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EDITORIAL

Close encounters with errors of the second kind: evaluating risks and benefits of long-term dual antiplatelet therapy

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This editorial refers to 'Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual-antiplatelet therapy after stent implantation: a pre-specified anaylsis from the PRODIGY (Prolonging Dual-Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial'[†], by F. Costa *et al.*, on page 1242.

In a letter published in 1935 in the journal *Nature*, Ronald Fisher, one of the fathers of modern statistical theory, described the phenomenon that had become known as 'errors of the second kind'—that is, 'the logical fallacy of believing that a hypothesis has been proved to be true, merely because it is not contradicted by the available facts . . . .'.[1] He would go on to write, 'It would . . . add greatly to the clarity with which the tests of significance are regarded if it were generally understood that tests of significance, when used accurately, are capable of rejecting or invalidating hypotheses, in so far as these are contradicted by the data; but that they are never capable of establishing them as certainly true.' In the realm of randomized clinical trials, errors of the second kind, more commonly referred to as Type II error, are typically addressed during the assessment of statistical power for a given sample size. However, Type II error remains a critical consideration in the interpretation of trial results, particularly in subgroup assessments, which invariably are less highly powered than parent studies. Eighty years after Fisher's description of Type II error, Costa *et al.* provide a new opportunity to examine critically what constitutes sufficient evidence to declare that a treatment has no beneficial effect, this time in the context of evaluating the risks and benefits of prolonged dual antiplatelet therapy after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes (ACS) vs. those with stable coronary artery disease (CAD).[2]

Patients with ACS are at higher risk for subsequent ischaemic events in both the short and long term than those with stable presentations, and may therefore derive greater benefit from extended duration dual antiplatelet therapy.[3] As a reflection of the perceived difference in risk and benefit of dual antiplatelet therapy among ACS vs. stable CAD patients, the European revascularization guidelines recommend 12 months of therapy after PCI in ACS patients, compared with 6 months for drug-eluting stent-treated stable CAD patients.[4] In light of these differences, Costa *et al.* examined whether the impact of 6 vs. 24 months of dual antiplatelet therapy on ischaemic and bleeding outcomes was similar for ACS vs. stable CAD patients in the PRODIGY trial, a randomized open-label trial that included 1465 patients with ACS and 505 patients with stable CAD. The study sought to answer three primary questions. (i) Does long-term vs. short-term dual antiplatelet therapy reduce ischaemic events in ACS and stable CAD patients? (ii) Does long-term therapy increase bleeding consistently in ACS and stable CAD patients? (iii) Is the effect of long- vs. short-term therapy on net clinical adverse events (NACE), i.e. the combination of death, myocardial infarction, cerebrovascular accident, or BARC (Bleeding Academic Research Consortium) 2, 3, or 5 bleeding, similar for ACS and stable CAD patients? The evidence provided by the study in answer to each of these questions requires careful interpretation.

Does long-term dual antiplatelet therapy reduce ischaemic events in ACS and stable CAD patients?

The PRODIGY trial randomized patients 30 days after PCI to 6 vs. 24 months of dual antiplatelet therapy.[5] The trial was powered to detect a 40% reduction in ischaemic events occurring between

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1 and 24 months. However, because treatment was identical between study arms for the first 5 months after randomization (all received dual antiplatelet therapy during this time), events occurring during that time period could only serve to dilute any observable treatment effect. In examining the rates at which events accumulated, more than one-third of events in the trial occurred within the first 5 months after randomization. As such, continued dual antiplatelet therapy would have needed to eradicate the vast majority of events after 6 months in order to achieve a 40% reduction over the 1–24 month period of follow-up. Based on this design, the primary study was almost certainly underpowered to detect even greater differences in ischaemic events than what was initially envisaged.

Issues of Type II error afflicting primary studies can only become compounded in the examination of subgroups. In the study of Costa *et al.*, long-term dual antiplatelet therapy was associated with no statistically significant difference in death, myocardial infarction, or cerebrovascular accident in either the ACS or stable CAD group. However, among ACS patients, the 95% confidence intervals (CIs) for the treatment effect include the potential for a >30% reduction in the primary endpoint. In the stable CAD group, representing a modest total of 505 patients, CIs are even wider and provide little evidence to support definitive conclusions regarding the presence or absence of ischaemic benefit for long-term dual antiplatelet therapy in either the ACS or stable CAD populations.

Does long-term dual antiplatelet therapy increase bleeding consistently in ACS and stable CAD patients?

