MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90)

ADDENDUM

This report was commissioned by the NIHR HTA Programme as project number 08/97/01

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DOES NOT CONTAIN IN CONFIDENCE DATA

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1 ADDENDUM: RESULTS OF PROBABILISTIC SENSITIVITY ANALYSES

1.1 Methods

The AG model was developed as an MS 2007 Excel application, since this facilitated rapid model development and modification within a limited timescale following the availability of the detailed results of trial data (especially from the CAPRIE[1] trial) produced by the manufacturer of clopidogrel. Although modest in its design (a maximum of ten key events for each of 2,000 simulated patients), it became apparent that the limitations of Excel 2007 in the Windows Vista operating environment caused serious restrictions in two respects: the speed at which the model could be recalculated, and the size of workbook that could be accommodated.

These problems became critical in the context of carrying out PSA on the AG model results, where it proved necessary to read random number sets from an external data file rather than from within Excel and to severely restrict the number of replications carried out. Commonly PSA simulations involve many thousands of replications aimed at achieving stability of results. Instead we used a pre-processing technique previously developed in the context of an earlier MTA project, which employs a much smaller replication random number set designed to ensure full coverage of the distributional space for each parameter together with guaranteed means, variances and correlations with related parameters. By trial and error we determined that a standard set of 100 such replications produced stable and reliable PSA results, and limited processing times to manageable proportions (typically 45 minutes for each candidate strategy within each population).

Employing identical random number sets for each parameter / comparator / scenario combination ensures direct comparability of results both within and between strategies. One consequence of using such a small number of replications is that the cost-effectiveness acceptability curve (CEAC) charts obtained are somewhat 'grainy' in definition compared to the smoother charts produced from larger numbers of replications. However, the results obtained appear to confirm the expectation that the careful use of these variance reduction techniques leads to reliable outcomes in all cases.

In order to limit the amount of PSA processing required to support decision-making, the AG has restricted attention within each population by not considering any strategy which was subject to dominance or extended dominance within the deterministic analysis i.e. limiting attention only to strategies on the cost-effectiveness frontier.

In all cases but one, consideration was given only to analyses using the full branded price of clopidogrel, on the grounds that previous results had indicated that (with the exception of one subpopulation of 'IS only' patients), a reduced price of clopidogrel does not alter the choice of optimal strategy.

1.2 PSA findings for optimal strategies

The results of PSA are compared with the earlier deterministic findings in Table 1-1. The two sets of ICERs governing the selection of the optimal strategy rather than the 'next best' option are very similar in all cases and show no evidence of consistent bias in either direction. Moreover, in all cases the estimated ICERs fall markedly below the 'standard range' of cost effectiveness (£20,000 - £30,000 per QALY gained).

For three of the four patient populations (MI only, PAD only and MVD) the probability of optimal cost effectiveness is close to 100% when the WTP exceeds £20,000 per QALY. In the case of the IS only population, probabilities are somewhat lower but still well above 50%. It is noticeable that in those smaller patient groups where intolerance to either ASA or MRD leaves only a single antiplatelet treatment option, the incremental net benefit is much greater than when comparing between competing antiplatelet treatment strategies, confirming that using any of the available treatments is preferable to not treating at all.

Figure 1-1 to Figure 1-10 indicate the relative cost-effectiveness performance of each of the eligible treatment strategies for each patient population group across a range of WTP values.

Table 1-1 Comparison of deterministic and probabilistic model results (assuming branded price clopidogrel and TA90 guidance not applied)

Patient population	Treatment strategy		ICER (£/QALY)		At £20,000/QALY WTP threshold		At £30,000/QALY WTP threshold	
	Optimal	Next best	Deterministic	PSA	Prob. cost-effective	INMB	Prob. cost-effective	INMB
MI only	ASA ⇒ Clop	ASA	£6,381	£6,250	100%	£1,134	100%	£1,958
MI only (ASA intolerant)	Clop	No APT	£12,802	£12,037	98%	£1,911	100%	£4,311
PAD only	Clop ⇒ ASA	ASA ⇒ Clop	£9,769	£9,975	98%	£3,559	100%	£7,110
PAD only (ASA intolerant)	Clop	No APT	£4,563	£4,367	100%	£12,145	100%	£19,914
MVD	Clop ⇒ ASA	ASA ⇒ Clop	£10,432	£11,121	100%	£1,790	100%	£3,806
MVD (ASA intolerant)	Clop	No APT	£2,189	£2,064	100%	£12,747	100%	£19,853
IS only	MRD+ASA ⇒ ASA ⇒ Clop	MRD+ASA ⇒ ASA	£16,894	£16,833	79%	£46	89%	£190
IS only (ASA intolerant)	Clop ⇒ MRD	Clop	£7,142	£6,443	96%	£2,576	96%	£4,277
IS only (MRD intolerant)	ASA ⇒ Clop	ASA	£6,797	£6,185	85%	£1,347	65%	£2,322
IS only (MRD intolerant – generic clopidogrel)	Clop ⇒ ASA	ASA ⇒ Clop	£3,970	£4,676	85%	£989	87%	£1,635

