NHS
Bradford and Airedale

TA Committee B
NICE
By email

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18 July 2011

Dear TA Committee B,

Response from NHS Bradford and Airedale to NICE ACD on Tigacrelor

Thank you for the opportunity to comment on this ACD. As the nominated PCT Commissioning Advisor to this TA, our comments are below. These comments are split into two sections:

1. Clinical effectiveness, also incorporating safety.

There are some specific issues with respect to effectiveness and safety that we feel haven't been fully factored into the economic appraisal (particularly the sensitivity analysis); these may have an important bearing on the real world effectiveness. Obviously this drug does have market authorisation in Europe. However, having now read the FDA review in detail, we are of the opinion that the insight it gives can simply be ignored. There are important clinical and statistical nuances in the interpretation that may have an important bearing on the clinical effectiveness of this drug. The commentary of the FDA review re the primary end point rate in US v non US requires further investigation in our opinion. There was some discussion about the adequacy of loading dose of clopidogrel used in the US (which IS different to standard UK practice). We feel this needs to be fully explored. Whether the findings of PLATO would be reproducible in countries with adequate clopidogrel dosing does not seem fully established. This is an important point, and we would wish to see it explored.

2. Affordability and economics -

There are many important issues with respect to different methods of appraising value for money, population impact and affordability. Whilst we accept that affordability is not within the remit of the TA Committee it is a critical consideration.

Our view is that this is clearly an important drug, and represents an advance. We would hope these comments are useful in informing further deliberations of the TA Committee going forward

Yours sincerely
[redacted]

[redacted]
NHS Bradford and Airedale

1 Clinical Effectiveness

There are some obvious, and well documented, weaknesses of the PLATO trial. Whilst we accept that the PLATO trial was large, well conducted and clearly represents an important advance, we feel these weaknesses may limit the real life effectiveness of Ticagrelor.

The TA Committee did discuss some of these issues, but I believe the view in the room was “it is licensed in Europe, therefore NICE does need to accept that data on effectiveness”. We can understand this, but even so feel the internal / external validity issues may have a bearing on the real life clinical effectiveness. This obviously has a bearing on the cost effectiveness and the “outcomes” that this technology “buys” in real life.

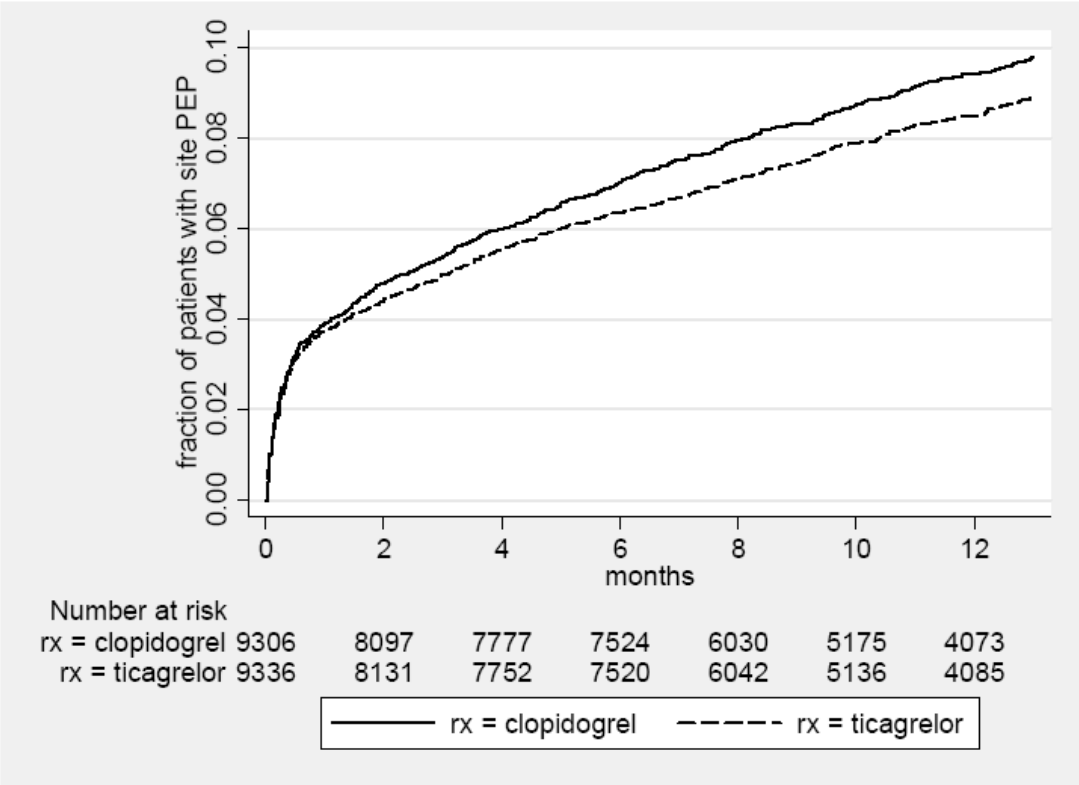
These issues are highlighted below

1a. FDA review Marciniak D. Submission to FDA. June 29 2010.

