Role of Ranolazine in Reducing Angina, Subsequent Revascularization, and Healthcare Expenditures in Stable Ischemic Heart Disease

Angina pectoris is the most common manifestation of stable ischemic heart disease (SIHD) and affects approximately 8.7 million adults in the United States.[1] Not only does the prevalence of angina pectoris increase with age, but it is an important prognostic marker of increased cardiac events which, in turn, results in a significant reduction in quality of life and increased healthcare costs. Angina pectoris is also one of the most common targets for therapeutic interventions in the treatment of symptomatic coronary artery disease (CAD). Unlike acute myocardial infarction (MI), revascularization confers no mortality benefit in the vast majority of SIHD patients and, therefore, lifestyle interventions, risk factor modification, and intensive pharmacotherapy as secondary prevention have been the preferred initial strategy.[2,3] The successful implementation of this combined therapeutic approach has been termed optimal medical therapy (OMT) and entails a multifaceted and comprehensive application of multiple therapeutic agents targeting differing aspects of the disease process. For such patients with CAD, apart from reducing the risk of death or MI, the most important treatment is one that reduces the burden of chest pain and myocardial ischemia improving exercise capacity and overall quality of life.

The major classes of traditional antianginal agents include beta-blockers (BB), calcium channel blockers (CCB), and long-acting nitroglycerin (LAN), and both current US and European clinical practice guidelines have advocated a step-wise algorithm using these agents.[4,5] In particular, both the US and European guidelines have recommend BBs as the initial agent (or first line therapy), which are largely derived by extrapolating evidence of mortality benefit in patients with prior MI or in patients with left ventricular systolic dysfunction as the justification for this therapeutic recommendation. In general, nondihydropyridine CCBs followed by LANs are considered as suitable alternatives if patients cannot tolerate BBs, whereas the European guidelines differ slightly in that they recommend BBs and CCBs as comparable first-line agents, yet similarly propose a step-wise algorithm for pharmacotherapy of angina. More recently, however, Ferrari, Manolis, and others have advocated a more pathophysiologically directed approach to using various antianginal agents that take into account the effects of therapies on heart rate, blood pressure, and conduction, rather than using the designation of a hierarchical, step-wise application of first-line and second-line therapies.[6-8] Importantly, there has been a paucity of randomized studies in the contemporary era comparing various antianginals to support this hierarchical approach of first- and second-line antianginal therapies, and it is noteworthy that the agent with the most efficacy data to support its use in chronic angina is actually ivabradine, although this agent is not approved for use to treat angina in the United States.[9-12]

Another therapeutic agent, ranolazine, is likewise currently considered a second-line therapeutic agent that is approved for chronic angina. It inhibits the late inward sodium current and thus reduces intracellular calcium overload, which both promotes improved oxygen consumption in ischemic myocardium and facilitates diastolic relaxation. Ranolazine is hemodynamically neutral in that it does not affect heart rate or blood pressure, which makes it an attractive antianginal agent in patients who may be prone to hypotension or bradycardia. Several clinical trials have demonstrated improvement in exercise tolerance and reduction in angina frequency with ranolazine as monotherapy[13] or in addition to standard antianginal combination therapy.[14] The therapeutic effect appears to be greatest in those with a high burden of angina and less so in patients postrevascularization where angina is infrequent.[15] Interestingly there also appears to be other salutary effects with reductions in glycosylated hemoglobin in patients with diabetes and arrhythmic events.[16] Based on current US and European guidelines, ranolazine is considered as an adjunctive therapy in patients with angina despite the use of BB or CCBs.