WTP= willingness to pay; INMB= incremental net monetary benefit; APT = antiplatelet therapy; QALY= quality adjusted life year; ICER= incremental cost-effectiveness ratio; ASA= aspirin; MRD= modified release dipyridamole; MI= myocardial infarction; IS= ischaemic stroke; MVD= multivascular disease; PAD= peripheral arterial disease; CLOP= clopidogrel

1.3 Cost-effectiveness acceptability displays

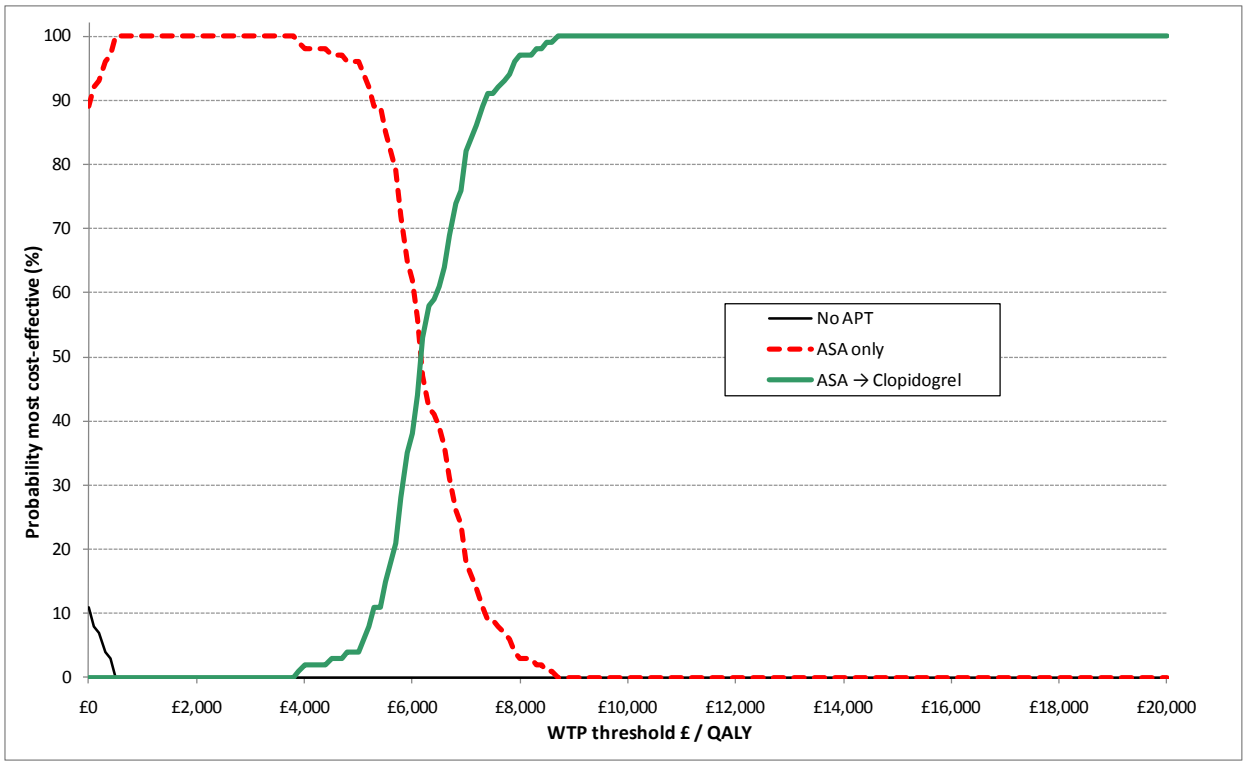

Figure 1-1 CEAC for MI only population (branded clopidogrel price, TA90 guidance not applied)