The FDA Reviewers report is very insightful. We have taken the liberty of copying my impression of the key chunks here:

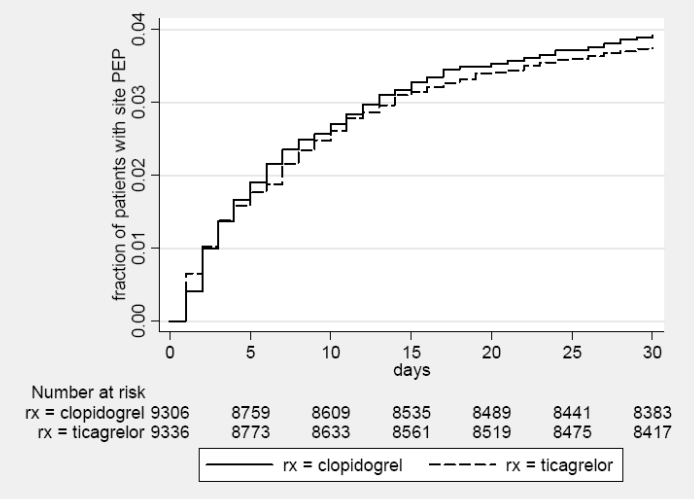
> “Site-Reported MACE
>
> As a check I counted CV death, MI, and stroke events (MACE) as reported by the sites without the ICAC adjudication. For these site-reported statistics I also implemented two variations from the sponsor’s classification of CV deaths: (1) The sponsor counted bleeding deaths as CV deaths. While that is reasonable for the primary endpoint (PEP) to estimate a net benefit, for an endpoint to explore efficacy effects alone I believe that it is preferable to exclude bleeding events not related to a cardiovascular or cerebrovascular event. Hence I excluded gastrointestinal bleeds but included non-traumatic intracranial hemorrhages. (2) **The sponsor counted all unknown deaths as CV deaths, again reasonable for a PEP for net benefit. I counted sudden unknown deaths as CV deaths but excluded completely unknown deaths.** I show the K-M plot for this site-reported MACE in Figure 4.

Figure 4: Time to Site-Reported First MACE



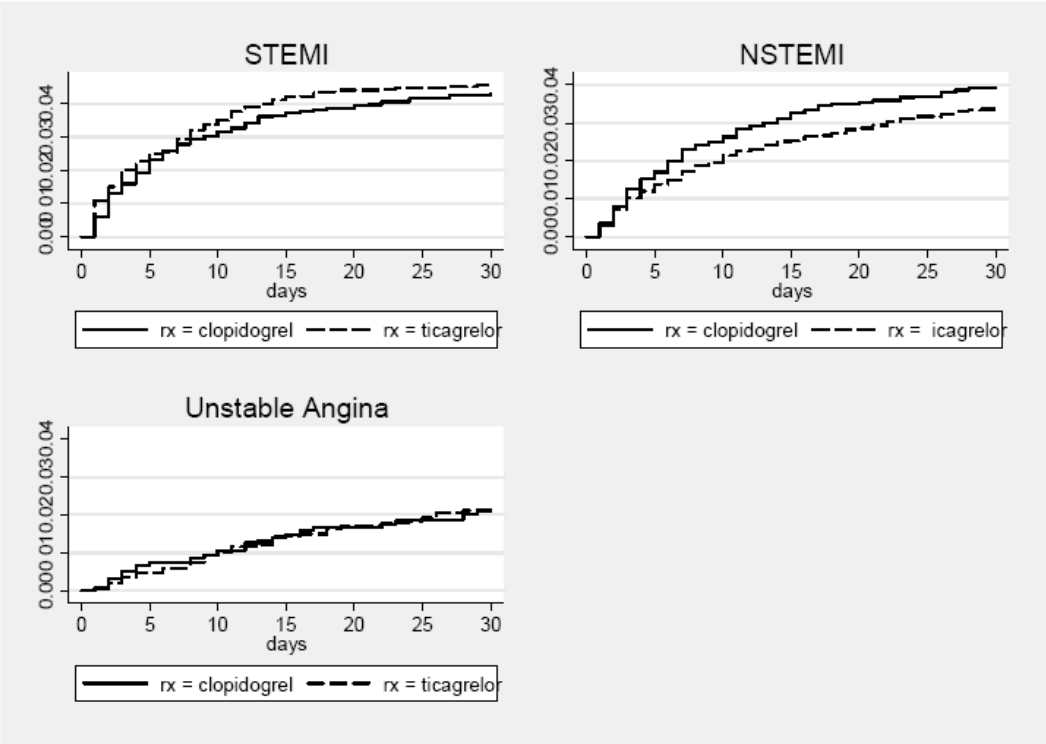
The possible benefit of ticagrelor is much less impressive for site-reported events and not statistically significant (p about 0.095 by log rank). For site-reported events there is only a slight benefit regarding MIs (relative risk (RR) about 0.94), a detriment regarding strokes (RR about 1.2), with the best benefit regarding CV deaths (RR 0.85). Note that the curves do not diverge early. In fact, there is little divergence for the first 30 days as shown in Figure 5."

