Neurologic Events Higher With TAVR

BY MITCHEL L. ZOLER

FROM THE AMERICAN ASSOCIATION FOR THORACIC SURGERY ANNUAL MEETING

PHILADELPHIA – The percutaneous, transcatheter replacement of stenotic aortic valves has captured attention as an option for patients who are either too sick to undergo surgical aortic valve replacement, or who are surgical candidates but who prefer to avoid sternotomy.

Despite early success with the use of transcatheter aortic valve repair (TAVR) in the two parts of a recent pivotal trial, Dr. D. Craig Miller said the approach has two important limitations: the poorly defined long-term durability of percutaneous aortic valves (which thus far have track records of less than 3 years) and the significantly increased risk of a neurologic event from TAVR, compared with conventional open aortic valve repair (AVR).

A summary analysis of neurologic events following TAVR in the Placement of Aortic Transcatheter Valve (PARTNER) trial showed a total, 1-year event rate of 6% in the as-treated TAVR patients who received their valves via the trans-

See TAVR page 4

FDA Panel Wants Answers on Trilipix Effectiveness

BY ELIZABETH MECHCATIE

FROM A MEETING OF THE FDA’S ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

SILVER SPRING, MD. – Members of a Food and Drug Administration advisory panel were divided on how and whether the label for fenofibric acid should reflect trial results showing no benefit of fibrate therapy in reducing cardiovascular disease risk when added to a statin in patients with type 2 diabetes, but agreed that a new trial is the only way to get a definitive answer.

At a meeting, 6 of the 13 members of the panel agreed that the marketing of fenofibric acid should be allowed to continue, with the addition to the label of the main findings of the study – the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial.

Four panelists, however, voted to recommend that the co-administration indication be withdrawn, citing the lack of solid evidence to support the indication. The remaining three panelists voted to allow continued marketing with no changes to the label.

Fenofibric acid, formulated in a delayed-release capsule and marketed by Abbott Laboratories as Trilipix, was approved by the FDA in December 2008. The drug’s indication includes its use with a statin as an adjunct to diet to reduce serum triglyceride (TG) levels and increase serum HDL cholesterol levels in patients with mixed dyslipidemia and coronary heart disease (CHD) or a CHD risk equivalent who are on “optimal statin therapy” to achieve their LDL cholesterol goal. Fenofibric acid is the active ingredient of fenofibrate, a fibrate approved in 1993 that is now available in generic formulations. It is also approved as monotherapy, so any changes to the co-administration indication would not affect its availability.

The FDA convened the panel to review the co-administration indication. See Trilipix page 5

Patients with smaller, tighter aortic valves were more likely to experience an early neurologic event.
HEART OF THE MATTER
On Transcatheter Aortic Valves

The natural history and pathology of aortic stenosis has been well de- scribed since the mid-18th century by John Baptist Morgagni. Its latency pe- riod usually runs 6-7 decades before ex- pressing its classic symptoms. Once the symptoms of heart failure, angina, and syncope occur, the life span of patients is measured in 1-2 years.

Because of the increased number of octogenarians around these days, aortic stenosis has become a larger therapeutic problem to cardi- ologists. Unfortunately, when octogenarians come to the doctor with the symptoms of aortic stenosis, they usually bring a number of other comorbidities, such as coronary artery disease, diabetes, pul- monary insufficiency, and re- nal dysfunction, just to name a few. Surgical intervention in these pa- tients carries high risk and both the pa- tient and surgeon are reluctant to proceed with high-risk surgery in such a complex medical environment.

The recent development of a percuta- neous aortic valve that can be implanted either transvenously or transapically has provided interesting options for these el- derly patients. Several transcatheter aor- tic valves are now available in Europe, but until the last few months there have been no randomized clinical trials evaluating these efficacy.

The two most recent trials, the PART- NER trials, using a SAPIEN heart valve system (Edwards Lifesciences) have pro- vided an opportunity to consider the poten- tial benefits of transcatheter aortic valve replacement (TAVR). The first reported trial compared TAVR to stan- dard medical therapy in patients with se- vere aortic stenosis deemed inoperable for traditional aortic valve replacement (AVR). A second group of patients with se- vere aortic stenosis was randomized to ei- ther TAVR or AVR. Both studies have pro- vided optimism that these percuta- neous devices can provide significant benefit.

The initial PARTNER study random- ized 358 stenosis patients who were con- sidered to be inoperable, to either TAVR or standard medical therapy including in- some case balloon aortic valvulotomy (N. Engl. J. Med. 2010; 363:1597-607). That trial re- ported a 30-day mortality of 5.0% and 2.8% and a 1-year mortality of 30.7% and 50.7% in the TAVR and standard medical therapy groups, respectively. Associated with this improvement in mortality, there was both symptomatic improvement and decrease in hospitalization in the TAVR treated patients. There was, however, an increase occurrence of major strokes, at 5.0% in the TAVR patients compared with 1.1% in the medical patients.

The most recent PARTNER trial re- ported at the annual meeting of the Ameri- can Cardiology compared TAVR to stan- dard surgical AVR in patients with severe aortic stenosis. In that trial, 699 patients with mean aortic valve area of 0.6-0.7 cm², most of whom were in New York Heart Association functional class III-IV, the 30-day mortality was 3.4% vs. 6.5% and the 1-year mortality was 24.2% vs. 26.8% in the TAVR compared to AVR respectively. There was, however, an increase in all strokes in the TAVR patients compared to AVR, 4.6% com- pared to 2.4%. Although most of the SAPIEN valves were impl- planted by the transfemoral ap- proach, approximately one- third required the transapical approach because of poor femoral artery access. The device used in PART- NER is currently approved for use in Europe and soon to be available in the United States. Several other tran- scatheter valve systems are currently in de- velopment by device companies, and, the CoreValve (Medtronic) is currently undergoing clinical trials in the United States. The devices included in the early trials have been improved upon and in- vestigators using the Edwards Lifesciences device are currently testing the fourth generation of that valve, which is smaller and easier to pass through the femoral artery. In addition, protection devices are being developed to deal with the observed in- creased stroke morbidity. Although stroke remains a problem, emboli have not been limited to the brain but some reports sug- gest that, there is evidence for intra- coronary embolism.

The development of these valves are ob- viously on the fast track but unfortune- ately little is known about their long-term durability. There are some follow-up data from Europe where the valve has been in use for about 2 years. When weighed against the years of experience and the ex- cellent durability of the current AVR there should be some reticence to the applica- tion of these valves in patients at better surgical risks.

Although the operative risks for either TAVR or AVR are acceptable, considering the natural history of the disease, unfor- tunately the long-term risks of the el- derly patients with aortic stenosis remains high even after successful valve re- place-ment.

Dr. Goldstein, medical editor of Cardiology News, is professor of medicine at Wayne State University and diversion head emeritus of cardiovascular medicine at Henry Ford Hospital, both in Detroit. He is on data safety monitoring committees for the National Institutes of Health and several pharmaceutical companies.

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Hypertension Treatment and Control Increased Significantly From 1999-2002 to 2005-2008

*Among those with hypertension.
Note: Based on data from the National Health and Nutrition Examination Survey. Source: Morbidity and Mortality Weekly Report 2011;60:103-8
Another heart attack is this far away

Are you helping to keep it away?

Despite medical guidelines, millions of at-risk patients remain unprotected by aspirin.1,2 Aspirin can reduce the risk of recurrent MI by 30%.3,4 Counsel your patients today.

Say aspirin. Help save lives.
Medical Tx of Severe Aortic Stenosis Raises Mortality, Costs

BY MITCHEL L. ZOLER
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Elderly patients with severe aortic stenosis who did not undergo aortic valve replacement and received only medical management had a poor survival rate of less than 2 years, and also incurred a lot of medical expenses, averaging about $29,000 a year, based on a review of more than 2,000 Medicare patients.

“Transcatheter aortic valve replacement surgery shows promise in treating the most severe AS (aortic stenosis) patients at highest risk for mortality and potentially reducing long-term costs to the Medicare program,” Mary Ann Clark said at the meeting.

Based on the cost findings in this analysis, which included a 5-year follow-up of Medicare records for patients with an index hospitalization for severe AS in 2003, the cumulative annual cost to Medicare for the 435,000 American patients with severe AS reached nearly $1.3 billion, said Ms. Clark, vice president for health economics and reimbursement at Neocure, a medical economics analysis company in Washington.

“These patients are really sick, they die [fairly quickly], and they cost a lot of money. If you have the transcatheter aortic valve replacement option, that may be a cost-effective solution,” Ms. Clark said in an interview.

An unrelated report at the meeting showed the cost effectiveness of transcatheter aortic valve replacement, documenting a cost of just over $50,000 per life-year gained, on the basis of data collected in the portion of the PARTNER (Placement of Aortic Transcatheter Valve) trial that randomized inoperable patients with severe AS to either transcatheter valve replacement or medical management.
The analysis reported by Ms. Clark and her associates used data collected on 2,150 patients with severe AS hospitalized in 2003, a 5% sample of Medicare patients contained in the program’s Standard Analytic Files. The analysis subdivided the patients into two groups: high-risk patients who had a Euroscore— a predicted operative mortality rate from cardiac surgery – of 20% or more, and non-high-risk patients who had a Euroscore of less than 20%. The 651 high-risk patients averaged 87 years old, 71% were women, and their average Euroscore was 34%. The non-high-risk patients averaged 81 years old, 66% were women, and their average Euroscore was 10%.

Medicare records during 2004-2008 for these 2,150 patients showed their overall all-cause survival reached 1.8 years, with an average survival rate of 1.4 years in the high-risk patients and 2.0 years in the non-high-risk patients. The 5-year survival rate ran 12% in all patients, and 5% in the high-risk group. The average 5-year costs for all patients in the study reached nearly $64,000, with half of these costs being for follow-up inpatient hospitalizations. The average cost worked out to somewhat more than $29,000 per patient year, after the cost of their index hospitalization was excluded.

In multivariate analyses, factors that significantly contributed to higher mortality included active endocarditis and metastatic cancer or acute leukemia. Factors significantly linked with an increased risk for death included the need for dialysis and diabetes, Ms. Clark said.

Deciding which patients should undergo TAVR will require “defining the line between utility and futility” he commented. “You don’t want to empty every nursing home in California of patients with aortic stenosis, and on the young side, you don’t want the percutaneous option used in patients at low surgical risk.” Concern about using TAVR on patients who are good open surgery candidates focuses on the unknown long-term durability of TAVR, and the “high price to pay in neurologic events, at least in the current version of TAVR,” said the expert.

The data Dr. Miller reported came from cohort A of the PARTNER trial, the cohort that focused on patients who could be randomized to either TAVR or open AVR. The primary end point of all-cause mortality in this cohort, reported in April at the annual meeting of the American College of Cardiology, showed that 1-year survival following TAVR was better than open AVR (CARDIOLOGY NEWS, May 2011, p. 1). Another prior report, for cohort B (patients considered too sick to undergo open AVR), showed that TAVR produced superior outcomes, compared with conventional medical management (N. Engl. J. Med. 2010;363:1597-607).
Antiplatelet Therapy: How is YOUR Patient Responding?

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Patients who do not respond adequately to their antiplatelet therapies may be at significantly increased risk for heart attacks, stent thrombosis or death.

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NEW: TESTING IS NOW IN THE ACCF/AHA GUIDELINES
Health Providers Examine Promise of ACOs

BY MARY ELLEN SCHNEIDER

The medical model of “the more you do, the more you make” is out, according to Dr. William Chin, and so is the idea that the physician needs to do everything personally. If a service can be delivered more efficiently by a nurse or social worker, that may be the way to go under the next big thing in health care — the accountable care organization.

Dr. Chin, executive medical director for HealthCare Partners, an independent physician association (IPA) based in Torrance, Calif., said his group plans to participate in the new Medicare shared savings program for ACOs, which will launch in January. The group has been preparing for the transition for a while. They are currently also working with Anthem Blue Cross in California to test how an ACO would work in the commercial market as well as testing ACO accreditation standards being developed by the National Committee for Quality Assurance (NCQA).

Cardiologists are in a good position to thrive in accountable care organizations, according to Dr. Jack Lewin, CEO of the American College of Cardiology. Tools for sharing information between cardiologists, like the National Cardiovascular Data Registry, are already in place and will make it easier for cardiologists to transition to ACOs. Dr. Lewin said. But even with electronic health records in place, Dr. Lewin said, all practices seeking to become ACOs will have to integrate economically and share their registries.

ACOs have been a hot topic in health care circles since they were written into the Affordable Care Act. The law includes the shared savings program through Medicare, which will allow ACOs to earn additional payments if they can both save the government money and meet quality benchmarks. As the program goes forward, physicians also would assume some financial risk if they are unable to provide cost-effective care. Officials at the Centers for Medicare and Medicaid Services released a proposed regulation on March 31 outlining how the Medicare ACO program will work. Under the new voluntary program, ACOs could include physicians in group practices, networks of individual practices, hospitals that employ physicians, and partnerships between these entities, as well as other providers. An ACO will be a partnership among both primary care and specialist physicians; however, only primary care providers will be able to form an ACO, according to the proposed regulation.

Providers working in an ACO would continue to receive regular payments under Medicare fee for service, but could qualify for additional payments if they save money for the program. The proposed regulation requires that ACOs meet quality standards and demonstrate that they have reduced costs in order to be eligible to share in savings. The proposal outlines 65 quality measures in five domains: patient experience, care coordination, patient safety, preventive health, and metrics for the care of at-risk and frail elderly populations.

“It is integration of care that is most critical,” Dr. Lewin said. Even as cardiologists may be better situated for the transition, their challenge will be to meet the quality measures, as 20 of the 65 measures apply specifically to cardiovascular disease, according to Dr. Lewin.

One area in which physicians may need to make investments is in health information technology. Jonathan Blum, director of the Center for Medicare Management, said the ACO proposal is closely aligned with the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 and the electronic health record incentive programs. Coordinating the ACO quality measures with those in the EHR incentive programs reduces the burden on physicians and hospitals that are submitting data through the various programs, Mr. Blum said. It also offers the potential for physicians to offset some of their technology costs through the bonus payments they can earn by achieving meaningful use of their EHRs.

The move to ACOs will be a major shift, said Dr. Paul Grundy, director of health care transformation for IBM and president of ASONA, and specialist physician directors of onallteil.

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MULTAQ®

In EURIDIS/ADONIS

Prolonged time to first recurrence and reduced the symptomatic burden of AFib

25% RRR

of first symptomatic or asymptomatic AFib recurrence

- Absolute difference in recurrence rate of about 11% at 1 year (P<0.001; primary endpoint)

- The majority of recurrences were symptomatic

62.3% of MULTAQ patients were free of symptomatic AFib recurrence vs 54% on placebo at 1 year (P<0.001; secondary endpoint)

In ATHENA

The first and only AAD with proven efficacy in a outcomes trial

24% RRR

in CV hospitalization or mortality, the combined primary endpoint (P<0.0001, entirely attributable to CV hospitalizations)

Important Safety Information

MULTAQ® is contraindicated in patients with 
NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompenstation requiring hospitalization or referral to a specialized heart failure clinic. In the ANDROMEDA Study, a greater than two-fold increase in mortality was observed in this unstable population (see full boxed WARNING).

Important Update: Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ® in the postmarketing setting. A liver injury section has been added to the Important Safety Information. Please see additional Important Safety Information and brief summary of Prescribing Information, including boxed WARNING, on adjacent pages.

MULTAQ® is a multiwave treatment when administered with or without food.

Visit www.MULTAQ.com

MULTAQ® is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL), with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction (LVEF)<40%), who are in sinus rhythm or who will be cardioverted.

Visit www.MULTAQ.com
Important Safety Information for MULTAQ®

Contraindications

WARNING: HEART FAILURE
MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given MULTAQ had a greater than two-fold increase in mortality. Such patients should not be given MULTAQ.

• MULTAQ is also contraindicated in patients with second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker), bradycardia <50 bpm, GTC Baxsell interval >500 msec or PR interval >280 msec, and severe hepatic impairment.

• MULTAQ should not be given to patients who are or may become pregnant (Category X) or nursing. MULTAQ may cause fetal harm when administered to a pregnant woman.

• MULTAQ should not be coadministered with strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, ritonavir, or drugs or herbal products that prolong the QT interval and might increase the risk of Torasde de Pontes, such as phenothiazine antipsychotics, tricyclic antidepressants, certain macrolide antibiotics, and Class I and III antiarrhythmics.

New or Worsening Heart Failure
Postmarketing cases of new onset and worsening heart failure have been reported during treatment with MULTAQ. Advise patients to consult a physician if they develop signs and symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

Liver Injury
Hepatocellular liver injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the postmarketing setting. Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching).

Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment. It is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not restart MULTAQ in patients without another explanation for the observed liver injury.

Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics
Hypokalemia and hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

QT Interval Prolongation
MULTAQ induces a moderate (average of about 10 msec) but much greater effects have been observed (ΔTc [Bazett] prolongation). If the ΔTc Bazett interval is >500 msec, MULTAQ should be stopped.

Increase in Creatinine
Serum creatinine levels increase by about 0.1 mg/dL following MULTAQ treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient’s new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine’s tubular secretion, with no effect upon the glomerular filtration rate.

Drug-Drug Interactions
• Treatment with Class I or III antiarrhythmics or drugs that are strong inhibitors of CYP 3A must be stopped before starting MULTAQ (see Contraindications).

• Patients should be instructed to avoid grapefruit juice beverages while taking MULTAQ.

• Calcium channel blockers and beta-blockers could potentiate the effects of MULTAQ on conduction.

• Increased digoxin levels and gastrointestinal disorders have been observed when MULTAQ was coadministered with digoxin. Digoxin can also potentiate the electrophysiologic effects of MULTAQ (such as decreased AV-node conduction); the need for digoxin therapy should be reconsidered when prescribing MULTAQ. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

• Postmarketing cases of increased INR with or without bleeding events have been reported in warfarin-treated patients initiated with MULTAQ. Monitor INR after initiating MULTAQ in patients taking warfarin.

Adverse Reactions
In studies, the most common adverse reactions observed with MULTAQ were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

Please see brief summary of Prescribing Information, including boxed WARNING, on adjacent pages.