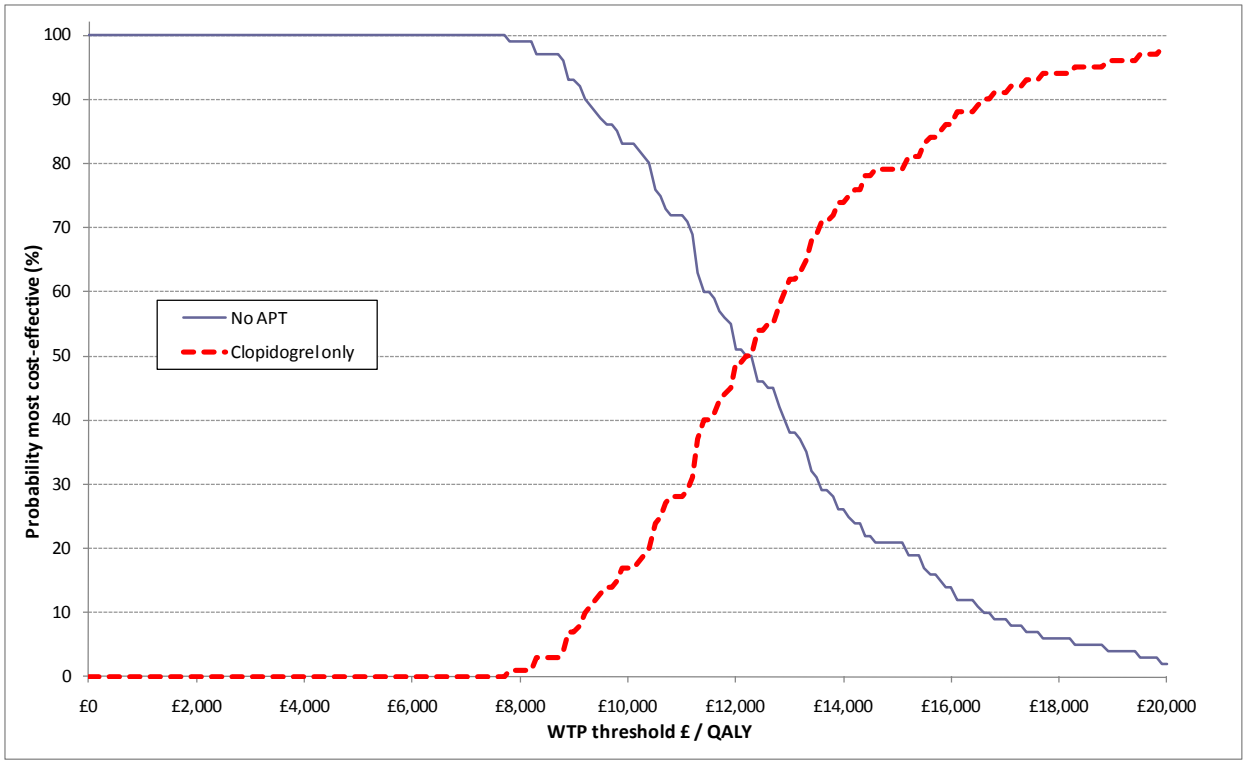

Figure 1-2 CEAC for MI only ASA-intolerant population (branded clopidogrel price, TA90 guidance not applied)

