

Greater Clarity From Nuclear Images Coming Soon

BY ROBERT FINN
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SAN FRANCISCO — The near future of nuclear cardiology will be a bright one, with several important developments expected within the next 3 years, Manuel D. Cerqueira, M.D., said at a cardiovascular imaging conference sponsored by the American College of Cardiology.

New technology and improvements to current technology will lead to more in-

formation and greater efficiencies, reported Dr. Cerqueira of the Cleveland Clinic.

Dr. Cerqueira highlighted a number of advances:

► Attenuation from the breast and diaphragm and scatter from the liver and gut are big problems, especially in women and obese patients. Scanners with combined single-proton emission computed tomography (SPECT) and CT are beginning to address these issues.

Several constituents of vulnerable plaques are inviting targets for radiotracers, including clotting components and LDL and HDL cholesterol.

A combined, six-slice, SPECT/CT provides high-quality SPECT images with attenuation, scatter, and resolution correction. It also provides calcium scoring and CT coronary angiography.

But these scanners are expensive, they're quite large, and they require shielding, he said.

"We had to basically take two imaging rooms and combine them to put this system in place," Dr. Cerqueira said.

He added that new, smaller systems tailored to the practice setting will soon become available.

► PET scanners and combined PET/CT scanners will also make important contributions to cardiology. PET has much higher spatial resolution than SPECT,

about 4-5 mm, vs. 16 mm. Attenuation correction can be quite accurate with these systems, and they can be used to make precise measurements of absolute myocardial blood flow and coronary flow reserve.

This is especially important in the context of balanced disease, which is otherwise difficult to diagnose.

► Single acquisition rest/stress testing using two isotopes may soon become a reality.

Dr. Cerqueira envisions a protocol involving an initial infusion of 4.5 mCi of thallium-201, followed 30 minutes later by a stress test.

At the conclusion of the stress test

would be an infusion of 9.0 mCi of technetium-99m, followed 30 minutes later by the acquisition of a rest image.

► Just a stress study, with no accompanying rest study, could be used to improve efficiency in certain patients.

The best candidates would be patients judged to be of low risk on the basis of risk factors, calcium scoring, or biomarkers. If the stress study proved to be normal, they would not need a rest study, according to Dr. Cerqueira.

On the other hand, if the stress study results proved to be abnormal, management decisions could be made on the basis of that study alone, or a rest study could be ordered.

► New systems to image vulnerable plaques may soon become a reality. Several constituents of vulnerable plaques provide inviting targets for radiotracers, he commented.

These include LDL cholesterol, oxidized LDL cholesterol, HDL cholesterol, membrane components of macrophages such as metalloproteinases, G-protein signaling or tyrosine kinase from smooth muscle cells, and clotting components, Dr. Cerqueira said.

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.

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).

Noninvasive Angiography a Reality With CT

BY ROBERT FINN
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SAN FRANCISCO — With CT angiography, "patients literally go home with a Band-Aid and a bottle of water" after just 20 minutes, Matthew J. Budoff, M.D., said at a cardiovascular imaging conference sponsored by the American College of Cardiology.

With high sensitivity and specificity and images that rival the resolution obtainable with traditional coronary angiography from the catheterization lab, CT angiography will allow many more patients to avoid an invasive procedure, said Dr. Budoff of Harbor-UCLA Medical Center, Torrance, Calif.

After an injection of 80-100 mL of non-ionic iodinated contrast solution, up to 4,000 two-dimensional images can be obtained within 20-30 seconds as the patient holds his or her breath. The entire procedure takes 20 minutes, and interpretation takes another 10 minutes, according to Dr. Budoff.

Sophisticated workstations assemble the stack of 2D images into a three-dimensional reconstruction. Interpretations are made on the basis of the 3D reconstruction with reference to the 2D images.

Dr. Budoff started working with CT angiography in the mid-1990s. In those days it took 3 weeks of full-time computation to assemble a single 3D reconstruction. This same function takes just 30 seconds today.

And these workstations allow the cardiologist to rotate the heart image in three dimensions, to zoom in to interesting features, and to easily reference the original 2D data from any point of

interest, he said at the conference.

The initial studies of four-slice CT angiography revealed the limitations of this early technique. Only 30% of patients had all three major arteries available for analysis, and in detecting stenosis the sensitivity was just 58% with 76% specificity.

Nowadays, as 16-slice and even 64-slice CT angiography become available, the sensitivity and specificity have improved considerably. Studies have calculated sensitivities as high as 97% and specificities as high as 94%.

Most important, the negative predictive value is 98%-100%.

"The benefit of CT angio is that when the coronaries look normal, the coronaries are normal," Dr. Budoff said at the meeting.

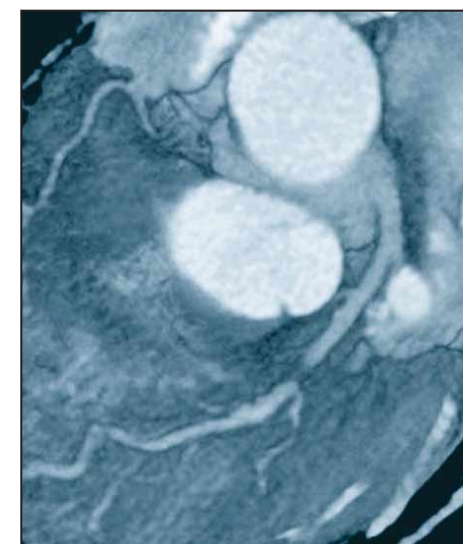
The temporal resolution of the CT images is about 175 milliseconds, so reducing the heart rate to below 60 beats per minute is important for accuracy and interpretability.

Most centers use 100 mg metoprolol 1 hour prior to the study and/or a 5-mg intravenous metoprolol push every 5 minutes until the patient achieves a slow heart rate.

A regular rhythm is also important. If there's a regular rhythm, with multiple detectors obtaining images at specific parts of the heart cycle, the modality reaches an effective frame speed of 15 images per second.

This is slower than the cath lab, but fast enough that the images are free of motion artifact.

CT angiography may be the best technique for imaging the results of bypass grafting as the anastomoses are clearly visible.



CT angiography reveals high-grade stenosis (dark area) in the mid-left anterior descending artery.

Other clinical indications for CT angiography are: in cases of equivocal results following stress testing; to evaluate patency post angioplasty, post stent, and post bypass surgery; in cases of congenital abnormalities and anomalous coronaries; before and after atrial fibrillation ablation; and before placing a biventricular pacer.

CT angiography is not without its disadvantages, however. It's not very good for visualizing vessels with diameters less than 1.5 mm.

It is subject to artifacts from extensive calcification, stents, or extensive clips after bypass grafting.

And it subjects patients to a relatively high dose of radiation—about 9.3-11.3 mSv, compared with 2.1-2.3 mSv for the cath lab and 0.1 mSv for a chest x-ray, Dr. Budoff said.

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