The Challenges with Chronic Angina
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Should therapies to treat chronic stable angina reduce the risk of major cardiovascular events such as death and myocardial infarction? Although this may be a laudable target, the majority of treatments that are currently in use, such as nitrates, calcium-channel blockers, and beta-blockers, have not been proved to achieve this goal. Still, these agents have been recommended as first-line therapy for angina because of their presumptive safety in this context and their ability to lower blood pressure, reduce symptoms, and improve quality of life.

The occurrence of angina is associated with reduced quality of life and increased resource use. Angina, although common, is also a very subjective symptom. Therefore, Food and Drug Administration approval for antiangina therapies requires an objective test, such as a treadmill test, to define the degree of ischemia, as well as blinding with the use of a placebo control. To assess safety outcomes, such as death and myocardial infarction, approval requires large studies that follow patients long-term. This rigorous process may be a reason why only one new agent has been approved for the treatment of angina in the United States in the past two decades. Unfortunately, we are left with few therapies available to treat patients with chronic angina, which probably contributes to more use of revascularization.

Among the newer medications available to treat angina, including ranolazine, nicorandil, ivabradine, and trimetazidine, only ranolazine, which is recommended as a second-line agent, is available in the United States. Ivabradine, an agent that reduces heart rate in a dose-dependent manner by acting on current through the I_f channel, has an antiangina effect shown in studies with the use of standard stress testing. Ivabradine has also been tested for the management of heart failure in a trial that enrolled 6505 patients with a heart rate of more than 70 beats per minute, clinical heart failure, and an ejection fraction of at least 35%, which showed a significant reduction in the risk of death from cardiovascular causes and hospitalization for heart failure.

The Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial, the results of which are now published in the Journal, addressed whether ivabradine, by reducing heart rate, could affect the rate of death from cardiovascular causes and nonfatal myocardial infarction among patients with stable coronary disease. Patients were included if they had a heart rate of 70 beats per minute or more, a left ventricular ejection fraction of 40% or more, and an age of 55 years or more; they were followed for an average of slightly more than 2 years. The majority of enrolled patients had angina of Canadian Cardiovascular Society (CCS) class II or higher (12,049 patients [63%]) and prior revascularization (68%). The vast majority of patients were treated with standard preventive therapies, including antiangina therapies. The dose of ivabradine was adjusted to achieve a target heart rate of 55 to 60 beats per minute during the first few months.

This was a well-conducted trial, with minimal change in beta-blocker therapy in both groups during the study. At 3 months, the patients in the ivabradine group had a heart rate that was an average of 10 beats per minute lower than the mean heart rate of those in the placebo group, which was maintained throughout. Not surprisingly, ivabradine caused more bradycardia than did placebo, which led to a higher overall rate of study-drug discontinuation (21% vs. 14%). Although
the observed difference in heart rate was impressive, there was no significant reduction in the incidence of the primary end point — a composite of death from cardiovascular causes or nonfatal myocardial infarction — with ivabradine, as compared with placebo (6.8% vs. 6.4%, P=0.20).

The most surprising finding in this study was the significant increase in the incidence of the primary end point among patients with angina of CCS class II or higher who were randomly assigned to ivabradine (7.6%, vs. 6.5% with placebo; P=0.02 for interaction). The increase in risk was similar for the separate components of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine did significantly reduce the occurrence of angina in this cohort, a finding that is consistent with those of smaller mechanistic studies. Although this is a subgroup of an overall neutral trial, it is a group of more than 12,000 patients, who were studied where the therapy is approved and in use outside the United States.

How should we approach this challenge? It is well established that we should be very cautious in interpreting subgroup results, because the results may be spurious, particularly if they are directionally different,7 which was not observed in the SIGNIFY trial. The next natural step would be to carry out a second study, as was done by the ivabradine investigators for the indication of heart failure,8 to ascertain whether this angina subgroup is really one in which we should exercise caution. This is unlikely to happen, unless a regulatory agency forces the issue before allowing further use of ivabradine for more severe forms of angina. Before taking such a drastic step, it would be of paramount importance to analyze the SIGNIFY trial in greater detail to better define what drove the outcomes among patients with severe angina who had been randomly assigned to ivabradine.

What action should physicians who have ivabradine available to them take on the basis of this subgroup finding? Our recommendation is to exercise caution among patients with more severe forms of angina and to consider adjusting beta-blocker doses to effective levels before initiating ivabradine. The experience from the trial of ivabradine in heart failure suggests that nearly 60% of patients were receiving inadequate doses of beta-blockers and that the majority of benefit with ivabradine was among patients who could not take beta-blockers or who were taking a lower dose.9 Whether this holds true for patients with angina is unknown, but this cautious approach may be reasonable until we understand this finding better.

It should also not escape us that we need more therapies for patients with chronic angina in order to improve their symptoms and quality of life, particularly in the United States. We wish these therapies to be efficacious. What we may need to consider is the level at which an individual patient might be willing to trade some potential risk of major nonfatal cardiovascular events for less angina and better quality of life.

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