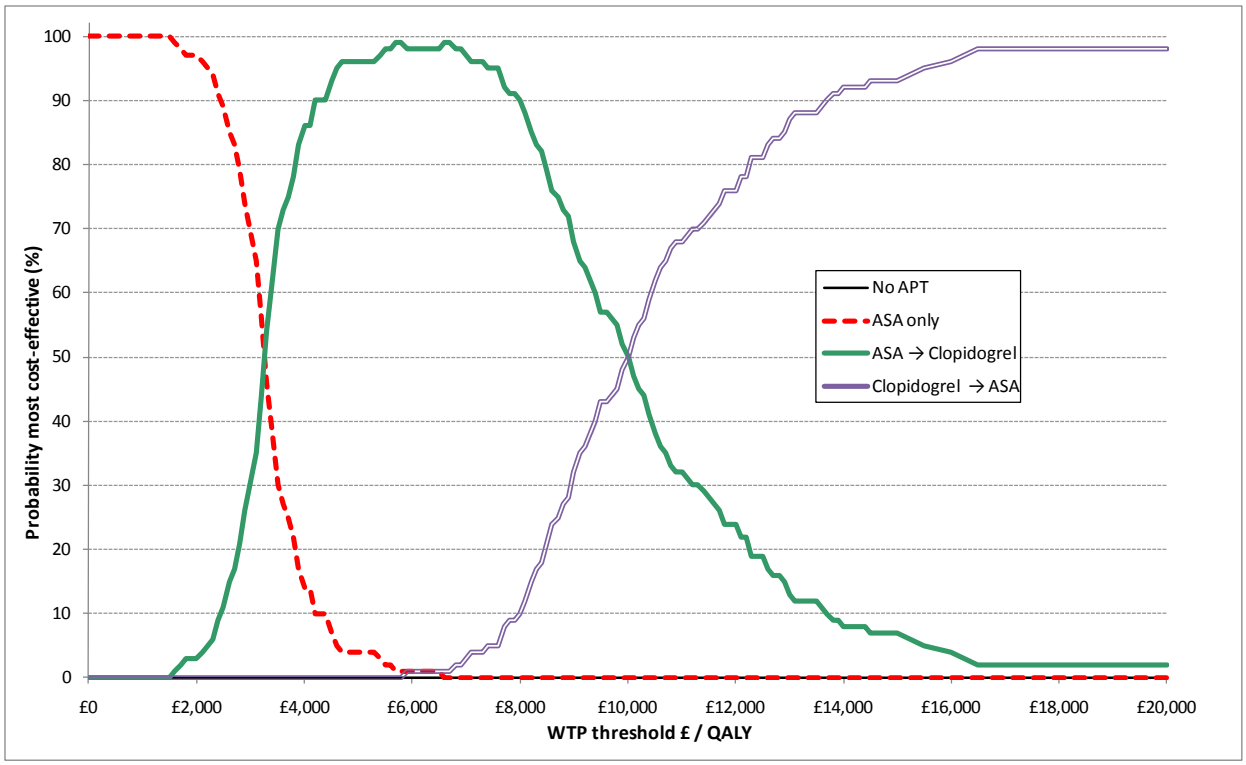

Figure 1-3 CEAC for PAD only population (branded clopidogrel price, TA90 guidance not applied)

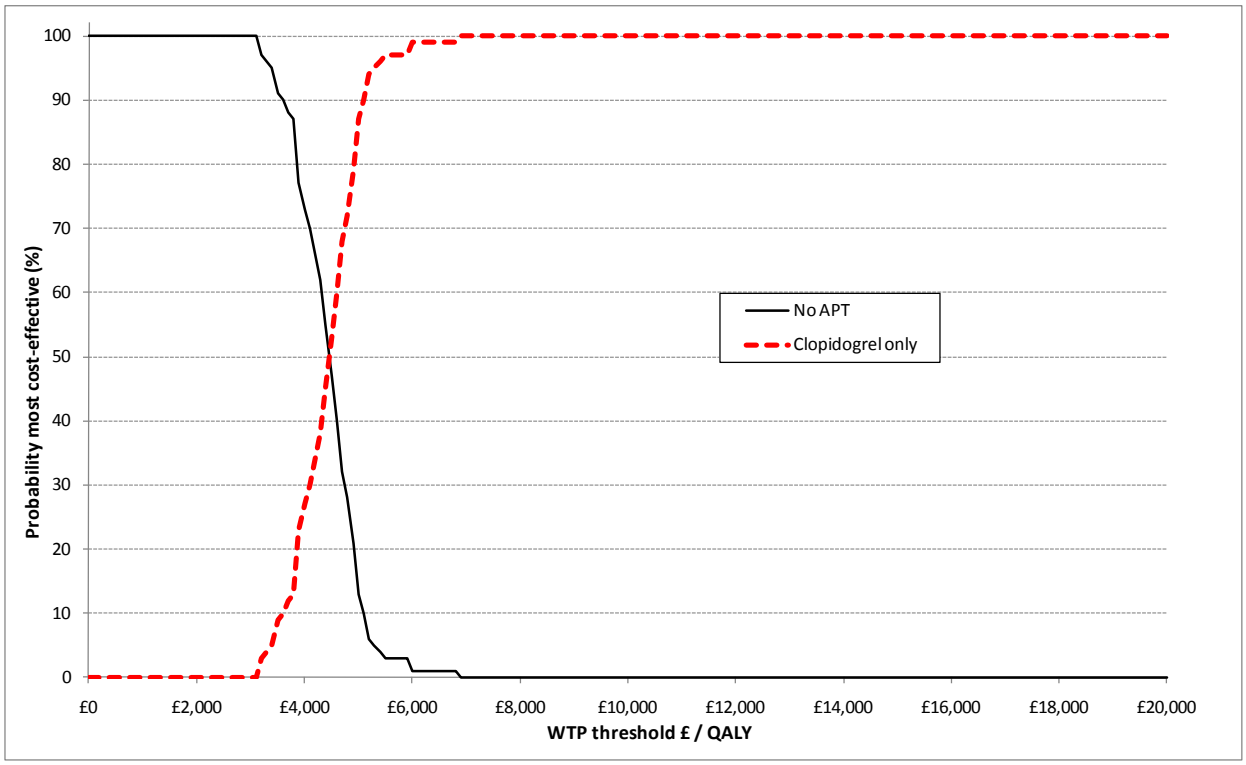

Figure 1-4 CEAC for PAD only ASA-intolerant population (branded clopidogrel price, TA90 guidance not applied)

