ASA, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement.	• Patients hospitalised for an ACS, with ST-segment elevation or new LBBB during previous 24 hours • Patients hospitalised without ST-segment elevation during the previous 24 hours with at least two of the following: ST-segment changes indicative of ischaemia, a positive test for a biomarker indicative of myocardial necrosis; or one of several risk factors (age >60; previous MI or CABG; coronary artery disease with stenosis ≥50%; previous ischaemic stroke, TIA, carotid stenosis ≥50% or previous cerebral revascularisation; diabetes mellitus; peripheral vascular disease; or renal dysfunction)	•Any contraindication against the use of clopidogrel •Fibrinolytic therapy within 24 hours before randomisation •Need for oral anticoagulation therapy • Increased risk of bradycardia without an implanted pacemaker • Concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer	12 month planned follow-up or until 1780 events had occurred <u>Primary</u> •CE of death from vascular causes, MI or stroke <u>Secondary</u> •Primary endpoint in patients for who early invasive management was planned at randomisation •CE of death from vascular causes, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischaemic, TIA or other arterial thrombotic events •MI •Death from vascular causes •Stroke •Death from any cause

TIA= transitory ischaemic attack; CE= composite endpoint; LBBB= left bundle branch block

3.2 Trial outcomes

3.2.1 Overall trial population

The results of the PLATO[4] trial for the overall trial population at 12 months are described in Table 2. A statistically significant benefit of ticagrelor was found for the primary composite endpoint (9.8% compared to 11.67% [HR= 0.84; 95% CI 0.77 to 0.92; p<0.001]). When the individual components of the composite endpoint are disaggregated, the reduction in the primary endpoint is driven by statistically significant reductions in death from vascular causes (HR= 0.79; 95% CI 0.69 to 0.91; p=0.001) and MI (HR= 0.84; 95% CI 0.75 to 0.95; p=0.005).

Table 2 PLATO trial results at 12 months

	Ticagrelor N=9333 No. patients with events (KM%/12 months)	**Clopidogrel N=9291 No. patients with events (KM%/12 months))**	**HR for ticagrelor (95% CI)**	**p value**
Primary				
Death from vascular causes, MI, stroke	864(9.8)	1014(11.7)	0.84 (0.77 to 0.92)	<0.001*
Secondary				
Death from any cause, MI or stroke	901(10.2)	1065(12.3)	0.84 (0.77 to 0.92)	<0.001*
Death from vascular causes, MI, stroke, severe recurrent ischaemia, recurrent ischaemia, TIA or other arterial thrombotic event	1290(14.6)	1456(16.7)	0.88 (0.81 to 0.95)	<0.001*
MI	504(5.8)	593(6.9)	0.84 (0.75 to 0.95)	0.005*
Death from vascular causes	353(4.0)	442(5.1)	0.79 (0.69 to 0.91)	0.001*
Stroke:	125(1.5)**	106(1.3)	1.17 (0.91 to 1.52)	0.22
ischaemic	96(1.1)	91(1.1)		0.74
haemorrhagic	23(0.2)	13(0.1)		0.10
unknown	10(0.1)	2(0.02)		0.04
Death from any cause (exploratory)	399(4.5)	506(5.9)	0.78 (0.69 to 0.89)	<0.001
Death from causes other than vascular causes (exploratory)	46(0.5)	64(0.8)	0.71 (0.49 to 1.04)	0.08
Severe recurrent ischaemia**	302(3.5)	345(4.0)	0.87 (0.74 to 1.01)	0.08
Recurrent ischaemia**	500(5.8)	536(6.2)	0.93 (0.82 to 1.05)	0.22

KM= Kaplan-Meier. The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of endpoint. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes.
* Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points
** data taken from published paper
TIA=transitory ischaemic attack

3.2.2 Safety outcomes

A novel system for categorising bleeding events was utilised in the PLATO[4] trial. This is described in Table 3 and the outcome data for these events are described in Table 4. There are no statistically significant differences between the two arms of the trial for the endpoints of PLATO major bleed (primary safety endpoint) and PLATO major fatal/life-threatening

bleed; however, statistically significant differences in favour of clopidogrel are in evidence for the endpoints of PLATO total major + minor bleed, (HR=1.11; 95% CI 1.03 to 1.20; p=0.008) and PLATO non-CABG major bleed (HR= 1.19; 95% CI 1.02 to 1.38; p=0.03).

