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Choices for potent platelet inhibition in patients with diabetes mellitus

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Diabetes mellitus provides challenges to clinicians seeking to optimize the efficacy of pharmacological therapies for the management and prevention of atherothrombotic events. On the one hand, it drives the progression of atherosclerosis, leading to the highly thrombogenic rupture and erosion of plaques, at the same time as increasing the thrombogenicity of blood through modulation of platelet reactivity, enhancement of plasma coagulability and impairment of endogenous fibrinolysis.[1] On the other hand, it is associated with reduced pharmacodynamic action of traditional oral antiplatelet therapies, aspirin and clopidogrel, through increased platelet turnover and, in the case of clopidogrel, impairment of hepatic active metabolite generation, thus rendering these therapies less effective despite the clinical imperative for more effective treatment.[1] It was therefore inevitable that more effective treatments should be developed for diabetes patients as well as others at high risk of atherothrombotic events. This concept is well illustrated in the work of Angiolillo and colleagues who here have compared the pharmacodynamic properties of prasugrel and ticagrelor in diabetes patients.[2]

A key component of the rationale for comparing prasugrel's and ticagrelor's effects in diabetes patients is the different patterns of benefits seen in the diabetes subgroups in the pivotal phase 3 studies of these drugs compared to clopidogrel.[3, 4] With prasugrel, a particularly marked early benefit in reduced thrombotic events was seen in the diabetes subgroup whereas, with ticagrelor, there was a more progressive accrual of benefit over 1 year, including progressive reduction in mortality. However, differences in study design can explain much of the difference in the patterns of early benefit: the clopidogrel

regimen was substantially different between the two studies, with prasugrel being compared to a 300-mg loading dose of clopidogrel, often given after completion of percutaneous coronary intervention (PCI), whereas ticagrelor was compared to pretreatment with a clopidogrel loading dose of 300 to 600 mg. Given the higher thrombotic risk and lesser efficacy of clopidogrel in diabetes patients, it is clear that a 300mg loading dose administered after PCI is "too little, too late" so would be predicted to drive a higher event rate compared to more effective pretreatment regimens. Nevertheless, it was important to establish whether or not any differences in early and sustained platelet inhibition exist between prasugrel and ticagrelor in diabetes patients.

The phase 3 results for both prasugrel and ticagrelor point to breakthroughs in oral antiplatelet therapy. The key to prasugrel's success is its more efficient production of active metabolite compared to variable and unreliable clopidogrel active metabolite production.[5] Although the second step in prasugrel active metabolite formation relies on hepatic cytochrome P450 (CYP) enzymes, in the same way that both steps in clopidogrel active metabolite formation do, the availability of several different CYP pathways for generating prasugrel active metabolite and the lack of alternative pathways for inactivation of prasugrel and its intermediate metabolite mean that sufficient levels of this active metabolite can be produced in order to bind irreversibly to most of the $P2Y_{12}$ receptors on circulating platelets. This irreversible inhibition must occur before the active metabolite levels fall to subtherapeutic levels within a few hours after prasugrel absorption as a consequence of its short distribution half-life (about 30-60 minutes) (Figure 1).

The explanation for ticagrelor's success is different. Ticagrelor belongs to a class of drug that is distinct from the thienopyridines prasugrel and clopidogrel and relies on sustained plasma levels of both ticagrelor and, to a lesser extent, its active metabolite to provide potent platelet $P2Y_{12}$ inhibition (Figure 1).[5] As a consequence of its reversible binding to an allosteric site on $P2Y_{12}$ distinct from the ADP binding site, its inhibitory effects resolve when plasma levels of ticagrelor and its active metabolite fall to subtherapeutic levels such that the inhibitors dissociate from the platelet $P2Y_{12}$ receptors. Plasma half lives of 6 to 12 hours for both inhibitory molecules ensures consistent and sustained $P2Y_{12}$ inhibition with twice-daily ticagrelor dosing.[6, 7] Beyond $P2Y_{12}$ inhibition, ticagrelor also possesses a second property, which is a weak inhibition of cellular adenosine uptake via equilibrative nucleoside transporter 1 (ENT-1).[8] How much this contributes to the clinical effects of ticagrelor remains to be established but it may explain some of the clinical efficacy as well as some of the adverse effects such as dyspnea.

