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Multiple Technology Appraisal (MTA)

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: **Prof. Nick Curzen**

Name of your organisation
BCIS

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Yes
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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[redacted]

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 [i] [ii]]. These data have stimulated interest in the development of P2Y12 inhibitors that are more potent and faster acting than clopidogrel. There are 2 theoretical ways to respond to the knowledge that in perhaps 20% of people treated with clopidogrel, that they may exhibit HTPR and thus be at risk of ST & other ischaemic events.[iii] [1] Change to a more potent P2Y12 inhibitor for all patients, and accept that in doing so there may be an elevated risk of important bleeding or [2] give all patients clopidogrel, which is cheap & may well have a lower bleeding risk, but measure the phenotypic response to this drug with a view to switching those patients with HTPR to a stronger agent… thus personalising P2Y12 therapy.

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). [iv] [v] These properties made it a good candidate to replace clopidogrel for these indications. Subsequent data have provided insight into the potential value of prasugrel as the

default P2Y12 inhibitor for ACS/PCI in ACS. The original guidance by NICE (TA 182) was mainly based upon the results of the TRITON study. Since then, data have emerged that raise important questions about the efficacy of prasugrel in the context of 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 (ticagrelor, ?cangrelor) and there also remains the option of investigating properly the role of personalising therapy in this context by performing a UK trial of platelet function testing for clopidogrel patients as described above.

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

The TRITON-TIMI 38 trial [vi] compared prasugrel against 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 ($p=0.002$). On the basis of these headline 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. This change in P2Y12 inhibitor use in the context of primary PCI for ST elevation myocardial infarction (STEMI) may not, in fact, be well supported by the available data. The trial data require close scrutiny, especially since such a heterogeneous group of patients were included (see below)

Other published works on subgroups from the TRITON-TIMI 38 trial have reported on efficacy and drug safety[vii] . 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 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 [viii] 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.

<u>Data that casts some doubt on the role of prasugrel as the default P2Y12 inhibitor in ACS/STEMI</u>

1. TRITON trial data

(a) The trial population as a whole

To begin, the primary efficacy endpoint consists of three components: of these, non-fatal MI rates dominate the overall headline benefit of prasugrel. Specifically, non-fatal MI occurred in 9.5% of the
clopidogrel group and 7.3% of the prasugrel group ($p<0.001$). By contrast, the rates for cardiovascular death were 2.1% and 2.4%, respectively ($p=0.31$) and for stroke were 1.0% and 1.0% ($p=0.93$). While it is clear that the rate of ST was indeed significantly lower in the prasugrel group (2.4% vs 1.1%, $p<0.0001$), the rest of the non-fatal MI is poorly defined. The question should therefore be asked: *Does the reduction in nonfatal MI of this type justify the excess fatal and serious bleeding that would be incurred by a wholesale switch from clopidogrel to prasugrel?*

(b) The Primary PCI population from TRITON

Even greater concern about the justification for a wholesale switch to prasugrel from clopidogrel for primary PCI arises from a 2009 Lancet paper in which the analysis of the STEMI subgroup of the TRITON-TIMI 38 trial was reported.[ix] The headline result was that prasugrel was superior to clopidogrel in STEMI patients. However, closer inspection shows that the difference in the STEMI patients who had true primary PCI as practised in the UK was *not* statistically significant (8.2% clopidogrel

vs 6.6% prasugrel, p=0.1440). Evidently, this is a subgroup of a subgroup, and there is indeed a trend to suggest benefit. However, allowing for this, *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?* This question is particularly pertinent given the trial design: the late administration of the study drug, with only 25% of patients receiving the drug before the PCI guidewire was passed, should have given a stronger, more rapid onset P2Y12 inhibitor a massive efficacy advantage over clopidogrel. So why isn't there a large (statistically significant) difference in outcome in the primary PCI cohort in TRITON? If the answer is that it is underpowered to detect a difference in the primary PCI group, then surely we need (and should expect) persuasive data from an adequate randomised trial before a wholesale change in DAPT therapy in this group, particularly given the potential for increased bleeding complications?

2. Other clinical data

(a) Does prasugrel act as fast as expected in STEMI?

A body of data is growing that casts doubt on the premise that prasugrel does in fact act as rapidly and as potently in the context of STEMI/ACS as pharmacodynamic data has originally suggested from populations of healthy subjects or patients with stable CAD. For example, in one pharmacodynamic study recently published, the onset of action of antiplatelet effect of prasugrel in STEMI patients was much slower than expected, with 34.6% of patients exhibiting HTPR at 2 hours.[x] Furthermore, in a recent study in which ACS patients who exhibited HTPR to clopidogrel were randomised to either ticagrelor or prasugrel, the speed of onset of antiplatelet efficacy was significantly slower for prasugrel compared to ticagrelor. [xi]

(b) Does prasugrel work better 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[xii] and ACCOAST.[xiii] 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

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(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*.

(c) Is the assumption that the response to prasugrel in ACS patients is homogeneous and therapeutic correct?
There are now data describing important prevalence of HTPR to prasugrel in the ACS population. Specifically, one study describes HTPR to prasugrel in 25.2% of a study population of ACS patients treated with prasugrel, and this was associated with adverse clinical outcome.[xiv]

Conclusion

Since the last NICE TA, further data are available about prasugrel in the context of ACS. This leads to the following conclusions:
1. Prasugrel reduces ST & other types of non-fatal MI in a heterogeneous population of ACS patients receiving PCI with stents. It does not reduce mortality but definitely increases fatal and life-threatening bleeding.
2. There are no data to support prasugrel as a default P2Y12 inhibitor in PPCI for STEMI.

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3. The speed and potency of pharmacodynamic action of prasugrel in ACS patients are both lower than predicted from healthy subjects or patients with stable CAD. The intuitive early advantage of prasugrel over clopidogrel in these patients is therefore less than expected and may explain why prasugrel has not been clinically superior in the primary PCI STEMI subpopulation of TRITON, or in NSTE populations in TRILOGY or ACCOAST.

4. data suggest that a significant proportion of ACS patients taking prasugrel have HTPR with associated adverse outcome.

5. Given these data, it is now difficult to justify the recommendations made in the original prasugrel TA. Instead I recommend that the following recommendations are now justified:

(a) Prasugrel is a reasonable P2Y12 inhibitor to use in ACS in patients shown to have HTPR on clopidogrel, provided that their individual phenotypic response to prasugrel is then checked.

(b) Prasugrel is an option for patients who have ST whilst on a combination of aspirin and clopidogrel.

(c) Prasugrel remains a good option in diabetic patients with ACS

Unanswered questions

It is clear that further data are required to answer the following questions that will inform clinical practice:

1. Is the strategy of giving all ACS patients clopidogrel and then using a near patient test of platelet function to change only those with HTPR to prasugrel or ticagrelor associated with better clinical outcome and lower cost and bleeding?

2. Is ticagrelor superior to prasugrel in ACS patients?

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