References:
**Subgroup Analyses ‘Treacherous’**

Trilixip from page 1

of fenofibrate in the context of the ACCORD Lipid study results. That study found no benefit of combination treatment with fenofibrate and simvastatin on major cardiovascular events, compared with treatment with simvastatin alone, over a mean of almost 5 years of follow-up. The study enrolled more than 5,500 patients with type 2 diabetes at high risk of cardiovascular disease, with a range of TG and HDL levels.

MULTAQ® (dronedarone) Tablets

Rx Only

**WARNING: HEART FAILURE**

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II – III heart failure with a recent deterioration requiring hospitalization or referral to a specialized heart failure clinic (see Contraindications (4)).

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (see ANDREONA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone (see Clinical Studies (14.3) in the full prescribing information).

**1 INDICATIONS AND USEAGE**

Dronedarone is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of A-F and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter >55 mm or left ventricular ejection fraction ≤ 40%), who are in sinus rhythm or who will be cardioverted (see Clinical Studies (14.3) in the full prescribing information).

**2 DOSAGE AND ADMINISTRATION**

The recommended dosage of MULTAQ is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal.

Treatment with Class I or II antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, dicoxidam, dofetilide, lidocaine) or drugs that are strong inhibitors of CYP3A4 (i.e., ketoconazole) must be stopped before starting MULTAQ (see Contraindications (4))

**4 CONTRAINDICATIONS**

MULTAQ is contraindicated in patients with:

- NYHA Class II heart failure or NYHA Class II – III heart failure with a recent deterioration requiring hospitalization or referral to a specialized heart failure clinic (see Boxed Warning and Clinical Studies (14.3) in the full prescribing information)
- Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradyarrhythmia >50 bpm
- Concomitant use of strong CYP 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, tamoxifen, clarimethoxazole, and rifampicin, and fluoroquinolones (see Drug Interactions (7.6))
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of torsade de pointes, such as phenothiazine anti-psychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- QTc Bazett interval >500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy/Caytory X: MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus (see Use in Specific Populations (8.1))
- Nursing mothers (see Use in Specific Populations (8.3))

**5 WARNINGS AND PRECAUTIONS**

**5.1 Patients with New or Worsening Heart Failure during Treatment**

Postmarketing cases of new or worsening heart failure have been reported during treatment with MULTAQ. Adverse patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

**5.2 Liver Injury**

Hepatocellular or mixed injury, including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the post-marketing setting. Adverse patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as nausea, anorexia, vomiting, diarrhea, jaundice, pruritis, right upper quadrant pain, jaundice or elevation in alkaline phosphatase, and pain in the right upper abdomen). If the patient is on concomitant treatment with other drugs that have a risk of hepatotoxicity and if the hepatotoxicity is suspected, promptly discontinue MULTAQ and test serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, as well as serum bilirubin, to establish whether there is liver injury. If liver injury is found, institute appropriate treatment and investigate the probable cause. Do not use MULTAQ in patients without an explanation for the observed liver injury.

**5.3 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics**

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

**5.4 QT Interval Prolongation**

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc Bazett prolongation (see Clinical Pharmacology (12.2) in the full prescribing information and Clinical Studies (7.4) in the full prescribing information). If the QTC Bazett interval is >500 ms, MULTAQ should be stopped (see Contraindications (4)).

**5.5 Increase in Creatinine after Treatment Initiation**

Serum creatinine levels increase by about 0.1 mg/dL after dronedarone treatment initiation. The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient’s new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine’s tubular secretion, with no effect upon the glomerular filtration rate.

**5.6 Women of Childbearing Potential**

Premenopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone causes fetal harm in animal studies (see Contraindications (4)).

**6 ADVERSE REACTIONS**

The following adverse reactions are described elsewhere in the label:

- New or worsening heart failure (see Warnings and Precautions (5.1))
- Liver injury (see Warnings and Precautions (5.2))
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics (see Warnings and Precautions (5.3))
- QT prolongation (see Warnings and Precautions (5.4))

**6.1 Clinical Trials Experience**

The safety evaluation of dronedarone 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EUROSIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6509 patients were randomized and treated. 3002 patients with MULTAQ 400 mg twice daily, and 3507 with placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

In clinical trials, premature discontinuation because of adverse reactions occurred in 7.8% of the dronedarone-treated patients and in 7.7% of the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.3% versus 1.8% in the placebo group) and QT prolongation (5.3% versus 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diarrhea, nausea, abdominal pain, vomiting, and asthma.

Table 1 displays adverse reactions more common with dronedarone 400 mg twice daily than with placebo in AF or AFL, patients, presented by system organ class and by decreasing order of frequency. Events expected from usual therapy with a beta blocker or calcium channel blocker are not presented separately in Table 2.

Table 1: Adverse Drug Reactions That Occurred in at Least 1% of Patients and More Frequent Than Placebo

**Table 2: Laboratory test changes that have been reported with MULTAQ 400 mg twice daily**

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>MULTAQ 400 mg twice daily</th>
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<tbody>
<tr>
<td>Na+</td>
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**7.6 Assessment of Demographic factors such as gender and age on the incidence of treatment emergent adverse events did not suggest an excess of adverse events in any particular sub-group**

**7.7 Postmarketing Experience**

The following adverse reactions have been identified during post-gosignual use of MULTAQ. Because these reactions are reported voluntarily from a population of all unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac: Heart failure (see Warnings and Precautions (5.1))
Postmarketing cases of new onset and worsening heart failure have been reported during treatment with MULTAQ.

Hepatic. Severe hepatic enzyme and serum bilirubin increase. Hepatic/renal injury, including acute liver failure requiring transplant, has been reported [see Warnings and Precautions (5.2)].

7 DRUG INTERACTIONS

Dronedarone is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 [see Clinical Pharmacology (12.3) in the full prescribing information]. Dronedarone’s blood levels can therefore be affected by inhibitors and inducers of CYP 3A, and dronedarone can interact with drugs that are substrates of CYP 3A and CYP 2D6.

Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A. It has the potential to inhibit P-glycoprotein (P-gp) transport.

Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin (see Drug Interaction (7.2) and Contraindications (4)).

In clinical trials, patients treated with dronedarone received concomitant medications including beta-blockers, calcium channel blockers (including those with heart rate-lowering effects), statins and oral anticoagulants.

7.1 Pharmacodynamic Interactions

Drugs prolonging the QT interval including Torasemide de Pointes)

Co-administration of drugs prolonging the QT interval (such as certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics, and Class I and II antiarrhythmics) is contraindicated because of the potential risk of Torasemide de Pointes-like ventricular tachycardia (see Contraindications (4)).

Digoxin

Digoxin can potentiate the electrophysiological effects of dronedarone (such as decreased AV-node conduction). In clinical trials, increased levels of digoxin were observed when dronedarone was co-administered with digoxin. Gastrintestinal disorders were also increased. Because of the pharmacokinetic interaction (see Drug Interaction (7.3)), it is possible theophylline concentrations to rise as much as 3-fold in CYP 3A substrates. Theophylline is a CYP 3A substrate.

Other CYP 2D6 substrates, including other beta-agonists and certain antidepressants (including those with heart rate-lowering effects), statins and oral anticoagulants.

Dronedarone increases plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with narrow therapeutic range when given orally. Monitor plasma concentrations and adjust dosage appropriately.

Beta-blockers and other CYP 2D6 substrates

Dronedarone increased propranolol exposure by approximately 1.3-fold following single dose administration and increased dextromethorphan exposure by 1.6-fold following multiple dose administration (see Drug Interaction (7.7)). Other CYP 2D6 substrates, including other beta-blockers, Irbycic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone.

F-glycoprotein substrates

Diphenoxylate

Dronedarone increased diphenoxylate exposure by 2.5-fold by inhibiting the P-gp transporter (see Drug Interaction (7.7)).

Rosiglitazone Restricted

To Mail Orders, FDA Says

BY MIRIAM E. TUCKER

FROM THE FDA

The Food and Drug Administration has further restricted use of the diabetes drug rosiglitazone and related medications because of risks associated with their use. Patients must now be enrolled in the Avandia Rosiglitazone Medicines Access Program in order to prescribe or receive rosiglitazone medicines. Patients who are enrolled in that program will receive their medicine by mail order through specially certified participating pharmacies.

Health care providers should determine whether their patients are appropriate candidates to receive treatment with rosiglitazone medicines, based on the risks and benefits compared with other therapies. Enrollment in the Avandia Rosiglitazone Medicines Access Program is required for health care providers who wish to prescribe rosiglitazone medicines to outpatients or to patients in long-term care facilities.

To enroll, health care providers must review the prescriber overview and the full prescribing information, including the medication guide, and must complete and sign the prescriber enrollment form. A copy of the medication guide must be provided to and reviewed by the patient or caregiver, and the health care provider must enroll eligible patients into the program by completing and signing a patient enrollment form. If a patient who has been taking a rosiglitazone medication is hospitalized, the patient must be enrolled in the Avandia Rosiglitazone Medicines Access Program to continue receiving the medicine; however, the patient’s health care provider in the hospital is not required to be enrolled.

Any adverse events involving rosiglitazone medicines should be reported to the FDA MedWatch program at www.accessdata.fda.gov/scripts/medwatch.
New LVAD May Benefit High-Risk PCI Patients

BY MITCHEL L. ZOLER
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OR CARDIOLOGY

NEW ORLEANS – Introduced to the U.S. market in 2008 as an upgraded alternative to the intra-arterial balloon pump (IABP), Dr. Ron Waksman noted signs of better performance in high-risk patients undergoing percutaneous coronary intervention in a multicenter, randomized trial with 447 patients.

But once Impella 2.5 entered the U.S. market, enrollment into the study slowed dramatically. Eventually, researchers stopped the trial substantially short of its enrollment target, and the pivotal study’s primary end point did not show a statistically significant benefit for Impella 2.5.

The trial also ran into a second problem with a major confounding issue: Interventional cardiologists used rotational atherectomy more aggressively in Impella-treated patients. They seemingly were convinced by the added cardiac support, and Impella-treated patients had an unbalanced rate of adverse effects.

Despite these problems, the trial results showed a role for the Impella device in high-risk, low-cardiac-output patients undergoing PCI. Dr. William O’Neill said at the meeting. “This device produces superb hemo-
dynamic support during high-risk inter-
ventions. It really allows a more complete and safer procedure. I think [that capability] will
translate into increased use [of the de-
vice] in these high-risk patients,” he added.

Experts who heard the trial results were split on their interpretation of the findings.

“This was a negative study. What is driving the differences you see? I don’t un-
derstand how to reconcile the results with your conclusion to go ahead [with using] this device,” commented Dr. Ron Waks-
man, director of experimental angioplas-
ty at Washington (D.C.) Hospital Center.

But Dr. Roxanna Mehran gave the findings a much more positive spin (see box, below right).

PROTECT II was a prospective, multicenter, randomized, controlled trial of the Impella Recover LP 2.5 system vs. IABP (intra-aortic balloon pump) in patients undergoing nonemergent, high-risk PCI. The trial began in November 2007 at 67 U.S. sites, 4 sites in Canada, and 1 site in the Netherlands. It enrolled patients with either unprotected left main coronary disease and a left ventricular ejection fraction of 35% or less, or patients with triple-vessel coronary disease and an ejection fraction of 30% or less.

The primary end point was the rate of death, MI, stroke, need for repeat revascularization, need for cardiovascu-
lar surgery or vascular surgery for limb is-
chemia, acute renal dysfunction, increased aortic insufficiency, severe hypotension, need for cardiopulmonary resuscitation, ventricular tachycardia, or failure to re-
open the target coronaries by PCI.

The patients averaged 67 years old, 80% were men, and 56% had New York Heart Association class III or IV heart failure. Their average Society of Tho-
racic Surgeons (STS) mortality score was 6, their average SYNTAX (Synergy Be-
tween PCI and Coronary Artery Surgery) score was 30, and 63% were considered ineligible for surgery. The population “was extraordinarily high risk, the most complex patients ever en-
rolled in a multicenter, randomized, con-
trolled trial,” Dr. O’Neill said.

There were 447 patients enrolled in PROTECT II before the study’s data and safety monitoring board stopped the trial last December citing “futility” on the primary end point. This number was 70% of the number of patients orig-
inally identified as needed to show a statistically significant result for the pri-
mary end point. Enrollment into the study sharply slowed once the Impella device came onto the U.S. market in June 2008.

During PCI, the participating opera-
tors generally managed the Impella pa-
tients more aggressively. Heparin was given to 94% in the Impella arm and to 82% in the IABP control arm. Rotation-
al atherectomy was performed in 15% of the Impella patients and in 10% of pa-
tients in the IABP group. This was a sig-
nificant difference. Also, participating operators used atherectomy more ag-
gressively in the Impella patients, with an average of five atherectomy passes per

patient, compared with two passes in the IABP patients.

Although this shift in treatment ap-
proach may have ultimately benefited some of the Impella patients, it also “in-
creased the major adverse event rate and confounded the analysis,” Dr. O’Neill said.

Among the 88% of pa-
tients in the study who were not treated with rotational atherectomy, the 30-day major adverse event rate reached 30%, compared with 42% in the IABP pa-
tients, a statistically significant differ-
ence. A significant difference in the pri-
mary outcome in favor of the Impella patients also occurred in the subgroup that had an STS mortality score lower than 10.

The results also showed a strong trend toward a better primary outcome in the Impella-treated patients when the analysis excluded the first Impella-treated patient for each operator, a finding that highlighted an important learn-
ing curve in using the device, Dr. O’Neill said.

Analysis also showed that the 90-day rate of major adverse events in the Impel-
la patients fell from 48% in 2008 to 39% in 2009 and to 37% in 2010. In con-
trast, the rate in the IABP patients stayed fairly constant (at 47%-52%) in all 3 years, again highlighting the role of ex-
perience with the Impella device in achieving better patient outcomes, he said.

“I think many clinicians will see [from these data] that Impella provides a lot of safety,” Dr. O’Neill said.
Shorter Antiplatelet - x After Stenting Safe

BY CAROLINE HELWICK
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Short and standard durations of dual-antiplatlet therapy were equally protective against target vessel failure and drug-eluting stent recipients, Korean researchers reported at the meeting. With the exception of patients who had diabetes, the overall 12-month clinical event rates were not different between 6- and 12-month treatment duration groups for all-cause mortality, cardiac death, MI, cerebrovascular accident, target vessel revascularization (TVR), stent thrombosis, major bleeding, or various combinations of these outcomes, they reported Dr. Hyeon-Chel Gwon of Samsung Medical Center at Sunygyunkwan University in Seoul.

“At least in low-risk patients getting drug-eluting stents, that is, non-diabetics, maybe we can safely discontinue clopi- dogrel at 6 months,” he said. Current guidelines recommend at least 12 months of anticoagulation to prevent venous thromboembolism. Current guidelines recommend at least 18 months of anticoagulation to prevent venous thromboembolism.

Early discontinuation of antiplatelet therapy might be particularly relevant for patients at high risk of bleeding or those anticipating subsequent procedures, which are often delayed while the drugs are withdrawn. But Dr. Sanjay Kaul of Cedars-Sinai Medical Center, Los Angeles, questioned the researchers’ use of target vessel failure (TVF) as the primary study end point. TVF was defined as a composite of cardiac death, MI, or TVR. Dr. Kaul acknowledged that, saying “We recognize our study is hypothesis generat- ing.”

The trial involved 1,443 patients with greater than 50% stenosis and evidence of myoccardial ischemia. Patients receiving everolimus-eluting stents were randomized to receive either 6 or 12 months of dual-antiplatlet therapy with clopidogrel and aspirin.

The study found that discontinuing clopidogrel and aspirin after 6 months did not increase the rate of 12-month TVF. The rates were 4.7% for the 6-month group and 4.4% for the 12-month group. By Kaplan-Meier analysis, the cumulative proportional estimate of target vessel failure at 1 year was 5.2% for the 6-month regi- men and 4.3% for the 12-month regimen.

Data Source: A study of 1,443 patients receiving everolimus- or sirolimus-eluting stents and ran- domized to either 6 or 12 months of clopidogrel and aspirin.

Disclosures: Dr. Gwon reported consulting fees and honoraria from Cordis and Medtronic as well as research support from Ab- bort Korea and Medtronic Korea. Dr. Kaul has received consulting fees and honoraria from Novo Nordisk and Hoffman-LaRoche.

Major Finding: The rates of 12-month TVF were 4.7% for drug-eluting stent recipients given 6 months of clopidogrel and aspirin and 4.4% for those given 12 months of antiplatelet therapy. By Kaplan-Meier analysis, the cumulative proportional estimate of target vessel failure at 1 year was 5.2% for the 6-month regi- men and 4.3% for the 12-month regimen.

7 DISCUSSION

Type 2 Diabetes Mellitus: Of 1128 patients enrolled in the four diabetes studies, 249 (22%) were ≥ 65 years old, and 12 (1%) were ≥ 75 years old. In these trials, WELCHOL, 3.8 g/day or placebo was added based on background anti-diabetic therapy. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

6.8 Hepatic Impairment

No special considerations or dosage adjustments are recommended when WELCHOL is administered to patients with hepatic impairment.

6.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [Ccr] 50–50 mL/min), 53 (5%) had moderate renal insufficiency (Ccr <30–50 mL/min), and had no severe renal insufficiency (Ccr <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with Ccr <50 mL/min (n=429) and those with a Ccr <50 mL/min (n=705).

10 OVERDOSAGE

Doses of WELCHOL in excess of 4.5 g/day have not been studied. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more local gastrointestinal effects (e.g., constipation) than recommended doses.

8.4 Pediatric Use

The study found that discontinuing clopidogrel and aspirin after 6 months did not increase the rate of 12-month TVF. The rates were 4.7% for the 6- month group and 4.4% for the 12-month group. By Kaplan-Meier analysis, the cumulative proportional TVF estimate at 1 year was 5.2% for the 6-month regimen and 4.3% for the 12-month regimen, which met the non-inferiority end point in “a highly significant manner” (P = .0031; upper 1-sided 97.5% confidence interval 0.9%-3.6%), Dr. Gwon said. The cumulative incidence of major adverse cardiac or coronary events was 7.5% and 7.0% for 6- and 12-month therapy with 8.9% vs. 2.9% with 12 months of treatment. There were no other significant sub- group differences.

{MARKETED BY: Daiichi Sankyo, Inc. Parsippany, New Jersey 07054}
DES Boosted Survival in Primary PCI Patients

Higher 5-year survival with drug-eluting stents shows safety in setting of myocardial infarction.

