Coronary artery disease (CAD) continues to have a significant impact on society. The latest update by the American Heart Association estimates that 83.6 million American adults have some form of cardiovascular disease (CVD) with an anticipated 15.4 million attributed to CAD. A portion of patients with CAD experience predictable chest pain, which occurs as a result of physical, emotional, or mental stress, more commonly referred to as chronic stable angina (CSA). Based on the most recent estimates, the incidence of patients who experience CSA is about 565,000 and increases in the male population through the eighth decade of life.1

Although it may be common, treatment options for patients with CSA are limited, as these patients may not be ideal candidates for coronary artery bypass graft or percutaneous coronary intervention (PCI) and may often prefer less invasive treatments. It has also been demonstrated that optimal medical management results in similar cardiovascular outcomes when compared with optimal medical management combined with PCI.2-3 Therefore, optimizing medical management is a reasonable alternative for these individuals.

Pharmacists have been successful in implementing collaborative practices for the management of various conditions, including anticoagulation, diabetes, hypertension, and hyperlipidemia.4-7 Pharmacists are heavily involved with cardiovascular risk reduction and management, so it seems opportune that they also treat CSA.8 The latest estimated direct and indirect costs for CVD and stroke were well over $315 billion for 2010, and it is anticipated that the costs will continue to rise.1 Because CSA is typically a medically managed disease and due to its huge medical expense, the development of a pharmacist-managed collaborative practice for treating CSA may prove to be beneficial for both clinical and pharmacoeconomic outcomes.

CLINIC DEVELOPMENT AND PRACTICES
In June 2007, following the approval of ranolazine by the FDA, the VA adopted nonformulary criteria for ranolazine use (Appendix).9,10 In order for patients to receive ranolazine, health care providers (HCPs) within the North Florida/South Georgia Veterans Health System (NFSGVHS) network were required to submit an electronic nonformulary consult using the computerized patient record system (CPRS). Select clinical pharmacists who had knowledge of the health system’s nonformulary criteria and who were granted access to the electronic consults responded to the requests.

The consults primarily consisted of an automated template that required providers to fill out their contact information and the name of the requested nonformulary medication, dose, and clinical rationale for requesting the specified medication, including any previous treatments that the patient could not tolerate or on which the patient failed to achieve an adequate response. It was highly

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recommended but not required that the HCPs include other supporting information regarding the patient’s cardiovascular status, such as results from diagnostic cardiac catheterization, stress tests, electrocardiograms (ECGs), or echocardiograms if not readily available from the CPRS. If procedures or tests were conducted at outside facilities, then this information was supplied in the request or obtained with the patient’s consent. However, this information was not necessarily required in order to complete the nonformulary consult. Nonformulary requests for ranolazine were typically forwarded to the clinical pharmacists who specialized in cardiology.

A pharmacist-oriented collaborative practice was established to increase cost-effective use, improve monitoring by a HCP because of the drug’s ability to prolong the corrected QT (QTc) interval, and to more firmly establish its safety and efficacy in a veteran population. This practice operated in a clinic, which was staffed by a nurse, postdoctoral pharmacy fellow, clinical pharmacy specialist in cardiology, and a cardiologist. The nurse was responsible for obtaining the patient’s vitals and ECG and documenting them in the CPRS. The pharmacy fellow interviewed the patient and obtained pertinent medical and historical information before discussing any clinical recommendations with the clinical pharmacy specialist.

The recommendations consisted of drug initiation/discontinuation, dose adjustments, and assessing and ordering of pertinent laboratory values and ECGs, which took place under the scope of the clinical pharmacy specialist. The focus of the ECG was to assess for any evidence of excessive QTc prolongation. Due to the variable and subjective nature of CAD, a cardiologist was available at any time and was used to review any relevant information and further discuss any treatment recommendations.

Based in the NFSGVHS Malcom Randall Veterans Affairs Medical Center (VAMC) in Gainesville, Florida, clinic services were primarily offered to patients of that facility due to the limited number of cardiology providers and services offered at other NFSGVHS locations. Despite being driven by requests for ranolazine, especially after cardiac catheterization when further cardiac intervention may not have been feasible, all patients were allowed to enroll in the clinic at the discretion of their primary care provider (PCP) for optimization of their CSA regimen with the intent of adding ranolazine when appropriate.