Figure 5: Time to Site-Reported First MACE – 30 Days



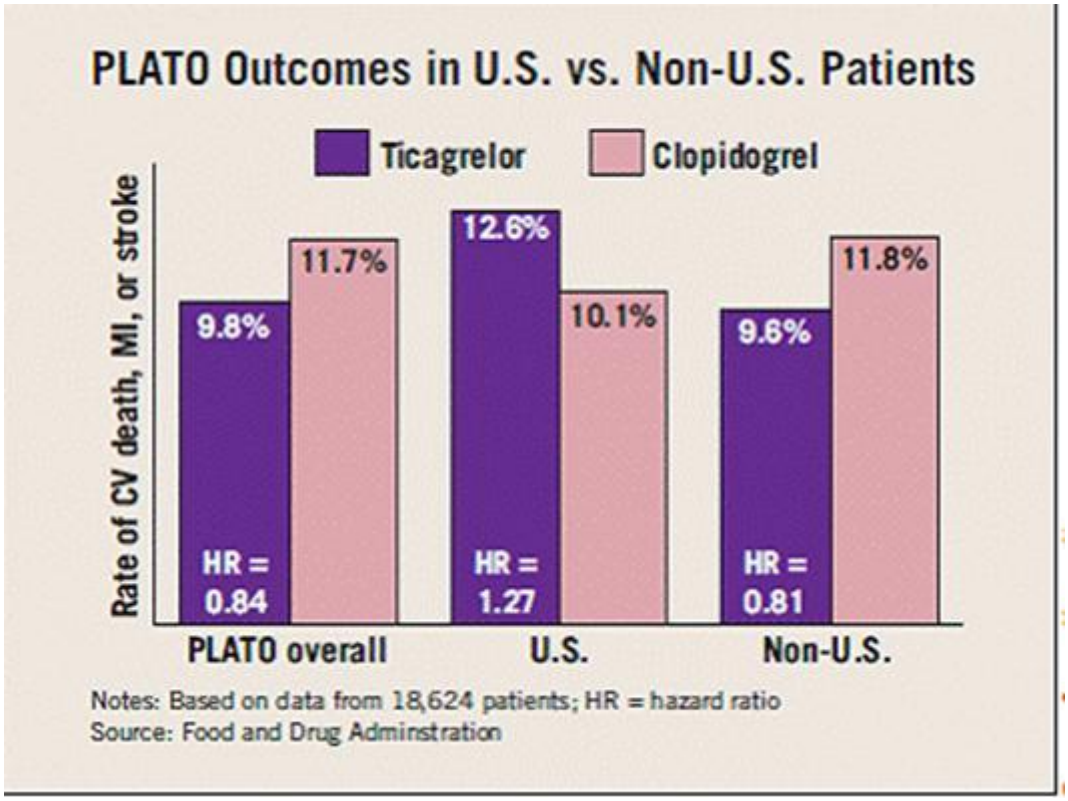
The time course in Figure 4 and Figure 5 is quite different from what we have seen with the thienopyridines in ACS. Typically there has been an almost immediate benefit that rapidly accrues during the early days. The benefit (in prasugrel / clopidogrel) beyond 30 days is harder to establish. For ticagrelor there appears to be little variation early by type of index event as shown in Figure 6.

Figure 6: Time to Site-Reported First MACE by Index Event Type



Response in US v non US v PLATO as a whole.

