

## **Ticagrelor - the physicians' perspective**

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***on behalf of the British Cardiovascular Intervention Society and British Cardiovascular Society***

How best to optimally manage acute coronary syndromes (ACS) has become the focus of interest for cardiovascular physicians and in particular for Interventional cardiologists. The pathobiological consequences of atheromatous plaque disruption require the management of both the generated thrombus and of the coronary narrowing. PCI with stents can itself aggravate the prothrombotic environment. There has been much research leading to international, continental, national and local guidelines in an attempt to provide best standard of care using adjunctive pharmacotherapy for the 250 000 or so patients who present with ACS each year in the UK.

ACS management in terms of adjunctive pharmacotherapy is currently split into pre-intervention and peri-/post-intervention. Percutaneous coronary intervention (PCI) is a cornerstone of treatment following the RITA 3 trial (1) amongst others. Current NICE guidance on ACS suggests that the intervention should be done within 96 hours for medium and high risk cases. Most patients with non-ST-elevation myocardial infarction (NSTEMI) presenting with chest pain (+/- ECG changes) undergo troponin measurement and risk scoring once it is available (TIMI or GRACE risk score). Some also use a bleeding risk score (e.g. the CRUSADE score). During this pre-PCI phase patients are currently and routinely started on clopidogrel (normally 600 mg loading with 75 mg unless they are unlikely to be taken to the cath lab in which case they will be loaded with 300 mg). Patients will also be routinely given aspirin and low molecular weight heparin. At PCI they frequently have the culprit lesion(s) treated with a stent and increasingly this is a drug eluting stent (DES). Some administer abciximab (ReoPro) based on the ISAR-REACT-2 trial (2) which concluded: In high-risk patients with NSTEMI-ACS undergoing a PCI after pre-treatment with 600 mg clopidogrel, adverse events occurred less frequently with abciximab and the early benefit was maintained at 1 year after administration. However with recent concerns regarding the attributable deaths from bleeding (3) the use of abciximab in NSTEMI patients has fallen in the UK.

Post-procedure aspirin and clopidogrel (75 mg) are given for 12 months even when bare metal stents (BMS) are deployed (normally, dual antiplatelet therapy - DAPT - is given for one month after

BMS in stable patients) based on previous NICE guidance for ACS patients. Recent data from the CURRENT-OASIS-7 has led some interventionists to administer clopidogrel at 150 mg od for the first week following the procedure (4).

For ST-elevation myocardial infarction (STEMI) the current preferred proposed management strategy is prompt transfer to the cath lab (within guideline mandated times (5)). Aspirin is usually given as soon as the diagnosis has been made and, until recently, clopidogrel is administered either just before or just after angiography and subsequent angioplasty with stenting ("primary angioplasty", or PPCI). Many units use abciximab at the time of PPCI, but following the HORIZONS trial data on net clinical benefit bivalirudin is increasingly being used instead of abciximab.

Following recent NICE guidance on PRASUGREL (6) this agent is being taken up by Units in the UK. It has a more rapid onset of action than clopidogrel (important in the context of PPCI where speed is essential) and is more potent but even more importantly overcomes the variable response of individuals to clopidogrel. The term "clopidogrel resistance" is often used but this important occurrence with its potential clinical consequences should be limited to those for whom the anti-platelet drug does not achieve appropriate inhibition of platelet aggregation (IPA); i.e. it has a sub-optimal pharmacological effect despite standard proven effective dosing and compliance. Patients may present acutely, sub-acutely or in the longer term with stent thrombosis (ST) which has been associated with a ~50% rate of acute myocardial infarction (AMI) or death. Thus while ST occurs at a rate of at least 0.6% p.a., since there are 85 000 PCIs per annum in the UK, the clinical events associated with ST represent up to 250 serious events or more p.a.

Thus while it is clear and of no doubt that dual anti-platelet therapy is pivotal to the short, medium and longer term prevention of serious adverse events following stent implantation, individual variation in platelet response to clopidogrel (due to the need for this drug to be metabolised in the liver and thus subject to inhibitory pathway interactions, and/or possibly genetic defects in metabolism) have led to the realisation that more potent and more reliably inhibitory drugs may have important roles in optimising the outcome after PCI. Obtaining a good immediate angiographic and clinical result after PCI stenting is not enough if the patient (invariably not tested for their platelet responsiveness) suffers a catastrophic acute stent thrombosis (which tends to be an acute event even if it presents late after the PCI). The use of prasugrel has been targeted through NICE approval to the STEMI patient due to its rapid onset of action and ability to overcome the variable platelet responsive to clopidogrel. It has also been approved through data review during the NICE appraisal process for use in those patients presenting with and treated for stent thrombosis (albeit this is treating once the consequences of the ST myocardial infarct have occurred to reduce the risk

of recurrent events) and for diabetic patients presenting with NSTEMI, where the data were convincing for the level of superiority over clopidogrel. It was not approved for use in all NSTEMI patients as there had, in the TRITON study been no pre-loading with clopidogrel as is routine in clinical practice, so the superiority of prasugrel over clopidogrel was felt to be unproven.

