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EDITORIAL COMMENT

Optimal $P2Y_{12}$ Inhibitor for Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction

Network Meta-Analysis in the Data-Free Zone: Do You Believe in Magic?*

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With the availability of an increasing number of potent antiplatelet and antithrombotic agents, clinicians are offered a large number of choices and potential drug combinations to be applied during percutaneous coronary intervention (PCI) as well as during follow-up to reduce risks associated with atherothrombotic events. In the absence of head-to-head randomized clinical trial for each available drug, Rafique et al. (1) in this issue of *JACC: Cardiovascular Interventions*, have performed a network meta-analysis aiming to compare the efficacy and safety of antiplatelet agents—clopidogrel, prasugrel, ticagrelor, and cangrelor—in the context of primary PCI for ST-segment elevation myocardial infarction (STEMI).

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SUMMARY OF CLAIMS

On the basis of primary and secondary endpoint analyses in the hospital, at 1 month and at 1 year, the findings were mostly anticipated, but some reported observations are provocative. Not surprisingly, prasugrel and ticagrelor were more efficacious than clopidogrel at 1 year, whether used at standard or high dose. Major bleeding was low (2.61% at 1 month, 4.32% at 1 year) and did not differ among prasugrel, ticagrelor, and clopidogrel, which came as the first surprise. The investigators assume that bleeding rates are lower in younger patients with STEMI than in those with non-ST-segment elevation myocardial infarction, who often have comorbidities. Even more provocative, prasugrel was superior to ticagrelor with respect to major adverse cardiac events at 1 month and all-cause mortality at 1 month and 1 year. Data on cangrelor were too few to allow a significant conclusion.

On the basis of their analysis, the investigators offer a number of strong statements. Judge for yourself:

- "The principle findings of our network analysis are that at 1-month and 1-year follow-up, prasugrel was associated…with lower mortality and major adverse cardiac events than ticagrelor."

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- "Prasugrel was superior to ticagrelor, particularly in conjunction with bivalirudin and drug-eluting stents."
- "These results point to better outcomes with prasugrel without significant increase in major bleeding."

As a result, Rafique et al. (1) recommend that a direct randomized comparative trial be performed in this patient subset. If shown to be true, the superiority of prasugrel to ticagrelor would imply that both U.S. and European practice guidelines may need to be revisited (2,3).

FACTS AND FIGURES

Primary PCI studies performed between 2003 and 2014 were included, involving up to 88,402 patients; of these, 32,005 were enrolled in 14 randomized trials and 56,397 in registries or observational studies. The overall event rate was 5.74% (n = 5,077), higher in nonrandomized (n = 3,416 [6.06%]) than in randomized studies (n = 1,661 [5.19%]). Multiple efficacy and safety endpoints were compared, with fluctuating denominators: all-cause mortality, new myocardial infarction, target vessel revascularization, their combination as major adverse cardiac events, cardiovascular mortality, stroke, stent thrombosis, any bleeding, and major bleeding. Adjudication of new myocardial infarction after an index STEMI is associated with known definition instability within and among studies (4). Data on cardiovascular death, target vessel revascularization, any bleeding, and stroke were not robust. Three time points were considered, with varying patient denominators for each event. For all-cause mortality, data were available for 19,438 patients in the hospital, 60,510 patients at 1 month, and 41,766 patients at 1 year. As a result, event rates tended to fluctuate: for instance, mortality was 3.16% in the hospital, 2.47% at 1 month, and 5.51% at 1 year; the rate of target vessel revascularization went from 3.54% in the hospital through 1.78% at 1 month to 5.00% at 1 year.

Thus, the conclusions that prasugrel and ticagrelor are superior to clopidogrel on one hand and that prasugrel is superior to ticagrelor on the other hand are based on somewhat unstable foundations. Of note, the reported findings pertain essentially to primary PCI, with limited if any information on patients treated by pharmacoinvasive strategies or with late presentation.

Let us now discuss whether the present analysis and its conclusions are robust enough to support a change in guidelines and practice. To this end, one must review specific methodological aspects of Bayesian network meta-analyses.

VALUE AND LIMITATIONS OF THIS NETWORK META-ANALYSIS

Network meta-analyses have been introduced as a way to address the limitations of conventional pairwise meta-analyses when head-to-head trials are either lacking or are limited in the overall number of patients included, or when multiple treatments warrant simultaneous assessment to enable their informative ranking. As such, these complex studies have the potential to play an important role in the improvement of the decision-making process by optimizing the use of existing data in fields in which large-scale randomized trials comparing multiple treatment simultaneously are unlikely to ever be performed. The "magic" of this methodology is that it can potentially anticipate the outcome of trials that have not been performed. As such, these analyses aim at reducing the size of "data-free" zones.

So is the evidence provided by the network meta-analysis of Rafique et al. (1) sufficient to warrant a change of current guideline recommendations (2,3) and establish a priority for prasugrel over ticagrelor in patients with STEMI undergoing primary PCI? Our short answer is no.