A critical part of the FDAs seeming concern about granting market access to this medicine is the seeming differential between US patients and non US patients. The graph below is well cited and highlights the apparent advantage of clopidogrel in US patients (lower event rate) compared to non US and PLATO overall. We would consider this does require further investigation.



Taking into account the view expressed in the TA Committee meeting that “it is licensed here, therefore the US FDA view is not important”, we do feel that the issues highlighted by the FDA reviewer need careful consideration as they may have a bearing on the real world effectiveness.

Our interpretation of the FDA report is that they were less impressed with data on efficacy – and there are important nuances in both the clinical and statistical interpretation of the data that might easily be overlooked, but would have a bearing on the real life effectivness.

1b. Sub Groups – not all outcomes in the sub group analyses reached statistical significance

Efficacy of Ticagrelor v clopi in various pre-planned sub-group analyses of PLATO was clear - although not all reached statistical significance (taken from DTB review article):

- patients in whom invasive management was planned at randomisation (9.0% vs. 10.7% at 360 days, HR 0.84, 95% CI 0.75 to 0.94; NNT 59);
- those with STEMI and planned primary PCI (9.4% vs. 10.8%, HR 0.87, 95% CI 0.75 to 1.01);

- those with diabetes (HR 0.88, 95% CI 0.76 to 1.03);
- those with creatinine clearance below 60mL/minute (17.3% vs. 22.0%, HR 0.77, 95% CI 0.65 to 0.90; NNT 21).

There seem uncertainties with respect to the optimal treatment schedule for different sub groups, and treatment duration – first line, second line in clopi non responders (genetic testing?)

1c Time to event

The benefit of ticagrelor over clopidogrel was apparent within the first 30 days of therapy and persisted throughout the study period.
The FDA reviewer questioned whether
 The treatment benefit was driven by statistically significant reductions in both vascular death (4.0% vs. 5.1%; p=0.001) and MI (5.8% vs. 6.9%; p=0.005). Ticagrelor does not appear
to have an effect on stroke outcomes (HR 1.17, 95%CI 0.91-1.52, p=0.22).

1d Exclusion criterion used in PLATO

The SMC review highlighted that PLATO did not exclude patients already receiving treatment with clopidogrel and may have included a small proportion of patients who were poor responders to clopidogrel and therefore at higher risk of an ischaemic event.
Clopidogrel patients also received different loading doses depending on whether or not they had already been receiving clopidogrel, and at the discretion of the investigator if undergoing PCI.
Loading dose of clopidogrel is an issue - 70% of patients in PLATO did not have loading dose of 600mg of clopidogrel which is current clinical practice in the UK, Obviously this might have a bearing on the contextualisation of the results.

1e Follow up – quoting from Marciniak / FDA review:

"There was one aspect of PLATO study conduct that was not good: the follow-up rate. By the sponsor's statistics, about 5% of the patients died while about 82% had a final study visit ("completers" per the sponsor's terminology). **Hence about 13% of the patients (100% - 5% - 82%) had incomplete follow-up for determining**

the primary endpoint of CV death, myocardial infarction (MI), or stroke by the sponsor's tallying."

"These rates of incomplete follow-up are concerning. They greatly exceed the differences between arms in rates for any of the endpoints. If the endpoint results were consistent, then we would be less concerned about the follow-up rates. However, the efficacy results are inconsistent by region and the time course of the effects are inconsistent with those from the thienopyridine ACS trials."

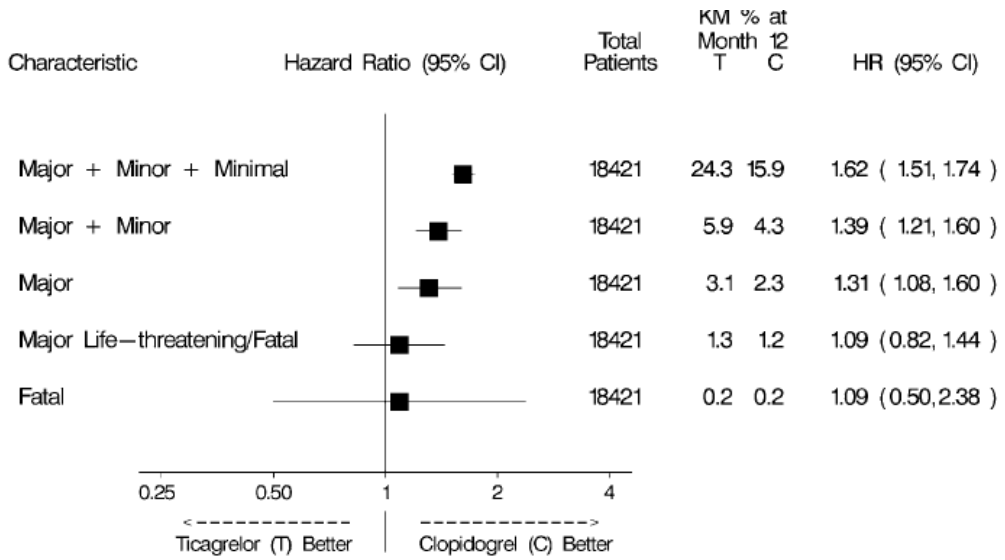
"This problem with incomplete follow-up rates has been an issue for other recent CV outcome trials. While we are sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials."