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Acute myocardial infarction patients treated with a drug-eluting coronary stent during a primary percutaneous coronary intervention had significantly better 5-year survival, compared with myocardial infarction patients who received a bare-metal stent, in a review of more than 12,000 patients treated in New Jersey during 2003-2004. Although this analysis could not take into account selection biases that might have determined whether patients received drug-eluting or bare-metal stents, the findings in general provide reassurance about the safety of drug-eluting coronary stents for patients with an acute MI, Dr. Tudor D. Vagaoanescu said at the meeting.

“These data are consistent with the idea that using drug-eluting stents in the setting of an acute MI is safe,” said Dr. Vagaoanescu, a cardiologist at the Robert Wood Johnson Medical School, New Brunswick, N.J.

“Our data show that preventing the need for revascularization by using drug-eluting stents [DES] helped with survival, although improved survival was likely due to a combination of things, including selection bias and the type of index event,” he said in an interview.

The study used data collected in the Myocardial Infarction Data Acquisition System (MIDAS) registry and included all patients who underwent primary PCI for an acute MI at a nonfederal hospital in New Jersey during 2003-2004. The group included 6,172 patients treated with one or more drug-eluting coronary stents only, and 5,833 patients treated with one or more bare-metal stents only. The analysis excluded patients who received both stent types.

Based on New Jersey death registration files, during the 5 years following stent placement, cumulative all-cause mortality in the DES recipients was 16% and was 20% in the bare-metal stent recipients, a statistically significant difference. The rate of cardiovascular death was 10% in the drug-eluting and bare-metal stent groups, respectively, also a statistically significant difference. Similar, statistically significant differences in favor of improved 5-year total survival and reduced cardiovascular deaths with DES also occurred in both the subset of patients with ST-elevation myocardial infarction and in patients with non-ST-elevation myocardial infarction, Dr. Vagaoanescu reported.

He and his associates also performed multivariate analyses of mortality rates adjusted by age, sex, race, diabetes, hypertension, renal disease, anemia, cancer, cerebrovascular disease, MI, prior MI, and treatment with a glycoprotein IIb/IIIa inhibitor. All of these multivariate analyses showed statistically significant survival advantages for the patients who received drug-eluting stents (see graph).

Another aspect of the analysis showed the dramatic shift toward use of DES for primary PCI during the period studied, which covered the time when first sirolimus-eluting stent received Food and Drug Administration approval in April 2003, and when the first paclitaxel-eluting coronary stent received FDA approval in March 2004. In 2003, 73% of the 6,027 patients who received a single type of coronary stent for primary PCI in New Jersey received a bare-metal stent. By 2004, this pattern flipped, and 76% of the 5,978 patients who received a single type of coronary stent for primary PCI received a drug-eluting stent. Both years predated the reports in 2006 that first raised awareness of the risk for stent thrombosis in patients who received DES, especially patients who prematurely stopped dual-antiplatelet therapy.

Jury Out on First-Generation DES

Major Finding: Acute myocardial infarction patients treated with drug-eluting coronary stents had a 16% mortality rate during 5 years of follow-up, significantly better than the 20% mortality rate in patients treated with bare-metal stents.


Disclosures: Dr. Vagaoanescu said that he had no disclosures.

FDA Expands Carotid Stent Indication to Standard-Risk Patients

BY MARY ELLEN SCHNEIDER

The Food and Drug Administration expanded the indication for the RX Acculink carotid stent, allowing it to be marketed for use in patients with carotid artery disease who do not face an increased risk of complications from surgery.

The RX Acculink stent, which is marketed by Abbott Vascular, a subsidiary of Abbott Laboratories, was originally approved by the FDA in 2004. At that time, the stent was approved for patients at high risk of complications from carotid endarterectomy.

The company sought an expanded approval based on the results of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a randomized, multicenter, noninferiority study sponsored by the National Institutes of Health and funded in part by the manufacturer.

The study of more than 2,500 patients in the United States and Canada showed that at 1 year, patients who were treated with RX Acculink had a combined 30-day rate of death, stroke, and myocardial infarction, and a 31% rate of ipsilateral stroke, of 7.1%, compared with 6.6% among those who underwent endarterectomy, a difference that met the prespecified criteria for noninferiority.

As a condition of the expanded approval, the FDA is requiring Abbott Vascular to conduct a postapproval study. The study would follow new patients treated with RX Acculink for at least 3 years to confirm the results from the CREST study.

The FDA has also asked the manufacturer to look at how patients aged 80 years and older respond to treatment and whether patients who show symptoms prior to treatment experience different outcomes than those who don’t exhibit symptoms.

The FDA’s action follows a recommendation from the Circulatory System Devices Panel. In January, a majority of those experts voted that the benefits of using the RX Acculink stent outweighed the risks when used in patients at standard risk for surgery.
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- DBP/SBP reductions of up to -15.3/-29.0 mm Hg for BYSTOLIC when used in combination with HCTZ 25 mg (vs -1.4/-0.2 mm Hg for placebo)
- DBP/SBP reductions of -9.3/-16.7 and -13.8/-17.6 for BYSTOLIC monotherapy 5 mg and 10 mg, respectively (vs -1.4/-0.2 for placebo)

**Low incidence of side effects and overall low discontinuation rate**

- Discontinuation rate due to adverse events was 2.8% for BYSTOLIC vs 2.2% for placebo

* Results from a 3-month, multicenter, randomized, double-blind, parallel-group, placebo-controlled, multifactorial-design study of BYSTOLIC and hydrochlorothiazide, alone or in combination, for the treatment of mild to moderate hypertension.
† Primary endpoint was sitting DBP at trough. Mean values at baseline: sitting DBP at trough, 102.1 mm Hg; sitting SBP at trough, 158.1 mm Hg (N=240; n=100).
‡ Primary endpoint was sitting DBP at trough. Mean values at baseline: sitting DBP at trough, 100.5 mm Hg; sitting SBP at trough, 158.1 mm Hg (N=240; n=59).

BYSTOLIC is indicated for the treatment of hypertension. BYSTOLIC may be used alone or in combination with other antihypertensive agents.

**Important Safety Information**

**Adverse Reactions**
- The most common adverse events with BYSTOLIC versus placebo (approximately ≥1% and greater than placebo) were headache, fatigue, dizziness, diarrhea, nausea, insomnia, chest pain, bradycardia, dyspnea, rash, and peripheral edema. The most common adverse events that led to discontinuation of BYSTOLIC were headache (0.4%), nausea (0.2%), and bradycardia (0.2%).

**Contraindications**
- BYSTOLIC is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product.

**Warnings and Precautions**
- Do not abruptly discontinue BYSTOLIC therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction, and ventricular arrhythmias have been reported following the abrupt discontinuation of therapy with beta blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other beta blockers, when discontinuation of BYSTOLIC is planned, carefully observe and advise patients to minimize physical activity. Taper BYSTOLIC over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, restart BYSTOLIC promptly, at least temporarily.
- BYSTOLIC was not studied in patients with angina pectoris or who had a recent MI.
- In general, patients with bronchospastic diseases should not receive beta blockers.
- Because beta blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta blockers should generally continue treatment throughout the perinoperative period. If BYSTOLIC is to be continued perinoperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene are used. If beta-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
- The beta-blocking effects of BYSTOLIC can be reversed by beta agonists, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with beta blockers.
- Beta blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Advise patients subject to spontaneous hypoglycemia and diabetic patients receiving insulin or oral hypoglycemic agents about these possibilities.
- Beta blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta blockers in these patients may be followed by an exacerbation of symptoms or may precipitate a thyroid storm.
- Beta blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.
- Because of significant negative inotropic and chronotropic effects in patients treated with beta blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure of patients treated concomitantly with these agents.
Warnings and Precautions (continued)

■ Use caution when BYSTOLIC is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc). When BYSTOLIC is co-administered with an inhibitor or an inducer of CYP2D6, monitor patients closely and adjust the nebivolol dose according to blood pressure response. The dose of BYSTOLIC may need to be reduced. When BYSTOLIC is administered with fluoxetine, significant increases in d-nebivolol may be observed (ie, an 8-fold increase in AUC and a 3-fold increase in \(C_{\text{max}}\) for d-nebivolol).

■ Renal clearance of nebivolol is decreased in patients with severe renal impairment. In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients receiving dialysis.

■ Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. BYSTOLIC has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

■ Patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine while taking beta blockers.

■ In patients with known or suspected pheochromocytoma, initiate an alpha blocker prior to the use of any beta blocker.

Drug Interactions

■ Do not use BYSTOLIC with other beta blockers.

■ Both digitalis glycosides and beta blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

■ BYSTOLIC can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

Use in Specific Populations

■ Use BYSTOLIC during pregnancy only if the potential benefit justifies the potential risk to the fetus. BYSTOLIC is not recommended during nursing.

■ The safety and effectiveness of BYSTOLIC have not been established in pediatric patients.

■ In a placebo-controlled trial of 2128 patients (1067 BYSTOLIC, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens, consider discontinuation of BYSTOLIC.

Please see brief summary of full Prescribing Information on last page of this advertisement.


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BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE HEART RHYTHM SOCIETY

SAN FRANCISCO — Declaring a patient “tired” of atrial fibrillation on the basis of a lack of symptoms following atrial fibrillation ablation may be the difference between jumping the gun, the DISCERN AF study indicates.

Implantable loop recorders used in DISCERN AF (Discerning the Impact of Symptomatic and Asymptomatic Episodes Post Radiofrequency Ablation of AF) clearly documented that the proportion of AF episodes that are asymptomatic markedly increases after ablation, Dr. Atul Verma reported at the meeting. “The observation that state is making patients less able to detect their arrhythmia,” observed Dr. Verma, DISCERN AF principal investigator and an electrophysiologist at Southlake Regional Health Center in Newmarket, Ont. DISCERN AF was an eight-center, prospective Canadian study in which 50 patients with symptomatic AF received a Medtronic Reveal XL inertial cardiac sensor monitor at least 3 months before they underwent a standard first-time AF ablation procedure. Eighty percent of patients had paroxysmal AF. “The subjects’ mean left atrial size was 41 mm. Dr. Verma presented the study results through 18 months of postablation follow-up, but there will be a subsequent report, because the devices will be left in place for a total of 30 months post ablation.

Patients kept a detailed standardized diary of their episodes of onset and end of their arrhythmic symptoms. Every 3 months the implantable loop recorder data were downloaded, and all recorded episodes were blindly adjudicated and compared to entries in the symptom diary.

Radiofrequency ablation effectively reduced total AF burden. Indeed, the total AF/atrial flutter burden decreased from a mean of 2 hours per day per patient preablation to 0.3 hours per day per patient postablation, an 86% reduction. But while 52% of all AF/flutter episodes preablation were asymptomatic, that proportion climbed to 79% post ablation. The ratio of asymptomatic-to-symptomatic AF episodes preablation was 1:1.1; post ablation, it jumped to 3:7.1.

Similarly, 36% of the total AF/flutter burden patients shouldered preablation consisted of asymptomatic arrhythmias, while postablation was 68% of the burden was asymptomatic. The ratio of asymptomatic-to-symptomatic AF/flutter burden postablation was 0.6:1; post ablation, it was 2:1.

Patient self-reports corresponded to an implantable loop recorder–documented episode of AF only 47% of the time. On the basis of self-reported symptoms only, 58% of patients were free of AF postablation. However, the implantable monitor data showed that the true figure was 46%. In other words, after AF ablation 12% of study participants had AF recurrences that were exclusively asymptomatic, Dr. Verma continued.

Asymptomatic episodes were shorter than symptomatic, lasting 4 and 6 hours, respectively. They also involved a significantly lower heart rate and less heart rate variability. In a multivariate analysis, all three of these factors were independent predictors of asymptomatic AF recurrences. But postablation AF recurrences were a threefold more powerful predictor of lack of symptoms than any of the other three predictors.

There is something about the postablation syndrome that is making patients less able to detect their arrhythmia.’’ — Dr. Verma

These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to BYSTOLIC. Adverse reactions common in the population generally have been included. Because of the different patient populations treated voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship with the use of this medication, and, accordingly, these reactions are not included. ONCE THERAPEUTIC RESPONSE IS STRONGLY INDICATED, MACHINE CONTROLLED VENTILATION SHOULD BE CONSIDERED AND CHRONOTROPIC MODULATION WITH β-AGONISTS, PEFUSION, OR VENTILATION MODULATION WITH THE USE OF A VENTILATOR WITH A HIGH INHOCAPACITANCE END-PIECE CAN BE CONSIDERED. DRUGS OR PROCEDURES THAT POTENTIATE THE PULMONARY RESISTANCE CAN BE CONSIDERED. DRUGS OR PROCEDURES THAT POTENTIATE THE PULMONARY RESISTANCE CAN BE

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AF Boosts Nonaccidental Fall Risk in Elderly

BY BRUCE JANCIN
FROM THE ANNUAL MEETING OF THE HEART RHYTHM SOCIETY

SAN FRANCISCO – A history of atrial fibrillation independently more than triples the risk of a nonaccidental fall in the elderly, an emergency department study has shown.

Of 459 consecutive elderly patients who presented to a large emergency department with a chief complaint of a fall, 225 had a fall deemed to be nonaccidental—that is, a fall not explained by mitigating circumstances such as a loose paving stone or a collision with a skateboarder.

A history of atrial fibrillation (AF) was present in 20.4% of those with a nonaccidental fall, compared with 10.6% of the 234 elderly patients who presented with an accidental fall, Dr. Joya A. Ganguly reported at the meeting.

The study population had a median age of 81 years. Patients not older than that who had a nonaccidental fall were 3.36-fold more likely to have a history of AF, compared with those who had an accidental fall. In addition to being more likely to have a history of AF, patients with a nonaccidental fall were also more likely to have a neurologic disorder and to be on three or more medications.

In contrast, there were no differences between patients in the nonaccidental and accidental fall groups in terms of blood pressure, heart rate, orthostatic hypotension, prior pacemaker placement, a history of heart failure, or the prevalence of AF at presentation, which was about 8% in both groups.

Dr. Ganguly concluded that these study findings suggest elderly patients with a history of AF might be good candidates for a fall prevention education program along the lines of the national program recently proposed by investigators at the University of Southern California as a cost-effective intervention (Clin. Geriatr. Med. 2010;26:751-66).

She said she had no relevant financial disclosures.
AF Linked to Systemic Inflammatory Diseases

**BY BRUCE JANCIK**

FROM THE ANNUAL MEETING OF THE HEART RHYTHM SOCIETY

SAN FRANCISCO — What do individuals with rheumatoid arthritis and inflammatory bowel disease have in common?

They suffer debilitating chronic diseases that throw off high levels of systemic inflammation. And what's more, they share a newly recognized predisposition to atrial fibrillation compared with the general population.

Major Finding: First study: Patients with AF were 65% more likely to have rheumatoid arthritis than were controls without AF, but were 35% less likely to have SLE. Second study: Patients with IBD had an 11-fold increased prevalence of AF compared with controls without IBD.

Data Source: 86,497 patients with the diagnosis of AF and 100,000 randomly selected control patients from the Nationwide Inpatient Sample database, 142 patients with IBD from Metro Health Medical Center in Cleveland and a large population of control patients without IBD from a Kaiser Permanente database.

Disclosures: Dr. Hebbbar and Dr. Pattanshetty declared having no financial conflicts of interest.

according to two studies presented at the meeting.

Dr. Prabhath Hebbbar and his coworkers used the Nationwide Inpatient Sample database for 2008, which contains discharge diagnoses for roughly 1,000 U.S. hospitals in 40 states, to identify 86,497 patients with the diagnosis of atrial fibrillation (AF) and 100,000 randomly selected controls without IBD.

More than half of atrial fibrillation is likely attributable to modifiable risk factors, including high blood pressure, obesity, and smoking, according to an analysis of the Atherosclerosis Risk in Communities Study.

The finding, which was based on a cohort of middle-aged American adults from communities in the ARIC study, highlights the need for primary prevention among this population.

"Moreover, because improvement in these behaviors would also favorably affect other AF risk factors, such as diabetes mellitus and impaired glucose tolerance, the reduction in the incidence of AF would be even greater than expected through BP lowering alone," wrote Rachel R. Huxley, D.Phil.

Dr. Huxley, an epidemiologist at the University of Minnesota, Minneapolis, and colleagues looked at nearly 20 years of follow-up from the ARIC survey, a prospective cohort study of atherosclerotic diseases in Forsyth County, N.C.; Jackson, Miss.; Washington County, Md.; and the suburbs of Minneapolis.

At baseline in 1988-1989, it included 15,792 men and women aged 45-64 years, selected by area probability sampling.

All patients underwent three triennial visits, and in the present study, AF cases were counted as those diagnosed at an incident study visit (not baseline assessment) by 12-lead ECG, or during follow-up with an ICD code for AF in a hospital discharge, or when AF was listed as any cause of death on a death certificate.

Those with baseline AF on electrocardiogram or history of AF were excluded, as were those with missing data.

The researchers characterized participants into one of three risk profiles. An "optimal" group had no history of cardiovascular disease, systolic BP below 120 mm Hg and diastolic less than 80 mm Hg without antihypertensive drugs; a body mass index less than 25 kg/m²; fasting serum glucose less than 100 mg/dL without antidiabetic drugs or history of diabetes; and no history of smoking.

"Borderline" participants had any of the following criteria: systolic BP 120-139 and/or diastolic BP 80-89 mm Hg without antihypertensives; BMI 25-30; fasting glucose 100-125 mg/dL without use of antidiabetics and no history of diabetes; and former smoker status.

Finally, participants regarded as having "elevated" risk profiles had any of the following: history of cardiovascular disease (heart failure or coronary heart disease); systolic BP at least 140 mm Hg, diastolic BP at least 90 mm Hg, or use of antihypertensives; BMI greater than 30; fasting serum glucose greater than or equal to 126; or use of antidiabetic drugs; history of diabetes; or current smoker status.

Among the 14,598 subjects (55% women; 25% black; mean age, 54.2 years) over a mean 17.1 years of follow-up who were included in the current analysis, there were 1,520 cases of incident AF.

Compared with those with no risk factors, the age-adjusted incidence rates were three times higher in those with one or more elevated risk factors (2.19 vs. 6.59 per 1,000 person-years, respectively), wrote the authors (relative hazard for optimal patient group, 0.33).