Several trials, including PRODIGY, have provided evidence that treatment with dual antiplatelet therapy increases bleeding complications.[5–7] Whether stable and unstable patients differ with regard to the long-term bleeding risks associated with continued dual antiplatelet therapy is a matter of current debate. Although bleeding rates in ACS patients are typically higher than those of patients undergoing elective PCI, the differences are often due to higher rates of early bleeding, including procedure-related bleeding.[8] In the PRODIGY trial, long-term dual antiplatelet therapy appeared to lead to a larger increase in bleeding events in stable CAD patients [hazard ratio (HR) 5.37, 95% CI 1.84–15.65, $P = 0.002$] compared with ACS patients (HR 1.75, 95% CI 1.11–2.74, $P = 0.01$). The data add to an emerging picture that patients with acute presentations, particularly those with ST-elevation myocardial infarction,[9] may be more resistant to the long-term bleeding risks of more intensive antiplatelet therapy.

Notably, more than half of all bleeding events in the PRODIGY trial were classified as BARC type 2 bleeding, minor (albeit actionable) bleeding that has been found to be prognostically unimportant in a secondary analysis of this trial.[10] Moreover, minor bleeding episodes not requiring any blood transfusion or intervention may be subject to biased ascertainment in an unblinded study such as this. Appropriately, the authors conducted additional analyses that included only BARC type 3 and 5 bleeding episodes. Using these categories, among ACS patients, 23 bleeds (3.1%) occurred in the 24-month treatment group compared with 17 (2.3%) in the 6-month group ($P = 0.34$), while for stable CAD patients, 11 bleeds (4.3%) occurred in the 24-month group compared with 2 (0.8%) in the 6-month group ($P = 0.03$). Strictly speaking, however, the interaction terms assessing the difference in bleeding effect of long-term therapy among ACS vs. stable CAD patients were not statistically significant regardless of the bleeding definitions employed, highlighting both the underpowered nature of these hypothesis-generating assessments (Type II error) and the potential for overstating the importance of borderline significant findings based on a small number of events, in the context of testing multiple hypotheses (Type I error).

Is the net effect of long- vs. short-term therapy, weighing ischaemic and bleeding events, similar for ACS and stable CAD patients?

When treatments in question can lead to distinct benefits and risks for patients—and particularly when there are trade-offs involved—there is an intuitive desire to combine these different effects into a single measure that summarizes the overall impact of treatment. Such a desire has led to the growing practice of using composite endpoints to assess 'net clinical benefit' in studies evaluating different durations of dual antiplatelet therapy.[11–14] These endpoints typically take the approach of simply tallying bleeding and ischaemic events into a single measure. Unfortunately, this tactic is fundamentally flawed, as it assumes that all events in the composite are of equal weight and violates the requisite concordance of contributing endpoints for interpretation of the composite. In the PRODIGY trial, the net adverse event endpoint included events as serious as death and as minor as BARC type 2 bleeding.

The scientific field of decision analysis is devoted to quantifying systematically and transparently the relative impact of different disease conditions and health states in order to identify optimal decisions in the presence of competing risks and benefits. Such approaches require that appropriate weights be assigned to different outcomes based on their prognostic impact and their importance to patients, accounting for potential uncertainty in each of these inputs.[15] While the practice of employing net clinical benefit endpoints has the appeal of simplicity, the assumptions behind this approach are so far removed from clinical plausibility to the point of rendering them unmeaningful.

Moving beyond the impasse

The identification of patient subgroups who will benefit from long-term dual antiplatelet therapy as well as those who can safely forgo it remains an important goal for the millions of patients undergoing coronary stent procedures each year. However, making progress in this quest requires that we first acknowledge that small trials cannot be used to declare that extending dual antiplatelet therapy provides no ischaemic benefit, 'merely because it is not contradicted by the available facts' provided by unpowered assessments, as Fisher once warned. The absence of evidence should once again not be considered evidence of absence, particularly in the presence of strong

evidence demonstrating protection against stent thrombosis and myocardial infarction with long-term dual antiplatelet therapy in the DAPT Study—the only study to date that was powered to make this assessment.[7] In the DAPT Study, the reduction in ischaemic events and the increase in bleeding with long-term treatment were consistent in both higher risk patients ($n = 4799$) enriched with ACS and low risk patients ($n = 5162$). Ultimately, determining how we weigh ischaemic benefits against the bleeding risks, while not denying the existence of either, will be critical to improving the management of our patients.

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