This lack of follow up is a concern in terms of real world efficacy.

1f Safety and adverse events

There are nuances in data re adverse events need full exploration – both clinically and H Econ case.

The safety issue common to platelet inhibitors is bleeding. Ticagrelor did produce more bleeding than clopidogrel as shown by the sponsor's statistics in Figure 11 (taken from FDA review).



Although there was no significant difference in rates of major bleeding between the two groups (11.6% with ticagrelor vs. 11.2% with clopidogrel), ticagrelor was associated with a higher rate of major bleeding that was unrelated to CABG during 12 months of treatment (4.5% vs. 3.8%, HR 1.19, 95% CI 1.02 to 1.38; NNH 143).

While major bleeds and less serious bleeds were substantially increased with ticagrelor, life-threatening and fatal bleeds were not significantly increased. The FDA primary clinical safety reviewer commented that most major bleeds were CABG-related (~ 75%) and most CABG bleeds were major (~85%). The risk of CABG-bleeding was increased in ticagrelor patients who did not wait until day 5 after stopping treatment to have CABG.

Patients taking ticagrelor were significantly more likely to suffer from non-procedure related bleeding (NNH=143) and breathlessness than those taking clopidogrel

For example, in PLATO, dyspnea was significantly more common among ticagrelor patients than clopidogrel patients. So it's possible that ticagrelor will be associated with higher resource use because the dyspnea leads to more diagnostic testing and more ER visits. Dyspnoea was reported more commonly in those treated with ticagrelor than clopidogrel (13.8% vs. 7.8%). We note that in PLATO few seem to have discontinued on account of this - 13.8% vs. 7.8% with clopidogrel, $p<0.001$; NNH 17, leading to discontinuation of treatment in around 1% of patients. We are of the view that discontinuation on account of side effects would be higher in real life than in a trial (motivated, well supported patients etc). Combined with rapid reversibility, this poses a

greater risk and are of the view that this needs to be fully explored in the economic analysis – probably through a sensitivity analysis.

Discontinuation of study drug due to adverse events occurred more frequently with ticagrelor (7.4% vs. 6.0%, $p < 0.001$), which was also associated with more episodes of fatal intracranial bleeding (0.1% vs. 0.01%, $p=0.02$) but with fewer episodes of other types of fatal bleeding (0.1% vs. 0.3%, $p=0.03$) than clopidogrel.

1g Risks and bleed rates - length of treatment seems important

PLATO study, ticagrelor was associated with a higher rate of major bleeding events unrelated to CABG than clopidogrel, including more instances of fatal intracranial bleeding. But the ticagrelor patients had fewer fatal bleeding events of other types, and overall bleeding rates were similar between the two groups.

Obviously the recommended treatment course is one year. Any analysis of clinical and cost effectiveness, and real world use would need to be mindful of patients who will be on the drug for a long time. Bleeding rates are always expressed as rates—frequency divided by time—so if a patient takes a drug for a longer period of time, the likelihood he will experience bleeding is higher

We would expect these issues to be built into the econ analysis, and are not clear it is at this moment. NHSBA would like assurance that the adverse event profile has been fully built into the economic analysis.

1h Onset / offset of action – causes concerns

The fast-offset drug might be well-suited to coronary artery bypass patients or perhaps patients who have multivessel disease and are going to probably undergo bypass. This advantage does not extend to chronic antiplatelet drug users.

As the effects of ticagrelor reverse rapidly, compliance may be particularly important for effective treatment, and patients may need additional counselling and surveillance in this respect.

> It is thought that about 20% of patients on clopidogrel don't adhere to their prescribed regimen. Although the "trough levels" of platelet inhibition are higher with

ticagrelor than for clopidogrel when a patient misses a single dose, the level of platelet inhibition with ticagrelor drops off rapidly if a patient misses three or four doses.

