Expert Opinion

Assessing Cardiac Risk Prior to Use of Triptans

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Whether to prescribe a triptan for a patient whose age suggests that they might have latent coronary artery disease is a common clinical problem.

CLINICAL HISTORY

This 60-year-old woman has had a history of severe migraines without aura since she was 25 years old. The attacks now occur once every 3 weeks or less, lasting up to a week without treatment. Sumatriptan, 6 mg, administered subcutaneously (SQ) completely relieves the headache and zolmitriptan, 5 mg, decreases the headaches to a dull level. Sumatriptan, 50 mg, administered orally, a sumatriptan 20-mg nasal spray, and rizatriptan, 10 mg, do not help. There is no history of hypertension, diabetes, ischemic heart disease, cerebrovascular disease, or hyperlipidemia.

Questions.—Can the use of sumatriptan SQ or zolmitriptan be safely continued into the patient's 60s? Should she have some type of cardiac screening, and if so, what? If she were male or had one or more cardiac risk factors, would your recommendations be the same?

EXPERT COMMENTARY

Few studies address whether triptans are safe for patients aged 60 years or older. Most of our safety data regarding the triptans come from prospective cohort studies, postmarketing data, and case reports in younger patients. The vast majority of the safety data come from the use of sumatriptan, since it has been on the market the longest. I will first discuss the available safety data and then try to develop a rational diagnostic and therapeutic approach to this patient.

A recent prospective cohort study[1] reported safety data on the use of sumatriptan SQ in patients aged 16 to 82 years. This study involved 12339 patients, of whom 100 to 200 were 60 years or older. A total of 185579 attacks of migraine were treated with sumatriptan SQ. The following cardiac events were reported: three myocardial infarctions, six episodes of angina, and four episodes of dysrhythmia. It was unlikely that the cardiac events were caused by the use of sumatriptan because the events occurred 24 or more hours after its administration, and by that time the drug should have been eliminated from the body. Therefore, one could conclude that the risk of cardiovascular complications is quite low in patients aged predominantly 16 to 60 years receiving sumatriptan SQ. This study, however, included an inadequate number of patients older than 60 years for the safety of the triptans in this age group to be assessed.

Postmarketing data have been obtained to ascertain the potential cardiovascular risk of sumatriptan. Such data need to be interpreted cautiously because a temporal association between a drug and an event does not prove a causal relationship. This is especially true with cardiovascular events because they commonly occur in the general population, and could occur independently of drug administration. Thirty-nine cardiovascular deaths were reported between

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1991 and 1996 in patients who had received sumatriptan 24 hours or less prior to their death. The occurrence of serious cardiac events such as angina, arrhythmias, and myocardial infarction was less than one per million. During the years 1991 through 1996, 5 million migraineurs treated over 100 million migraine attacks (GlaxoWellcome data). Therefore, the postmarketing data would also suggest that cardiovascular events are rarely associated with the use of sumatriptan.

There have been case reports of patients aged 30 to 60 years experiencing cardiovascular events in close temporal relation with the administration of sumatriptan. The reported events have included myocardial infarction,[2,3] unstable angina,[4] arrhythmias,[5] and cardiac arrest.[6] Whereas many of the cardiac events have occurred in patients with previously unrecognized coronary artery disease,[4,6] some have occurred in patients with minimal or no coronary artery disease.[2,3,5] It has been postulated that vasospasm has been responsible for these cardiac events and that diseased coronary vessels are more prone to vasoconstriction with use of the triptans than normal vessels. This led to the recommendation that the triptans are contraindicated in patients with known coronary artery disease or Prinzmetal's angina. It has also been recommended that a cardiac evaluation be given to those at risk of unrecognized coronary artery disease prior to the use of triptans. These patients would include: (1) men older than 40 years, (2) women older than 50 years, and (3) those with cardiac risk factors. However, no mention is made of what an *appropriate* cardiac evaluation might entail.

The first step in determining whether one can safely prescribe triptans to patients aged 60 years or older would be to evaluate their cardiac risk. Diamond and Forrester published a study that documents the prevalence of coronary artery disease in asymptomatic patients and in those with nonanginal, atypical, and anginal chest pain. The results of this study in patients aged 60 to 69 years are shown in Table 1. For example, the prevalence of coronary artery disease in a woman aged between 60 and 69 years with atypical chest pain would be 54%. This study also provides a means to estimate the prevalence of coronary artery disease in patients who are asymptomatic but who have a variety of cardiac risk factors (Table 2). For example, an asymptomatic 60-year-old woman with five risk factors has an estimated prevalence of coronary artery disease of 13% to 31%.