Ticagrelor is the third generation of anti-platelet agent to be tested in ACS patients and all trials to date have used clopidogrel as the comparator control group. It is unlikely that a head-to-head trial comparing ticagrelor with prasugrel will be forthcoming.

The first consideration regarding the PLATO trial is that it was designed to reflect UK (and European) practice. Patients were pre-loaded with clopidogrel (600 mg) (7), although it appears this was only in 46% of patients and only 16.6% received 600 mg Clopidogrel. The headline results showed significant benefit over clopidogrel, almost certainly because it provides effective treatment to clopidogrel non-responders. Platelet reactivity was below the cut points previously associated with ischemic risk as measured by light transmittance aggregometry, VerifyNow P2Y12 assay, and vasodilator-stimulated phosphoprotein phosphorylation in 98% to 100% of patients after ticagrelor therapy versus 44% to 76% of patients after clopidogrel therapy (8). While the benefits of clopidogrel over aspirin alone (in the CURE trial) and prasugrel over clopidogrel (in the TRITON trial) were driven by significant differences in rate of enzyme defined myocardial infarction, in the PLATO study at 12 months, while the composite primary end point (death from vascular causes, myocardial infarction or stroke occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84;95% confidence interval [CI], 0.77 to 0.92;  $P < 0.001$ ) the difference was that in the predefined hierarchical testing of secondary end points there was also (uniquely for such studies) a significant difference in death from vascular causes (4.0% vs. 5.1%,  $P = 0.001$ ). Interestingly the rate of death from any cause was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel;  $P < 0.001$ ).

There has been much debate regarding the possible causes of this mortality benefit to date with ticagrelor but with no simple explanation ("other non-platelet" related, possibly nitric oxide based, effects often being quoted), it might be presumed to be due to the more potent anti-platelet effects of ticagrelor compared to clopidogrel. However this explanation is difficult since there was no apparent significant difference in the rates of major bleeding (11.6% and 11.2%, respectively;  $P = 0.43$ ), although on careful analysis of the data there is a difference with ticagrelor being associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%,  $P = 0.03$ ), including more instances of fatal intracranial bleeding and fewer fatal bleeds of other types.

Comparison across studies does suggest greater platelet inhibition with ticagrelor (platelet aggregation at 4 hours T 90mg = 30%, T 180 mg = 20%; P 10mg = 40%, P 60 mg = 30%; versus C 300 mg 84%, C 600mg = 70%).

The primary results to 12 months for TRITON and PLATO appear very similar with a HR of 0.84 and 0.81 and p values 0.0003-4 compared to clopidogrel although the major differences between these trials was in the trial design, with preloading of clopidogrel and benefit in survival with PLATO. In both studies there was an increase in non CABG bleeds (2.4% P versus 1.8% C in TRITON; and 2.8% T versus 2.2% C in PLATO). Overall, however, bleeding was not increased in PLATO. All cause mortality was 3.0% P versus 3.2% C in TRITON  $p=0.62$ , in contrast to 4.5% P versus 5.9% C in PLATO  $p<0.001$ .

The benefits of Ticagrelor may be seen as complimentary to those with Prasugrel although the headline results for the two trials appear similar for ACS populations. The HR for Prasugrel compared to clopidogrel for the end-points of CV death, MI and stroke at 15 months was 0.79 (0.65–0.97), NNT=42 for the STEMI patients, and 0.85 (95% CI = 0.74–0.97), NNT=59 for Ticagrelor compared to clopidogrel. For Ticagrelor the benefit is seen best in the NSTEMI population particularly in those managed invasively. In PLATO, the rate of end-points for STEMI patients managed invasively was T: 8.1% (250/3278) versus C: 9.5% (293/3297), HR 0.86 (0.72, 1.01); for patients with NSTEMI managed invasively rates were T: 10.2% (242/2564) versus C: 12.2% (284/2481), HR 0.82 (0.70, 0.97) (FDA analysis). Additional analysis (ref 10 fig 5) suggests that patients without diabetes might do better than those with diabetes.

There have been concerns over the side effects of Ticagrelor but we understand these are reversible, and treatment was interrupted in only a few patients. The rapid onset and offset has been demonstrated by the PLATO Investigators (11). Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel; this was sustained during the maintenance phase and was faster in offset after drug discontinuation. This means that if a patient needs a non-cardiac or cardiac operation then discontinuation of the anti-platelet agent can be undertaken closer to the proposed procedure with greater safety with regard to bleeding. This was clearly shown in the CABG PLATO data where reduction in bleeding appeared to be the driver of mortality benefit with equal numbers of patients in each group receiving the randomly allocated agent in the 7 days prior to the CABG.

Ticagrelor is an important additive agent to the adjunctive therapy available in ACS. Mortality benefit with no overall excess bleeding is a very important consideration as are its rapid onset and rapid offset duration of action. Prasugrel has recently been approved for patients presenting with STEMI and ST and diabetic patients with NSTEMI. Ticagrelor is superior to clopidogrel for patients with acute coronary syndromes and may be clinically more desirable in special groups such as those who need anti-platelet protection leading up to CABG.

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