If GI bleeding complication, leading the GI specialist to immediately take the patient off the antiplatelet drugs

With a slow-offset drug, there may be time for the cardiologist to consult with the GI specialist about the antiplatelet regimen, but taking a patient off of a fast-offset drug could put him or her at risk for MI and stroke very quickly.

1i BD dosing - compliance in the real world - may attenuate the effectiveness

especially if effects wear off quickly - an advantage can be turned into a disadvantage compared to clopi – PLATO demonstrated that more patients on ticagrelor than clopidogrel discontinued due to adverse events (7.4% vs. 6.0%, p<0.001; NNH 71).

patients deemed unlikely to comply with the twice-daily regimen of ticagrelor were excluded from the pivotal PLATO study

We disagree with the conclusions of the Committee in 4.6 on compliance. Patients are always advised to take medicines as their doctor prescribes, there is a huge wealth of anecdotal clinical experience and peer reviewed evidence making clear that whilst such instructions are given that compliance is often poor. This is an important point in this particular medicine.

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The DTB article summarised the “greater risk of non-procedural major bleeding and other treatment-related side-effects (dyspnoea, bradyarrhythmia, increased serum levels of uric acid and creatinine) compared with clopidogrel, raise questions about its safety, particularly over the longer term.”

Obviously such medium and long term safety issues ode need to be explored by further study. By the time any such study reports the drug will be well established in UK clinical

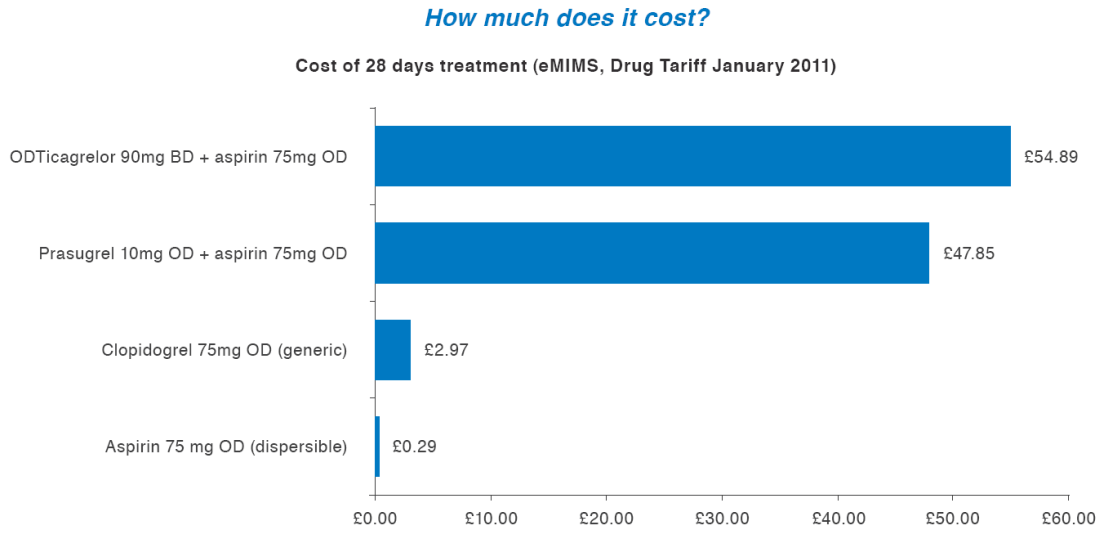
practice, thus the impact of any such study (unless the results were truly dramatic) would be minimal.

There have been a number of recent and very well cited examples of where medicines have received market authorisation in Europe that that subsequently turned out to do more harm than good. We would wish to see a cautious approach to the introduction of this medicine

2 Affordability and Economics. Real world economics versus "academic" health economics.

We accept that NICE is precluded from considering affordability. It is, however, an issue that NHS commissioners need to consider very seriously. Indeed it is a prime consideration

2a The difference in drug acquisition cost is stark, and well documented.



2b Budget impact

NHSBA has seen various estimations of budget impact. Here we highlight the likely budget impact using the manufacturers own model.

