Letters

TO THE EDITOR

Microvascular Function in Ischemic Heart Disease
There May Be Room for Improvement

We have read with great interest the papers written by Sara et al. (1) and Patel et al. (2), as well as the editorial by Yoo and Samady (3), related to physiological testing in ischemic heart disease. Knowledge of the physiological basis of ischemic heart disease is extensive, and few gaps can be found with regard to traditional coronary risk factors, the development and progression of coronary plaques, and the processes of atherothrombosis that can affect the coronary tree. Meaningful improvements in noninvasive tests provide us with invaluable screening information, and coronary angiography reinforced with fractional flow reserve and instantaneous wave-free ratio allow us to decide the most appropriate approach. Finally, the exceptional progress in the pharmacological armamentarium combined with great advances in percutaneous and surgical techniques have achieved very successful results. There is, however, a lack of information related to the phenomena that occur in the microvasculature, and there is also some pessimism because the studies carried out to date that explored potential effective therapies have not brought positive results. In our opinion, there may be room for improvement in those patients with obstructive coronary disease who require long-term antiplatelet therapy, and the benefits of ticagrelor in comparison with other antiplatelet agents should be investigated. Its molecular similarity to adenosine increases the plasma levels of the latter (4), and this action could have a beneficial effect in decreasing the microvascular resistance. The strong relationship between microvascular resistance and prognosis has been previously demonstrated. In the PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial, as is pointed out in the main paper, there was no apparent heterogeneity in the efficacy of ticagrelor at either dose with respect to the risk of the primary composite endpoint across all of the major subgroups: age, sex, race, weight, type of index myocardial infarction, time from qualifying myocardial infarction to randomization, history of percutaneous coronary intervention, presence or absence of diabetes, presence or absence of multivessel coronary disease, presence or absence of chronic kidney disease, aspirin dose, and geographic region. However, the heterogeneity in the efficacy of ticagrelor in relation to the presence of high microvascular resistance has never been explored. The annual risk for stable patients after the first 12 months when treated with aspirin as the only antithrombotic drug in addition to an optimal secondary prevention is only on average 1.0% to 2.0% for nonfatal myocardial infarction, 1.0% for cardiovascular mortality, 0.5% for ischemic stroke, and 0.5% for stent thrombosis (5), and it may be difficult to demonstrate benefit when we compare different antiplatelet strategies in these patients as could have occurred in PEGASUS. The double property of ticagrelor with platelet inhibition and also its adenosine-like effect could be more effective in the subgroup of patients with high microvascular resistance. Although it would be difficult to stratify patients according to the microvascular resistance in real practice, we might find that ticagrelor is more beneficial in this subgroup compared with other modalities of double antiplatelet therapy or even as single therapy instead of aspirin in the mid- and long term.

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Please note: Dr. Lozano has presented lectures on ticagrelor. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

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We recently showed that coronary microvascular dysfunction (CMD) is present in up to two-thirds of patients presenting with signs and symptoms of stable myocardial ischemia and nonobstructive coronary artery disease at coronary angiography (1). Although it is known that CMD is associated with adverse cardiovascular events, we agree that the evidence supporting therapies that improve CMD is lacking, as highlighted by Dr. Lozano and colleagues in their letter to the editor. Therapy may be directed at improving symptoms and/or reducing the risk of cardiovascular events, and although the majority of evidence focuses on the former, there certainly remains “room for improvement” in this area. Indeed, reports have shown that beta-blockers may improve chest pain in patients with CMD, but do not support the role of calcium channel blockers (2). Further, evidence is either inconsistent or lacking with regard to the efficacy of short- and long-acting nitrates in patients with microvascular angina, and among novel antianginals, ranolazine may be superior to ivabradine, but recently presented data by Bairey Merz et al. (3) suggest that ranolazine may still be inefficacious in managing chest pain associated with CMD.

Dr. Lozano and colleagues highlight a potential novel use for ticagrelor in the management of microvascular angina, which putatively enhances the bioavailability of adenosine (4), leading to microvascular vasodilation and improved myocardial perfusion. Thus, ticagrelor could create a therapeutic opportunity from the concepts that underlie diagnostic testing for CMD in which intracoronary injections of adenosine are used to induce hyperemia. However, although no study has evaluated the role of ticagrelor in managing microvascular angina, xanthines, which inhibit microvascular vasodilation by antagonizing adenosine receptors, have paradoxically been shown to improve chest pain in patients with CMD (5). It may be that adenosine-mediated smooth muscle vasodilation of functionally intact microcirculation distributes blood flow away from regions of CMD, exacerbating perfusion imbalance and explaining why xanthines may have a role in managing microvascular angina. The precise clinical role of ticagrelor and xanthines and the underlying molecular pathways involved require greater clarification with larger clinical trials, and may ultimately trigger a new direction in the search for therapies directed at CMD. Xanthines may also exhibit their analgesic effect through inhibition of cardiac nerve fibers, and if found to be more efficacious, may lead the way for the development of therapies directed at modulating neuropathic pain/pain perception, which is thought to be deregulated in patients with microvascular angina. Alternatively, if ticagrelor is more efficacious, it may open the door to evaluating drugs that modulate microvascular tone, potentially creating novel uses for commonly prescribed drugs, including cyclo-oxygenase inhibitors.

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REFERENCES

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The subject of our editorial regarding the paper by Sara et al. (1) was the use of intravascular imaging