In their study, Angiolillo *et al* demonstrate how the different pharmacokinetic characteristics of prasugrel and ticagrelor lead, in both cases, to a high mean level of platelet $P2Y_{12}$ inhibition at 2 hours after a loading dose in diabetes patients. Despite this, a minority of the patients exhibited high platelet reactivity at this time point indicating that they had not yet reached a steady state level of platelet inhibition. In the case of prasugrel, previous studies have suggested slower onset of action in stable patient populations[9, 10] compared to the healthy volunteer studies that indicate impressive effect at 1 hour and steady

state inhibition at 2 hours after loading dose.[11] Previous work suggested ticagrelor achieves steady state inhibition by 2 hours in patients with stable coronary artery disease,[7] so the results in the current study raise the question as to whether diabetes mellitus might be associated with slower absorption of ticagrelor in some patients. This is distinct from the effect of morphine which delays gastric emptying and therefore delays the intestinal absorption and onset of action of prasugrel and ticagrelor in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention (PPCI) (Figure 1).[10, 12, 13] The rate of onset of action of prasugrel or ticagrelor is particularly important in PPCI patients and the various factors that lead to delayed onset of action in these patients support the use of parenteral antithrombotic therapy to cover the time period during which the drugs are absorbed in order to prevent acute stent thrombosis.

Some doubts are raised in the current study as to whether or not ticagrelor provides greater platelet $P2Y_{12}$ inhibition during maintenance therapy compared to prasugrel. We are inclined to trust the results of the VerifyNow P2Y12 assay that showed a slightly greater level of inhibition with ticagrelor. There are multiple strands of evidence underlying this opinion. Firstly, there was a deliberate decision to develop a 10-mg daily maintenance dose of prasugrel compared to prasugrel doses of 15 mg or greater in order to minimize the excess of bleeding compared to clopidogrel therapy[14] and this explains offset of some of the platelet inhibition after the effects of the prasugrel loading dose have worn off.[9] This contrasts with the decision to develop a maintenance dose of ticagrelor that sustains the high levels of platelet inhibition seen following a

loading dose. [6][7] Secondly, several studies have previously observed higher levels of platelet $P2Y_{12}$ inhibition with ticagrelor compared to prasugrel maintenance therapy, including in patients with diabetes mellitus.[15] Thirdly, we have found the VerifyNow P2Y12 assay to be particularly discriminating and reliable in assessing therapeutic levels of platelet $P2Y_{12}$ inhibition compared to some of the other assays.[6, 16] Whether the observed differences in long-term levels of platelet $P2Y_{12}$ inhibition with the two drugs translate into relevant differences in efficacy and safety outcomes is unknown, particularly in view of potential or actual differences in effects unrelated to $P2Y_{12}$ inhibition, and this requires sufficiently powered head-to-head studies.

Angiolillo *et al* demonstrate how prasugrel and ticagrelor inhibit not only ADP-induced platelet aggregation but also platelet aggregation induced by agonists activating the receptor pathways for collagen, thromboxane A_2 and thrombin. This reflects the central role of the platelet $P2Y_{12}$ receptor in amplifying the responses mediated by numerous receptor pathways and explains why this receptor has proven to be such a successful target in the management of cardiovascular disease (Figure 1).[5] Whilst it is tempting to infer that this might mean aspirin can be abandoned as a co-medication with prasugrel or ticagrelor, such an inference must be cautioned against in high-risk patients, such as those with diabetes and history of acute coronary syndrome. The effects of aspirin are additive to those of a $P2Y_{12}$ inhibitor, particularly with regard to collagen-induced platelet activation (Figure 1), and the effects of $P2Y_{12}$ inhibition can be overwhelmed by high levels of platelet activation. Consequently it is important to wait for the results of clinical studies assessing $P2Y_{12}$ inhibitor monotherapy

and, furthermore, to look critically at results in subgroups at different levels of risk before judging that aspirin can be safely abandoned in high-risk individuals.

