MTA REPORT ADDENDUM 1

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ADDENDUM 1

This report was commissioned by the NIHR HTA Programme as project number 12/62/01

Completed 14th February 2014

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

In preparing the overview document prior to the first Appraisal Committee (AC) meeting for the appraisal of prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182) [ID648], the NICE technical team identified several issues on which they considered that clarification of the information in the Assessment Report would be helpful to the Committee. This addendum has been prepared by the Assessment Group (AG) to provide additional background to help the AC to fully understand the context of this review and the methods and parameters used in the AG's cost-effectiveness modelling.

2 DEFINITION OF THE DECISION PROBLEM AND PATIENT POPULATIONS

This section is relevant to Sections 4.1 (page 24) and 6.3.2 (page 73) of the Assessment Report and is intended to provide the rationale for the specific patient populations considered by the AG in the Assessment Report.

The final scope[1] issued by NICE (described in Table 4 of the Assessment Report) for this appraisal identifies the relevant population as patients with acute coronary syndrome (ACS) undergoing primary or delayed percutaneous coronary intervention (PCI). It further states that if the evidence allows, subgroups of patients will be considered, including people with UA/NSTEMI, STEMI and people with diabetes mellitus. Finally, the scope specifies that guidance will only be issued in accordance with the marketing authorisation.

The remit of the AG was to appraise the clinical and cost-effectiveness of prasugrel within its licensed indication for the treatment of ACS with PCI and was a review of an existing technology appraisal, TA182.[2]

No new randomised controlled trial (RCT) evidence for prasugrel has been published and the evidence base for the effectiveness of prasugrel remains unchanged from that considered for TA182.[2] The AG has therefore taken its starting position for this multiple technology appraisal (MTA) as a reassessment of the evidence from TA182.[2]

Core clinical cohort

The evidence for TA182[2] was based on a single RCT, the TRITON-TIMI-38[3] trial. The TRITON-TIMI-38[3] trial included 13,608 patients with ACS who were to be treated with PCI. The relevance of the evidence from the overall TRITON-TIMI 38[3] trial population was constrained by the marketing authorisation, which excludes patients with prior stroke or TIA and patients with active peptic ulcer disease, and restricts use in patients over the age of 75 years and in those weighing less than 60kg to a lower 5mg dose to limit the risk of severe bleeding.

In their evidence submission for TA182[2] the manufacturer identified a reduced population from the TRITON-TIMI-38[3] trial that they referred to as the ‘target population’ and the manufacturer considered the ‘target population’ to be the most relevant for providing data for the development of the economic model. The Evidence Review Group (ERG) and the AC agreed with this selection, as the excluded patients were either explicitly excluded from the marketing authorisation or were not supported by trial evidence (since the trial was based on the full 10mg dose). It is therefore this ‘target population’ that is the focus of the Assessment

Report and is described as the 'core clinical cohort' in the manufacturer's latest evidence submission (review of TA182[2]). This cohort comprised 10,804 (79%) of patients from the overall trial population.

Specific sub-populations identified in the Assessment Report

During the process of TA182,[2] an appraisal consultation document (ACD) was issued (June 2009) which restricted the use of prasugrel to patients undergoing PCI as primary treatment for patients with a STEMI event, as well as those suffering stent thrombosis whilst under treatment with clopidogrel. In a response to the ACD, the manufacturer of prasugrel suggested that several other high-risk patient groups should also be considered, in particular those diagnosed with diabetes.

In preparation for the second meeting of the AC, the Chair requested that the ERG should provide cost-effectiveness estimates relating to four mutually exclusive subgroups defined by the type of index event (STEMI vs UA/NSTEMI) and whether patients were diagnosed with diabetes mellitus or not. These results were provided by the ERG and then considered by the AC. The AC concluded that prasugrel could be recommended for three of the four subgroups, but that the results for UA/NSTEMI non-diabetic patients did not support a positive recommendation.

As the evidence base has not changed since the publication of TA182,[2] the AG has taken the view that the review of the existing guidance should involve a reassessment of the same subgroups of the same trial cohort, and has developed its economic model on this basis.

3 INDEPENDENT ECONOMIC MODEL

The purpose of this section is to provide further information relevant to the independent economic model in respect of the model design and structure (section 6.3.4 of the Assessment Report), the data source for the key patient groups of the core clinical cohort (page 36 of the Assessment Report) and parameter sources and values (section 6.3.6 of the Assessment Report).

