EDITORIALS

The Evolving Post-PCI Antithrombotic Therapies

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Prolonged dual antiplatelet therapy is the treatment of choice for patients with an acute coronary syndrome who have undergone percutaneous coronary intervention (PCI) with a drug-eluting stent.[1,2] The rationale is anchored in the understanding that drug-eluting stents impair the vascular healing process, because exposure of the metal in the stent serves as a nidus for stent thrombosis.[2,3] The technology for drug-eluting stents has evolved from early devices, which were associated with heightened thrombotic risk, to third- and fourth-generation devices.[2,4] These newer stents have been modified to retain their anti-restenosis properties while shortening their drug-eluting properties to minimize the exposure of the metal to platelets and fibrin.[2] Thus, they may allow for a shorter duration of dual antiplatelet therapy before the switch is made to single antiplatelet therapy.

Patients who are most vulnerable to the risks associated with prolonged dual antiplatelet therapy are those at heightened bleeding risk,[4,5] such as patients with an age of 75 years or older, a clinical indication for oral anticoagulant, stroke or transient ischemic attack, systemic conditions associated with increased bleeding risk (including cancer), long-term treatment with glucocorticoids and nonsteroidal antiinflammatory medications, a previous bleeding event, or documented anemia or receipt of blood transfusion. These criteria may form the basis for a shorter duration of dual antiplatelet therapy.

The trial by Valgimigli and colleagues, the results of which are now published in the *Journal*,[6] is a welcome exploration of the population of patients who are at high bleeding risk after the placement of a drug-eluting stent. This pragmatic trial involved 4579 patients, the majority of whom had stable heart disease (51% of the patients), who were randomly assigned to receive 30 days or 6 months of dual antiplatelet therapy (i.e., abbreviated therapy or standard therapy) and were then followed up to 1 year. The choice of the single antiplatelet therapy after randomization in the abbreviated-therapy group, at 30 days after PCI, was decided by the investigator and was predominantly clopidogrel (in 56% of the patients) or ticagrelor (in 14%); 31% of the patients in this group received aspirin as single antiplatelet therapy, a finding consistent with those from recent trials.[7,8]

The first of the three ranked primary outcomes was a composite outcome of net adverse clinical events that incorporated both ischemic events (death, myocardial infarction, and stroke) and major bleeding (defined as Bleeding Academic Research Consortium [BARC] type 3 or 5). The cumulative incidence was 7.5% in the abbreviated-therapy group and 7.7% in the standard-therapy group, which met the noninferiority criteria established for the trial (P<0.001). These findings were driven by a cumulative incidence of major bleeding that was approximately 30% lower in the abbreviated-therapy group than in the standard-therapy group.

The trial incorporated noninferiority testing for the first and second ranked primary outcomes, which deserves further discussion. Although noninferiority trials are a good choice for testing abbreviated treatment strategies against standard treatment strategies, their interpretation can be challenging.[9,10] Noninferiority testing requires a determination of an acceptable trade-off to declare the findings to be sufficiently similar to support the choice of a shorter duration of therapy. In this trial, the authors declared that noninferiority would be established if the upper boundary of the 95% confidence interval for the absolute difference for the first primary outcome of net adverse clinical events did not exceed 3.6 percentage points at an estimated cumulative incidence of 12.0% in the control group. In previous trials, tighter and relative boundaries for noninferiority testing have been advocated to preserve the majority of the benefit observed after stenting.[9,10]

Unfortunately, tighter boundaries require a larger trial population. Uncertainty arises when the event rate is lower than predicted, because an absolute upper margin is proportionally larger at a lower event rate. This uncertainty is highlighted by the fact that the actual cumulative incidence in the standard-therapy group was 7.7% — in a trial in which an absolute upper limit of 3.6 percentage points in the confidence interval is a higher-than-acceptable trade-off. Fortunately, the point estimate for this primary outcome was in favor of abbreviated dual antiplatelet therapy, although the upper boundary for the confidence interval for the absolute difference was up to 1.33 percentage points worse in absolute terms with abbreviated therapy than with standard therapy. The upper boundary of the confidence interval for the hazard ratio was consistent with a result up to 20% worse in relative terms with abbreviated therapy than with standard therapy.

These observations also apply to the composite ischemic outcome (the second ranked primary outcome), for which the observed cumulative incidence was 6.1% in the abbreviated-therapy group, as compared with 5.9% in the standard-therapy group, which was lower than the expected cumulative incidence of 8.0% in the control group. Although this finding was also noninferior, the wide 95% confidence interval for the hazard ratio encompassed a potential 30% higher incidence in the abbreviated-therapy group than in the standard-therapy group, which, although still statistically noninferior, is higher than some would consider to be a reasonable trade-off between bleeding events and ischemic events.