AZ Budget impact model. W Yorks. About £5m /yr in population of 2.1m - £240k / 100,000 pop

Budget Impact	2011	2012	2013	2014	2015	5-Year Total
Uptake of ticagrelor	100%	100%	100%	100%	100%	100%
Number of ticagrelor patients	8,190	8,190	8,190	8,190	8,190	40,950
Cost of ticagrelor:						
Drug costs	£2,914,616	£5,829,233	£5,829,233	£5,829,233	£5,829,233	£26,231,546
Cost of adverse events	£8,886	£17,772	£17,772	£17,772	£17,772	£79,975
Total cost of ticagrelor	£2,923,502	£5,847,005	£5,847,005	£5,847,005	£5,847,005	£26,311,522
Less cost of clopidogrel:						
Drug costs	£161,474	£322,948	£322,948	£322,948	£322,948	£1,453,266
Cost of additional CV events	£274,361	£548,721	£548,721	£548,721	£548,721	£2,469,246
Total cost of clopidogrel	£435,835	£871,670	£871,670	£871,670	£871,670	£3,922,513
Budget impact of ticagrelor	£2,487,668	£4,975,335	£4,975,335	£4,975,335	£4,975,335	£22,389,009

Summary of Impact of Ticagrelor in 2011

In 2011, using ticagrelor in 8,190 patients (100%) would result in:

- 57.3 fewer deaths, of which 45.0 are due to cardiovascular causes
- 45.0 fewer myocardial infarctions
- 5.8 fewer stent thromboses
- A budget impact of £2,487,668
- A cost per death avoided of £43,392
- In the PLATO study, no increase in overall major or fatal bleeding between ticagrelor and clopidogrel was observed*

*Please refer to summary of product characteristics for full information on bleeding rates

In NHSBA (520k registered pop) the estimated impact is therefore in the region of £1.25m. Assuming, at best, a flat budget scenario this equates to £1.25m of investment we will not be making in other cardiology services. This is equivalent to 1.4% of the total prescribing budget for NHSBA.

We note that the budget impact model is from the manufacturer therefore are of the impression it will be populated will with perhaps the most optimistic assumptions. It is not clear that the cost of treating side effects are built into the AZ model adequately – noting some of our concerns above.

Some commentators have noted that the net cost may be lower due to lower resource use savings……..less readmissions etc. This seems incorporated into the AZ model. It is of note that NHS commissioners will not realise this cost without concurrent reductions in capacity – bed base in hospitals. Put most simply, if the bed is there it will be filled with another patient. Therefore whilst there may be a net saving to the NHS, this will NOT be realised by NHS commissioners. Calculating how much capacity to remove so as to realise cash savings will be difficult.

NHS Bradford and Airedale currently spends approx £67m on circulatory problems (of which £22.6 is on CHD). The additional estimated £1.25m that this drug may incur will be found from savings elsewhere in the cardiology spend, with reductions in spend in other parts of the programme and certainly very limited new investment. NHS Commissioners are required to make judgements about the relative value of investments. We would seek support of secondary and primary care clinicians in doing this.

2c Population impact seems modest, for a high cost and opportunity cost.

The population impact of introduction of ticagrelor is also an important consideration. Using our own data we can estimate admissions for ACS seems relatively stable – see table below.

Admissions for ACS 2008 / 09 to 2010 / 11

ICD10 code (primary)	2008 09	2009 10	2010 11
I20 – UA	1447	1166	1070
I21 - AMI	726	656	485
I22 – subsequent MI	140	144	173
I24 – other acute ischemic HD	8	25	224
	2321	1991	1952

the recent studies give a perspective on mortality.

Wallentin (main PLATO study). The one year CV mortality (primary end point) is 9.8% in ticag vs 11.7% in clopi – an absolute risk reduction of 1.9% (NNT of 54).

The James SK et al (BMJ 2011) sub group analysis on effectiveness of Tica v clopi in ACS patients planned for medical management gives a different perspective on CV mortality risk. This indicates (table 3) that 12% of ticagrelor patients died at 1yr, compared to 14.3% of clopidogrel. An absolute risk reduction of 2.3%.

Taking data on the primary outcome of PLATO - composite end point CV death – the absolute risk reduction (compared to clopidogrel) is 1.9%

Just considering ACS patients, application of this data to our local population of 1070 ACS admissions that are admitted would indicate the following (using the James et al estimates from BMJ)

		current Management	Ticagrelor	Net benefit
ACS admissions	CV Deaths	153.01	128.4	24.61
1070		14.3% CV death at 1yr	12% CV death at 1yr	net reduction in deaths