For the borderline group, the incidence rate was 3.68, for a relative hazard of 0.50, compared with participants who had one or more elevated risk factors.

"Overall, the [population-attribution fraction] estimates indicated that having [one or more] elevated risk factor levels could explain 50% ... of AF events," added the authors (Circulation 2011;101:1161/CIRCULATIONAHA.110.009035).

Adding elevated and borderline levels together, that number jumped to 57%. The authors also sought to determine which of the relevant risk factors played the biggest role in incident AF.

Elevated blood pressure, experienced by 39% of the entire cohort, accounted for roughly one in five cases of AF (21.6%). "This rose to 24.5% if borderline levels of BP, which affected another 22.7% of the cohort, were also included," wrote the authors.

"Obesity and overweight explained 17.9% of all AF cases, and diabetes mellitus and impaired glucose tolerance combined accounted for the smallest fraction (3.9%) of the AF burden in this cohort," they added.

According to the authors, this study is the second to look at the relationship between modifiable risk factors and atrial fibrillation. A 1994 analysis, using data from the Framingham cohort, found that smoking, diabetes, hypertension, and prevalent coronary heart disease combined explained 44% of the AF burden in men and 58% in women, a conclusion that Dr. Huxley called "broadly comparable" to that of the current study.

They added that the study was limited by its inability to differentiate subtypes of AF, as well as by its reliance on hospital discharge codes to ascertain AF cases. However, if anything, this fact likely led to the "underascertainment of cases that perhaps were not severe enough to warrant hospitalization."
Totally Subcutaneous ICD ‘Viable Alternative’

BY BRUCE JANCIN
FROM THE ANNUAL MEETING OF THE HEART RHYTHM SOCIETY

San Francisco — An entirely subcutaneous implantable cardioverter defibrillator accurately detected and successfully converted all episodes of ventricular fibrillation in a multicenter Dutch study.

“For us, so far, it has been a viable alternative to conventional ICD systems in selected patients,” Dr. Lara Dabiri Abkenari said in presenting the study results at the meeting.

Since 2001, Dr. Luc Jordans, who was Dr. Abkenari’s senior coinvestigator in the study, went further: He said that “viable alternative” is too conservative an assessment now that a software upgrade has improved the detection algorithm and greatly reduced inappropriate shocks.

“This, we often see the subcutaneous ICD as the first choice,” said Dr. Jordans, professor of cardiology at Erasmus University, Rotterdam, the Netherlands.

The subcutaneous ICD has generated considerable interest among cardiologists and patients because – unlike conventional transvenous ICDs – it is easily implanted without fluoroscopy, it requires no vascular access, and the lead is simple to remove if necessary. A smaller experience with the subcutaneous system that was reported last year attracted a great deal of attention (N. Engl. J. Med. 2010;363:36-46). The system, by Cameron Health Inc., is approved for the European market and is under review at the Food and Drug Administration.

The system comprises a pulse generator, a subcutaneous lead that has two sensing electrodes, and about 8 cm of shock coil. It has no pacing or synchronization capabilities.

“This is for patients who need defibrillation. It’s restricted to patients who would not benefit from antithyocardia pacing,” explained Dr. Abkenari, an electrophysiology fellow and PhD candidate at Erasmus.

She reported on 98 patients (mean age, 56 years) who received the subcutaneous ICD and have been followed for a median of 9 months, during which the system identified 14 nonsustained ventricular arrhythmia episodes in 5 patients and treated 28 sustained episodes in 4 patients. The system also delivered 22 inappropriate shocks to eight patients because of oversensing.

The pulse generator box is placed in a left lateral thoracic subcutaneous pocket. The lead is tunneled from the pocket to the xiphoid process, where the tip of the electrode is sutured to a sleeve attached to the xiphoid fascia.

The generator box is substantially larger than those used in conventional transvenous ICDs. On a thin patient, the box is more obvious under the skin. The lateral position results in arm contact with movement, albeit with no pain.

Because the subcutaneous ICD preserves the vasculature, Dr. Abkenari sees the device as particularly attractive for relatively young, active patients who may need surgery later, such as individuals with hypertrophic cardiomyopathy who may one day need myomectomy or a heart transplant. The subcutaneous device has been placed in several children in the Dutch study with favorable results. Discussant Dr. Bruce L. Wilkoff expressed reservations about the current iteration of the subcutaneous ICD.

The 5% infection rate that resulted in device removal in the Dutch study is “most disturbing,” observed Dr. Wilkoff, director of cardiac pacing and tachyarrhythmia devices at the Cleveland Clinic and professor of medicine at Case Western Reserve University, Cleveland.

“The hope was that infection would be more easily managed with this system,” noted Dr. Wilkoff.

He also zeroed in on the four patients who required shocks for 28 sustained ventricular arrhythmic episodes. “It’s hard to imagine that those patients wouldn’t have benefited a little bit from ATP [antithyocardia pacing]. It seems to me that ATP may be an important component of what’s needed in a device.”

That being said, he cautioned that important new medical technologies rarely spring up full grown. Refinements made along the way can make all the difference between success and failure.

Nearly Half of ICDs in Massachusetts Placed Off Label

BY MITCHELL L. ZOLER
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

New Orleans — Nearly half of patients who received an implantable cardioverter defibrillator in Massachusetts during the period studied, represents “the first choice,” said Dr. Abkenari’s senior coinvestigator in the study, went further: He said that “viable alternative” is too conservative an assessment now that a software upgrade has improved the detection algorithm and greatly reduced inappropriate shocks.

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He also zeroed in on the four patients who required shocks for 28 sustained ventricular arrhythmic episodes. “It’s hard to imagine that those patients wouldn’t have benefited a little bit from ATP [antithyocardia pacing]. It seems to me that ATP may be an important component of what’s needed in a device.”

That being said, he cautioned that important new medical technologies rarely spring up full grown. Refinements made along the way can make all the difference between success and failure.

Nearly Half of ICDs in Massachusetts Placed Off Label

NEW ORLEANS – Nearly half of patients who received an implantable cardioverter defibrillator in Massachusetts during 1998-2008 had at least one clinical factor that categorized them as an off-label recipient, based on the exclusion criteria used in the clinical trials that established the efficacy of these devices.

The most common off-label use occurred in patients aged either 75 or older, about 8 cm of shock coil. It has no pacing or synchronization capabilities.

“This is for patients who need defibrillation. It’s restricted to patients who would not benefit from antithyocardia pacing, ... In a nutshell, it’s a shock box,” explained Dr. Abkenari, an electrophysiology fellow and PhD candidate at Erasmus.

She reported on 98 patients (mean age, 56 years) who received the subcutaneous ICD and have been followed for a median of 9 months, during which the system identified 14 nonsustained ventricular arrhythmia episodes in 5 patients and treated 28 sustained episodes in 4 patients. The system also delivered 22 inappropriate shocks to eight patients because of oversensing.

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That being said, he cautioned that important new medical technologies rarely spring up full grown. Refinements made along the way can make all the difference between success and failure.
Add-On ApoB Synthesis Inhibitor Cut LDL Levels

BY CAROLINE HELWICK
FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – In patients with hypercholesterolemia and high cardiovascular risk, the novel agent mipomersen administered as add-on therapy led to robust reductions in LDL cholesterol, based on the results of a double-blind, phase III study.

“In high-risk patients refractory to maximally tolerated statin therapy, the addition of mipomersen significantly reduced LDL-C and other atherogenic lipids and lipoproteins,” said Dr. William C. Cromwell of the Presbyterian Cardiovascular Institute in Charlotte, N.C.

Mipomersen is the first of a new class of agents called apolipoprotein B (apoB) synthesis inhibitors. In the study, the drug was administered subcutaneously once a week. Among its side effects were injection site reactions, increases in ALT levels, and steatosis.

The study included 158 patients at high risk for cardiovascular events who were unable to achieve target LDL-C levels with statins, bile-acid sequestrants, and niacin. At baseline, all patients were on maximally tolerated doses of a statin; 63 were on the maximal approved dose, and 25 were also receiving ezetimibe.

All subjects had LDL-C levels of at least 100 mg/dL and triglycerides below 200 mg/dL. They were randomized 2:1 to 200 mg subcutaneous mipomersen or placebo weekly for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28 or 2 weeks after the last dose if treatment was not completed.

LDL-C levels of less than 100 mg/dL were achieved by 77 (76%) mipomersen-treated patients, compared with 19 (38%) placebo-treated patients. LDL-C levels of less than 70 mg/dL were achieved by 51 (50%) and 4 (8%), respectively.

The percent reduction in LDL cholesterol from baseline to the primary efficacy time point was a 37% drop in the mipomersen arm and a 5% drop in the placebo arm, a significant difference.

“LDL-C levels decreased through the first 17 weeks of treatment and remained relatively low through week 28,” Dr. Cromwell observed. “Mipomersen’s lipid-lowering effects were independent of baseline LDL-C or race, and were similar for patients with and without diabetes.” The effect of the drug in the diabetic subset was robust. In the diabetes cohort, the mean decline in LDL-C from baseline was 51% for the 56 patients on mipomersen and 32% for the 29 on placebo.

Dr. Cromwell noted that the drug had a more pronounced effect in females and in patients whose age was above the median. However, mipomersen’s effects in males and in younger persons were still statistically significant and clinically meaningful.

Mipomersen also was associated with significant reductions from baseline values in apoB (38%), total cholesterol (26%), non-HDL cholesterol (36%), and lipoprotein(a) (24%). HDL-C levels did not change significantly from baseline.

Sixty of the 105 mipomersen-treated patients (57%) and 44 of 52 placebo patients (85%) completed treatment. A total of 26 mipomersen-treated patients and 2 placebo-treated patients discontinued due to on-treatment adverse events. Of the mipomersen noncompleters, seven discontinued due to a liver enzyme-related adverse event, and seven stopped because of an injection site reaction.

Injection site reactions were the most common adverse event, occurring in 78% of the mipomersen group and 31% of the placebo group. Flu-like symptoms occurred in 34% and 21%, respectively.

ALT elevations at least 3 times the upper limit of normal were observed in 14% of patients on mipomersen, versus none receiving placebo, but this occurred without concomitant significant bilirubin elevations, he said. For 10% of patients, ALT elevations occurred on consecutive measurements at least 7 days apart. One patient in the placebo arm had an ALT of at least 10 times the upper limit of normal.

Approximately one-third of patients had an increase in steatosis, defined as liver fat increasing by at least 5%; median percent change from baseline was 15%. “This does not represent a huge accumulation of fat. Instead, it is a signal that it’s there at 28 weeks, and it is not particularly worrying. In a series of patients with much longer exposures, there is a plateau in this increase."

Dr. Patrick Moriarty, a lipid specialist who is assistant professor of medicine at the University of Kansas, Kansas City, commented, “We treat many refractory patients, and I can tell you that a drug of this class is very much needed in this patient population. It will help get their lipid numbers down.” The fact that patients achieve good LDL-C reductions on top of statin therapy is very encouraging, he said.

Benefits of Lipid-Lowering Agents Persist After Trials End

BY CAROLINE HELWICK
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS — In major clinical trials of lipid-lowering drugs, the mortality benefit from medical therapy persists long after the studies end, according to a meta-analysis presented at the meeting.

Furthermore, placebo recipients who cross over to lipid-lowering therapy in the open-label phases of the studies show survival benefits as well, but never attain the protection achieved by being randomized to active treatment earlier on, according to Dr. William J. Kostis of Massachusetts General Hospital, Boston.

“Persons with risk factors for coronary artery disease should be treated early,” Dr. Kostis said in an interview. “The sooner you treat, the better.”

He and his colleagues identified randomized trials of lipid-lowering therapies that also contained an analysis of patient outcomes after the randomized portion of the trials had ended and an open-label phase had begun. Active treatment in involved statins, niacin, cholestyramine, or gemfibrozil. The analysis included eight clinical trials involving 44,255 patients, of whom 8,144 died during follow-up.

During the randomized phase of the trials, the mean all-cause mortality was significantly lower for the active treatment group (odds ratio, 0.84, as was cardiovascular mortality (0.72). The longer mortality in those initially receiving active therapy persisted during the open-label follow-up phase (OR, 0.90, as did the reduction in cardiovascular mortality (OR, 0.82).

New Insights Into SLE’s Cardiovascular Pathogenesis

BY BRUCE JANCIN
EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. — A distinct subset of proinflammatory activated neutrophils may play a pivotal role in the accelerated atherosclerosis of systemic lupus erythematosus.

The aberrant neutrophils (known as low-density granulocytes [LDGs]) synthesize increased amounts of interferon-alpha and other type I interferons in levels sufficient to kill vascular endothelial cells while at the same time disrupting the capacity of endothelial progenitor cells to differentiate into mature endothelial cells, Dr. W. Joseph McCune explained at the symposium.

The role of LDGs in patients with SLE was unclear until Dr. McCune and his colleagues developed a laboratory technique that isolated LDGs from peripheral blood mononuclear cells.

In earlier studies, Dr. McCune, professor of rheumatic diseases at the University of Michigan, Ann Arbor, and his colleagues showed that the number of circulating apoptotic endothelial cells is at least several-fold greater in SLE patients, than in controls, and is higher still in those with highly active lupus. The researchers also showed that lupus patients had a significantly impaired capacity for endothelial progenitor cells to differentiate into mature endothelial cells available for vascular repair.

Dr. McCune and coworkers recently isolated LDGs and normal-density neutrophils from 190 SLE patients and neutrophils from 110 healthy controls. These in vitro studies pinned down LDG function: namely, increased synthesis of type I interferons and induction of vascular damage (J. Immunol. 2010;184:3284-97).

In vitro, the depletion of LDGs restored the capacity of endothelial progenitor cells to properly differentiate into mature endothelial cells.

In a study in 120 SLE patients, serial measurement of carotid intimal medial thickness during 1.5 years of follow-up indicated that carotid narrowing progressed significantly more quickly in patients who produced high levels of type I interferon, Dr. McCune said. Framingham risk score, systolic blood pressure, and other predictors. Dr. McCune declared having no relevant financial interests.
CIMT Predicts Coronary Events in RA Patients

BY AMY ROTHMAN SCHONFELD
FROM A RHEUMATOLOGY MEETING SPONSORED BY NEW YORK UNIVERSITY

NEW YORK – Imaging seems to be the sine qua non of determining cardiovascular disease risk in patients with rheumatoid arthritis.

Dr. Jeffrey D. Greenberg noted that, over the last 10-15 years, epidemiologic studies have shown patients with rheumatoid arthritis (RA) have a doubled risk of MI and stroke and an increase in cardiovascular-related deaths. “An important issue we face is how can we risk stratify our patients to predict who will develop cardiovascular disease?” Imaging is a promising area that may help us develop biomarkers of risk or better understand pathophysiological mechanisms of RA.”

The need for precise tools with which to predict risk has become more urgent with the recently published findings that carotid ultrasound measurement of carotid intimal medial thickness (CIMT) has been found to predict coronary events in patients with RA, independent of traditional cardiovascular risk factors and manifestations of RA.

The study, conducted by Dr. Matthew R. Evans and his associates at Brooke Army Medical Center, Fort Sam Houston, Tex., found that there appears to be a dose-dependent relationship between plaque and risk, with a 2.5-fold increase with unilateral plaque and a 4.3-fold increase with bilateral carotid plaque, suggesting that atherosclerosis plays a significant role in acute coronary events in patients with RA (Arthritis Rheum. 2011 [doi:10.1002/art.30265]).

In discussing Dr. Evans’s research at his presentation at the meeting, Dr. Greenberg said that this is the first study to show the predictive value of measuring CIMT and plaque for cardiovascular events in RA patients.

In the Evans study, carotid ultrasounds were performed on 636 RA patients as part of the prospective ORALE (Outcome of Rheumatoid Arthritis Longitudinal Evaluation) study. These patients were followed for 3,402 person-years and, during that time, 84 patients experienced 121 new or recurrent acute coronary syndrome events. The rate of ACS events was 3.5/100 patient-years for this group. If only those without a prior history of ACS were analyzed, this group had 66 ACS events, with an incidence of 2.1 ACS/100 person-years.

Multivariate analysis of baseline factors associated with incident or recurrent ACS revealed that two markers of atherosclerosis were independent predictors of a subsequent coronary event. Having a past cardiovascular event raised the risk almost threefold (hazard ratio, 2.87) and CIMT also raised the risk significantly (HR, 1.61). After substituting carotid plaque for intimal-medial thickness, the investigators found a 2.5-fold increase in risk for unilateral plaque and almost a 6-fold increase in risk for bilateral plaque.

The findings confirmed that traditional demographic and cardiovascular risk factors also significantly predict coronary events as would be expected. These include male gender (HR, 1.94), diabetes (HR, 2.24), and hypertension (HR, 1.56).

Major Finding: Carotid intimal medial thickness is an independent predictor of coronary events in patients with RA. Unilateral plaque more than doubled the risk and bilateral plaque increased the risk more than four-fold.

Data Source: Prospective study of 636 patients with RA.

Disclosures: Dr. Greenberg receives consulting fees from Genentech.
Heart Involvement Missed in Systemic Sclerosis

BY BRUCE JANCIN
FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY SNOWMASS, COLO. — Cardiac abnormalities were detected by magnetic resonance imaging in three-quarters of an unselected consecutive series of systemic sclerosis patients, underscoring the impressive frequency of heart involvement in this collagen vascular disease.

“The heart is something we often forget in scleroderma. The heart disease is underestimated,” Dr. Fredrick M. Wigley said at the symposium.

The hallmark of cardiac involvement in systemic sclerosis (SSc) is fibrosis and inflammation. Cardiac MRI is unequaled at visualizing these features, he said.

“You can see fibrosis of the myocardium, pericardium, coronary circulation, and conduction system. Arrhythmias are common. Coronary vasospasm is thought to occur, particularly with cold conduction – the so-called Raynaud’s of the heart – leading to ischemic reperfusion injury and fibrosis of the heart,” said Dr. Wigley, professor of medicine and director of the scleroderma center at Johns Hopkins University, Baltimore. A resting tachycardia in patients with systemic sclerosis is a common clinical manifestation of cardiac involvement. Clinically evident heart disease carries an unfavorable prognosis, as do cardiac abnormalities detected via right heart catheterization or other invasive methods. The prognostic significance of asymptomatic abnormalities that are detected only on cardiac MRI and that are not evident at the bedside remains to be established. The noninvasive imaging technique has only recently been applied in systemic sclerosis.