Patients in outlying regions who met the criteria were supplied with ranolazine and continued to follow up with their HCPs as recommended by the criteria for use. Conversely, if patients from outside areas failed to meet the criteria, their PCPs were supplied with appropriate, alternative guideline-based recommendations for improving CSA with the option to resubmit the nonformulary consult. Recommendations regarding cardiovascular risk reduction were also sent to HCPs at that time, which included optimal endpoints for managing other conditions, such as diabetes, hypertension, and hyperlipidemia when necessary.

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| Table. Seattle Angina Questionnaire (SAQ) Scoresa,b |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| SAQ Dimension                  | Baseline Score (n = 35) | Baseline to 1 Month (n = 28) | Baseline to 3 Months (n = 26) | 1 Month | 3 Months |
| Physical limitation            | 33.56             | + 9.86            | +11.94            | Yes      | Yes      |
| Angina stability               | 36.43             | +39.29            | +32.69            | Yes      | Yes      |
| Angina frequency               | 34.00             | +26.79            | +25.38            | Yes      | Yes      |
| Treatment satisfaction         | 80.89             | +11.38            | +10.66            | No       | No       |
| Disease perception             | 41.90             | +16.85            | +18.59            | Yes      | Yes      |

Adapted from Reeder et al.17

aAll changes statistically significant at P < .001, based on the Wilcoxon signed rank test.
bDefined as a difference of at least 8 points on the physical limitation dimension, 25 points on the angina stability dimension, 20 points on the angina frequency dimension, 12 points on the treatment satisfaction dimension, and 16 points on the disease perception dimension.
ment from outside facilities. A thorough history and description of the patient's anginal symptoms were also taken at baseline and during follow-up visits. Once it was confirmed that the patients' electrolytes were within normal limits and there was no evidence of prolongation in the Bazett's QTc interval or major drug interactions, all patients who met criteria for ranolazine were initiated at 500 mg twice daily. The Seattle Angina Questionnaire (SAQ) was also completed by patients at the initiation of ranolazine and then again at follow-up visits. The SAQ is an 11-question, self-administered survey that measures functional status of patients with angina.

All patients initiated on or ensuing dose changes with ranolazine followed up with the clinic at 1 and 3 months with labs and ECGs obtained prior to ensure that there were no electrolyte imbalances or excessive QTc prolongation. Excessive QTc prolongation was defined as an increase of ≥ 60 milliseconds (msec) from baseline or > 500 msec. If this boundary was
exceeded, ranolazine was discontinued, or for those taking higher doses, it was reduced to the initial 500 mg twice daily as long as there was no previous excessive QTc prolongation. In cases where ranolazine was not added at baseline, doses of antianginal medications were titrated over appropriate intervals to improve angina symptoms with ranolazine subsequently added in conjunction with the nonformulary criteria.

A generalized treatment algorithm was followed by the clinic for the management of CSA (Figure). It was highly recommended that all referred patients have an active prescription in the CPRS for short-acting sublingual nitroglycerin 0.4 mg in case of any acute episodes. Although other forms of short-acting nitroglycerin were available, sublingual nitroglycerin 0.4 mg was the preferred formulary medication at the time of the study.

Depending on whether the patients met nonformulary inclusion or exclusion criteria, they were either initiated or optimized on ranolazine or other traditional antianginals, such as beta-blockers (BBs), dihydropyridine calcium channel blockers (DHP-CCBs), or long-acting nitrates (LANs). Beta-blockers were recommended as first-line treatment for patients with previous myocardial infarction (MI) and left ventricular dysfunction, in accordance with treatment guidelines and because of their benefits in treating patients with CSA.\textsuperscript{12,15}

Once patients were optimized on BBs and/or DHP-CCBs, LANs were added if patients experienced ≥ 3 bothersome episodes of chest pain weekly. Optimization for BBs meant an ideal heart rate of at least about 60 bpm without symptoms suggestive of excessive bradycardia, whereas optimization for all 3 classes (BBs, DHP-CCBs, and LANs) consisted of dose titration until the presence of drug-related adverse effects (AEs) or symptoms suggestive of hypotension. Because LANs have lesser effects on blood pressure (BP) compared with DHP-CCBs, they were preferred in patients with persistent anginal symptoms whose BPs were considered low or normal, according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines.\textsuperscript{16}