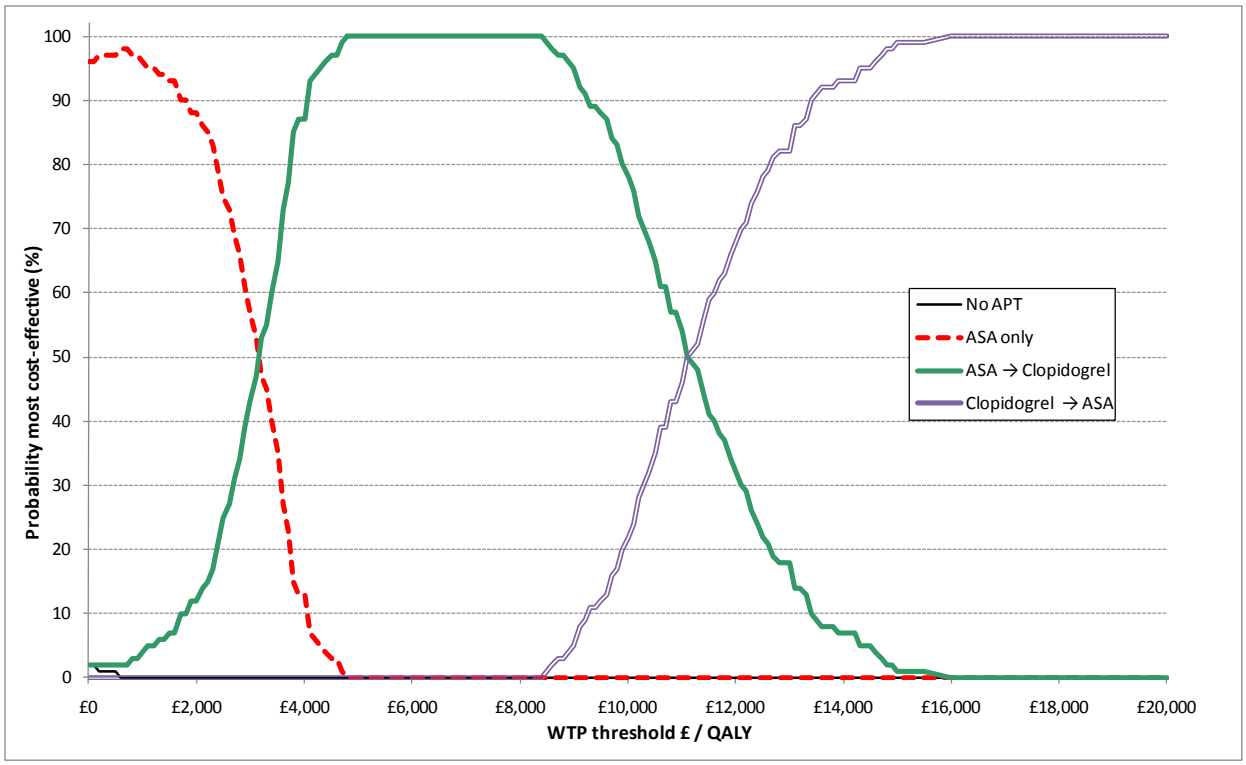

Figure 1-5 CEAC for MVD population (branded clopidogrel price, TA90 guidance not applied)