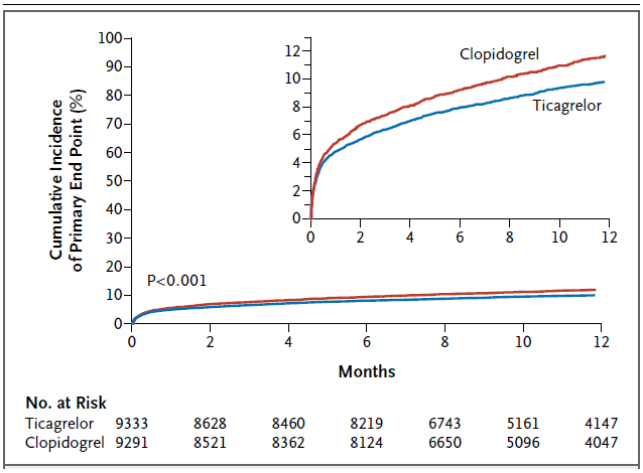
25 fewer deaths in a population of 1070 ACS admissions admitted. The net estimated drug cost is £686k (taking the figures on cost of ticagrelor and clopidogrel used above, and assuming all 1,100 are prescribed a 12m course of ticagrelor). This equates to

approximately £30,000 per CV death avoided, and NHS commissioners do need to consider the opportunity cost of investments foregone that might represent better value for money. Obviously such an analysis is obviously very sensitive to time horizon, and the horizon above is 1 year.

Obviously there are significant uncertainties in the epidemiology of ACS – and some discrepancies between different systems (eg HES and MINAP). In addition the actual decision to commence treatment with antiplatelet depends on risk stratification.

2d Economics and cost effectiveness

Despite the issues and weaknesses cited above, PLATO did report a mortality benefit, this is an obvious and important driver of the QALY side of the ICER equation. It is clear that the ACD concludes that ticagrelor is a highly cost effective use of resources. The absolute benefit is relatively meagre. See Table 1 from the Wallentin et al paper in NEJM.



That said, it is difficult to disagree with the findings of the ERG on their point estimates of ICER and CEACs. The methodology seems sound, though we would wish to see the sensitivity analysis cover in more detail some of the issues we highlight in section 1
It is worth noting that the ICERs are predicated on an NHS perspective. The ICERS will not work from a commissioner perspective unless the commissioner is able to realise savings from reduced admissions in cash terms – they will only do this through reduction in bed base in secondary care.

2e "Real world value for money" versus Incremental cost effectiveness ratios

The question that most, if not all commissioners will ask is whether the returns warrant the cost – an 18 fold cost difference compared to generic clopidogrel. The SMC review alluded to "drugs with a lower acquision cost". The SMC did not give any advice on where clopidogrel or ticagrelor might be preferentially used. The NICE ACD does not either. This issue of combining a relatively meagre absolute benefit with cost was adequately highlighted in the DTB review published recently.

> "To prevent one death from a vascular cause, stroke or myocardial infarction, 53 people would need to be treated with ticagrelor instead of clopidogrel for 12 months at a cost of £37,775; to treat the same number of people with generic clopidogrel would cost £1,626, so using ticagrelor would cost an extra £36,149 to prevent one death." (taken from NYRDTC report)

This is obviously uncomfortable territory, but NHS Commissioners must ask this question explicitly, and it cannot be ignored. This is a very good example of where a "pure academic" approach to economic appraisal must sync with the real issues of affordability in practice, and a financially driven approach to cost benefit appraisal within short time horizons. This is a concept that the NHS simply cannot ignore. NHS commissioners recognise and are supportive of an economic approach to valuation of benefit over clinically and epidemiologically appropriate time horizons. However, they MUST live within a budget envelope and a 1 year time horizon.

The budget impact of this drug is considerable. NICE clearly will find that it is highly cost effective – obviously that is very different from affordable. NHSBA and other NHS Commissioners will necessarily ask what services will be scaled back or cut, and whether the opportunity costs worth it? As a minimum, commissioners may seek to scale back the value of cardiology contracts, and may get into considering specific interventions. Given that the NNT for a non fatal MI is approx 44 it ought to be possible to calculate the likely reduction in admissions for MI this drug will yield, and thus the size of contract reduction that might be possible.

Most commissioners see this as a low priority development. From a commissioners perspective no there is not a compelling case for rapid introduction.

We find the DTB conclusion compelling:

> "Although ticagrelor appears to offer some benefits over clopidogrel in ACS, it is much more expensive, requires twice-daily dosing and has unknown long-term safety. Consequently, we cannot currently recommend ticagrelor as first-line therapy in the management of patients with ACS."

[redacted], [redacted]

NHS Bradford and Airedale

Refs

James et al. *BMJ* 2011;342:d3527 doi: 10.1136/bmj.d3527. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial

Wallentin et al. n engl j med 361;11. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Marciniak T. Sumbission to FDA. Ticagrelor for acute coronary syndromes, NDA 22-433

Ticagrelor for acute coronary syndrome. *DTB* 2011;**49**:66-68 doi:10.1136/dtb.2011.02.0035