Scleroderma patients at greatest risk for clinically severe cardiac involvement are those with myopathy and rapidly progressing skin disease, according to the rheumatologist.

Dr. Wigley highlighted a recent study by investigators at Lille 2 (France) University that effectively demonstrated the power of cardiac MRI in detecting heart involvement in SSc. The French investigators examined 52 consecutive unselected scleroderma patients with both Doppler echocardiography and cardiac MRI. One or more cardiac abnormalities were found on cardiac MRI in 75% of the patients, while Doppler detected the abnormalities in only 48% of the patients.

Moreover, only cardiac MRI permitted precise analysis of the patterns of cardiac involvement in SSc, as it was able to distinguish between the fibrotic, inflammatory, and microvascular components. Interestingly, patients with limited cutaneous SSc had cardiac MRI abnormalities that were similar to those with diffuse cutaneous disease.

Seven of the 40 patients without pulmonary arterial hypertension were found to have right ventricular dilatation on cardiac MRI, underscoring the point that right ventricular dilatation is not specific for this common respiratory manifestation of SSc.

Study participants had a mean 11.2-year disease history since developing Raynaud’s phenomenon. The longer a patient’s disease duration, the greater the number of cardiac segments with kinetic abnormalities and delayed contrast enhancement on MRI (Ann. Rheum. Dis. 2009;68:1878-84).

Dr. Wigley said that while to date no therapy has been shown to alter the natural course of cardiac disease in patients with scleroderma, French investigators strongly believe calcium channel blockers are cardioprotective, and they have documented increased myocardial perfusion in nifedipine-treated SSc patients.

He receives consulting fees and/or research grants from Actelion, Amara, Kinemed, Medimmune, Novartis, Orion, Pfizer, and United Therapeutics.

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2009 ACC/AHA Update for STEMI

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• body weight <60 kg
• propensity to bleed
• concomitant use of medications that increase the risk of bleeding (eg, warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs])

Suspect bleeding in any patient who is hipertensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient. If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.


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JUNE 2011 • CARDIOLOGY NEWS
CABG Relieves Angina Better Than PCI

BY MARY ANN MOON
FROM THE NEW ENGLAND JOURNAL OF MEDICINE

In patients with complicated coronary artery disease, coronary artery bypass graft surgery provided greater relief from angina at 6 and 12 months after revascularization than did PCI with paclitaxel-eluting stents. This benefit with CABG was consistent across a broad range of patient characteristics, said Dr. David J. Cohen of the University of Missouri–Kansas City and his associates in the randomized SYNTAX trial, in which 1,800 patients with three-vessel or left main coronary artery disease underwent either CABG or PCI with paclitaxel-eluting stents. The rate of the primary efficacy end point of death, MI, stroke, or repeat revascularization was significantly lower with CABG at 1 year. The current analysis was a quality of life substudy of SYNTAX that included 903 patients who had been assigned to PCI and 897 who received CABG. At baseline, 12% of the subjects had daily angina and 20% had no angina; the remaining subjects had occasional angina. The primary quality of life end point was the score on the Seattle Angina Questionnaire angina frequency sub-scale. The improvement in this score was slightly but significantly greater with CABG than with PCI at 6 and 12 months. “There were marked benefits with PCI as compared with CABG in general health-related quality of life as assessed by the SF-36 as well as EQ-SD [European Quality of Life 5-Dimensions instrument] at 1 month, but these differences had largely disappeared by 6 months,” Dr. Cohen and his colleagues reported (N. Engl. J. Med. 2011:364:1016-26).

CONTRAINDICATIONS
- Effient is contraindicated in patients with active pathological bleeding, such as from a peptic ulcer or intracranial hemorrhage (ICH), or a history of transient ischemic attack (TIA) or stroke, and in patients with hypersensitivity to prasugrel or any component of the product

WARNINGS AND PRECAUTIONS
- Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued. Effient should also be discontinued for active bleeding and elective surgery
- Premature discontinuation of Effient increases risk of stent thrombosis, MI, and death
- Thrombotic thrombocytopenic purpura (TTP), a rare but serious condition that can be fatal, has been reported with Effient, sometimes after a brief exposure (<2 weeks), and requires urgent treatment, including plasmapheresis

ADVERSE REACTIONS
- Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction

Please see Brief Summary of Prescribing Information on subsequent pages.

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RAPS: Radial Artery Tops Saphenous Vein Graft

By Patrike Wendling
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Long-term data from the Radial Artery Patency Study show that radial arteries, compared with saphenous veins, are associated with reduced rates of functional and complete graft occlusion in patients undergoing coronary artery bypass surgery.

Radial arteries also are associated with lower rates of graft disease, lead author Dr. Stephen E. Frestes said during a late-breaking trial session at the meeting.

The issue of which conduit provides the best long-term graft outcomes has been a subject of debate. Several trials reported that radial artery grafts are no better than saphenous vein grafts, including a Veterans Affairs study showing similar 1-year graft patency among 757 patients undergoing first-time, elective coronary artery bypass surgery (JAMA 2011;305:167-74). One-year data from the Radial Artery Patency Study (RAPS) showed that complete graft occlusion was significantly reduced in radial artery grafts compared with saphenous vein grafts (8.2% vs. 13.6%), but that partial occlusion was essentially the same (12.3% vs. 13.4%) between the two conduits (N Engl J Med 2004;351:2302-9).

When Dr. Frestes was asked how to reconcile the results of RAPS with those from the VA study, he replied that the VA study was conducted almost exclusively in men (99%), vein grafts performed better than predicted, and there were very high rates of evidence-based medicine. Adherence to secondary preventive medicine in RAPS, but the trial accrued much earlier, from November 1996 to January 2001. The mean age of the 269...

Conclusions

- Radial artery grafts may provide better durability than saphenous vein grafts in long-term coronary artery bypass surgery.
- Further studies are needed to confirm these findings.
Major Finding: Functional graft occlusion at 5 years was 12% in radial artery grafts and nearly 19% in saphenous vein grafts.

Data Source: Multicenter, randomized Radial Artery Patency Study in 269 patients.

Disclosures: The Canadian Institutes of Health Research funded the study. Dr. Freams reported no conflicts.

patients in the current analysis was 10 years, and 15% were women. ARA enrolled 540 patients with isolated triple-vessel disease and a left ventricular fraction of more than 35% from 12 Canadian centers and 1 in New Zealand. Randomization was unique in that it was performed within patients, between sides, at the discretion of the cardiac surgeon at Sunnybrook Health Sciences Centre and research director at the Schullich Heart Centre at Sunnybrook, Toronto. Patients were randomly assigned to receive either a radial artery to the right coronary artery and a saphenous vein to the circumflex territory or a saphenous vein to the right coronary artery and a radial artery to the circumflex territory. Long angiography was performed on 440 patients at 1 year and on 269 patients at a mean of 7.6 years after surgery. In the current analysis, all patients who had a TIMI (Thrombolysis In Myocardial Infarction) Score of 0-2, and were considered patent with a TIMI score of 3.

At 5 years, the primary end point of functional graft occlusion was significantly decreased in radial artery grafts at 12%, compared with saphenous vein grafts at 18.8% (odds ratio, 0.64). Dr. Freams did not report any significant radial artery grafts also became completely occluded at 9%, compared with saphenous-vein grafts at 18% (OR, 0.50).

Among 164 patients who had completely patent grafts at follow-up, graft patency was associated with both coronary for proximal and distal anastomosis lesions. There were fewer body-girth lesions at 6.7% in radial arteries, vs. saphenous veins at 15.2% (OR, 0.42). Consequently, radial artery grafts were significantly less likely to be either stenotic or completely occluded at 22%, compared with saphenous vein grafts at 34% (OR, 0.58), he said.

Target vessel stenosis, an important risk factor for graft occlusion at 1 year, was evaluated in a subgroup analysis. Target vessel stenosis were classified as a priori as those with 70%-90% narrowing and those with at least 90% narrowing. Although graft occlusion was reduced almost 50% for either graft in target vessels with at least 90% narrowing, radial artery grafts had much lower (8.8%) and complete (6.3%) occlusion rates, as did saphenous vein grafts (14.6% and 14.5%, respectively), in the more severely narrowed vessels.

The incidence of cardiac death beyond 1 year was 5%, of nonfatal myocardial infarction was 1.5%, and of major adverse cardiac events was 15%. Dr. Freams pointed out that the clinical event findings were descriptive rather than explanatory since each patient received both graft types.

Overall survival in the entire cohort was 96% at 5 years, 91% at 7.5 years, and 78% at 10 years. Event-free survival was 95%, 90%, and 78%, respectively.

“[This study] lends credence to utilizing the radial artery, with obvious cavvagesical place to an initially highly obstructed vessels so there is not competitive flow and to maintain patency for the longest period of time,” Dr. James McClurken, professor and vice-chair of surgery at Temple University in Philadelphia, said in a panel discussion. “This is not quite as good as internal mammary artery patency data, but certainly better than vein-graft data.”

Fellow discussant Dr. Steven Bolling, a thoracic surgeon at the University of Michigan, Ann Arbor, said he expects the data will shift practice and increase utilization of the radial artery graft.

When asked about this point at a press conference, Dr. Freams said that radial artery utilization varies by jurisdiction anywhere from 10% to 24% in some centers, with more than 95% for the internal mammary artery. He noted that the evidence to date on radial artery grafts has been mixed and comes mainly from observational studies.

“The body we presented is the first multi-institutional, longitudinal, randomized comparison, so this is fairly unique data,” he said. “Hopefully, it will be persuasive.”
Use of Hearts From High-Risk Donors Waning

BY SUSAN LONDON
FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

SAN DIEGO – Heart transplant recipients in their 70s have outcomes that are generally similar to those of their counterparts in their 60s, new data show.

In a retrospective study of 18,534 wait-listed older adults, the rates of post-transplant complications in septuagenarians were much the same as those in sexagenarians, except that the former were in fact less likely to experience rejection. And on average, the septuagenarians lived roughly 8 years after getting their new heart, which is not much shorter than the 9.8 years seen in sexagenarians, according to results reported at the meeting.

“Selected septuagenarians – and I underscore the word selected – with advanced heart failure derive great benefit from heart transplantation,” said lead investigator Dr. Daniel Goldstein. “This is not every 70-year-old [who is] going to walk into your office.”

The findings raise the thorny ethical issue of expanding age limits on eligibility for heart transplantation, as organs are scarce and every heart given to an older adult is one that is not given to a young person, he noted.

One approach would be to limit transplantation to those septuagenarians who have the best risk profile. Another would be to use an alternative list, as first tested by the University of California, Los Angeles, whereby older recipients are given hearts that are typically rejected by younger recipients.

“I don’t see being able to do this without having an alternative list situation,” UCLA is the perfect model,” asserted Dr. Goldstein, a cardiothoracic surgeon at the Montefiore Einstein Center for Heart and Vascular Care at Montefiore Medical Center in the Bronx, N.Y. “It would be hard to get an 18-year-old donor and give the heart to a 70-year-old, but if you take in a heart that nobody else wants, I think it’s a little more palatable.”

With the aging of the population and the epidemic of heart failure among old-er adults, this dilemma is likely to intensify, he noted.

Centers generally use an age cutoff of 65 years for cardiac transplantation eligibility. But an informal survey of centers in the New York City and New Jersey area suggests that “there is great variability in who we think is too old for transplantation,” he said. “It’s clear that more centers are doing away with chronological age criteria.”

In the study, the investigators analyzed data from the UNOS (United Network for Organ Sharing) database for 1987-2010, first looking at trends among 18,534 adults aged 60 years or older put on the waiting list for a primary, single-organ heart transplantation. Results showed that “in the current era, septuagenarians are being transplanted more frequently, without a doubt,” Dr. Goldstein said. The number undergoing transplantation increased almost every year, and their median age was 71 years.

Consider Ethics, Consequences

The boundaries of reasonable medical care are being pushed daily, and it now appears that heart transplantation can be done safely with acceptable survival in septuagenarians. Do these recipients receive the same transplant survival benefit as sexagenarians? Not quite, but it’s pretty close. The small survival differences between the septuagenarians and sexagenarians suggest that age (and perhaps selection bias) should allow for older pa-tients to be considered, in certain circumstances, as candidates. What sets organ transplantation apart from other heroic interventions (e.g., experimental chemotherapy for patients with metastatic cancer) is that donor organs are an exquisitely limited commodity. The ethics of increasing the recipient pool by including older patients must be considered, and this change may have significant consequences for younger patients on the wait list.

Dr. Sethish Murthy is an ACS fellow and surgical director of the Center for Major Airway Disease at the Cleveland Clinic.

Survival Data Show Viability of Transplants in Older Patients

BY SUSAN LONDON
FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

SAN DIEGO – Transplantation physicians may be increasingly avoiding the use of hearts from donors who have high-risk characteristics, even as demand for transplantable hearts continues to outstrip supply, suggests a retrospective study of more than 42,000 heart trans-plan t recipients.

The percentages of transplanted hearts from donors who have characteristics that are associated with an elevated risk of poor outcomes for the recipient (such as older age or hypotension) initially increased during the recent 2-decade study period. But thereafter, they plateaued or fell – in some cases to levels seen at the start of the period.

There are two possible explanations for the declining use of hearts from high-risk donors, lead investigator Dr. Joseph N. Nativi told attendees of the meeting.

“One hypothesis is that there is a concern about adverse outcomes” for recipients who would be given these hearts, in the wake of publications describing actual experience with their use, he explained.

“The second hypothesis is that, probably, we have another option to offer these patients, that is, the increasing utilization of left ventricular assist devices,” Dr. Nativi said.

“So for a patient who is critically ill, instead of offering them a high-risk donor, now we have the luxury in some centers to offer them an alternative, that is, mechanical support,” he added.

There have been several key milestones in efforts to make more organs available for transplantation in the United States, according to Dr. Nativi, a fellow in cardiology with the University of Utah and the Utah Transplantation Affiliated Hospitals Cardiac Transplant Program in Salt Lake City.

The Crystal City Conference in 2001 resulted in a formal recommendation to expand the use of hearts from high-risk donors (Circulation 2002;106:836-41). In addition, the Organ Donation Breakthrough Collaborative in 2003 encouraged increased consent and donation by individuals with high-risk features (Crit Care Nurs. Q. 2008;31:190-210).

“These efforts are resulting in the expansion of acceptable donor criteria toward high-risk donors,” he said. “But the high-risk donor still remains a matter of controversy.”

In the year after the collaborative, there was an increase in the number of all types of organs donated – with the sole exception of hearts. “So we are still struggling to find donors for heart recipients,” Dr. Nativi commented.

To assess temporal patterns in the use of hearts from high-risk donors, the investigators analyzed data from the U.S. Scientific Registry of Transplant Recipients identifying adult patients who underwent single-organ heart transplantation in 1987-2009.

They were divided into three eras by transplantation date: era 1 (1987-1996), when standard donor criteria were used; era 2 (1997-2003), when there was increasing acceptance of the high-risk donor, and reports about the use of organs from such donors increased; and era 3 (2004-2009), after the collaborative was established.

Results were based on 42,023 patients who underwent transplantation during the study period (42% in era 1, 32% in era 2, and 26% in era 3), Dr. Nativi reported.

In multivariate analyses that included more than 40 donor characteristics as well as a transplant center’s patient volume, recipients were more likely to die in the first year post transplantation if their donor was older than 40 years of age (hazard ratio, 1.2), was female (HR, 1.2), had a cerebrovascular cause of death (HR, 1.6), or had a history of hypertension (HR, 1.3).

Temporal trends showed a biphasic pattern for three of these high-risk characteristics, with the percentage of hearts having the characteristic increasing significantly between era 1 and era 2, but then decreasing significantly between era 2 and era 3.

For example, the percentage of hearts from donors older than 40 years averaged 21%, 30%, and 28% in eras 1, 2, and 3, respectively. The pattern was similar for hearts from donors who were female (29%, 31%, and 27%) and those having a cerebrovascular cause of death (26%, 29%, and 23%).

The percentage of hearts from donors having hypertension increased from 4% to 11% between eras 1 and 2, and again from 11% to 13% between eras 2 and 3. But in clinical terms, the latter change was really more of a plateau, according to Dr. Nativi.

Major Finding: Relative to sexagenarians, septuagenarians had both shorter 9.8 years seen in sexagenarians, except that the former were in fact less likely to experience rejection. And on average, the septuagenarians lived roughly 8 years after getting their new heart, which is not much shorter than the 9.8 years seen in sexagenarians, according to results reported at the meeting.

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Continued on page 28
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- The most common adverse reactions are flushing, diarrhea, nausea, vomiting, increased cough and pruritus.

Please see brief summary of full Prescribing Information on adjacent pages.


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ADVERSE REACTIONS

Because clinical studies are conducted under various varying conditions, adverse reactions observed in the clinical studies of a drug cannot be predicted exactly from those reactions reported during clinical research. A drug’s responsiveness varies with individual patients; therefore, a patient’s responsiveness to a drug can differ from that observed in clinical research. The following adverse reactions, representing a range of what was observed in clinical studies, have been selected on the basis of their potential clinical significance in the therapeutic use of NIASPAN. The frequency of adverse reactions observed in clinical studies is usually equal to or less than the frequency of similar drug treatments used in clinical studies of similar patients.

Clinical Studies Experience

In the placebo-controlled clinical trials of NIASPAN, adverse reactions were compared with adverse reactions in patients receiving placebo. The frequency of adverse reactions observed in the placebo-controlled clinical trials of 426 patients range from 10% to 30% in a short-term study of 10 weeks. In this study, the patients were divided into placebo and NIASPAN groups. Patients who received NIASPAN were compared with patients who received placebo in the clinical trials as follows: 6% (14/245) of NIASPAN patients discontinued due to adverse reactions versus 0% of placebo patients. These discontinuations were due to adverse reactions of flushing, pruritus, and diarrhea.

NIASPAN has been associated with an increased incidence of anaphylaxis (see Warnings and Precautions). In placebo-controlled clinical trials of NIASPAN, 1% (n = 3/303) of patients reported an allergic reaction, 0.66% (2/303) of patients reported rash, and 0.33% (1/303) of patients reported gastrointestinal reactions. In addition, 0.33% (1/303) of patients reported flushing. These reactions were managed with supportive care and antihistamines, and no fatalities were reported.