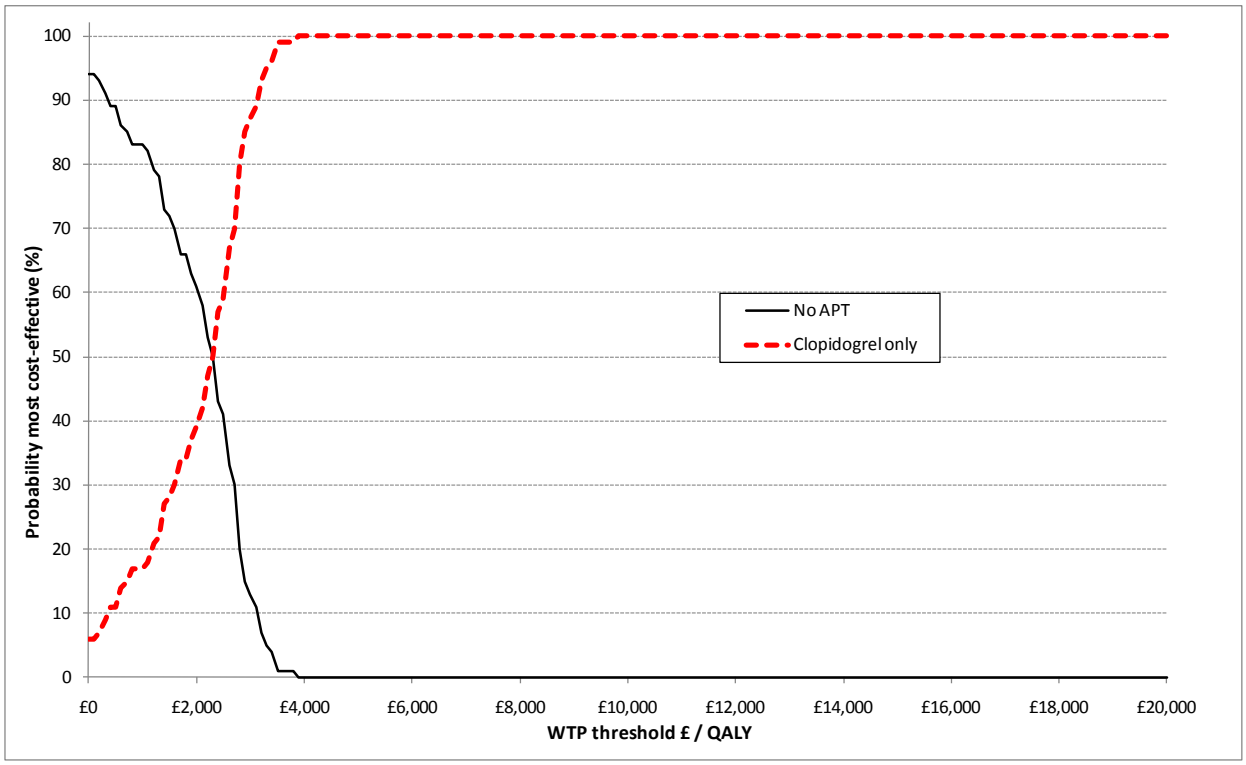

Figure 1-6 CEAC for MVD ASA-intolerant population (branded clopidogrel price, TA90 guidance not applied)

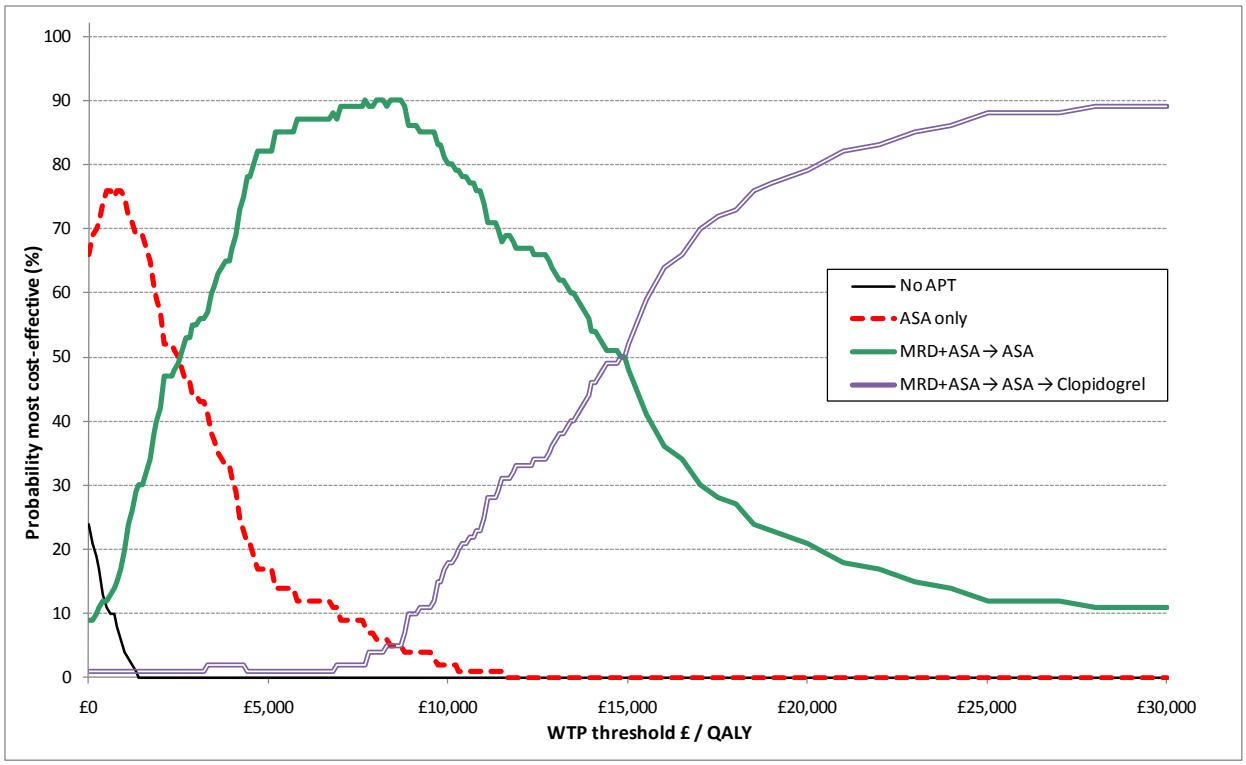

Figure 1-7 CEAC for IS only population (branded clopidogrel price, TA90 guidance not applied)