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Figure legend

Figure 1. Absorption and effects of the orally-active antiplatelet drugs aspirin, clopidogrel, prasugrel and ticagrelor. A_{2A}- Adenosine receptor 2A; AA – Arachidonic acid; ADP – Adenosine diphosphate; CAM – Clopidogrel active metabolite; CIM – Clopidogrel inactive metabolite; ENT1 – Equilibrative nucleoside transporter 1; GPVI – Glycoprotein VI receptor; $P2Y_{12}$- Platelet $P2Y_{12}$ ADP receptor; PAM – Prasugrel active metabolite; PAR1 – Protease-activated receptor 1; PAR4 – Protease-activated receptor 4; TAM – Ticagrelor active metabolite; TPα – Thromboxane receptor [α isoform]; TxA_2 – Thromboxane A_2.

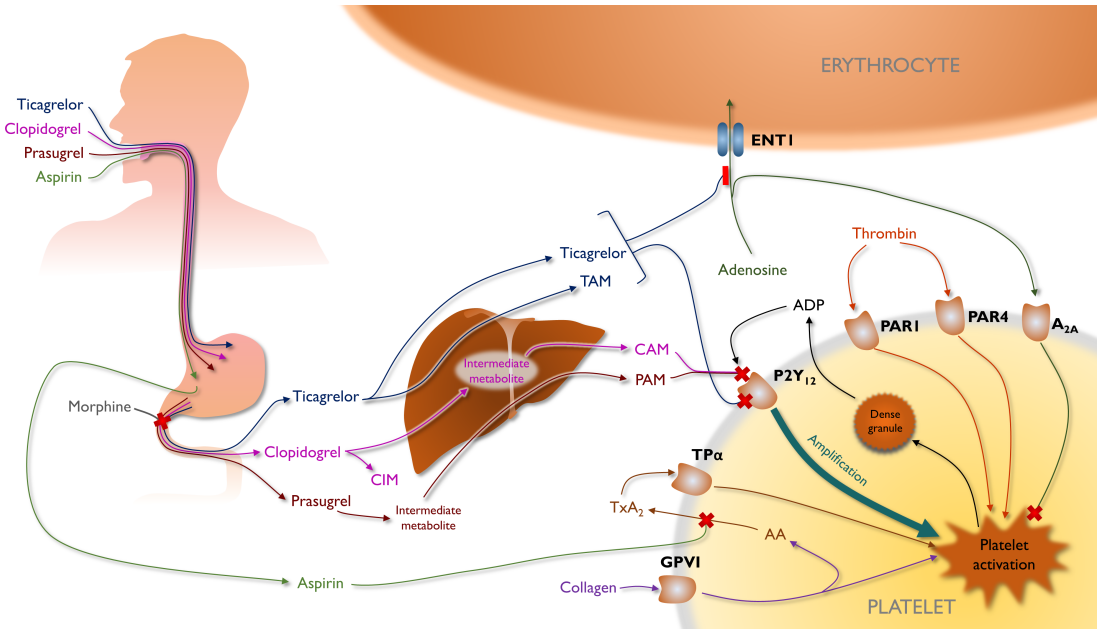
ERYTHROCYTE
ENT1
Ticagrelor
Clopidogrel
Prasugrel
Aspirin
Adenosine
Thrombin
Ticagrelor
TAM
ADP
PAR1
PAR4
A2A
CAM
PAM
P2Y12
Intermediate metabolite
Morphine
Ticagrelor
Dense granule
Amplification
Clopidogrel
CIM
TPα
Prasugrel
Intermediate metabolite
TxA2
AA
Platelet activation
GPVI
Collagen
Aspirin
PLATELET

Figure 1