If patients with normal or controlled BP continued to have symptoms of angina despite optimal doses of BBs and LANs, an appropriate dose of a DHP-CCB was administered and titrated for as long as the patients tolerated the treatment. If titration of antianginal agents was limited due to the presence of other antihypertensives, then the patient’s medication regimen was modified as necessary to allow for an increased dose of the BB or DHP-CCB due to these medications’ abilities to improve angina symptoms while also lowering BP. If patients achieved an acceptable reduction in their angina symptoms, they were discharged from the clinic, whereas those with contraindications to other classes were referred to their PCP or cardiologist.

Patients successfully treated with ranolazine (defined as a noticeable reduction in angina symptoms in the absence of intolerable AEs and excessive QTc prolongation after 3 months) were discharged from the clinic and instructed to follow up with their PCP at least annually. If the patient was discharged from the clinic at the baseline dose, it was recommended to the HCP that he or she follow up within 3 months after any dose increases. Any patient whose symptoms were consistent with unstable angina (described as occurring in an unpredictable manner, as determined by the clinical pharmacy specialist, lasting longer in duration and/or increasing in frequency, and those who experience symptoms at rest) were immediately evaluated and referred to a cardiologist. Patients who continued to have unacceptable rates or episodes of angina despite an optimal medical regimen were referred to Cardiology for consideration of other treatment modalities.

**RESULTS**

The initial report of this study population was described by Reeder and colleagues.\textsuperscript{17} Fifty-seven patients were evaluated for study inclusion, of which 22 were excluded due to ranolazine being managed by an outside HCP or because an SAQ was not obtained at baseline. All study participants were males with an average age of 68 years and were predominantly white (86%). All patients had a past medical history significant for hypertension and hyperlipidemia. More than half (57%) had a prior MI and multivessel disease, although only 1 patient had an ejection fraction of < 35%. The majority of patients enrolled were being treated with BBs (97%) and LANs (94%) with a little more than half prescribed CCBs (60%). A large percentage (97%) of patients were also taking aspirin and a statin.

Improvements in angina symptoms as measured by the SAQ and safety measures, which included details of AEs and discontinuation rates following the initiation of ranolazine within the clinic, have previously been published.\textsuperscript{17} In summary, it was found that the addition of ranolazine to an optimal medical regimen for CSA improved all dimensions of the SAQ scores at 1 and 3 months compared with baseline (Table).
Additionally, it was noted that higher doses may not have been as well tolerated in the veteran population, despite that only a small number of eligible patients were captured. This was because 5 of 7 patients whose dose was increased to 1,000 mg twice daily after 1 month required withdrawal as a result of AEs or lack of efficacy. The AEs reported included dizziness, abdominal pain, blurry vision, nausea and vomiting, dry mouth, and dyspnea.

The pharmacists were able to ensure that relevant electrolytes were replaced during the treatment period and also minimized the number of clinically significant drug interactions. Twenty-one patients received medications at baseline that had known interactions with ranolazine. Two patients required discontinuation of other medications: sotalol and diltiazem. At the time this study was conducted, diltiazem was contraindicated when given concomitantly but has since been allowed per manufacturer recommendations as long as the dose of ranolazine does not exceed 500 mg twice daily. Electrolyte replacement was also required in 3 patients, 2 of whom had hypomagnesemia.

**CONCLUSION**

Pharmacists have been influential in managing a variety of chronic diseases. When instituted into collaborative practice agreements, CSA is another unique condition that pharmacists can play a role in treating. Given that pharmacists are heavily involved with cardiovascular risk reduction, combined with the higher cost of ranolazine and the need for monitoring due to its AEs, QTc interval prolongation, and significant drug interactions, the benefits of having pharmacist-oriented clinics can ensure the safe and effective use of medications in the treatment of CSA.

**Author disclosures**

The authors report no actual or potential conflicts of interest with regard to this article.

