

Scoring System Can Predict Cardiac Mortality

BY BETSY BATES

Los Angeles Bureau

LOS ANGELES — Specific findings on adenosine stress myocardial perfusion imaging can be combined with other risk factors to offer precise guidance about whether a patient would obtain a significant survival advantage with early revascularization, Rory Hachamovitch, M.D., said at a meeting sponsored by the American College of Cardiology.

VYTORIN® (ezetimibe/simvastatin)

VYTORIN: There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See *Ezetimibe and Simvastatin* below.)
Ezetimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pregnancy**). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See **CLINICAL PHARMACOLOGY, Special Populations** and **ADVERSE REACTIONS**.)

ADVERSE REACTIONS

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated. Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials. Table 1*

Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
Body as a whole – general disorders				
Headache	6.4	6.0	5.9	6.8
Infection and infestations				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
Musculoskeletal and connective tissue disorders				
Myalgia	2.9	2.5	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

** All doses.

Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

Ezetimibe: Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole – general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including angioedema and rash; elevated creatine phosphokinase; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely, myopathy/rhabdomyolysis (see **WARNINGS, Myopathy/Rhabdomyolysis**).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole – general disorders:* asthenia; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances. *Ear and labyrinth disorders:* vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting.
Hepatobiliary disorders: hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

Metabolism and nutrition disorders: anorexia.

Skin and subcutaneous tissue disorders: alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction.

Eye disorders: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see **WARNINGS, Liver Enzymes**). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see **WARNINGS, Myopathy/Rhabdomyolysis**).

Concomitant Lipid-Lowering Therapy

In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)

In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see **CLINICAL PHARMACOLOGY, Special Populations** and **PRECAUTIONS, Pediatric Use**).

Dr. Hachamovitch outlined the simplest of three new prognostic adenosine scores he validated in a group of 5,873 consecutive patients who underwent adenosine stress, dual-isotope single-photon emission computed tomography (SPECT) scanning, and were followed for a mean 2.2 years.

The simple score uses a patient's age, percent of ischemic myocardium, percent of fixed myocardium, presence or absence of dyspnea, resting ECG results, resting and peak stress heart rates, and scan results following early revascularization to predict 2-year mortality from cardiac causes.

Because revascularization can be plugged into the equation or left out, the formula can offer specific guidance as to the clinical management of an individual patient, said Dr. Hachamovitch of the clinical cardiovascular medicine unit at the University of Southern California, Los Angeles.

He offered the example of an 80-year-old man with atypical angina, assessing points to account for his age, the fact that 30% of his myocardium is ischemic, and other clinical characteristics and scan findings.

His final score was plotted on the x-axis of a graph against the 2-year Kaplan Meier Survival Curve on the y-axis.

The hypothetical patient received a total of 150 points if he underwent medical therapy, for a survival score of 91%, meaning he had a 9% chance of dying of cardiac causes in the ensuing 2 years.

When revascularization was factored into the formula, the patient's score dropped to 85 points, and his 2-year survival estimate rose to 97%.

The derivation of such a formula has been dependent on years of research into risk stratification for cardiac patients based on nuclear scan findings, said Dr. Hachamovitch at the meeting, which was cosponsored by the American Society of

Nuclear Cardiology and Cedars-Sinai Medical Center.

This research has determined predictors of both relative and absolute risk reduction based on nuclear perfusion study results. Following Dr. Hachamovitch's talk, his findings were published (*J. Am. Coll. Cardiol.* 2005;45:722-9).

The relative benefit of revascularization over medical therapy after nuclear imaging is dependent on the extent and severity of the myocardium at risk.

The absolute benefit of revascularization—number of lives saved per 100 treated—depends on left ventricular ejection fraction (LVEF) and underlying clinical risk factors.

