Expert submission for NICE review of guidance re:

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (TA182 issued October 2009)

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Background to original NICE Guidance:

Since the 1990s the combination of aspirin and (the P2Y12 platelet receptor) clopidogrel has been a standard therapy for (a) patients with acute coronary syndrome (ACS) as a medical therapy and (b) in patients receiving coronary stents in order to protect them from subsequent ischaemic events including stent thrombosis (ST) and myocardial infarction (MI). Increasing data have described heterogeneity in the individual antiplatelet response to clopidogrel, and furthermore a link has been demonstrated between (the minority of) patients who exhibit high on-treatment platelet reactivity (HTPR) on clopidogrel and subsequent ischaemic events, including ST. [Reviewed in references [1 2]]. These data have stimulated interest in the development of P2Y12 inhibitors that are more potent and faster acting than clopidogrel. Prasugrel is a third-generation thienopyridine that achieves higher levels of platelet inhibition more rapidly and consistently than standard- or high-dose clopidogrel in healthy volunteers and stable patients with coronary artery disease (CAD). [3 4] The original guidance by NICE (TA 182) was based upon the results of the TRITON study. Since then, data have emerged about the lack of efficacy of prasugrel in the context of non STE- ACS, and these data should now be taken into consideration, given that there are other viable options for the role of potent P2Y12 inhibitor in this context.

Clinical data that supports the use of prasugrel for ACS/PCI in ACS

The TRITON-TIMI 38 trial [5] compared prasugrel to clopidogrel in 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled PCI. The results demonstrated a significant (absolute 2.3%; $p<0.001$) reduction in the combined primary endpoint of cardiovascular death, myocardial infarction (MI) and stroke. Specifically, 138 fewer primary endpoint events were seen in the prasugrel group over the median duration of follow-up at the expense of 35 more TIMI major bleeding events in the prasugrel group ($p=0.03$). There were 21 fatal bleeds in the prasugrel group compared with five in the clopidogrel arm ($p=0.002$). The largest net clinical benefits were seen in the groups with diabetes mellitus and those presenting with ST elevation MI. On the basis of these data and subsequent supportive guidance from NICE , prasugrel is now used as the default P2Y12 inhibitor in over 50% of units providing primary PCI services in the UK.

Other published works on subgroups from the TRITON-TIMI 38 trial have reported on efficacy and drug safety[6] . In a cohort of patients “defined by worldwide regulatory agencies” the group of patients in TRITON-TIMI 38 without previous stroke, <75 years old, and weighing >60 kg had substantial reductions in ischemic events with prasugrel compared to clopidogrel. Although relative bleeding excess was seen in this population, absolute rates and differences in bleeding were attenuated. Of clinical relevance, patients outside of this core group randomised to prasugrel

showed no net clinical benefit. The authors concluded that, "these data indicate that use of prasugrel in a core clinical cohort that has been defined by regulatory action will maximize the benefit of prasugrel and limit the risk of adverse outcomes".

In a further subgroup analysis [7] of 12844 patients in the TRITON-TIMI 38 data receiving at least one coronary stent, therapy with prasugrel resulted in fewer ischaemic outcomes including stent thrombosis than with clopidogrel. These findings were statistically robust irrespective of stent type, and the data affirm the importance of intensive platelet inhibition in patients with intracoronary stents.

2. Other clinical data

(a) Is prasugrel effective in non ST elevation ACS (NSTE) patients?

Since the above appraisal guidance was issued there have been two randomised controlled trials of prasugrel in the treatment of acute coronary syndromes – TRILOGY[9] and ACCOAST.[10] The TRILOGY study was a randomised controlled trial to evaluate the relative efficacy and safety of prasugrel and clopidogrel in a medically managed unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) acute coronary syndrome population *not* managed with acute coronary revascularization. The findings showed *prasugrel did not significantly reduce the frequency of the primary end point* (death from cardiovascular causes, myocardial infarction, or stroke among patients under the age of 75 years), as compared with clopidogrel, and similar risks of bleeding were observed between the two groups.

The ACCOAST study enrolled 4033 patients with NSTE acute coronary syndromes and a positive troponin level who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization. Patients were randomly assigned to receive prasugrel (a 30-mg loading dose) before the angiography (pretreatment group) or placebo (control group). When PCI was indicated, an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI and 60 mg of prasugrel was given in the control group. The study reported that *pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but did increase the rate of major bleeding complications*.

(b) Is the use of prasugrel in ST elevation MI patients justified?

In 2009 an analysis of the STEMI subgroup of the TRITON-TIMI 38 trial was reported in the Lancet.[8] The headline result was that prasugrel was superior to clopidogrel in STEMI patients. The difference in the STEMI patients who had true primary PCI was *not* statistically significant (8.2% clopidogrel vs 6.6% prasugrel, p=0.1440) although the test for heterogeneity between subgroups treated by primary and 'secondary' PCI was negative. These findings have led UK researchers and experts in this

field to question as to whether these data are robust enough to justify the change from clopidogrel for all patients undergoing primary PCI for STEMI.

Summary

- Although data for the use of prasugrel in ST elevation MI *treated by primary PCI* are equivocal, the data supporting the use of prasugrel for STEMI treated by a variety of means (as still occurs in the UK) remain strong and there are no robust new data to challenge the original guidance defining the patient population for whom prasugrel may be prescribed.
- The benefit of prasugrel therapy is limited to patients without any of the following clinical criteria: > 75 years, <60kg and history of TIA or stroke
- Trial data subsequent to the guidance do not support extending the use of prasugrel to all patients with NSTE-ACS – whether treated medically or by urgent revascularisation
- There is evidence from subgroup analysis for efficacy of prasugrel over clopidogrel in the reduction of stent thrombosis in patients receiving an intracoronary stent for treatment of ACS

Conclusion

Since the last NICE TA, few further data have become available about prasugrel in the context of NSTE-ACS. No important new data are available for the context of ST elevation MI. On behalf of BCIS we suggest that it remains fair to conclude that:

1. Prasugrel reduces major adverse cardiac events and stroke in high risk ACS patients receiving PCI with stents. There is no evidence that it reduces mortality. It actions are at the expense of an increase in fatal and life-threatening bleeding in patients >75 years old, <60Kg and with a past history of TIA or CVA in whom its use should not be recommended.
2. Prasugrel remains an option for patients who have ST whilst on a combination of aspirin and clopidogrel.
3. Prasugrel should remain a treatment option in patients with ST elevation treated by primary PCI or by other means and in diabetic patients with ACS of any variety (STEMI, Non-STE ACS, unstable angina)
4. Future studies should be performed to assess whether ticagrelor is superior to prasugrel in ACS patients.

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