Discontinuing clopidogrel: Abrupt or tapered cessation?

Peter L. Thompson
Heart Research Institute, Sir Charles Gairdner Hospital, University of Western Australia, Perth, Western Australia, Australia

Despite the recent availability of alternative antiplatelet therapies to inhibit the P2Y12 receptor, such as prasugrel and ticagrelor, clopidogrel remains the most widely used drug to partner aspirin in dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) (1). The availability of generic clopidogrel further entrenches it as the most widely used P2Y12 inhibitor.

There are many unanswered questions on when and how DAPT should be ceased after PCI (2) with some guidance anticipated from the DAPT (3) and ISAR SAFE (4) trials due to be reported later this year. Current guidelines for DAPT post-PCI recommend continuation of DAPT for 12 months after insertion of a drug-eluting stent and shorter duration after insertion of a bare-metal stent (5, 6). Early unanticipated cessation of DAPT due to non-adherence or bleeding is far less safe than temporary cessation under physician supervision (7). An unanswered question concerns the mode of physician supervised withdrawal of clopidogrel. While the risk of stent thrombosis is low, the risk of this potentially catastrophic complication can cause anxiety for patients and physicians, and anything to reduce the risk is worth exploring. Some evidence from platelet activity studies (8) and observational cohort studies (9) has suggested that sudden cessation may be associated with a "rebound" effect.

In this issue of Thrombosis and Haemostasis Fiedler et al. report the results of a randomised trial to evaluate whether tapered cessation of clopidogrel after treatment with a drug eluting stent is less risky than abrupt cessation (10). The trial randomised 783 patients, 392 patients to tapered cessation and 390 to abrupt cessation. The event rate at 90 days was low, with only 14 (1.8%) patients having a major adverse cardiac event (MACE) in that time, nine patients (2.3%) in the tapered cessation group and five (1.3%) in the abrupt cessation group (p=0.284). The trial had planned to recruit 3,000 patients, but was stopped because of slow recruitment. The trial was well conducted and there was outcome information available on every patient who entered the trial. The authors are to be congratulated on persisting with the trial over five years and reporting carefully on the results of a "negative" trial.

However, it is clear that this trial does not provide clinically useable evidence to guide the physician in deciding whether to taper or abruptly cease clopidogrel after the guideline recommended duration of DAPT. There were not enough endpoints in the trial to answer the question posed.

Several factors explain the lack of a discernible result from the trial. It was limited by lack of funding and apparent lack of referring physician enthusiasm for the trial and had to be terminated because of slow recruitment. More concerning, the trial may never have had the power to answer the question it was tackling. While stent thrombosis is a feared complication of DAPT cessation, the reality is that this is an infrequent occurrence. The design of the trial assumed an event rate far in excess of that actually observed. One of the assumptions behind the ISAR CAUTION trial was that there would be a 5% MACE rate within two months post cessation. This is much higher than post PCI event rates in modern practice, which has adopted wider use of new generation stents with lower rates of stent thrombosis (11). Previous reports of high event rates in observational series included patients with higher risk from early generation stents and did not distinguish inappropriate cessation of clopidogrel as a result of non-adherence or emergency cessation as a result of bleeding, from appropriate cessation under physician guidance. The latter carries a far lower risk with one large registry showing no increase in events after physician supervised interruption or cessation (7).

The trial was also partly conceived from the observation that platelet aggregability may rebound on cessation of clopidogrel. Recent studies have questioned the validity of platelet aggregation testing in clinical care and monitoring of platelet function does not improve outcomes (12), and the relevance of the apparent rebound in platelet activity on cessation of clopidogrel remains uncertain.

Could these limitations have been predicted at the time of design of the trial? Perhaps the inadequate sample size could have been anticipated, but in the rapidly changing field of interventional treatment of coronary artery disease "Prediction is very difficult, especially if it’s about the future" (13).

We need more clinical trials to guide the duration of DAPT and how to manage the situations where DAPT must be withdrawn. At this stage, despite some suggestive observational and platelet function data, there does not appear to be any advantage in tapering off clopidogrel compared with its abrupt cessation.

Conflicts of interest
None declared.

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References