To come to the conclusion that prasugrel appears superior to ticagrelor at 1 month and 1 year, the investigators used direct evidence from 4 small, head-to-head pharmacodynamic trials investigating surrogate endpoints (with fewer than 200 patients cumulatively randomized). These limited data were pooled with a larger set of nonrandomized data from post hoc analyses of studies that were not specifically designed to compare $P2Y_{12}$ antagonists. Importantly, most of these studies reported clinical endpoints only up to 30 days, and the number of analyzable events was small. On this background, a vast proportion of the investigators' conclusions, particularly (but not only) those pertaining to 1-year follow-up, are sustained by the "indirect" evidence generated by means of the Bayesian framework, with the obvious unknowns and potential bias of comparisons across studies that included different populations, definitions, protocols, and practices. Unfortunately, the investigators did not report sensitivity analyses contrasting the direct and indirect evidence from the network, nor a systematic bias assessment including reporting of the quality of the studies analyzed. Also missing is important information about heterogeneity and publication bias. In addition, the choice of detaching the nodes of clopidogrel and ticagrelor into

different strategies on the basis of dose (i.e., standard vs. high) or timing (i.e., upstream), although intuitive and appealing from a clinical standpoint, may have introduced further analytic challenges in the stability of the Bayesian framework and may jeopardize the power of specific comparisons within the network. All of these issues were obviously amplified in the subgroup analyses, which makes it problematic to accept the investigators' contention that prasugrel works better than ticagrelor, particularly in patients on bivalirudin or treated with drug-eluting stents.

A robust answer to the question of whether 1 of the new $P2Y_{12}$ blockers is better for primary PCI can be provided only by a dedicated randomized trial in patients with STEMI. However, how badly does one need the results of such trial in order to address current clinical challenges?

WHICH RANDOMIZED TRIAL NEXT?

As appropriately mentioned by Rafique et al. (1), oral antiplatelet agents suffer from severe limitations in patients with STEMI, which can be overcome with the use of intravenously administered agents.

Reduced absorption due to delayed intestinal transit, nausea and vomiting, and potential drug interactions with morphine all represent specific challenges to the efficacy of oral $P2Y_{12}$ antagonists in the setting of STEMI (5). This is reflected by the large proportion of patients who still exhibit high platelet reactivity 2 h after a loading dose of clopidogrel, prasugrel, or ticagrelor (6,7). In many patients with STEMI who are pre-treated with antiplatelet agents upstream of primary PCI, prasugrel or ticagrelor still requires 4 to 6 h to achieve a full platelet-inhibitory effect (7), which exceeds the short time window for reperfusion and myocardial salvage. As a result, primary PCI is frequently performed during this vulnerability window, in the absence of adequate platelet inhibition. This may explain in part the unsatisfactory reperfusion outcomes observed in a nonnegligible proportion of patients with STEMI after primary PCI.

Pharmacodynamic studies have suggested that prescribing crushed ticagrelor or prasugrel induces more rapid platelet inhibition. This faster onset of action may partially bridge the gap between the oral intake of intact tablets and their delayed onset of action (8,9). Along this line, intravenous compounds may be even more effective in bridging patients to the full effect of oral antiplatelet agents (10). Glycoprotein IIb/IIIa antagonists are currently recommended mostly for bailout use in STEMI, with a few exceptions (2). Against this recommendation, the utility of an upstream "blocking and bridging" strategy (i.e., bolus with no infusion) with glycoprotein IIb/IIIa antagonists has been proposed to improve the level of platelet inhibition when the action of oral $P2Y_{12}$ antagonists is anticipated to be deficient or delayed (11,12). In contrast, intravenous cangrelor has the potential to become the "in-cath-lab" $P2Y_{12}$ inhibitor of choice for patients with STEMI undergoing primary PCI to promote faster platelet inhibition, with a possible benefit on reperfusion outcomes.

Direct comparative studies between prasugrel and ticagrelor have only been performed in small biological studies, showing a comparable degree of platelet inhibition (7). The ongoing ISAR-REACT 5 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) trial (NCT01944800) will compare the 2 drugs in patients with acute coronary syndrome. However, this study will not focus on patients with STEMI but will include those with non–ST-segment elevation acute coronary syndromes as well, and the 2 drugs will be used as tested in their original phase 3 study, after angiography in non–ST-segment elevation acute coronary syndromes and upstream in STEMI for prasugrel, upstream in any patient for ticagrelor. Therefore, it will be difficult to assign any difference in results to the drug itself or to the treatment strategy. Last, it seems unlikely that a large enough dedicated comparative randomized trial will ever be performed, for 2 important reasons: funding of such a trial will be difficult, and, most important, today, identifying a winner among oral antiplatelet drugs with delayed onset of action, be it prasugrel or ticagrelor, is no longer a major, clinically relevant issue.

BURNING CLINICAL QUESTIONS AND RELEVANCE FOR PRACTICE

In any urgent clinical setting, oral drugs have obvious limitations, as summarized earlier, and in the STEMI setting, intravenous drugs such as glycoprotein IIb/IIIa antagonists and newer $P2Y_{12}$ blockers such as cangrelor could be the solution to overcome those limitations. However, today's dilemma is that cangrelor has not been used in clinical trials together with new oral antiplatelet agents. Because cangrelor is not recommended in patients who have been orally pre-treated with new $P2Y_{12}$ antagonists, its introduction in local STEMI networks will pose new questions, including the comparative effectiveness and safety of pre-hospital use of prasugrel or ticagrelor versus "in-cath-lab" use of intravenous compounds. Evidence is lacking about the benefit of intravenously administered drugs (both glycoprotein IIb/IIIa

antagonists and cangrelor) in primary PCI on top of more potent oral $P2Y_{12}$ blockers. At the same time, all the evidence of benefit with new oral drugs has been obtained against clopidogrel.

The new treatment paradigm that needs to be validated by proper clinical trials can be sketched as follows. This strategy involves a synergy of efficacy and safety between intravenously and orally administered agents. In patients with acute thrombotic events, use of an antiplatelet agent with a fast onset of action, a predictable effect, and a fast offset is the best option, which will be provided by an intravenously administered drug. During primary PCI for STEMI and the early in-hospital phase, the intravenous drug will cover the gap in platelet inhibition before the full effect of the oral drug. As to improving long-term prognosis, the intensity and duration of oral antiplatelet therapy will be tailored to each patient's need, balancing ischemic and bleeding risks.

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