Resistance to what, does it matter? How do we study it?

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This editorial refers to ‘Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation†’ by M.J. Price et al., on page 992

The importance of platelets and thrombosis in the pathophysiology of acute ischaemic coronary syndromes has been well appreciated. This information has formed the backbone of the guidelines on treatment of acute ischaemic coronary syndromes has been well appreciated. The importance of antiplatelet regimens in patients undergoing PCI revascularizations; (ii) stent placement is the procedure of choice for PCI revascularization; (iii) stent thrombosis is a significant problem for a very small percentage of patients undergoing PCI, but, when it occurs, it can have catastrophic implications for the patient, with death or myocardial infarction occurring in 50–60% of patients; (iv) drug-eluting stents were introduced to prevent restenosis but were found to be susceptible to stent thrombosis again at a low to very low frequency rate; (iv) recent data have indicated that stent thrombosis occurs with both bare metal and drug-eluting stents.

After the importance of antiplatelet regimens in patients undergoing PCI was recognized, there was rapid adoption of dual antiplatelet strategies in patients treated with stents; this included initially aspirin and Ticlopidine, but then was switched to aspirin and clopidogrel because of an improved safety profile with the latter. Uncertainties remained concerning the duration of therapy as well as the specific regimen to be used. This importance was emphasized by early reports with drug-eluting stents that discontinuation of dual antiplatelet therapy could be associated with stent thrombosis. It again must be remembered that stent thrombosis may also occur with bare metal stents. Finally, it was recognized that some patients even when on antiplatelet strategies developed stent thrombosis. This has led to the concept first of aspirin resistance and now clopidogrel resistance. The issues of resistance to aspirin or in this case clopidogrel resistance are multiple and complex. Questions include:

- The definition of resistance—is it a dichotomous variable or, like many biological processes, a linear variable which has an increasing hazard ratio of an event with increasing resistance?
- How is resistance measured? This is of crucial importance if the measurement techniques have a great bearing on the definition of the incidence of resistance.
- What is the confounding effect of variable drugs?
- When should resistance be assessed and in whom?
- Perhaps most important is the link between definition and measurement of resistance and a physiological event such as stent thrombosis in a drug-eluting stent. This latter issue is compounded by the fact that the number of adverse events is low. There may be multiple other factors involved, such as adequacy of deployment technique and overlapped stents, as well as the specific segment to be stented. The ability to predict an individual at risk and the ability to develop alternative strategies is incredibly important in this regard.

The article by Price et al.† illustrates many of the salient issues: (i) a small number of patients (380); (ii) a small number of events occurred (only nine events) which required statistical techniques which have the potential to ‘model noise’; (iii) very selected patients were studied with only stable angina or stable ischaemia which is very different from most clinical series; (iv) inability to adjust for the confounding variables such as adequacy of stent deployment technique; and (v) definition of clopidogrel resistance which was defined in a very different population.

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Despite these issues, in this initial foray, Price et al.16 have documented that by using a point-of-care assay, post-treatment reactivity of platelets in patients on clopidogrel is associated with increased event rates. This study serves the purpose of stimulating more and larger efforts to study the issue of clopidogrel platelet reactivity by developing either new regimens of the same drug or new drugs which have different, more predictable, and more powerful effects on platelet function, such as prasugrel. It still must be remembered that optimizing the initial implant of any stent is the cornerstone to improving patient safety and outcome.

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References