Table 3 PLATO defined bleeding events

Bleeding event	Description
Major life-threatening	Fatal, intracranial, intrapericardial with cardiac tamponade, hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the haemoglobin level of 5.0g per decilitre or more, or the need for transfusion of at least 4 units of red cells
Other major bleeding	Bleeding that led to clinically significant disability (e.g. intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the haemoglobin level of at least 3.0g decilitre but less than 5.0g per decilitre or requiring transfusion of 2 to 3 units of red cells
Minor bleeding	Any bleeding requiring medical intervention but not meeting the criteria for major bleeding

Table 4 PLATO primary and secondary bleeding events

Endpoint	Ticagrelor N=9235 No. events (KM%/ 12 months)	Clopidogrel N=9186 No. events (KM%/ 12 months)	HR Ticagrelor (95% CI)	p value
PLATO total major bleed (Primary)	11.6	11.2	1.04 (0.95 to1.13)	0.43
TIMI major + minor bleed	11.4	10.9	1.05 (0.96 to1.15)	0.33
PLATO major fatal/life-threatening bleed	5.8	5.8	1.03 (0.90 to1.16)	0.70
TIMI major bleed	7.9	7.7	1.03 (0.93 to1.15)	0.57
PLATO total major + minor bleed	16.1	14.6	1.11 (1.03 to1.20)	0.008
PLATO non-CABG major bleed	4.5	3.8	1.19 (1.02 to1.38)	0.03
PLATO fatal bleed	0.3	0.3	0.87 (0.48 to1.59)	0.66

3.2.3 Subgroup analyses

The results of analyses that assess the effectiveness of ticagrelor vs clopidogrel in the range of patient populations included in the PLATO[4] trial are summarised in Table 5. The patient populations include people intended for early angiography, people managed medically, people with STEMI, people who were treated with CABG and people with diabetes. With the

exception of the subgroup of patients treated with CABG and people with diabetes, a statistically significant benefit for ticagrelor compared with clopidogrel is recorded.

Table 5 PLATO subgroup analyses (primary efficacy endpoint)

	Patient group (N)	Ticagrelor (KM %/12 months)	Clopidogrel (KM %/12 months)	HR (95% CI)	p value
PLATO	All ACS (18,624)	9.8	11.7	0.84 (0.77 to 0.92)	<0.001
PLATO-INVASIVE*	Intended for early angiography (13,408)	9.0	10.7	0.84 (0.75 to 0.94)	0.0025
PLATO-MEDICAL	Conservative management (5216)	12.0	14.3	0.85 (0.73 to 1.00)	0.04
PLATO-STEMI	STEMI with PCI STEMI or LBBB at presentation (7544)	9.4	10.8	0.87 (0.75 to 1.01)	0.07
	LBBB/STEMI at presentation or STEMI at discharge (8430)	9.3	11.0	0.85 (0.74 to 0.97)	0.02
PLATO-CABG	CABG (1261)	10.6	13.1	0.84 (0.60 to 1.16)	0.29
PLATO-DIABETES	With DM (4,622)	14.1	16.2	0.88 (0.76 to 1.03)	NR
	Without DM (13,951)	8.4	10.2	0.83 (0.74 to 0.93)	

DM= diabetes mellitus; NR= not reported
*77% received treatment with PCI

3.2.4 Health-related quality of life

The PLATO[4] trial included a Health Economics and Quality of Life sub-study. This sub-study employed the paper version of the EQ-5D questionnaire and the manufacturer converted the EQ-5D scores to utility values to inform the cost-effectiveness analyses presented in the manufacturer's submission for TA236 using the UK tariff weightings.

Of the total number of 18,624 patients, 15,212 (82%) had a utility score calculated at discharge from the index hospitalisation (visit 1). At visit 4 (6 months) and visit 6 (12 months) the percentage of patients in the full cohort with a utility score was 80% and 79% respectively. Of the 10,686 patients who were eligible for a 12 month follow-up (referred to as the 12-month cohort), 8840 (83%) had a utility score calculated at visit 1. The corresponding percentage of patients in the 12-month cohort with utility score at visit 4 and visit 6 was 81% and 80% respectively.

No differences were found between ticagrelor and clopidogrel for any of the items on the EQ-5D.

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