AN is indicated for use in patients who have a high-risk profile for cardiovascular disease and who cannot be managed with low-dose niacin. In the placebo-controlled clinical trials, 13% (4/30) of patients discontinued due to flushing. In the placebo-controlled clinical trials, 12% (4/35) of patients discontinued due to rash. In the placebo-controlled clinical trials, 11% (4/36) of patients discontinued due to pruritus. In the placebo-controlled clinical trials, 10% (3/30) of patients discontinued due to gastrointestinal reactions.

INFORMATION FOR PATIENTS

Reduce the dose of NIASPAN to the lowest effective level that achieves the desired degree of LDL cholesterol reduction and HDL cholesterol elevation. NIASPAN can cause flushing, pruritus, rash, and other symptoms of hyperemia. Flushing may vary in severity from a mild sensation of warmth or a feeling of mild warmth, pruritus, and rash. Flushing may occur at the time of NIASPAN therapy initiation or during any dosage increase and may be associated with exacerbation of hyperlipidemia. Flushing usually occurs within 1 hour after taking NIASPAN but may occur any time after administration of NIASPAN. Flushing may occur with or without pruritus.

NIASPAN can cause nausea, vomiting, diarrhea, constipation, abdominal discomfort, and dyspepsia. NIASPAN can cause pruritus or rash, particularly in elderly patients. NIASPAN can cause flushing. Flushing may occur at the time of NIASPAN therapy initiation or during any dosage increase and may be associated with exacerbation of hyperlipidemia. Flushing usually occurs within 1 hour after taking NIASPAN but may occur any time after administration of NIASPAN. Flushing may occur with or without pruritus.

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Use of NIASPAN in pregnant women should be limited to situations in which the potential benefits outweigh the potential risks. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant. NIASPAN is not indicated for use in patients who are breastfeeding. NIASPAN is not indicated for use in patients who are pregnant.
LVH in Donor Does Not Raise Risk of Death

BY SUSAN LONDON
FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

San Diego – Cardiac transplant recipients who are given hearts from donors with left ventricular hypertrophy are not at increased risk of death, Dr. Omar Wever-Pinzon reported at the meeting.

In a retrospective, nationwide study of more than 2,500 adults who underwent cardiac transplantation during 2006-2010, nearly half of the donor hearts had LVH.

Recipients who had been given hearts with LVH did not have poorer survival overall than did their counterparts who had been given hearts without this high-risk characteristic. But getting a heart with LVH did reduce survival if, in addition, the donor was older than 55 years or the graft had a longer ischemic time.

“Overall survival of recipients of donor hearts with LVH is similar to those without LVH, which indicates that the current donor selection and allocation algorithms successfully mitigate the risk that donor LVH could pose to recipient survival,” Dr. Pinzon said. However, “the combination of donor LVH with certain other high-risk characteristics can result in excess mortality.”

Because few donor hearts had moderate or severe LVH, “I think we have to be very careful” when using those hearts, he added. But hearts having an interventricular septum and posterior wall thickness up to 1.3 cm “may be safe in the absence of other high-risk characteristics.”

The scarcity of donor hearts coupled with growing knowledge about the impact of various donor characteristics on recipient outcomes “has led to strategies to make more hearts available for transplantation, according to Dr. Pinzon.

“Thanks to these strategies, patients with left ventricular hypertrophy, considered a high-risk characteristic, are more likely now to become donors,” he added. However, some studies have raised concerns that such hearts are more susceptible to ischemic graft injury, which could translate into poorer outcomes for the recipients.

Using data from the United Network for Organ Sharing and the Organ Procurement and Transplantation Network, the investigators studied 2,626 adult patients who underwent heart transplantation in 2006-2010. On the basis of the thickness of the interventricular septum and posterior wall, donor hearts were classified as having no LVH (less than 1.1 cm) or LVH that was mild (1.1-1.3 cm), moderate (1.4-1.6 cm), or severe (1.7 cm or greater).

The transplant recipients were 52 years old on average, and 78% were men. The donors were 33 years old on average, and 72% were men.

Fully 44% of the donor hearts had some degree of LVH, reported Dr. Pinzon of the UTAH (Utah Transplantation Affiliated Hospitals) Cardiac Transplant Program in Salt Lake City. The LVH was mild in most cases (38%) but occasionally was severe (10%).

Relative to their peers who had been given donor hearts without LVH, recipients who had been given donor hearts with LVH had a higher body mass index and a higher ratio of donor-to-recipient BMI, had been on the waiting list for a longer time, and were more likely now to receive a graft ischemic time exceeding 4 hours.

During a follow-up period of 3.3 years post-transplantation, 13% of the recipients died or underwent retransplantation.

In univariate and multivariate analyses, neither recipients of donor hearts with mild LVH nor recipients of donor hearts with moderate or severe LVH were more likely to die than their counterparts whose donor hearts did not have any LVH, Dr. Pinzon reported.

However, recipients’ risk of death increased with the age of their donor (hazard ratio, 1.01) and with their own serum creatinine level, and with pulmonary artery pressure (HR, 1.01).

Also, they were more likely to die if their donor had used tobacco (HR, 1.32), or if they themselves were older than 55 years of age (HR, 1.30) or had been on extracorporeal membrane oxygenation support (HR, 6.0).

Further analyses revealed an interaction between donor heart LVH and donor age. Of recipients whose donor was older than 55 years, those getting a heart with any LVH had roughly six times the risk of death. But there was no such association in recipients from younger donors.

There was also an interaction between donor heart LVH and graft ischemic time. Of recipients whose graft had an ischemic time of 4 hours or longer, those receiving a heart with moderate or severe LVH had twice the risk of death.

Men Receiving Women’s Hearts Have Higher Mortality

BY SUSAN LONDON
FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

San Diego – For men undergoing heart transplantation, the sex of their donor may mean the difference between life and death, according to a pair of large retrospective cohort studies.

The studies, which were reported at the meeting, each analyzed data from more than 60,000 recipients over periods spanning several decades.

Their conclusion: Men were more likely to die if they received a heart from a female donor vs. a male donor, with the elevation in risk largely resulting from excess deaths in the first year. Over-all mortality was 13% higher for these men after potential confounders were taken into account.

In contrast, women undergoing heart transplantation had a similar risk of death regardless of whether their donor was male or female.

A possible explanation for this finding, according to Dr. Ingo Kaczmarek, a cardiac surgeon at the Transplantation Center Munich of Ludwig-Maximilians University of Munich and the lead investigator of one of the studies, is that women’s hearts are smaller than men’s, even given the same body height and weight (J. Am. Coll. Cardiol., 2002;39:560-6).

Additionally, medication nonadherence may play a part. “In our population … I can tell you that females take their medication and males don’t,” he said. “And that might be a big confounder that you can’t measure.”

Although her study took donor characteristics into account, it is still possible that the smaller size of female hearts played a role, agreed Dr. Kran K. Khush, lead investigator of the other study. “But I think there are probably also some immunological processes involved and sex differences that we don’t completely understand,” she added.

This new information helps explain why some patients fare better than others after heart transplantation, but it would not necessarily alter her practice, said Dr. Khush, a cardiologist and instructor in cardiovascular medicine at Stanford (Calif.) University.

“I would worry about it clinically, but I’m not sure that would preclude me from accepting a female graft for a male recipient, because as we all know — when you have a very sick recipient who is in imminent danger of dying, you just want to have a heart for that patient,” she commented. However, she added, perhaps given a situation where several high-priority patients on the waiting list were otherwise similar, sex matching might be something to consider.

Dr. Khush and her colleagues analyzed data from the International Society of Heart and Lung Transplantation (ISHLT) database for the years 1990-2008, restricting analyses to 60,584 adult recipients having at least 2 years of follow-up post-transplantation.

Fully 79% of the heart transplant recipients were men. On average, the men were 52 years old and the women were 49 years old at the time of transplantation.

Men’s odds of acute rejection within 2 years of transplantation were higher if their donor was female vs. male before adjustment for more than a dozen potential confounders (odds ratio, 1.22), although not after adjusting for their peers who had been given donor hearts without LVH, recipients who had been given donor hearts with LVH had a higher body mass index and a higher ratio of donor-to-recipient BMI, had been on the waiting list for a longer time, and were more likely now to receive a graft ischemic time exceeding 4 hours.

During a follow-up period of 3.3 years post-transplantation, 13% of the recipients died or underwent retransplantation.

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However, recipients’ risk of death increased with the age of their donor (hazard ratio, 1.01) and with their own serum creatinine level (HR, 1.31) and pulmonary artery pressure (HR, 1.01).

Also, they were more likely to die if their donor had used tobacco (HR, 1.32), or if they themselves were older than 55 years of age (HR, 1.30) or had been on extracorporeal membrane oxygenation support (HR, 6.0).

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There was also an interaction between donor heart LVH and graft ischemic time. Of recipients whose graft had an ischemic time of 4 hours or longer, those receiving a heart with moderate or severe LVH had twice the risk of death.
Psoriasis Boosts Framingham Risk Score 6%

BY MITCHEL L. ZOLER
FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY
NEW ORLEANS – Patients with severe psoriasis face a 6% higher 10-year risk for a cardiovascular event than do comparable people without psoriasis, according to the findings of a prospective cohort study of nearly 18,000 people.

This added CV risk can have substantial implications, as it can move psoriasis patients into a higher Framingham Risk Score category and shift the way physicians need to think about CV risk management of these patients, Dr. Nehal N. Mehta said at the meeting.

Dr. Mehta implements aggressive lifestyle interventions for these patients, and also suggests the consumption of fiber, red yeast rice, soy, phytoestrogens, fish oil, and niacin. If a patient’s LDL cholesterol or BP remains at a questionable high level, he discusses the option of starting treatment with a statin or an antihyperpertensive medication, making clear that these steps have not yet been endorsed by most society management guidelines.

“Ultimately, about 5% of my psoriasis patients end up on a statin,” said Dr. Mehta, a cardiologist and director of the inflammatory risk clinic in preventive cardiology at the University of Pennsylvania, Philadelphia.

Dr. Mehta and his associates derived an estimate of CV disease risk attributable to psoriasis by reviewing follow-up data maintained on 3,603 patients with severe psoriasis and 14,330 control participants without psoriasis enrolled in the General Practice Research Database, a collection of records from more than 5 million people seen by U.K. general practice physicians. The researchers excluded people with a history of CV events. The average age of all the people in the analysis was about 50 years and, on average, people were followed for about 3 years.

In a multivariable analysis that controlled for diabetes, hypertension, hyperlipidemia, age, gender, body mass index, and smoking status, the risk for a MI, stroke, or death from a CV cause was 53% higher in the psoriasis patients than in the controls, a statistically significant difference. This higher CV risk in patients with psoriasis matched the 50% increased risk proposed last year for patients with rheumatoid arthritis and other forms of inflammatory arthritis including psoriatic arthritis (Ann. Rheum. Dis. 2010;69:325-31).

To translate the 1.53 relative risk into an attributable risk, Dr. Mehta and his associates multiplied that factor against the background CV risk for someone in the general population of the study to derive an adjusted risk. They then subtracted the background risk from the adjusted risk. Over a 10-year period, this translated into an excess risk for a cardiovascular event of 6.2%.

To illustrate the potential impact of this estimate, the researchers then applied it to a consecutive sample of 103 psoriasis patients seen in Dr. Mehta’s psoriasis clinic at the Penn Heart and Vascular Center, including nine patients with psoriatic arthritis. (See graph.)

Dr. Mehta had no disclosures.

‘Enormous Complexity’ of CV Meds Impairs Adherence

BY MARY ANN MOON
FROM ARCHIVES OF INTERNAL MEDICINE
Patients with cardiovascular disease face “enormous complexity” in managing their prescriptions, and it directly interferes with their adherence to medication, a study has shown.

Streamlining this complexity may improve adherence, and thus morbidity and mortality, in this patient group, said Dr. Niteesh K. Choudhry of the division of pharmacoepidemiology and pharmacoeconomics, Brigham and Women’s Hospital and Harvard Medical School, Boston, and his associates.

Using prescription claims data from CVS Caremark during a 1-year period, the investigators assembled a nationally representative cohort of patients taking long-term cardiovascular medications. They chose patients taking a statin, an angiotensin-converting enzyme inhibitor or a renin angiotensin receptor blocker (ACEI/ARB), or both, because these agents “represent the two most widely sold therapeutic classes to treat cardiovascular disease in the United States.”

Therapeutic complexity was assessed by measuring the total number of prescriptions filled, the number of fills for medications in different drug classes, the number of physicians who wrote prescriptions, the number of pharmacies used, the number of pharmacy visits the patients made, and the number of daily medication doses that were prescribed.

The researchers also estimated patient adherence by calculating the number of days the medication was available.

The statin cohort comprised 1,827,395 patients and the ACEI/ARB cohort comprised 1,480,304 patients. A total of 20% of the total sample took both classes of drugs.

The mean patient age was 63 years, and the cohort was evenly divided between men and women. Mean income was greater than $50,000 per year, and most patients received drug coverage directly through employer-sponsored insurance or a health plan. Thus, the study findings may not apply to uninsured patients.

During a 3-month “complexity assessment” period, patients filled a mean of 11 medications in six different drug classes; had prescriptions written by four or more prescribers; filled prescriptions at both retail pharmacies and via mail order; and filled a mean of 11 medications in six different drug classes, the investigators reported.

Overall, mean medication adherence was 69% with statins and 66% with ACEI/ARBs.

After adjustment for demographic factors, comorbidities, and copayments, patients who visited more pharmacies and those who filled fewer medications per visit were found to be substantially less adherent to their prescribed therapy.

For example, each additional pharmacy at which a patient filled a prescription was associated with a nearly 2% reduction in statin adherence. Patients who filled the fewest prescriptions per pharmacy visit — those who had the least refill consolidation — had adherence rates that were 8% lower than adherence rates of patients who had the highest refill consolidation.

“The magnitude of these effects [was] particularly large for patients who had newly initiated therapy and who filled their prescriptions at both retail pharmacies and via mail order,” the investigators wrote.

“These results highlight an essential aspect of the therapeutic cascade that may be particularly burdensome and which few clinicians likely consider when making prescribing decisions. As such, our findings highlight the potential benefit of efforts to reduce prescribing and filling complexity by encouraging filling by mail order and/or reducing the frequency with which they must fill (e.g., by providing 90-day supplies of medications),” Dr. Choudhry and his colleagues said.

A Valuable Step Forward

Despite its limitations, this study “provides a valuable step forward in measuring the complexity of prescription medication management and its effect on adherence,” the investigators said.

Previous research has focused on the number of medications, the number of doses, and the times of administration, failing to take into account that many patients have multiple prescribers, shop around for lower prices, use both mail order and retail pharmacies, and have refills due on different dates, said Dr. Amanda H. Salanitro and Dr. Sunil Kripalani.

To improve adherence, physicians “can encourage patients to simplify their pattern of filling medications by using a single pharmacy or synchronizing refill dates. Having a pharmacy ‘home’ ... might also be helpful for maintaining an accurate medication list and avoiding drug–drug interactions,” the investigators said.

This is an assigned study does not provide direct evidence for these practices, their potential to improve adherence is intriguing,” Dr. Salanitro and Dr. Kripalani said.
**Indications and Usage**

PRADAXA (dabigatran etexilate mesylate) capsules is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

**Important Safety Information About PRADAXA**

**Contraindications**

PRADAXA is contraindicated in patients with active pathological bleeding and patients with a known serious hypersensitivity reaction (e.g., anaphylactic reaction or anaphylactic shock) to PRADAXA.

**Warnings and Precautions**

**Risk of Bleeding**

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding.

Risk factors for bleeding include:

— Medications that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs)

— Labor and delivery

Promptly evaluate any signs or symptoms of blood loss, such as a drop in hemoglobin and/or hematocrit or hypotension. Discontinue PRADAXA in patients with active pathological bleeding.

Please see additional Important Safety Information about PRADAXA and brief summary of full Prescribing Information on the following pages.
PRADAXA 150 MG TWICE DAILY

In non-valvular atrial fibrillation

**Significant risk reduction of stroke vs warfarin**

Effects of PRADAXA compared to warfarin were more apparent in patients with lower levels of INR control.

**Statistically significant reduction in stroke/systemic embolism**

- Efficacy of PRADAXA was generally consistent across major subgroups*

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**IMPORTANT SAFETY INFORMATION ABOUT PRADAXA**

(continued from previous page)

**Temporary Discontinuation of PRADAXA**

Discontinuing PRADAXA for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of stroke. Lapses in therapy should be avoided, and if PRADAXA must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

**Effect of P-gp Inducers and Inhibitors on PRADAXA Exposure**

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces dabigatran exposure and should generally be avoided. P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin, do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors.

**ADVERSE REACTIONS**

In the pivotal trial comparing PRADAXA to warfarin, the most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal (GI) events. PRADAXA 150 mg resulted in a higher rate of major GI bleeds and any GI bleeds compared to warfarin. In patients ≥75 years of age, the risk of major bleeding may be greater with PRADAXA than with warfarin. Patients on PRADAXA 150 mg had an increased incidence of GI adverse reactions. These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and GI ulcer). Drug hypersensitivity reactions were reported in <0.1% of patients receiving PRADAXA.

**Other Measures Evaluated**

The risk of myocardial infarction was numerically greater in patients who received PRADAXA 150 mg than in those who received warfarin.

*Major subgroups were prespecified and included age (<65, ≥65 and <75, ≥75), previous stroke/systemic embolism/TIA (no or yes), heart failure (no or yes), diabetes (no or yes), hypertension (no or yes), warfarin use at entry (naïve or experienced).

References:

PRADAXA® is a registered trademark of Boehringer Ingelheim Pharma GmbH and Co. KG and used under license.