Table 1.—Prevalence of Coronary Artery Disease in Patients Aged 60 to 69 Years*

Symptoms	Men, %	Women, %
Asymptomatic	12	8
Nonanginal chest pain	28	19
Atypical chest pain	67	54
Anginal chest pain	94	91

*Data from Diamond and Forrester.[7]

The second step would be to determine whether to perform a cardiac evaluation in a 60-year-old patient receiving a triptan. The simplest and easiest screening test would be a baseline electrocardiogram (ECG). I believe that a baseline ECG is justified in this age group because it can sometimes identify those with coronary artery disease. Any of the following abnormalities could potentially signify underlying coronary artery disease: (1) Q waves or poor R wave progression suggesting a past infarction, (2) T wave inversions or ST depression suggesting ischemia, or (3) bundle-branch blocks suggesting a conduction abnormality. Some physicians would recommend a baseline ECG as well as a second ECG af-

Table 2.—Estimated Prevalence of Coronary Artery Disease With Risk Factors

No. of Risk Factors*	Men, %	Women, %
1	9-11	2-3
2	11-29	1-9
3	12-40	2-13
4	20-49	7-22
5	35-53	13-31

*Risk factors include hypertension, left ventricular hypertrophy, glucose intolerance, smoking, and hypercholesterolemia. The estimated risk is for a 60-year-old patient. The prevalences were estimated by multiplying the 6-year incidence data from the Framingham study[10] by a factor of 1.05.

ter a dose of a triptan, however, a study by Hillis and MacIntyre[8] found that ischemic changes on ECG were found in only 0.2% of patients who had an ECG performed after the administration of sumatriptan. Therefore, I would not recommend checking an ECG after the administration of a triptan because of the low yield of such a procedure.

Another potential screening test would be noninvasive cardiac stress tests such as a graded exercise test, exercise thallium scintigrams, exercise echocardiography, dobutamine echocardiography, dipyridamole thallium scintigrams, and exercise radionuclide angiograms. The sensitivities and the specificities of the various tests are listed in Table 3. Any of the above tests would be adequate to exclude obstructive coronary artery disease except the graded exercise test, which has too low a sensitivity in this circumstance. The decision as to which test to select may also depend on the experience of a given institution with a particular cardiac test.

Whether to order a noninvasive cardiac test depends on the pretest likelihood that the patient has coronary artery disease. If the patient has a 10% pretest likelihood of coronary artery disease, a positive thallium scintigram increases the likelihood of disease to 45%, whereas a negative test decreases the likelihood to 2%. This test would not have been helpful in the situation under discussion. If the patient has a likelihood of disease of 50%, a positive test increases the likelihood of disease to 88%, whereas a negative test decreases the likelihood of disease to 16%. This test would then clearly be helpful to confirm or rule out disease. Given the operating characteristics of the above noninvasive cardiac tests (with the exception of the graded exercise test), it would be necessary to have a 30% or greater pretest probability of coronary artery disease for the test to have a reasonable predictive value.

Table 3.—Sensitivity and Specificity of Noninvasive Cardiac Stress Testing*

Test	Sensitivity	Specificity
Graded exercise	0.53	0.83
Exercise thallium scintigram	0.83	0.89
Exercise radionuclide angiogram	0.85	0.80
Exercise echocardiogram	0.88	0.81
Dobutamine echocardiogram	0.86	0.79
Dipyridamole thallium scintigram	0.86	0.80

*Data from Weissler.[9]

This brings us back to our patient and to the question of whether to further evaluate her for coronary artery disease. I would first order a baseline ECG. If the ECG suggested coronary artery disease, I would proceed with a noninvasive cardiac test. If it was normal and the patient was asymptomatic, I would not proceed with further noninvasive cardiac tests because even with five risk factors for coronary artery disease, her pretest probability of coronary artery disease would only be 13% to 30%. If, however, she had experienced atypical or typical anginal pain, I would proceed with further cardiac testing as her pretest probability would be 54% and 91%, respectively.

If this patient was male, I would have performed further noninvasive cardiac testing under the following circumstances: (1) an ECG with evidence of ischemia or past infarction, (2) four to five risk factors in an asymptomatic patient, (3) atypical or typical angina, (4) in those with diabetes because of their predisposition to silent ischemia, or (5) in those with known peripheral vascular disease.

I would end with the following note of caution. A negative noninvasive cardiac test provides a reasonable measure of security that the patient does not harbor coronary artery stenoses of 50% or more. It does not, however, exclude the presence of subcritical stenoses of 50% or less. It is presently unknown whether these subcritical stenoses increase the risk of cardiac events when triptans are used. Therefore, I believe that caution should be exercised when prescribing these medications in asymptomatic patients with a high risk of atherogenesis. The physician and patient must realize that even a negative cardiac evaluation may not absolutely exclude the possibility of a cardiac event. One may first wish to prescribe abortive medications that have no known cardiac risk to those with a high risk of atherogenesis. If these medications fail and the patient has a great deal of disability with his or her migraines, then one might consider the use

of a triptan after a negative cardiac evaluation. This should only be done after carefully weighing the risks and benefits of such therapy with the patient.

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