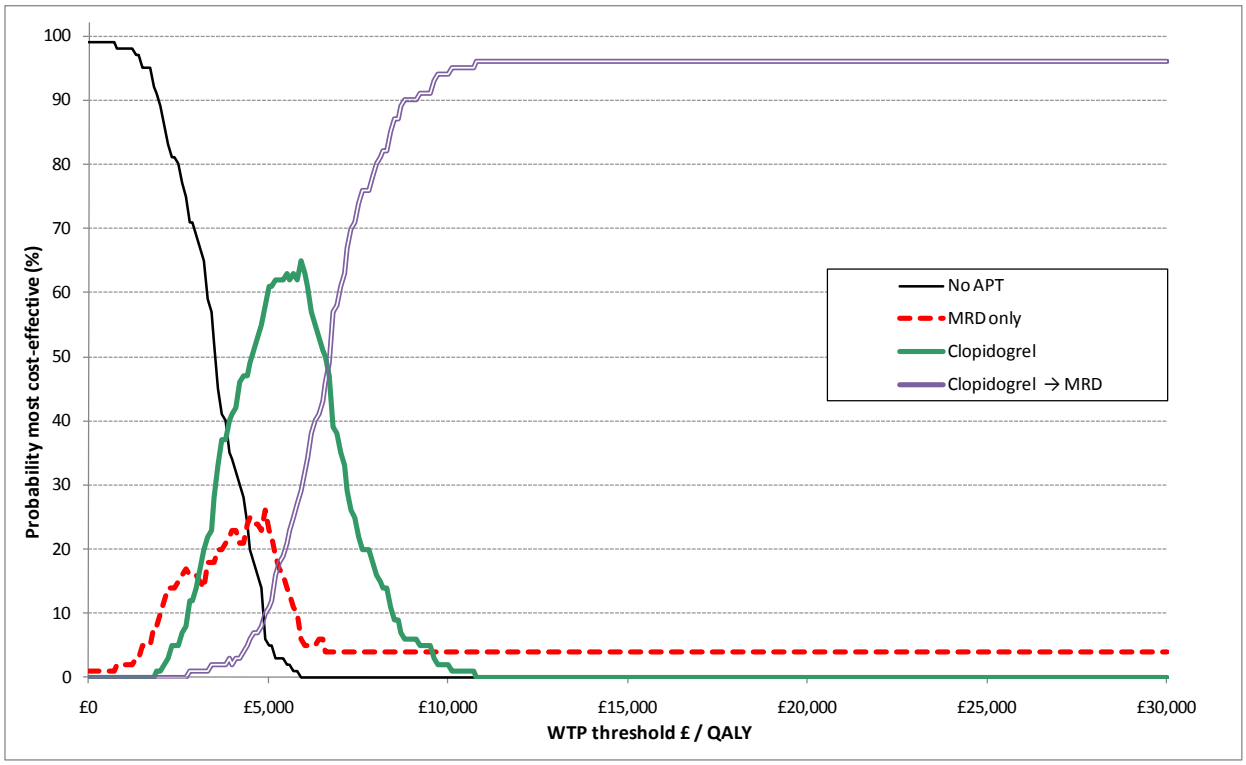

Figure 1-8 CEAC for IS only ASA-intolerant population (branded clopidogrel price, TA90 guidance not applied)