"Hence, if you want to figure out who is in need of revascularization, look for ischemia. If you want to know how big an impact on their survival that revascularization will be, look at LVEF and clinical risk factors," said Dr. Hachamovitch. ■

Perfusion Scans Warrant Immediate Notification

BY BETSY BATES

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LOS ANGELES — High-risk findings on myocardial perfusion studies require an immediate telephone call from a nuclear cardiologist to the referring physician, even when the temptation is to perform more tests to clarify the extent of cardiac viability, said Robert C. Hendel, M.D., at a meeting sponsored by the American College of Cardiology.

Dr. Hendel presented the case of a 31-year-old man, 6' 4" tall, 244 pounds, who presented with exertional chest pain. He had a history of radiation therapy for Hodgkin's disease.

During cardiac function tests, the patient was only able to proceed 4.5 minutes on the Bruce protocol before he experienced chest pain with ST-segment changes lasting about 15 minutes.

The patient's nuclear single-photon emission computed tomography (SPECT) images showed significant ischemia and large regions of decreased perfusion. Yet,

in the interaction session attended by nuclear cardiologists, just over half of audience members voted that they would respond by immediately calling the referring physician.

Other attendees split their votes among other options, including repeating the SPECT using pharmacologic stress, performing additional imaging to assess viability, or reporting the likelihood of single-vessel disease.

Clearly, those in attendance were influenced by the patient's young age and the fact that more studies might provide more precise information.

However, the study's findings, combined with the patient's response to the cardiac function test, should be enough to warrant an immediate consultation with the referring physician, said Dr. Hendel at the meeting, which was cosponsored by the American Society of Nuclear Cardiology and Cedars-Sinai Medical Center.

"This is a very high-risk study," he said. "Our responsibility is to pick up the phone

and communicate that kind of information."

In the case he presented, consultation with the referring cardiologist led to a referral to coronary angiography. The patient was found to have extensive coronary artery disease, including high-grade narrows (greater than 95%) in the proximal left anterior descending coronary artery involving the bifurcation of a large first diagonal branch.

"This high-risk anatomy was unsuitable for percutaneous coronary intervention, and he was referred for bypass surgery," said Dr. Hendel following the meeting.

One week after his SPECT study, the patient underwent five-vessel bypass graft surgery. "He is doing well now, without symptoms."

Dr. Hendel, a former president of the American Society of Nuclear Cardiology who practices with Midwest Heart Specialists in Fox River Grove, Ill., said nuclear cardiologists should lower their threshold for immediately conveying ominous test results to referring physicians. ■

Women Undergoing Angioplasty for MI at High Risk

ORLANDO — Women undergoing primary angioplasty for acute MI continue to have significantly higher mortality than men, even in the contemporary era of potent antiplatelet therapy regimens and high-pressure stent deployment, according to a large and comprehensive patient series from the New York State Coronary Angioplasty Reporting System Registry.

In a cohort of 9,015 consecutive acute MI patients—29% of them women—who underwent primary percutaneous coronary intervention (PCI) in

New York state during 1997-1999, unadjusted in-hospital mortality was 6.7% in women and 3.4% in men. Mean hospital length of stay was also significantly greater in the women: 7.5 days, compared with 6 days for men, Jeffrey S. Berger, M.D., reported at the annual meeting of the American College of Cardiology.

The composite major adverse cardiovascular event rate—comprising death, emergency coronary artery bypass surgery, catheter-site complications, need for renal dialysis, stroke, abrupt vessel closure,

or stent thrombosis—was 10% in women, compared with 5.7% in men, added Dr. Berger of Beth Israel Medical Center, New York.

However, women as a group were at higher risk of complications related to urgent PCI than were men. They were significantly older, by a mean of nearly 7 years. They also had higher prevalences of diabetes, hypertension, and peripheral vascular disease and were more likely to have a history of stroke.

Yet even after adjusting for all of these potential con-

founders in a multivariate logistic regression analysis, investigators still found female gender remained a strong independent risk factor for adverse outcome, with an associated 42% increased relative risk of in-hospital mortality.

A major caveat regarding the state registry is that the data are nonrandomized and retrospective, so it's possible that significant differences between men and women undergoing primary PCI for MI remain uncontrolled for and unrecognized.

—Bruce Jancin

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