Canadian Journal of Cardiology 35 (2019) 1283–1285

Editorial

"Ticagrelor or Prasugrel, Doctor?" The Basis for Decision in Clinical Practice

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See article by Welsh et al., pages 1377–1385 of this issue.

Selecting the best long-term antithrombotic regimen after ST-segment elevation myocardial infarction (STEMI) in patients treated with the use of primary percutaneous coronary intervention (pPCI) is complex. An exponentially growing body of literature provides clinicians with validated tools to support individualization of dual-antiplatelet therapy (DAPT) strategies based on patients' characteristics to optimize the trade-off between ischemia and bleeding.[1] Huge strides have been made to tailor antithrombotic management after STEMI, yet the answer to a simple conundrum encountered by cardiologists on a daily basis remains elusive: "Ticagrelor or prasugrel, doctor?"

We know that DAPT with aspirin and a P2Y12 receptor antagonist prevents recurrent thrombotic events after acute coronary syndromes treated with PCI.[2] We also know that both ticagrelor and prasugrel offer incremental ischemic protection over clopidogrel at the cost of a higher risk of major bleeding.[3,4] Within this background, international guidelines consistently recommend DAPT with the use of ticagrelor or prasugrel after pPCI, unless both are contraindicated.[5-7] What we do not know, however, is whether one of the latter 2 agents prevents more clinical events than its counterpart in the long run.

The only randomized controlled trial comparing clinical outcomes between ticagrelor and prasugrel in patients with acute coronary syndrome (ACS) treated with the use of PCI was the Comparison of **Pra**sugrel and Tica**g**relor in the Treatment of Ac**ute** Myocardial Infarction (PRAGUE-18) trial. The study was terminated early for futility roughly halfway through the recruitment target, after 1230 participants were randomized to either agent (89% had a STEMI at the time of enrollment). Virtually identical rates of the primary end point, a composite of all-cause death, reinfarction, stroke, serious bleeding requiring transfusion or prolonging hospitalization, or urgent target vessel revascularization were observed at 7 days in both groups (4.1% ticagrelor vs 4.0% prasugrel; $P = 0.939$). Rates of the individual ischemia and bleeding end points were also closely similar. At 1 year, rates of the composite of cardiovascular death, myocardial infarction (MI), or stroke were not materially different either.[8]

After PRAGUE-18, the answer to our quest to find the best long-term P2Y12 antagonist after pPCI for STEMI remains unresolved because: 1) the 1-year comparison between both agents was contaminated by a significantly higher proportion of participants in the ticagrelor group who switched to clopidogrel after discharge for economic reasons; and 2) the study was grossly underpowered based on a comparison of the expected and observed event rates.

Although it is informative, as a result of these limitations the PRAGUE-18 trial remains inconclusive. Lacking solid evidence from properly designed randomized controlled trials, observational studies tried to inform clinical practice on this conundrum. In this issue of the *Journal*, Welsh et al. present a post hoc analysis of the **Th**r**o**mbec**t**omy with PCI versus PCI **Al**one in Patients with STEMI Undergoing pPCI (TOTAL) trial exploring the impact of prasugrel and ticagrelor on ischemia and bleeding end points in patients treated with the use of pPCI.[9] Importantly, because the randomization scheme in TOTAL did not include P2Y12 inhibitor type, antiplatelet agent choice was left to the discretion of the treating physician. Reflecting the patterns of practice at the time the study was conducted, most of the 9932 participants included in this secondary analysis were discharged on clopidogrel (65.5%), and a minority were discharged on ticagrelor (22.0%) or

Received for publication May 6, 2019. Accepted May 21, 2019.

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See page 1285 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.05.027

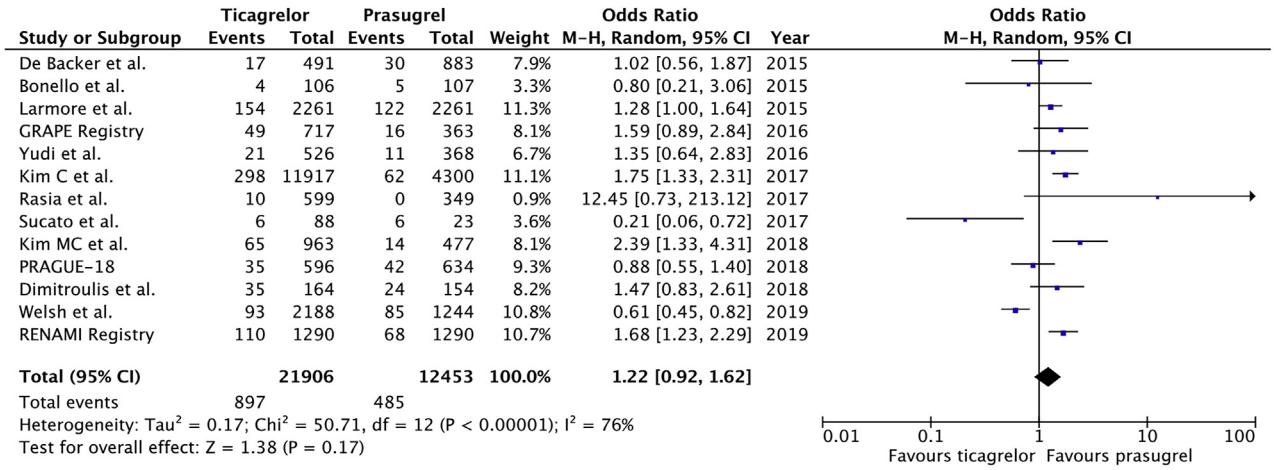

Figure 1. Comparative effectiveness of ticagrelor and prasugrel after PCI for acute coronary syndrome. Details of the studies are available in Supplemental Table S1. MH, Mantel-Haenszel.