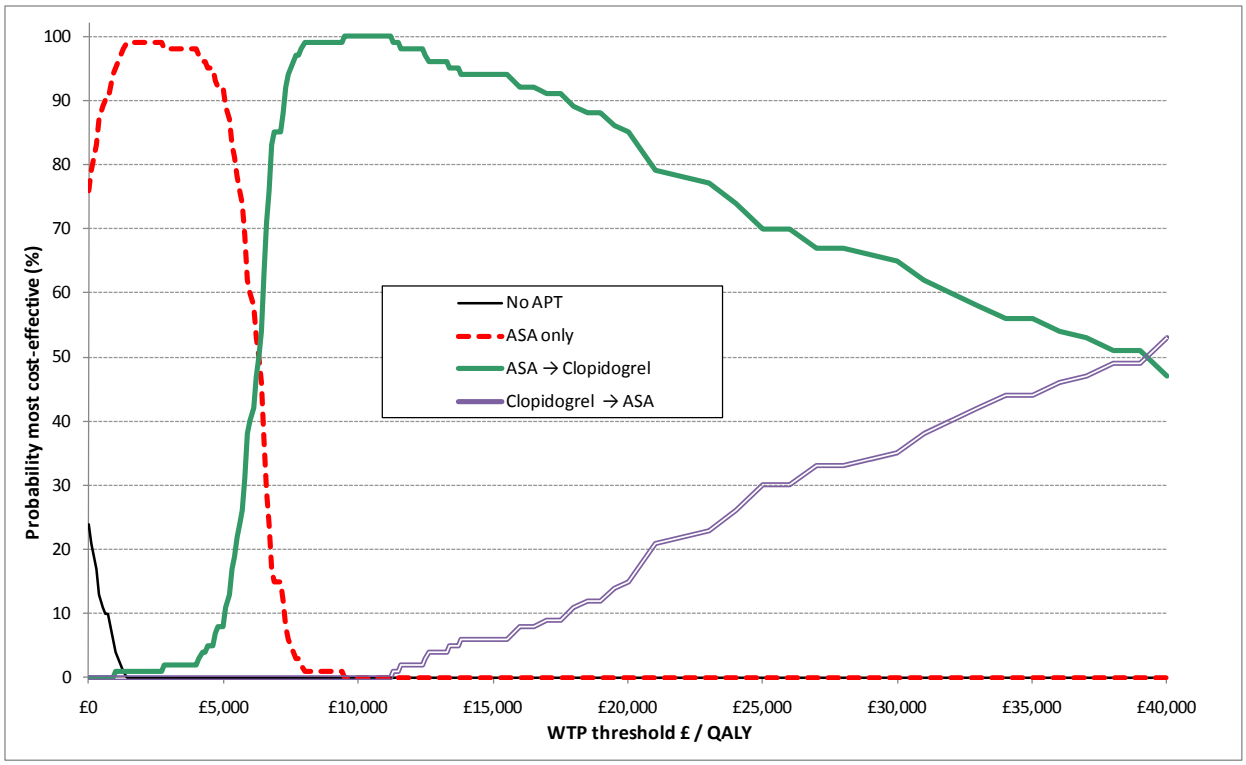

Figure 1-9 CEAC for IS only MRD-intolerant population (branded clopidogrel price, TA90 guidance not applied)

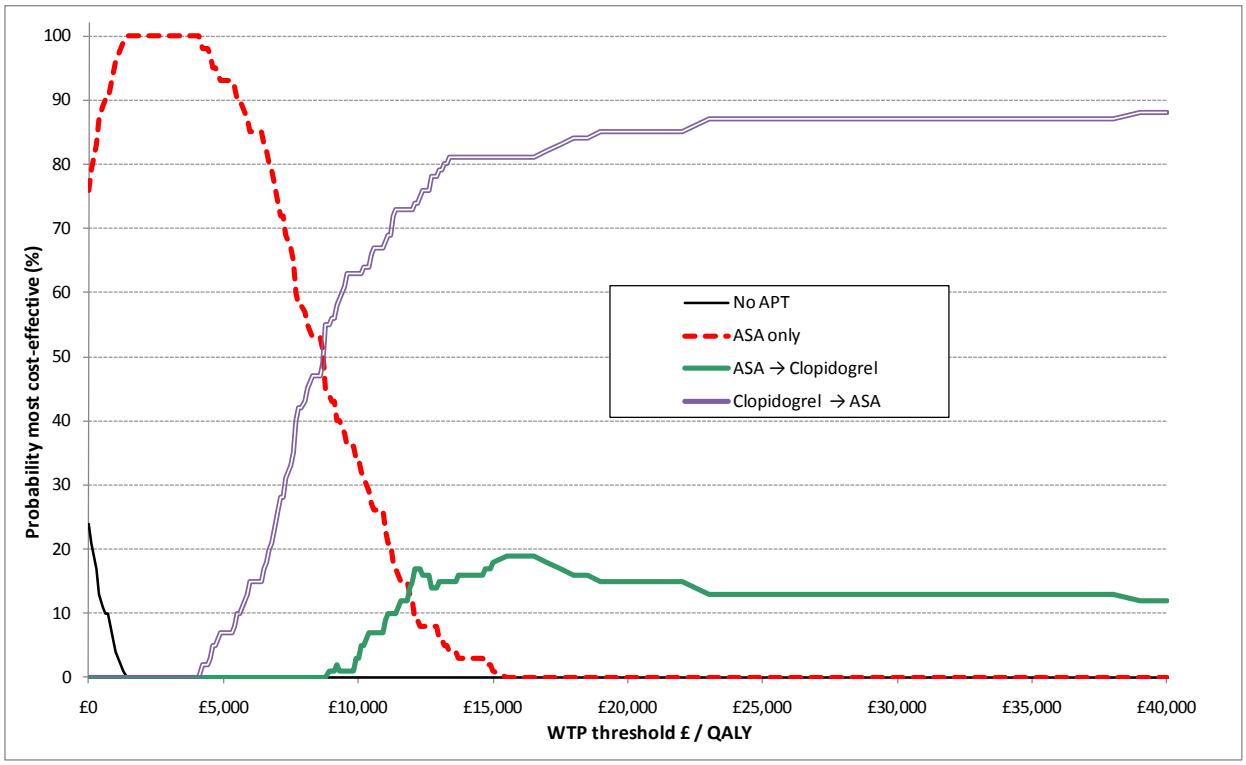

Figure 1-10 CEAC for IS only MRD-intolerant population (generic clopidogrel price, TA90 guidance not applied)

1.4 Summary of PSA results

The PSAs undertaken by the AG are fully consistent with the results obtained by deterministic use of the AG model. In addition they have confirmed that the optimal strategies previously described may be considered robust with respect to known parameter uncertainty. In particular, the apparent sensitivity of results in the PAD only population to uncertainty in event risk variables is not reflected in greater decision uncertainty when considered in the context of all other model parameters.

2 REFERENCES

1. 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(9038):1329-39.