The 1669 patients who were treated with oral anticoagulation represent a trial-within-a-trial concept because they were assigned to receive treatment durations that were different from those in the remaining patients. In the abbreviated-therapy group, these patients continued to receive antiplatelet monotherapy for up to 6 months, which was similar to the regimen in the overall trial. However, these patients in the standard-therapy group received dual antiplatelet therapy for 3 months, as opposed to 6 months, and then switched to monotherapy. There was no sample-size adjustment for this subgroup in the protocol. The effect of this important subgroup on the overall trial results is not yet available but will be important for the full interpretation of the trial results.

The finding that the use of abbreviated dual antiplatelet therapy may be reasonable in patients at increased bleeding risk should also be viewed in the context of the use of the Ultimaster drug-eluting stent (Terumo). However, abbreviated therapy may not be applicable to all later-generation drug-eluting stents, so caution should be used before short dual antiplatelet therapy is adopted more broadly.

The findings of Valgimigli and colleagues are important and move us toward a shorter and simpler antithrombotic strategy after PCI. Concomitant shorter antiplatelet monotherapy in the context of chronic disease after the implantation of a drug-eluting stent represents a major shift. This news is welcome for patients at high risk for bleeding after stent placement.

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Clinical Translation of Basic Science in Asthma

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Basic science has enriched our understanding of the pathophysiology of severe asthma. Clinical translation of these discoveries has resulted in biologic therapies that target key components of asthma-related disease pathways. For example, identification and validation of biomarkers such as elevated blood eosinophil counts made it possible to implement tailored biologic treatments targeting the function of cytokines such as interleukin-5, interleukin-4, and interleukin-13.[1] The success of these strategies has prompted investigations of other molecules that are active in the pathogenesis of severe asthma. The results of two pertinent trials are reported in this issue of the *Journal*.

In a randomized, controlled, phase 2a trial, Brightling and colleagues[2] assessed the monoclonal antibody risankizumab in the inhibition of the cytokine interleukin-23, which is implicated in the proliferation of CD4+ type 17 helper T (Th) lymphocyte cells, neutrophil recruitment, Th2 cytokine production, and delayed resolution of inflammation.[4] The authors hypothesized that blocking the activity of interleukin-23 would reduce the risk of severe asthma exacerbations. However, asthma-related outcomes were worse in the risankizumab group than in the placebo group. Downstream biologic responses to risankizumab were detectable (altered interleukin-23 gene–related expression was observed), which implies attenuation of apposite pathways, nonetheless without discernible clinical benefit.

Wechsler and colleagues[3] evaluated the monoclonal antibody itepekimab against the alarmin interleukin-33. Itepekimab was also combined with dupilumab (an inhibitor of interleukin-4 receptor [R] α) to block both upstream (interleukin-33) and downstream (interleukin-4 and interleukin-13) pathways. The primary end point was an event indicating loss of asthma control.[3] Both the itepekimab and dupilumab monotherapies led to a lower incidence of events indicating loss of asthma control and to improved lung function. However, the combination of itepekimab and dupilumab was not superior to either treatment alone. Clinical translation of manifestly sound scientific rationale did not result in the anticipated success — why not?

The key question is whether the trial design allowed for the detection of therapeutic benefit. Both trial designs were similar to those of previous successful trials that targeted individual cytokines in severe asthma.[1] Furthermore, patient numbers and therapeutic doses appeared to be adequate. In the trial of risankizumab, the dose was selected on the basis of demonstrated efficacy in psoriasis and Crohn's disease.[5,6] Itepekimab therapy showed a benefit with respect to improved outcomes that was broadly similar to that of dupilumab therapy, and it is likely that a lack of additive benefit for the combination of biologic agents cannot be attributed to underdosing of itepekimab.

Our understanding of basic science provides several clues as to why these therapies did not work as predicted (Fig. 1). Targeting the interleukin-23 and Th17 axis with risankizumab can reduce development of pathogenic Th17 cells; however, interleukin-23 is not critical for the development of Th17 cells and, in contrast to pathways operated by interleukin-5 and interleukin-4Rα, interleukin-23 has only a limited auxiliary role in amplifying type 2 responses.[4,7] It is possible that the trial conducted by Brightling and colleagues failed because signaling through alternative disease pathways nullified