In this issue of the *American Journal of Cardiology*, Meyer et al use administrative claims data to examine the effectiveness of ranolazine versus traditional antianginal agents as second- or third-line therapies to reduce the frequency of subsequent (or downstream) revascularization and medical costs in SIHD patients.[17] Their findings highlight a number of important issues in the management of SIHD. Among 108,741 SIHD patients identified between 2008 and 2016, only about 15% were treated with more than 1 class of antianginal drugs. The under-utilization of multiple antianginals is in keeping with other studies using real-world data where up to 30% of patients were on no antianginals at all before revascularization.[18] Unfortunately, important metrics impacting the robustness of OMT such as doses of medications, frequency of antianginal dose titration, and compliance before revascularization could not be ascertained in their study. As expected, the majority of patients were treated with BB as first-line therapy. However, the authors constructed 4 cohorts based upon which antianginal drug was added as a second- or third-line agent. Ranolazine formed one of these add-on treatment groups whereas the remaining 3 control groups were based on whether BBs, CCBs, or LANs were utilized as the additional agent. Inverse probability weighting based on propensity score was employed to balance the ranolazine and traditional antianginal therapy cohorts on patient clinical characteristics. The key assumption was that all potential confounders that affect treatment choice were accounted for, although obviously this was challenging in a population in which antianginal therapy was heavily skewed to BB use.

For example, it is possible patients deemed poor candidates for revascularization were selectively given ranolazine—that is, a feature that would reduce revascularization rate unrelated to the therapeutic effect of the medication. This is an inherent limitation related to the study design and the use of data derived from an administrative claims database, which the authors have acknowledged. Another limitation is the potential for misclassification bias when using third party payer claims data rather than auditing hospital records to confirm actual study outcomes. However, the size of the population and the geographically broad data collected should limit the effect of localized practice variation. Moreover, the authors have provided information to demonstrate that all study groups were adequately matched for important indicators of CAD severity. As Meyer et al suggest, given the size of the study it is likely that this bias would have equally affected all groups. Importantly, in this real-world setting, it is noteworthy that the effectiveness of ranolazine in reducing the need for subsequent revascularization (and hence lower healthcare costs) was more pronounced than for other interventions, except for CCBs, whereas BBs were the least effective.

As noted above, the findings from Meyer et al are at variance with the current step-wise algorithm for OMT that favors certain antianginal agents as first-line when there is scant evidence to support such an approach, although one that promotes an apparent bias toward older medications with proven effect in certain CAD patient subsets (e.g., post-MI secondary prevention), albeit not specifically proven to be of benefit for angina relief. Evidence to date suggests equivalence among the various antianginal drug classes in reducing the incidence of angina and improving functional status, whereas more recent and emerging data focus increasingly on tailoring the most appropriate antianginal agent to the co-morbidities and risk profile of the individual patient.[6,8]

What is the take home message to practicing cardiologists and how does this study inform our views of managing patients with SIHD? As this study and others clearly demonstrate, lower downstream procedural utilization is an important driver of reduced healthcare expenditures in SIHD patients in whom no one particular therapy seems to have advantages in improving survival or reducing the subsequent risk of MI. Hence, treating angina more effectively with antianginal agents lessens the likelihood (or need) for subsequent revascularization which, in turn, lowers costs and healthcare expenditures. And yet, a significant proportion of patients are not on adequate OMT, both before and after undergoing revascularization.[19] The potential reasons for this lower than expected utilization of OMT are multiple and include patient and physician misperceptions of the benefits of OMT and its treatment efficacy in SIHD,[20] expediency of treatment effect, challenges relating to medication tolerance and adherence, third party payer bias favoring the perceived benefits of revascularization procedures, and physician concerns regarding medical-legal consequences of poor outcomes that could be ascribed to avoiding or deferring revascularization.[21] However, the value and benefit to adopting more rigorous medical therapy in improving outcomes and

alleviating angina in patients with SIHD has been firmly established. The present study highlights the role ranolazine may have in promoting both angina relief as well as reduced procedural utilization.

In summary, treating angina pectoris effectively is an important therapeutic goal that is universally supported by cardiology clinical practice guidelines. Ranolazine is an effective antianginal agent that may improve not only symptom control, but may also limit the need for subsequent myocardial revascularization which, in turn, may lower downstream healthcare expenditures. In the absence of definitive evidence supporting a more prescriptive and hierarchical approach to medical therapy selection as has existed previously, the more widespread use of ranolazine may be a worthy consideration in patients with symptomatic SIHD.

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