5. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the ACC Foundation/AHA Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50–103.
6. Artinian N, Fletcher GF, Mozaffarian D, et al., on behalf of the AHA Prevention Committee of the Council on Cardiovascular Nursing. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults. A Scientific Statement from the American Heart Association. Circulation 2010;122:406–41.
7. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, and Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Stroke 2011;42;517–84.
8. Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010;170:1024–31.
9. Taylor F, Ward K, Moore THM, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011;1:CD004816.
10. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in randomized trials. Lancet 2010;376:1670–81.
11. Möhlenkamp S, Lehmann N, Moebus S, et al. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011;57:1455–64.
12. Garg J, Messerli AW, Bakris GL. Evaluation and treatment of patients with systemic hypertension. Circulation 2002;105:2458–61.
13. Mancia G, DeBacker G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the ESH and of the ESC. Eur Heart J 2007;28:1462–536.
14. Möhlenkamp S, Lehmann N, Greenland P, et al., on behalf of the Heinz Nixdorf Recall Study Investigators. Coronary artery calcium score improves cardiovascular risk prediction in persons without indication for statin therapy. Atherosclerosis 2011;215:229–36.

Ranolazine and Silent Ischemia

I read with interest the paper by Stone et al. (1), in which the authors investigated the relationship between ST-segment depression and the rate-pressure product during exercise. Based on their findings, they suggested that ranolazine's beneficial action is most likely primarily due to improvement of regional coronary blood flow in areas of myocardial ischemia. I do not refute that statement, but I would like to remind the readers that the current hypothesis of the mechanism of action of ranolazine is that it works only after myocardial ischemia has been present. When that happens, the late sodium channel remains open, leading to intracellular sodium overload, and the sodium–calcium exchanger then leads to intracellular calcium overload, which results in increased calcium ions intracellularly and impaired diastolic relaxation and increased tension. Ranolazine inhibits the myocardial late inward sodium current associated with ischemia and thus breaks up the cycle (2).

The authors emphasize in their article that under low stress conditions of exercise where there was mild ischemia, the ranolazine did not seem to be effective; however, as the ischemia became more pronounced, the anti-ischemic effects of ranolazine became more marked.

My question to the investigators is this: Since it has been shown many times that patients with chronic stable angina have multiple episodes of asymptomatic cardiac ischemia, is it possible or probable that these multiple episodes of silent cardiac ischemia are prevented from becoming manifest symptoms of myocardial ischemia (i.e., angina) by the drug ranolazine?

I suspect that the only way one could find the answer is to have chronic ambulatory electrocardiogram (ECG) monitoring of these patients. I know that patients who were in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial (3) had 7 days of ambulatory ECG monitoring, but the published study revealed that only arrhythmias were assessed. Would it be possible to go back and investigate those ambulatory ECGs to see whether or not silent ST-segment depression was present on several occasions without any manifestations of angina?

***C. Richard Conti, MD**

*Division of Cardiovascular Medicine
Department of Medicine
University of Florida
P.O. Box 100277
Gainesville, Florida 32610-0277
E-mail: conticr@medicine.ufl.edu

doi:10.1016/j.jacc.2010.11.084

REFERENCES

1. Stone PH, Chaitman BR, Stocke K, SanoJ, DeValut A, Koch GG. The anti-ischemic mechanism of action of ranolazine in stable ischemic heart disease. J Am Coll Cardiol 2010;56:934–42.
2. Nash DT, Nash SD. Ranolazine for chronic stable angina. Lancet 2008;372:1335–41.
3. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al., for the MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non–ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775–83.

Reply

Dr. Conti raises an interesting conceptual point regarding our paper (1) concerning the implications of treatment with ranolazine. If ranolazine were to render each ischemic episode less severe than an ischemic episode in the absence of ranolazine, then despite a reduction in symptomatic ischemia (i.e., angina), ranolazine may be associated with more frequent asymptomatic ischemia and, by inference, may expose the patient to an increased risk of cardiac events.

The fundamental premise implicit in this question, however, that asymptomatic episodes of myocardial ischemia represent less severe ischemia than symptomatic episodes, has not been demonstrated in any clinical study. Episodes of asymptomatic ischemia recorded during ambulatory electrocardiogram (ECG) recordings demonstrate the same ECG characteristics of ischemia severity as episodes of symptomatic ischemia (2). There is no evidence to support the notion that asymptomatic ischemia is asymptomatic because it is less severe than symptomatic ischemia and, consequently, does not reach an "angina threshold."

As Dr. Conti noted, patients in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial had 7 days of continuous ECG recordings following admission with a non–ST-segment elevation acute coronary syndrome.