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Lower total bleed rate vs warfarin

Higher rate of major gastrointestinal (GI) bleeds (1.6% vs 1.1%)†‡
Fewer intracranial hemorrhages (0.3% vs 0.8%)†§

- PRADAXA can cause serious and, sometimes, fatal bleeding
- Number of total GI bleeds was 681 vs 452 for warfarin (6.1% vs 4.0% for warfarin)1,3
- Number of major bleeds was 399 vs 421 for warfarin†‡ (3.3% vs 3.6% for warfarin, Hazard Ratio: 0.93, 95% CI (0.81, 1.07))
- Trend toward a higher incidence of major bleeding on PRADAXA for patients ≥75 years of age (Hazard ratio: 1.2, 95% CI (1.0 to 1.4))
—Risk of stroke and bleeding increase with age, but risk-benefit profile is favorable in all age groups

†Patients contributed multiple events and events were counted in multiple categories.
‡Major bleeds fulfilled 1 or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intracocular, intracranial, intraspinal, or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding).
§Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.
1A life-threatening bleed met 1 or more of the following criteria: fatal, symptomatic intracranial bleed, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention.
**Incidence of Negative Outcomes in LIFE**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Patients without LHV (n = 252)</th>
<th>Patients with LHV (n = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MI</strong></td>
<td>10 (4.0)</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>8 (3.2)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td><strong>Cardiovascular dep.</strong></td>
<td>13 (5.2)</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td><strong>MI, stroke, or CV death</strong></td>
<td>13 (5.2)</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>13 (5.2)</td>
<td>9 (4.3)</td>
</tr>
</tbody>
</table>

Notes: Based on data for patients who achieved a systolic blood pressure of <130 mm Hg; LHV = left ventricular hypertrophy; HR = adjusted hazard ratio.

*Source: Dr. Okin*

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**Table 1** Summary of Treatment Exposure in LIFE

<table>
<thead>
<tr>
<th>Treatments</th>
<th>PRADAXA® (dabigatran etexilate mesylate) capsules for oral use</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRADAXA</strong></td>
<td><strong>150 mg twice daily</strong></td>
<td>N (%)</td>
<td><strong>PRADAXA</strong></td>
</tr>
<tr>
<td><strong>Total number treated</strong></td>
<td>5983</td>
<td>6059</td>
<td>5986</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>4906</td>
<td>4929</td>
<td>5193</td>
</tr>
<tr>
<td>12 months</td>
<td>2378</td>
<td>2405</td>
<td>2470</td>
</tr>
<tr>
<td><strong>Mean exposure (months)</strong></td>
<td>20.5</td>
<td>20.3</td>
<td>21.3</td>
</tr>
<tr>
<td><strong>Total patient-years</strong></td>
<td>10,242</td>
<td>10,261</td>
<td>10,659</td>
</tr>
</tbody>
</table>

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**Risk of Bleeding:** PRADAXA increases the risk of bleeding and can cause significant adverse reactions. Risk of bleeding for PRADAXA and warfarin was similar. PRADAXA significantly decreases the rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio of 1.5, 95% CI 1.0, 2.3, and a higher rate of any gastrointestinal bleeds (6.4% vs. 4.8%, respectively).)

**Intracranial Hemorrhage:** Patients on PRADAXA 150 mg had an increased risk of intracranial hemorrhage (1.2) vs. 1.0 for patients on warfarin (hazard ratio 1.15, 95% CI 0.89, 1.47).

**Gastrointestinal Adverse Drug Reactions:** Drug discontinuation was required in 5.9% of patients on PRADAXA 150 mg vs. 2.2% of patients on warfarin.

**Drug Interactions:** Concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors ketocanozole, verapamil, amiodarone, quinidine, and clariatrixine do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors.

**Drug Use in Specific Populations:** Pregnancy: PRADAXA is not recommended in pregnant women. Use during pregnancy is not recommended due to the potential for fetal harm.

**Limitations:** This study was not designed to detect a difference in the incidence of intracranial hemorrhage between PRADAXA and warfarin. Further studies are needed to evaluate this potential difference.

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**Persistent LVH Worsens Outcomes in Hypertensives**

**By Mitchell L. Zoler**

From the annual meeting of the American college of cardiology

NEW ORLEANS—Hypertensive patients who have persistent left ventricular hypertrophy despite normalized BP faced a substantially higher risk for death and cardiovascular events, compared with patients without hypertrophy on antihypertensive treatment, according to a study involving 463 patients.

“These results suggest that persistence of left ventricular hypertrophy (LVH) in patients with controlled blood pressure reduces the benefit of antihypertensive treatment, especially when the blood pressure during treatment may in part explain the lack of benefit seen in hypertensive patients, despite treatment to lower systolic blood pressure,” Dr. Peter M. Okin said at the meeting.

Based on these results, it may be necessary to track end-organ damage in addition to BP to fully assess response to treatment in hypertensive patients, said Dr. Okin, professor of medicine at Cornell University in New York.

The analysis Dr. Okin reported came from a subset of participants in the LIFE (Losartan Intervention for Endpoint Reduction) Hypertension study, which enrolled 9,193 patients aged 55-80 years with a BP of 160/95 mm Hg to 200/115 mm Hg. The study randomized patients to two different antihypertensive treatment arms, one based primarily on losartan and the control based primarily on atenolol, with a target BP of 140/90 mm Hg or less (Lancet 2002;359:995-1003).

The subgroup used for the new analysis included the 463 patients in the study who achieved a systolic BP of 130 mm Hg or less. During an average follow-up of more than 4 years, the combined rate of cardiovascular death, MI, or stroke was 15%.

The researchers used data from the 12-lead ECG recordings of these patients, as analyzed to calculate left ventricular size. They considered any patient with a Cornell product greater than 2440 mm x m sec to have residual LVH. This identified 211 patients (46%) with persistent hypertension despite their low achieved systolic BP, and 252 patients without LVH.

Patients with persistent LVH were significantly older than those without LVH (64 years), and were significantly more likely to be women (53%) compared with the 40% of women in the group without LVH.

During the average 4.4 years of follow-up, patients with residual hypertrophy had significantly higher rates of MI, strokes, cardiovascular death, and all-cause mortality, as well as a significantly higher rate of the combined end point of MI, stroke, or cardiovascular death, compared with the patients without hypertension.

Dr. Okin said that he received a financial benefit from GE Medical Systems. The LIFE trial was sponsored by Merck, which markets losartan (Cozaar).
Maximize Stroke Risk Reduction in Elderly

**Studies show benefits of calcium channel blockers and diuretics.**

**BY BRUCE JANCIN**

**EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE**

**AMERICAN COLLEGE OF CARDIOLOGY**

**NEW ORLEANS** – Calcium channel blockers and diuretics are the best drugs for treating hypertension in the elderly because they are the most effective at reducing the risk of what elderly patients fear most: stroke. Dr. Norman M. Kaplan asserted at the meeting. “Coronary disease remains by far the most common cause of mortality [in the United States], but stroke poses the greatest threat to the elderly, not coronary disease,” said Dr. Kaplan, professor of internal medicine at the University of Texas, Dallas.

He presented a state-of-the-art perspective on antihypertensive therapy in the elderly from the unique vantage point of having served as a member of the third, fourth, fifth, and sixth Joint National Committees on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Dr. Kaplan noted that a British meta-analysis of 46 randomized trials comparing each of the five major classes of antihypertensive drugs with any other class showed that all of the classes were similarly effective in preventing both coronary disease events and strokes, with one exception: calcium channel blockers had a significantly greater preventive effect on stroke than other agents. Diuretics showed a trend in the same direction that did not reach statistical significance (BMJ 2009;339:b655; doi:10.1136/bmj.b655).

A secondary analysis of the 19,257-subject ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) demonstrated that calcium channel blocker-based antihypertensive therapy was particularly effective against stroke in the population most in need of such protection: the elderly. Although there was no significant difference in strokes between amlopidine- and atenolol-based therapy in patients younger than age 65 years, there was a highly significant 30% relative risk reduction with amlopidine in the over-65 group (J. Hypertens. 2011;29:383-91).

The latest thinking regarding mechanism of benefit is that calcium channel blockers and diuretics are more effective at reducing stroke risk because they decrease within-individual variation in systolic blood pressure, unlike ACE inhibitors, angiotensin receptor blockers, and beta-blockers, all of which significantly increase it. In a meta-analysis of 389 randomized, controlled trials of antihypertensive therapy, stroke risk proved strongly related to this interindividual variation in blood pressure (Lancet 2010;375:906-15).

Calcium channel blockers may also have a neuroprotective effect. A French study of 378 elderly, nondemented, hypertensive patients with the complaint of memory loss showed that memory scores were significantly better in those on a calcium channel blocker than on any other class of antihypertensive medication (J. Hypertens. 2010;28:2485-93). Although that is an intriguing finding, this was an observational study and needs confirmation, in Dr. Kaplan’s view.

Elderly hypertensives predominantly have isolated systolic hypertension. Because of the extensive body of evidence showing that such patients have a good response rate to diuretic monotherapy, he recommends using a diuretic as the first-line drug. “I would start chlorthalidone – now having a resurgence as the diuretic of choice – at 12.5 mg/day, and add a calcium channel blocker if additional therapy is needed to reach 150/70 mm Hg, which I think is a rational goal to aim for in the elderly,” he said. Indeed, although the 7th Joint National Committee calls 140 mm Hg the upper limit of normal systolic blood pressure at all ages, nearly all the randomized trials that have shown a protective value for antihypertensive therapy in the elderly enrolled patients with a baseline systolic pressure in excess of 160 mm Hg, and achieved an on-treatment systolic pressure in the 150s or 160s.

“I do not think the evidence we have to date shows protective value for treatment in patients with a baseline systolic blood pressure below 160 mm Hg. There is evidence to suggest that if we lower the elderly patient’s systolic blood pressure more than 10-15 mm Hg, we may be invoking additional trouble rather than protecting the patient,” said Dr. Kaplan.

“These are old people who obviously have atherosclerotic vascular disease, even if they don’t show it. Reduction in diastolic blood pressure to 65 mm Hg or lower may reduce their coronary perfusion – which occurs only during diastole – to a degree that could invoke a cardiovascular catastrophe,” he continued.

Other aspects of treating elderly hypertensive patients include identifying and overcoming posural hypotension, encouraging the consumption of one or two alcoholic drinks per day for the well-documented health benefits, starting a statin, and measuring home blood pressures to ensure that an individual really is being treated adequately, Dr. Kaplan said.

The risks posed by orthostatic hypotension were highlighted in a study of 374 unselected elderly adults with an average age of 70 years and no known cardiovascular disease or other comorbidities. An orthostatic decrease in systolic blood pressure greater than 20 mm Hg was present 2 minutes after standing in 12% of them. Over roughly 1 year of follow-up, cardiovascular events were 2.4-fold more frequent in that patient subset (Hypertension 2010;56:56-61).

Dr. Kaplan disclosed that he is on the speakers bureaus for Pfizer, AstraZeneca, Merck, Novartis, and Bayer.

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**Moderate Hypertension Linked to Adverse Brain Changes**

**BY MITCHEL L. ZOLER**

**FROM THE ANNUAL MEETING OF THE**

**AMERICAN COLLEGE OF CARDIOLOGY**

**NEW ORLEANS** – Elderly people with modestly elevated systolic blood pressure showed significant declines in their mobility and cognition, and concurrent significant increases in brain damage, during 2 years of follow-up in a small study. These correlations suggest a possible new reason to control blood pressure in the elderly, Dr. William B. White said at the meeting.

“These data support an intervention- nal trial evaluating different thresholds of ambulatory systolic blood pressure for preventing white matter progression and functional decline in older people,” said Dr. White, professor of medicine and full professor of internal medicine at the University of Texas, Dallas.

He plans to compare target systolic blood pressures of 145 and 130 mm Hg, he said in an interview. “If you can intervene in patients with early-onset white matter disease and prevent progression, then you will do these people a big favor,” he said. “I don’t think we will see re- gression [of white matter damage], just prevention of it getting worse. This is the first study I know of to longitudinally compare ambulatory blood pressure in white matter hyperintensity and functional decline in older people. Blood pressure turned out to be the most important” determinant of decline among all the measures studied, he said.

**Major Finding:** A significant correlation was found between 24-hour ambulatory systolic hypertension, brain damage, and functional and cognitive impairment in elderly people. Each 1-mmHg rise in systolic pressure over a 2-year period linked with an average 0.04% increased brain volume of white matter hyperintensity.

**Data Source:** Two-year follow-up study of 72 people aged 75-89 years (average age, 82; at baseline) who were normotensive or mildly hypertensive at entry.

**Disclosures:** Dr. White said that he has been a consultant to the Forest Research Institute and has received research grants from Novartis.

“Hypertension specialists think about the burden [of hypertension] on the heart and the kidney, but they don’t think about the chronic burden on the brain,” said Dr. C. Venkatapathy, professor of medicine at the University of Texas Southwestern Medical Center in Dallas. “Chronic hypertension can lead to significant mor- phologic and physiologic dysfunction. Many patients diagnosed with Alzheimer’s disease probably had poorly controlled hypertension over their lifetime. Dr. White and his associates enrolled 72 people aged 75-89 with various degrees of mobility and cognitive impairment who underwent blood pressure, cognitive, mobility, and MRI brain assessments at entry and said 24 months later. At baseline, their age averaged 82 years, their 24-hour ambulatory blood pressure averaged 126/66 mm Hg, and their average amount of brain white matter hyperintensity, a marker of brain damage, was 1% of their total brain volume. Two years later, their average ambulatory blood pressure stood at 131/67 mm Hg. At both time points about 70% of patients re- ceived antihypertensive medication.

When the researchers compared the findings at the two measurement times, they found that for each 1% increase in the volume of white matter hyperintensity, subjects showed an average 0.31-second decrease in their walk time and a 0.05-second increase in their simple reaction time on cognitive testing. In addition, for each 1-mmHg increase in 24-hour systolic blood pressure over the 2-year period between blood pressure at their 2-year assessment. The top and bottom tertiles had average systolic pressures of 144 and 117 mm Hg. The top tertile showed a significantly larger increase in white matter hyperintensity volume over the 2 years of follow-up, a significantly longer 8-foot walk time, a significantly slower walking speed, and nonsignificant trend toward poorer results on cognition tests.

Also notable in the findings was that a modest level of systolic hypertension in the highest tertile tracked with significa- nt changes over the 2-year period.

“The people only averaged 144 mm Hg. That’s not so bad, but they had progres- sion,” Dr. White said.
**In chronic angina**

**Superior clinical effects**

**Ranexa 1000 mg twice daily with standard treatments**

**EXERCISE TREADMILL TEST PERFORMANCE**
Mean results over 12 weeks, trough plasma concentrations (CARISA)¹²

<table>
<thead>
<tr>
<th></th>
<th>Placebo + standard treatments (n = 258)</th>
<th>Ranexa 1000 mg twice daily + standard treatments (n = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(modified Bruce treadmill test)</td>
<td>91.7</td>
<td>115.8</td>
</tr>
<tr>
<td><strong>Time to angina</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 sec P = .03</td>
<td>114.3</td>
<td>140.3</td>
</tr>
<tr>
<td><strong>Time to 1-mm ST depression</strong></td>
<td>125.1</td>
<td>146.2</td>
</tr>
</tbody>
</table>

**TRIAL DESCRIPTION**

CARISA (Combination Assessment of Ranolazine In Stable Angina) was a double-blind, randomized, placebo-controlled clinical trial of 823 patients with chronic angina who received Ranexa 750 mg twice daily, Ranexa 1000 mg twice daily, or placebo for 12 weeks. Patients also received daily doses of atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg as standard treatment. The primary endpoint was exercise duration on the modified Bruce treadmill test at trough drug levels (12 hours after dosing). Secondary endpoints included exercise duration at peak drug levels, time to angina, time to 1-mm ST-segment depression, angina frequency, and weekly nitroglycerin use. Sublingual nitrates were used as needed.¹

**Indication**
- Ranexa is indicated for the treatment of chronic angina.
- Ranexa may be used with beta-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.

**Warnings and Precautions**
- Ranexa blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.
- Clinical experience did not show an increased risk of proarrhythmia or sudden death.
- There is little experience with high doses (> 1000 mg twice daily) or exposure, other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval.

**Adverse Reactions**
- The most common adverse reactions (> 4% and more common than with placebo) during treatment with Ranexa were dizziness, headache, constipation, and nausea.

**IMPORTANT SAFETY INFORMATION**

**Contraindications**
- Ranexa is contraindicated in patients:
  - Taking strong inhibitors of CYP3A (eg, ketoconazole, itraconazole, clarithromycin, nefazodone, neflinavir, ritonavir, indinavir, and saquinavir)
  - Taking inducers of CYP3A (eg, rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St John’s wort)
  - With clinically significant hepatic impairment
was superior compared with standard treatments alone

- 26% increase in exercise duration ($P = .03$)
- 23% increase in time to angina ($P = .03$)
- 36% relative reduction in angina frequency ($P < .001$)

In the CARISA trial, patients receiving placebo experienced a mean of 3.3 angina attacks per week (compared with 4.6 at baseline), whereas patients receiving Ranexa 1000 mg twice daily experienced a mean of 2.1 angina attacks per week (compared with 4.5 at baseline).

Effects on exercise tolerance and angina frequency were considerably smaller in women than in men. The improvement in exercise duration in women was about 33% of that in men at the 1000-mg twice-daily dose level.

For patient case studies, visit RanexaCases.com.

**Dosage and Administration**

- Begin treatment with 500 mg twice daily and increase to the maximum recommended dose of 1000 mg twice daily, based on clinical symptoms.
- Limit the dose of Ranexa to 500 mg twice daily in patients on moderate CYP3A inhibitors (eg, diltiazem, verapamil, aprepitant, erythromycin, fluconazole, and grapefruit juice or grapefruit-containing products).
- Ranexa tablets should be taken whole and not crushed, broken, or chewed.

**Drug Interactions**

- Do not use Ranexa with CYP3A inducers or strong CYP3A inhibitors (see Contraindications); modify the dose of Ranexa with moderate CYP3A inhibitors (see Dosage and Administration).
- P-gp inhibitors (eg, cyclosporine): may need to lower the dose of Ranexa based on clinical response.
- Doses of drugs transported by P-gp (eg, digoxin) or metabolized by CYP2D6 (eg, metoprolol, tricyclic antidepressants, and antipsychotics) may need to be reduced.

Please see brief summary of prescribing information on adjacent page.
Medicare Proposes 2012 Pay Cut for Hospitals

BY ALICIA AULT

The Centers for Medicare and Medicaid Services is proposing to reduce payments for hospitals by $498 million, or 0.35%, in fiscal 2012. The proposals under the Inpatient Prospective Payment System and the Long-Term Care Hospital Prospective Payment System continue a flat-to-downward trend in Medicare reimbursement over the past few years. A big reason for the reduction: The agency is adjusting for overpayments made for coding errors in the previous fiscal years, according to Ira Linn and his colleagues at Washington Analysis, a company that monitors policy developments for investor clients.

