

# Smoking, atherothrombosis and clopidogrel

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Smoking is well understood to increase the risk of atherothrombotic events by some two to threefold.<sup>1–3</sup> Putting it another way, in 2003 the SCORE project estimated that over a period of 10 years smokers compared with non-smokers have approximately twice the risk of a fatal cardiovascular event.<sup>4</sup> Set against this elevation in risk, it was reported in the mid-1980s that there was a smokers' paradox, in that smoking appeared to confer a reduced mortality following an acute myocardial infarction.<sup>5</sup> It was also noted, in accordance with the suggestions from studies such as SCORE, that smokers tended to be 10 years or so younger and such variables could account for the difference seen. A more recent analysis has concluded that reports of the smokers' paradox appear largely confined to the 1980s and 1990s, at which time fibrinolysis was the generally employed approach for reperfusion, whereas the paradox is not seen in more contemporary studies when patients are routinely treated with early invasive management.<sup>6</sup>

A more recent smokers' paradox has been the observation that the response to clopidogrel is enhanced in smokers over non-smokers.<sup>7</sup> This taps into current interest about ideas of resistance, or hyporesponsiveness, to antiplatelet therapies and in particular to clopidogrel. In general terms, there is a wealth of literature demonstrating variability of the effectiveness of clopidogrel as an antiplatelet agent as assessed *ex vivo*, but it has proved difficult to associate such variability to worsened outcomes on a patient by patient basis and to individualise treatment accordingly.<sup>8–10</sup> Park and colleagues<sup>11</sup> develop their recent observations about the underlying reasons for the

increased response to clopidogrel in smokers (*see page 1000*). Previously, they have reported that the enhanced response to clopidogrel is seen only in P450 CYP1A2 (–163C>A) A-allele carriers<sup>12</sup>. This is suggestive of a subset of individuals in whom a change in genotype leads to CYP1A2 being particularly inducible by cigarette smoke, so increasing the capacity to convert clopidogrel, which is a prodrug, to its active form. Park *et al*<sup>11</sup> report that cessation of smoking reduces the enhancement of clopidogrel responsiveness seen, providing further support to the idea that smoking induces a metabolic pathway. As recently reviewed, smoking has a number of negative vascular effects that can contribute to an increased risk of thrombosis.<sup>1</sup> These include, but are not limited to: an increase in vascular resistance and a reduction in endothelial function and the production of endothelial mediators such as nitric oxide and prostacyclin; increased inflammation of the vascular wall, noted by factors such as increases in fibrinogen, interleukin 6 and C-reactive protein; increased progression of atherosclerosis, associated with increases in low-density lipoprotein and total cholesterol; increased platelet reactivity and coagulation pathways, such as an increase in the circulating levels of fibrinogen; and clearly increases in oxidative stress associated, among other effects, with the production of a number of prothrombotic and pro-atherogenic mediators.<sup>13</sup> Cessation of smoking will generally impact on these negative vascular effects,<sup>1</sup> which may carry through to a greater or lesser extent on the platelet testing conducted by Park and colleagues.<sup>11</sup> Many of the atherothrombotic risk factors associated with smoking will be relevant to the platelet within the milieu of the blood vessel. For example, the effects on endothelial cell mediator production, or the composition of atherosclerotic plaques and their stability. The Verify Now platelet testing system used by Park *et al*<sup>11</sup> provides a measure of the ability of platelet P2Y<sub>12</sub> receptors to respond to ADP in a low shear

system outside of the body, when the mechanical forces and effervescent vascular mediators are absent. To that extent it informs us of the level of P2Y<sub>12</sub> receptor blockade, which with regard to clopidogrel may well reflect the ability of individuals to metabolise the production of the active P2Y<sub>12</sub> receptor blocking metabolite. To that extent the study of Park *et al*<sup>11</sup> informs us that smoking appears to increase P2Y<sub>12</sub> receptor blockade through an effect that may most rationally be attributed to the induction of a metabolic pathway that declines following cessation of smoking. However, as we do not have information regarding the circulating levels of clopidogrel active metabolite this cannot be definitively claimed. Within the circulation this higher level of P2Y<sub>12</sub> receptor blockade in smokers may help at least partly to compensate for the reductions in endothelial production of prostacyclin, as P2Y<sub>12</sub> receptor blockade sensitises platelets to the anti-aggregatory effects of prostacyclin.<sup>14</sup> This reminds us that in considering the effects of antiplatelet drugs we need to consider layers of complexity beyond the direct effects they have on the responses of platelets to soluble mediators *in vitro*. Furthermore, smoking could affect other aspects of platelet responses to ADP, even fundamental ones such as the surface expression of P2Y<sub>12</sub> receptors<sup>15</sup> or the programming of platelets at the level of formation from megakaryocytes. To achieve this broader understanding of the interactions between clopidogrel, smoking and platelets within the circulation markers of ongoing platelet activation *in vivo* would be of great assistance.<sup>16</sup> In particular, it would be interesting to see if clopidogrel has particular effects against these markers in different patient groups; a clear example being, for instance, the CYP1A2 group earlier identified by Park and colleagues.<sup>11</sup> Increasingly, the opportunity afforded by techniques such as transcriptomics may allow us to model more precisely the interactions between cigarette smoke, variations in genotype and therapeutic drug effectiveness.<sup>17</sup>

In conclusion, while the work of Park and colleagues<sup>11</sup> adds to the interesting story of the variability in responsiveness to antiplatelet drugs and associations between smoking and atherothrombosis, it should not be taken as indicating that smoking improves the effectiveness of antithrombotic therapy. The slight increase in platelet inhibition has not been associated with outcomes, and goes very little of the way that would be needed to

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correct the greatly increased risk of a thrombotic event.

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