prasugrel (12.5%). Baseline characteristics of the patients selected for each treatment resembled those of current clinical practice, with patients selected for a treatment with prasugrel being significantly younger, more frequently male, and less likely to have suffered a previous stroke. The primary end point was a composite of cardiovascular death, recurrent MI, cardiogenic shock, or new or worsening New York Heart Association functional class IV heart failure. After propensity-score adjustment, ticagrelor was associated with a 4.6% rate of the primary end point at 12 months, lower than both clopidogrel and prasugrel (8.5% and 7.1% respectively; $P = 0.02$ for both pairwise comparisons). Yet, when only the thrombotic complications expected to be prevented by more potent platelet inhibition were considered (ie, composite end point of cardiovascular death, MI, or stroke), there was no significant difference among the 3 agents. Rates of bleeding events were similar between prasugrel and the other 2 agents. Unexpectedly, ticagrelor was associated with fewer major bleeding events compared with clopidogrel (1.1% vs 1.8%, respectively; adjusted $P < 0.01$) but with an excess of minor bleeding (10.0% vs 6.1%, respectively; adjusted $P < 0.001$).

Welsh et al. should be congratulated for their effort to shed light into this evidence-free zone in cardiovascular medicine. Yet the observational design of the analysis raises several limitations to clinical extrapolation of these findings. First, antiplatelet agent selection by the treating physician was susceptible to a selection bias, which is impossible to completely adjust for even with the most complex statistical model. Perceived higher bleeding risk attributed to patient characteristics that were not captured within the TOTAL dataset, including a history of major bleeding or concomitant chronic oral anticoagulation, might have driven the choice of clopidogrel over more potent agents, explaining the higher rate of major bleeding observed with clopidogrel.[10,11] Second, DAPT duration was not reported and may have varied across treatment groups. At the time that the study was conducted, patients at higher risk of bleeding were more likely to receive a bare-metal stent (BMS) to allow shorter DAPT duration. Because substantially more patients in the clopidogrel group were treated with the use of a BMS, it is also possible that more of these patients were treated with DAPT durations of < 1 year, losing the ischemia protection conferred by the P2Y12 antagonist. Third, the statistical penalties for multiple comparisons applied by the investigators might have been paid with inconsistent findings that likely reflect a residual play of chance rather than a true causal association.

Indirect comparisons between thienopyridines and ticagrelor in the literature have provided inconsistent results.[12,13] In fact, when we included the findings of Welsh et al. with results in the previous literature on the subject in an updated meta-analysis, we could not find conclusive evidence for a difference in efficacy of the 2 potent P2Y12 antagonists after PCI for acute coronary syndrome (Fig. 1, Supplemental Table S1, Supplemental Fig. S1, and Supplementary Material). The suggestion from the Welsh et al. data that ticagrelor may be superior compared with the other 2 P2Y12 inhibitors may be biologically plausible and finds supports in mechanistic studies showing multiple beneficial pleiotropic properties of ticagrelor on endothelial function beyond mere platelet inhibition. However, this hypothesis should ultimately be confirmed in the context of a well performed and well powered randomised controlled trial. The ongoing **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **R**apid **E**arly **A**ction for **C**oronary **T**reatment (ISAR-REACT) 5 trial (NCT01944800; expected completion in January 2021) is currently randomizing 4000 patients with an ACS planned for an invasive strategy to maintenance doses of either ticagrelor or prasugrel and may shed further light on this controversial topic.[14] Until then, we think that both drugs can safely be used interchangeably in the absence of known hypersensitivity or side-effects. If a previous stent thrombosis or MI occurred while treated with one of these agents, its counterpart should, however, be favoured.[5] Also, ticagrelor is specifically contraindicated in patients taking a strong CYP3A4 inhibitor, and prasugrel is contraindicated in patients ≥ 75 years of age, with a history of transient ischemic attack or stroke, or with a body weight < 60 kg.

While awaiting the important results of the ISAR-REACT 5 trial, are there other unresolved issues to be addressed to optimize results after pPCI? Sure there are. One question that

remains open is the optimal aspirin dose for secondary prevention after a cardiovascular event. The **A**spirin **D**osing: **A** **P**atient-Centric **T**rial **A**ssessing **B**enefits and **L**ong-Term **E**ffectiveness (ADAPTABLE; NCT02697916) trial aims to answer this question, and its results are expected to be available in late 2020.[15,16] Another important point to be explored is the practice of prescribing triple-antithrombotic therapy (DAPT plus an oral anticoagulant) in patients with STEMI and apical dysfunction, which is entrenched in the culture of Canadian cardiologists.[17] Although this practice is not supported by clinical evidence and guidelines recommendations, the multicenter Management of STEMI with Anterior Wall **M**otion **A**bnormalities Usin**g** Triple Versus Double Antithrombot**ic** Therapy (MAGIC) observational study will likely provide an answer to this question and is expected to be completed in 2019.[18]

Meanwhile, digesting the results provided by the new analysis by Welsh et al., our suggestion is to use common wisdom when selecting a P2Y12 inhibitor. The current status of the evidence allows an interchangeable use of ticagrelor or prasugrel after pPCI unless specific contraindications or side-effects are present. While awaiting new data in this exciting field, to the question "Ticagrelor or prasugrel, doctor?" the best answer may well be: "Keep it simple!"

Funding Sources

Dr Marquis-Gravel is supported by the Canadian Institutes of Health Research and the Montreal Heart Institute Foundation.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.05.027.