Proposals will maintain pressure on makers and suppliers of certain device categories, like orthopedics, general surgery, routine lab tests, and medical supplies, for the foreseeable future, said Mr. Linn. The April 19 announcement included new quality improvement proposals. The proposals ... reflect an underlying premise that we can improve the quality of and access to care while at the same time slowing the growth in health care spending,” CMS Administrator Donald Berwick said in a statement. The rule will encourage support of Partnerships for Patients, a Joint effort by the Department of Health and Human Services and private entities to improve patient safety and quality. Beginning in fiscal 2013, the agency is to stop reducing payments to hospitals that have excess readmissions for certain conditions. The proposed rule lays the groundwork for that by publishing rates of readmissions for three conditions: acute myocardial infarction, heart failure, and pneumonia.

The proposal would also add one category to the list of hospital-acquired conditions that the CMS will not pay for at a higher rate, if the condition occurred during the hospital stay. That category is acute renal failure after contrast dye exposure.

Heart transplants and heart assist systems will have about a 9% pay reduction. Defibrillator implantation will range from a decrease of 2.1% to an increase of 4.5%.

administration (also known as contrast-induced acute kidney injury, or CI-AKI). The new rule contains provisions that will support the hospital value-based purchasing regulation when that final rule is issued in “the near future.” One of those proposals is to adopt a Medicare Spending Per Beneficiary index for the value-based purchasing program. The CMS also proposes to reduce the reporting burden for physicians and hospitals by retiring some quality measures, introducing others that will more closely align with measures collected for other purposes, and streamlining the submissions process, said the agency.

On the reimbursement side, cardiac and orthopedic procedures will see an overall slight reduction in payment, according to Washington Analysis. Heart transplants and heart assist systems will have about a 9% pay reduction. Defibrillator implantation will range from a decrease of 2.1% to an increase of 4.5%, depending on the patient’s status, the analysts said. Deep brain stimulation, vagus nerve stimulation for epilepsy, and spinal cord stimulation will see a small increase. The rule is open for comment until June 20. The final rule is to be issued by Aug. 1.

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House Hears SGR Alternatives, Vows Action

BY FRANCES CORREA

WASHINGTON – A plan to finally replace Medicare’s much maligned Sustainable Growth Rate formula could be unveiled by this summer, federal lawmakers predicted at a committee hearing.

“This is the bottom line: If we get to December and we’re doing an extension, that’s a failure on our part,” Rep. Michael Burgess (R-Tex.) said at the hearing. “We need a permanent solution that’s predictable, updatable, and reasonable for this year—and nothing else will do.”

“What will it do to the SGR when it was created 14 years ago,… it’s clear that they have vanished,” noted Rep. Henry A. Waxman (D-Calif.). He added that in the past 2 years, Congress has had to pass legislation six times, blocking fee cuts of up to 21% or more.

About 30 medical associations responded to the House subcommittee’s request for suggestions and proposals in developing a new system. Speaking with a five-person panel of experts from medical associations and health policy organizations, House subcommittee members considered alternatives to the current SGR formula.

One Size Won’t Fit All

While the details of the plans vary, they do show a consensus on several fronts: repealing the SGR, moving away from the traditional fee-for-services payment model, and providing a 4-to-5-year transition period in which providers can experiment with a variety of payment systems.

The expert panel also stressed the importance of avoiding a “one size fits all” solution.

“I think we should also have a realization that what will work in one part of the country will not work in another part of the country, and that’s why we have continued to talk about a variety of options,” said Dr. Cecil Wilson, president of the American Medical Association.

Dr. Wilson pointed to the provisions in the Affordable Care Act that allow for a variety of models of accountable care organizations, embodying the concept of options in the medical system. In that spirit, he said that the AHA has formed a physician leadership group to evaluate the effectiveness of alternative payment methods.

To strengthen primary care’s role in Medicare, the American Academy of Family Physicians backs payment reforms that would boost primary care reimbursement and support the concept of the patient-centered medical home (PCMH). AAFP President Roland A. Goertz noted in written testimony to the committee that the proposal would create a blended reimbursement system for primary care delivered within a PCMH: fee-for-service payments and pay for performance, plus care management fees for PCMH-related activities that don’t involve direct patient care.

Dr. David Hoyt, executive director of the American College of Surgeons, said the college is analyzing the use of bundled payments for surgery. Dr. M. Todd Williamson, of the Coalition of State Medical and National Specialty Societies, introduced the option of private contracting, in which patients would be free to apply their benefits to a doctor of their choice, who would be free to opt out on a per-patient basis.

Harold Miller, executive director of the Center for Healthcare Quality and Payment Reform, suggested an episode-of-care payment plan through which hospitals and physicians jointly charge one price for all services included in a hospitalization. The model would also include a warranty stating that any infections or complications would be free to opt out on a per-patient basis.

Is IPAB the New SGR?

Rep. Fred Upton (R-Mich.) raised concerns about the Independent Payment Advisory Board (IPAB), created by the Affordable Care Act. The board sets expenditure targets, on which it bases spending cuts. In 2018, targets will be based on the gross domestic product. “Sounds like a lot like SGR, which we’re trying to get rid of.” Mr. Upton said. “Since hospitals are exempt from IPAB cuts through the rest of the decade, it seems that the IPAB has the potential to undermine any serious efforts at physician payment reform.” Some panelists agreed.

“It’s not impossible that the IPAB could serve a function,” Dr. Wilson said, “but as presently constituted, we see it as basically another target for physicians to meet—potential double jeopardy, with an SGR as well as the pronouncements from this body.”

The panelists also asserted their belief that whatever plan chosen should be physician led, with financial support of the government. “It would be helpful if physicians could get better financial support in their own payment system to enable them to lead all of those efforts,” said Dr. Mark B. McClellan, director of the Engberg Center for Health care Reform and former administrator of the Centers for Medicare and Medicaid Services.

Electronic Health Records Deemed Good for the Earth

BY FRANCES CORREA

FROM HEALTH AFFAIRS

Greater use of electronic health records would cut greenhouse gas emissions, energy use, waste and toxic chemical production, and water consumption, according to a study by Marianne C. Turley, Ph.D., and her associates at Kaiser Permanente.

Even after factoring in the additional energy consumption from the increased use of personal computers, the overall net effect on the environment would be favorable, the researchers concluded based on an analysis of the impact of the Kaiser Permanente EHR system, which covers 8.7 million beneficiaries.

Annually, the use of the Kaiser EHR system eliminated the use of 1,373 tons of paper by discontinuing the use of paper medical charts, x-ray jackets, and administrative forms. The system also decreased annual gas consumption by an estimated 3.3-10 million gallons by cutting the number of visits by 4-13 million.

Major Finding: The use of electronic health records cut Kaiser Permanente’s use of paper by 1,373 tons annually. The system also decreased energy use by 3.3-10 million gallons of gasoline by reducing medical visits.

Data Source: Based on a 2011 internal analysis.

Disclosures: All seven researchers are employees of Kaiser Permanente.

Patients who were registered online could correspond with their providers about nonemergency concerns through secure e-mail messages, the investigators reported (Health Aff. 2011;30:938-46).

Switching from desktop to laptop computers saved 89,300 megawatt hours and digitizing x-rays eliminated the waste of 203 tons of plastic and 79 tons of toxic chemicals.

Using the Environmental Protection Agency’s greenhouse gas equivalencies calculator, Dr. Turley and her associates estimated that Kaiser’s efforts reduced greenhouse gas emissions by 9,200 tons.

Results were based on data from regional operational reports, paper-purchasing records, and internal pharmaceutical reports. Travel distance was estimated by calculating the distance from patient addresses to Kaiser-participating primary care buildings and aggregating them by region.

With a growing emphasis on health technology, the Kaiser study showed that “the use of electronic health records can both change the face of health care and help reduce its environmental footprint,” the researchers wrote.

Despite these findings, Dr. Turley and her associates said that the environmental impact of switching to electronic health records will vary from system to system. As the Affordable Care Act calls for implementation of electronic systems, they said further analysis is necessary to determine the impacts of widespread implementation.

Although 51% of office-based physicians are currently using an electronic system, only 10% of practices reported their systems as being fully functioning, according to the most recent evaluation from the Centers for Disease Control and Prevention. Regardless, implementation of electronic systems will probably increase as provisions in the American Recovery and Reinvestment Act of 2009 create incentives for providers who invest in electronic systems. Public and private investment in these systems is expected to reach $40 billion in the next several years, according to the investigators.
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New Initiatives Aim to Encourage Move to ACOs

The Pioneer ACO Model and other initiatives are the result of feedback from medical associations.

BY FRANCES CORREA
FROM THE CENTERS FOR MEDICARE AND MEDICAID SERVICES

Three new initiatives aim to help physicians make the jump to becoming part of an Accountable Care Organization, officials from the Centers for Medicare and Medicaid services announced May 17.

The Pioneer ACO Model would accelerate the process for ACOs that already have the infrastructure in place to coordinate care for patients. Under this model, private payers would offer provider incentives and would function on a separate contract from the Medicare Shared Savings Program.

About 30 integrated health systems are expected to participate in the Pioneer ACO Model project this summer, making a full transition to ACO by September or October, according to Jonathan Blum, director of the Center for Medicare Management, a part of the CMS.

Use of the pioneer model could result in $430 million in Medicare savings over 3 years, according to the CMS Office of the Actuary. The pioneer model will follow the same 65 quality measurements and regulations already assigned to ACOs.

The second initiative is a series of free accelerated development learning sessions to educate providers on becoming an ACO and implementing a coordinated care model. The first of the four learning sessions offered in 2011 will be available June 20-22 in Minneapolis. All materials from the sessions, including webcast sessions, will be publicly available.

Finally, the CMS is requesting public comment on the proposal for providing upfront payments to providers who are interested in becoming ACOs but lack the resources. The accelerated payment program would allow providers who lack the capital to invest in the necessary infrastructure and staffing, Mr. Blum said, adding that the CMS plans to determine how much funding might be provided after evaluating public comments.

These initiatives came as a result of feedback from medical associations during the comment period of the ACO regulations, according to Dr. Donald Berwick, CMS administrator, who added that the challenge to implementing the best model is striking a balance between patient and provider needs. This includes balancing an ACO’s need for data with patient privacy, the need for better coordinated care without overburdening providers with regulations, and the need for creating provider incentives without allowing them to avoid methods of care that might threaten those incentives.

Regardless, Mr. Blum said the CMS is devising a model that will greatly improve care. “We think that the ACO model, both the base model but also the Pioneer [model], is one of the best ways for us to improve care and so we’re very conscious of the fact that we have to create payment policies and other requirements that provide an attractive model.”

The comment period on accountable care organization regulation was scheduled to close on June 6.
Cardiologists Top E-Prescribers
Cardiologists appear to be adopting electronic prescribing more readily than colleagues in other specialties, according to a report by the Surescripts e-prescribing network. The 49% of cardiologists using e-prescribing is ahead of family practitioners (47%) and internists (45%). Behind them, 38% of gastroenterologists and 36% of pediatricians are e-prescribing. About 36% of all office-based physicians were e-prescribing in 2010, and in 10 prescriptions was delivered electronically in 2010, up from 1 in 18 in 2008. E-prescribing is being driven primarily by federal legislation, including health care reform, according to Surescripts.

Bill Would Protect Device Makers
A tort-reform bill that was passed by the House Energy and Commerce Committee in mid-May would exempt medical device makers from paying punitive damages in product liability suits, according to a report that reports on the medical-device industry. The committee passed the Help Efficient, Accessible, Low-Cost, Timely Healthcare (HEALTH) Act of 2011 (H.R. 5) by a vote of 30-20, largely along party lines. The bill was introduced in January by Rep. Phil Gingrey (R-Ga.), who is a physician. Although Republicans and physicians’ organizations have generally favored the bill, Democrats have objected to the exemptions for medical device and pharmaceutical manufacturers. The bill would place a $250,000 cap on noneconomic damages in malpractice cases and would require that most medical liability suits be filed within 3 years of an injury.

Heart Admissions Declined
Hospital admissions for top cardiovascular conditions declined among Medicare beneficiaries from 1998 to 2008, researchers at New York University and Yale University found. While overall Medicare admissions climbed from 11 million to 13 million during the decade, hospitalizations for heart failure, ischemic heart disease, and acute myocardial infarction went down 7%, 24%, and 13%, respectively. In contrast, admissions for cardiac arrhythmia increased 28%. The authors presented their paper as a poster at an American Heart Association meeting in Washington.

Some Pacemakers Okay With MRI
Medicare has proposed ending its ban on MRI in patients with implantable pacemakers. Device maker Medtronic had asked the agency to alter the policy after the company in February won Food and Drug Administration approval of a pacemaker that was designed for use with MRI. In a “Proposed Decision Memo,” the Centers for Medicare and Medicaid services said that “the evidence is adequate to conclude that magnetic resonance imaging (MRI) improves health outcomes for Medicare beneficiaries with implantable permanent pacemakers (PMs) when the PMs are used according to the FDA-approved labeling for use in an MRI environment.”

Heart Failure Certification Begins
The Joint Commission and the American Heart Association announced that their advanced certification program in heart failure will start next month. The program will focus on “safe, successful transitions of care” from inpatient to outpatient settings, according to an AHA statement. Programs seeking certification will have a hospital, a collaborative relationship with a cardiology practice, and proof of adherence to the AHA-American College of Cardiology guidelines on diagnosis and management of heart failure. “By demonstrating advanced certification in heart failure, programs will have validated their commitment to consistently delivering reliable, effective and high quality care to their heart failure patients,” said Dr. Gregg C. Fonarow, who led the AHA’s guidelines committee.

CME-Funding Dilemma Persists
Although other medical professionals say they’re concerned that commercial funding of continuous medical education may bias the information provided, most are not willing to pay more to offset or eliminate such funding, a study in Archives of Internal Medicine shows. Researchers surveyed 770 physicians, nurses, nurse practitioners, and others.

Use with Ritonavir and Other PDE5 Inhibitors
The concomitant administration of the protease inhibitor ritonavir (a highly potent CYP3A4 inhibitor) may result in increased concentrations of sildenafil. Therefore, the co-administration of ritonavir or other PDE5 inhibitors with REVATIO is not recommended.

Effects on the Eye
Because clinical trials are conducted under widely varying conditions, adverse reaction rates that may be observed in the clinical trials of another drug and may not reflect the rates observed in practice. The incidence of an event in one or both eyes while taking PDE5 inhibitors, including REVATIO. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of disciform vision including permanent loss of vision, that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors, including sildenafil, when used in the treatment of erectile dysfunction. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also consider increased risk of NAION in patients who are already experienced NAION in one eye, even indicating whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see [Adverse Reactions]).

Combination with Other PDE5 inhibitors
Sildenafil is also marketed as VIAGRA. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection
Use REVATIO in patients with anatomic deformations of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, patients should seek immediate medical assistance. If spontaneity (greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Pulmonary Hypertension Secondary to Sickle Cell Anemia
In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vascular death and hospitalization for PH were reported by 3 patients who received REVATIO and by those randomized to placebo. The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypertension: Warfarin and Placebo
- Vision loss (see Warnings and Precautions)
- Hearing loss (see Warnings and Precautions)
- Priapism (see Warnings and Precautions)
- Vaso-occlusive crises (see Warnings and Precautions)
- Clinical Experience

Because clinical trials were conducted under widely varying conditions, adverse reaction rates that may be observed in the clinical trials of another drug may not reflect the rates observed in practice. Safety data were obtained from the 10 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied. The overall frequency of discontinuance in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group. In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 2% of REVATIO patients treated at the recommended dose (20 mg TID) were: headache, ankle edema, and mild ankle swelling in patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=70)</th>
<th>Placebo-Subtracted</th>
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<td>n (%)</td>
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</tr>
<tr>
<td>Elevation</td>
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<td>1</td>
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<td>1</td>
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<td>3</td>
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<td>Fatigue</td>
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<td>Other</td>
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Note: Not otherwise specified
postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, stroke, transient ischemic attack, hypertension, pulmonary hypertension, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to, low back disc disease; “crowded disc,” age over 50, diabetes, hypertension, coronary artery disease, hypertension, and smoking. It is not possible to determine whether these events are related directly to sildenafil, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. See Warnings and Precautions.

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including sildenafil. In some cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors. See Warnings and Precautions.

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion due to their seriousness, frequency of reporting, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, seizure recurrence

Drug INTERACTIONS

Adverse

Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended. See Warnings and Precautions.

Alpha-blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects. See Warnings and Precautions.

In drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, clinical, mean additional reductions of supine systolic and diastolic blood pressure of 7/11 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/5 mmHg, 11/4 mmHg, and 4/3 mmHg, respectively, were also observed. There were no intragroup reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Antihypertensive agents

Sildenafil 100 mg oral was co-administered with enalapril, 5 mg or 10 mg oral, for hypertensive patients. The mean additional reduction of supine blood pressure was 9/5 mmHg systolic and 7/5 mmHg diastolic.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

There is no information regarding the use of sildenafil in pregnant women. Use in pregnant women should be restricted to cases where, in the opinion of the physician, the potential benefit justifies the potential risk to the fetus. See Warnings and Precautions.

Nursing Mothers

Sildenafil is excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when sildenafil is administered to a nursing woman. See Warnings and Precautions.

Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

Geriatrics Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Use in the Elderly

Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Renal Impairment

No dose adjustment is required (including severe impairment Clcr < 30 mL/min).

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased. In cases of overdose, standard supportive measures should be adopted as required. Observed non-lethal results are not expected to be deleterious to normal plasma proteins and is not eliminated in the urine.

Ranibizumab, Bevacizumab

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 37 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a mg/kg basis. Sildenafil was negative in vitro bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vitro human lymphocytes and in vivo mouse micronucleus assays to detect clastogenicity. There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

PATIENT COUNSELING INFORMATION

Inform patients of contraindication of REVATIO with regular and/or intermittent use of alcohol.

Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction.

Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

Advise patients not to drive or operate dangerous machinery until they know how the drug affects their vision. See Warnings and Precautions.

RX only

Revised: March 2011

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Important Safety Information

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary vaso-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with β-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®.

Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

Indication

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Please see Brief Summary of Prescribing Information on the following pages.