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The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, Frontline Medical Communications Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

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**Appendix. Nonformulary Criteria for Ranolazine Use Checklist**

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<thead>
<tr>
<th>Nonformulary Criteria for Use Checklist</th>
<th>Ranolazine</th>
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<td>VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives</td>
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The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

(For further details, refer to the drug monograph and update at www.pbm.va.gov or http://vaww.pbm.va.gov)

**FDA APPROVED INDICATION FOR USE**

Ranolazine is indicated in the treatment of chronic stable angina

**EXCLUSION CRITERIA (If one is selected, patient is not eligible)**

- Clinically significant hepatic impairment
- Receiving strong CYP 3A4 inhibitors including ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir.
- Receiving strong CYP 3A4 inducers including rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, or St. John’s wort.
INCLUSION CRITERIA (Both must be selected to be eligible)

- Anginal episodes an average of 3 or more times per week despite maximal or maximally tolerated anti-anginal drug therapy (Defined as treatment with a beta-blocker, long-acting dihydropyridine calcium channel blocker and a long-acting nitrate).
- A VA healthcare provider is actively involved in the monitoring and management of ranolazine therapy and will re-assess ranolazine’s therapeutic effectiveness and tolerability within 12 weeks after initiation of therapy.

PRECAUTIONS

- **QT-interval prolongation:** Ranolazine can prolong the QT interval in a dose-dependent manner. The mean increase (QTc) seen with 1000 mg twice daily was 6 milliseconds. There is little experience with ranolazine use in patients with pre-existing QT interval prolongation (Normal QTc <440 milliseconds). Use of ranolazine in these patients should be done with caution in the absence of safety data.
- **Drug-drug interactions:** Carefully review medications for possible drug-drug interactions prior to initiating ranolazine. Ranolazine is both an inhibitor of and a substrate for CYP 3A4 and P-glycoprotein and to a lesser extent CYP 2D6. Dose adjustment of the object drug or avoidance of ranolazine may be recommended. There is little experience with ranolazine in combination with other drugs known to prolong the QT interval (e.g. Class Ia [quinidine] or Class III [amiodarone, dofetilide, sotalol] antiarrhythmics, erythromycin and some antipsychotic agents [thioridazine, ziprasidone]). Use of these drugs with ranolazine should be done with caution in the absence of safety data.

DOSE AND ADMINISTRATION

- Initiate therapy with 500 mg twice daily. Dose can be increased to a maximum of 1000 mg twice daily but dose escalation has not consistently been shown to improve symptoms. Adverse events with ranolazine are dose related.
- The maximum recommended dose of ranolazine should be limited to 500 mg twice daily in patients on concurrent therapy with moderate CYP3A inhibitors (e.g., diltiazem, verapamil, aprepitant, erythromycin, fluconazole, grapefruit-containing products).
- Down-titration of ranolazine dose based on clinical response may be needed when used concurrently with P-glycoprotein inhibitors such as cyclosporine.

ISSUES FOR CONSIDERATION

- Ranolazine prolongs the QT interval and has multiple drug interactions and precautions for use. It should be reserved for patients who have not received an adequate response with other antianginal drugs and should be used in combination with beta-blockers, nitrates and dihydropyridine (e.g. felodipine, amlodipine or long-acting forms of nifedipine) calcium channel blockers.
- Ranolazine was not shown to be pro-arrhythmic in a high risk ACS population.
- Ranolazine has been shown to increase drug levels of simvastatin by 2-fold. For most patients, this interaction is not expected to be clinically significant, and a dosing adjustment has not been recommended by the manufacturer or FDA. However, anecdotal reports within VA have noted adverse events potentially related to the combination, particularly due to elevated levels of simvastatin. Clinicians may wish to consider this issue when monitoring and counseling patients who are on both ranolazine and simvastatin.

RENEWAL CRITERIA (The following must be selected for renewal)

The therapeutic effectiveness and tolerability of ranolazine should be assessed within the first 12 weeks of ranolazine therapy:

- An improvement in anginal symptoms and/or a reduction in sublingual nitroglycerin consumption is documented in the medical record (while receiving ranolazine).
- Patient is not experiencing treatment-limiting adverse effects.
REFERENCES