The manufacturer's decision model comprises two parts:

- A statistical model to represent the main clinical outcomes of the trial during the first 12 months of follow-up until the trial treatments clopidogrel or prasugrel have finished
- A long-term model based on modified life table data to represent survival for up to an additional 39 years.

The AG found the short-term statistical model to be an accurate representation of the reported trial outcomes and was content to employ the results of this part of the manufacturer's model unaltered. The specifications of the statistical outcome functions are

shown in Table 17 (page 59) of the AG report. However, the AG considers that the long-term life table extrapolation is unrealistically simple and does not adequately represent the likelihood of patients suffering multiple additional cardiovascular events in their lifetime and the associated disutility and costs associated with such events.

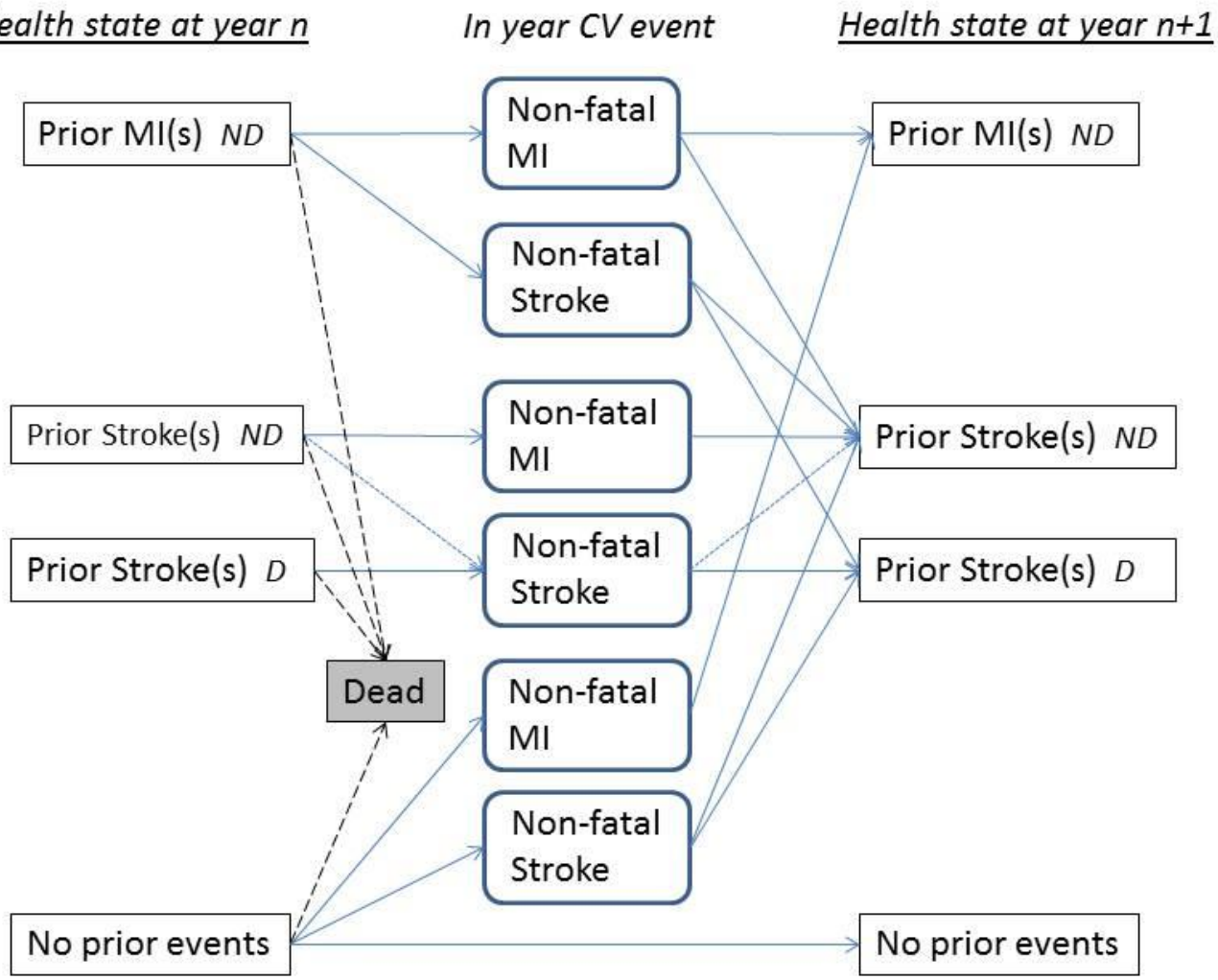
The AG has therefore extracted the outcomes from the manufacturer's short-term model for the four mutually exclusive subgroups of the 'core clinical cohort' and employed these as the initial conditions for surviving patients entering the AG's long-term state-transition model.

