MTA REPORT ADDENDUM 3

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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ADDENDUM 3

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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1 INTRODUCTION

A second pre-meeting briefing teleconference prior to the first appraisal committee (AC) meeting for prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (Review of TA182) took place on 21st February 2014. One of the points of discussion during the teleconference was an expert submission submitted to NICE by the British Cardiovascular Intervention Society (BCIS) and a clinical specialist statement from Professor Curzen. Both documents question the efficacy of prasugrel in patients with NSTEMI and cite evidence from two randomised controlled trials: TRILOGY[1] and ACCOAST[2]. Professor Curzen further questions the efficacy of prasugrel in patients with STEMI on an interpretation of the outcomes reported for the STEMI subgroup of patients from the TRITON-TIMI-38[3] trial.

The AG were asked to provide a commentary on the TRILOGY[1] and ACCOAST[2] trials and the outcomes for the STEMI subgroup of the TRITON-TIMI 38[3] trial.

2 THE TRILOGY TRIAL

The TRILOGY[1] trial was an RCT designed to compare the effectiveness of prasugrel (plus aspirin) with clopidogrel (plus aspirin) in 7243 patients with NSTEMI who were treated with medical management. The primary endpoint of the trial was a composite of death from cardiovascular causes, myocardial infarction, or stroke in patients under the age of 75 years and the results at 17 months demonstrated no statistically significant difference between the patients treated with prasugrel or clopidogrel (HR=0.9; 95% CI 0.79 to 10.5, p=0.21). Similar frequencies of bleeding events were reported in both trial arms.

The AG notes that the patient population recruited to the trial were patients with NSTEMI who were to be treated medically, i.e, who did not undergo PCI procedures. The AG is unclear as to the relevance of the patient population studied in the TRILOGY[1] trial to the patient population of interest to the present appraisal (people who are treated with PCI). Moreover, the AG notes that the marketing authorisation in the UK for prasugrel states that its use is for patients with ACS who are undergoing PCI.

3 THE ACCOAST TRIAL

The ACCOAST[2] trial was an RCT designed to assess the effectiveness of pre-treatment with prasugrel in 4033 patients with NSTEMI and positive troponin levels. Patients were assigned to two groups and prior to angiography were given either 30mg of prasugrel or placebo. When PCI was indicated, the pre-treated patients (30mg prasugrel group) were given a further 30mg of prasugrel and the placebo group 60mg of prasugrel. There was no

difference between the two groups for the composite primary endpoint of cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) at 7 days. However, the rate of TIMI major bleeding episodes (whether or not CABG-related) was significantly increased in the group pre-treated with prasugrel (HR=1.90; 95% CI 1.19 to 3.02, p=0.006). The trial authors concluded that pre-treatment with prasugrel did not reduce the rate of occurrence of the primary endpoint but the rate of major bleeding complications was statistically significantly increased.

The AG notes that following publication of the results of the ACCOAST[2] trial, the SPC[4] for prasugrel was changed on 18th December 2013. The SPC[4] now explicitly states that in UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI. The AG further notes that in the manufacturer's submission for the present appraisal, it is stated that the 30mg dose of prasugrel at randomisation followed by a further 30mg at the time of the procedure is an 'investigational and off label' dosing regimen.

4 THE STEMI SUBGROUP OF THE TRITON-TIMI-38 TRIAL

The statement from Professor Curzen commented on the reported primary outcome of the the STEMI subgroup from the TRITON-TIMI 38[3] trial. In the published paper[3], the outcomes of the STEMI subgroup were delineated into two groups: patients treated with primary PCI and patients treated with secondary PCI. Professor Curzen notes that although a statistically significant benefit was reported in patients undergoing secondary PCI, the corresponding outcome for patients undergoing primary PCI was smaller and did not achieve statistical significance (8.2% clopidogrel vs 6.6% prasugrel, p=0.1440). On this basis he asked

"….are these data, specific as they are to the primary PCI population, really robust enough to justify the change from clopidogrel for all patients undergoing primary PCI for STEMI?"

Table 1 summarises the data to which this comment refers. The AG suggests that further examination of the reported results is helpful in interpreting the context of the analysis, and can lead to a different interpretation.

Table 1 Key outcomes for the STEMI subgroup from the TRITON-TIMI-38 trial

	Clopidogrel			**Prasugrel**			**Diabetes proportion**
	Events	Patients	Rate	Events	Patients	Rate	
Primary PCI	101	1235	8.18%	79	1203	6.57%	16.8%
Secondary PCI	65	530	12.26%	36	528	6.38%	24.1%
Total	1765	1765	9.41%	115	1767	6.51%	19.1%

The event rates for both primary and secondary PCI patients treated with prasugrel are very similar (6.6% vs 6.4%, p=0.56) suggesting that prasugrel is equally effective in both primary and secondary PCI patients. However, for patients treated with clopidogrel there is a substantial difference in event rates (8.2% vs 12.3%, p = 0.006), a difference that appears to suggest that clopidogrel is more effective for patients treated with primary PCI than for those treated with secondary PCI. The AG considers that the key issue here is with the variability of the effectiveness of clopidogrel rather than the apparently stable efficacy of prasugrel.

One explanation for the excess of trial events for secondary PCI patients in the clopidogrel arm is that it is the result of an imbalance between the primary and secondary PCI groups of patients with diabetes mellitus (DM). The AG notes that 50% more of the secondary PCI patients had DM than did the primary PCI patients. The ratio of clopidogrel event rates shows an increase in trial outcome events of 43.5% for secondary PCI vs primary PCI.

The AG is aware of evidence that DM may be associated with a poorer response to treatment with clopidogrel, whereas the efficacy of prasugrel is unaffected by diabetic status.

The Optimus-3[5] trial sought to make a serial pharmacodynamics comparison of prasugrel vs clopidogrel in patients with type 2 diabetes and coronary artery disease. The investigators concluded:

"In patients with type 2 DM and CAD, standard-dose prasugrel is associated with greater platelet inhibition and better response profiles during both the loading and maintenance periods when compared with double-dose clopidogrel."

In a study of 485 consecutive ACS patients treated with PCI, Geisler et al[6] reported important differences in response to clopidogrel and concluded:

"The principal finding of this consecutive study is that diabetic individuals with ACS show a lower response to a 600mg clopidogrel loading dose…. Thus we found type 2 diabetes to be

associated with a decreased platelet response in a heterogenous patient cohort with symptomatic CAD."

The AG considers it reasonable to conclude that the apparent difference in clopidogrel events reported in the TRITON-TIMI-38[3] trial between primary and secondary PCI is simply the result of a bias in the proportion of patients with diabetes in the two subgroups, and that the true efficacy of clopidogrel and prasugrel in STEMI patients is more reliably estimated by comparing the overall average STEMI event rates in the TRITON-TIMI 38[3] trial (9.4% vs 6.5%, p=0.0007).

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