The detail of these outcomes data from the manufacturer's short-term model are fully described in Table 28 (page 77) of the AG report, covering 10314 patients in the original 'core clinical cohort' (but excluding additionally those with peptic ulcer disease who had been previously included in the manufacturer's analysis despite the explicit contraindication shown in the SPC). Costs, survival time and utility/disutility values during the first year (short-term) are estimated on the same basis as in the AG's long-term model. Specific clinical data relating to patients with STEMI, UA/NSTEMI or diabetes mellitus in the core clinical cohort were not available from the MS or the most recent publication.

The possible inter-state transitions from year to year in the AG's long-term model are represented in detail in Table 27 of the AG report. A graphic representation is provided below.

The main source of data used to populate the AG's long-term model is the CAPRIE[4] clinical trial. This was a double-blind placebo comparison of clopidogrel with aspirin involving 19,185 patients with atherosclerotic vascular diseases manifested as either ischaemic stroke (IS), myocardial infarction (MI) or symptomatic peripheral arterial disease. Only CAPRIE[4] data from 5,741 MI patients without prior history of other vascular events were used to populate the AG's long-term model. Follow-up of patients continued for up to 3 years (mean 1.9 years). The primary outcome was the first occurrence of IS, MI, or vascular death. Secondary outcomes included the first occurrence of IS, MI, amputation, or vascular death; vascular death; overall net benefit; any stroke (including primary intracranial haemorrhage), MI or death from any cause; death from any cause.

The manufacturer of clopidogrel kindly carried out extensive re-analyses of the CAPRIE[4] trial data as specified by the AG, in order to estimate independent event hazards adjusted to age, gender and event history. Full details of the estimated event rates (Appendix 10) and event fatality rates (Appendix 11) are provided in the full AG report for TA210.



D = disabled *ND* = not disabled If no event occurs in year patient remains in same health state

4 INDEPENDENT ECONOMIC ASSESSMENT: RESULTS

This section is relevant to section 6.4 of the Assessment Report (page 86 onwards) and describes the AG's concerns with the appropriateness of calculating an incremental cost-effectiveness ratio (ICER) for the overall 'core clinical cohort'.

The long-term model developed by the AG was adapted from a previous individual patient simulation model, using binary variables (male vs female, diabetes vs non-diabetes and STEMI vs UA/NSTEMI) to control relative risks and odds ratios of future events. This structure could only be translated into a cohort model by creating parallel homogeneous cohorts, and aggregating the separate results for the pre-planned subgroups, defined in the original appraisal of prasugrel. A direct adaptation of this model to accommodate an assessment of the overall 'core clinical cohort', based on averaging of binary risk variables is unlikely to give reliable results.

The AG is not convinced that an overall economic analysis encompassing very distinct subgroups (as discussed above) is appropriate. However, at the request of the NICE technical team the AG has provided an approximate analysis using a weighted average of the four subgroups for information, and the results are shown below.

Summary cost-effective results for prasugrel compared to clopidogrel at 40 years, using a weighted average of results for four mutually exclusive subgroups defined by (type of index event [STEMI vs UA/NSTEMI], and diabetes mellitus vs no diabetes mellitus):

	Clopidogrel	Prasugrel	Increment
Life-years	17.404	17.572	+0.168
Life-years (discounted)	12.353	12.457	+0.104
QALYs	14.660	14.806	+0.146
QALYs (discounted)	10.561	10.653	+0.092
Costs	£30,825	£31,101	+£276
Costs (discounted)	£20,261	£20,529	+£268
ICER per life-year (discounted)			£2,585
ICER per QALY (discounted)			**£2,913**

REFERENCES

1. National Institute for Health and Care Excellence. Prasugrel with percutaneous coronary intervention for treating acute coronary syndrome (review of TA182): Final Scope. NICE; 2013 [cited 2013 October]; Available from: http://guidance.nice.org.uk/TA/WaveR/141.
2. National Institute for Health and Clinical Excellence. Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention: TA182. NICE; 2009 [cited 2013 October]; Available from: http://publications.nice.org.uk/prasugrel-for-the-treatment-of-acute-coronary-syndromes-with-percutaneous-coronary-intervention-ta182.
3. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S*, et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2007; 357:2001-15.
4. The CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996; 348:1329-39.