Diabetic CHD Patients Need Lipid Lowering, Too

BY MIRIAM E. TUCKER Senior Writer

SAN DIEGO — Intensive lipid lowering is linked to fewer cardiovascular events in diabetic patients with established cardiovascular disease—and, as in nondiabetics, "lower is better."

That was the message from a subanalysis of 1,501 patients with diabetes who were among the 10,001 participants in Pfizer's Treating to New Targets (TNT)

study, reported by James Shepherd, M.D., at the annual scientific sessions of the American Diabetes Association.

The results suggest to me that we really should be quite aggressive with our intervention in our diabetic patients, not only with their glucose control, but also with their cardiovascular risk control," said Dr. Shepherd, professor of pathological biochemistry at the University of Glasgow,

In the original study, first reported in

March at the American College of Cardiology meeting, 10,001 patients with stable, established coronary heart disease (CHD) and a starting LDL cholesterol level of 130 mg/dL or less were randomized to receive either 10 mg or 80 mg of atorvastatin per day and were followed for a mean of 4.9 years, lowering mean LDL levels to 101 mg/dL and 77 mg/dL, respectively.

The high-dose regimen not only resulted in a 22% relative reduction in risk of major cardiovascular events, but also significantly reduced the relative risk of stroke by 35% and of heart failure by 26% (N. Engl. J. Med. 2005;352;1425-35).

In the TNT study, 753 diabetics were randomized to 10-mg atorvastatin, while the other 748 received 80 mg. At baseline, the two groups were well matched, with an average age of 63 years.

Compared with the overall study cohort, the diabetics were heavier and had a higher proportion of women.

They also were more likely to have hypertension, peripheral vascular disease, and a history of previous cerebrovascular accidents. However, their diabetes was relatively well controlled, with a hemoglobin A_{1c} of 7.4%, as was their mean blood pressure, at 135/77 mm Hg, Dr. Shepherd said.

At baseline, their mean LDL cholesterol level was about 150 mg/dL. After an 8-week open-label run-in period of 10-mg



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DR. SHEPHERD

atorvastatin, that level was reduced to just under 100 mg/dL.

The 753 who remained on 10-mg atorvastatin for the rest of the study had a final LDL cholesterol level of 98.6 mg/dL, compared with 76.7 mg/dL in the 748 randomized to 80 mg.

During the trial, the average triglyceride level was 177.9 in the 10-mg group, compared with 145.1 mg/dL in those on 80 mg/day. Levels of HDL cholesterol were not appreciably different between the two groups.

Differences in the rates of major cardiovascular events between the high- and low-dose atorvastatin appeared soon after randomization and remained significant the entire 4.9 years, with a relative risk reduction of 25%. Overall, 17.9% of the 10mg group had a major event, compared with 13.8% of those taking 80 mg.

Although the numbers for each individual end point were too small to reach statistical significance, most showed the same trend: 4.1% vs. 3.1% died of coronary heart disease, 8.1% vs. 6.6% had a nonfatal, nonprocedure-related MI, and 5.7% vs. 3.7% experienced a fatal or nonfatal stroke, Dr. Shepherd reported.

Cerebrovascular events were reduced by 31% overall, occurring in 10% and 7% of the 10-mg and 80-mg groups, respectively. Reductions were seen in both fatal and nonfatal stroke (5.8% vs. 4.3%) and in transient ischemic attacks (4.1% vs. 2.7%).

Although overall event rates were higher among the diabetics, the pattern of benefit with aggressive lipid lowering was similar to that of the entire TNT cohort, in whom overall major cardiovascular event rates were 10.9% with 80 mg and 8.7% with 10 mg, 2.5% vs. 2% for CHD deaths, 6.2% vs. 4.9% for nonfatal, non-Continued on following page

DAIICHI PHARMACEUTICAL CORPORATION

FLOXIN® Otic

(ofloxacin otic) solution 0.3% Brief Summary. Please see product insert for complete prescribing information.

INDICATIONS AND USAGE

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FLOXING Office (office) solution 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Otitis Externa in adults and pediatric patients, 6 months and older, due to Escherichia coli, Pseudomonas aeruginosa, and

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to Proteus mirabilis, Pseudomonas aeruginosa, and Staphylococcus aureus.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, and

CONTRAINDICATIONS
FLOXIN® Otic (ofloxacin otic) solution 0.3% is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS NOT FOR OPHTHALMIC USE. NOT FOR INJECTION.

NOT FOR INJECTION.
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

General: As with other anti-infective preparations, prolonged use may result in over-growth of nonsusceptible organisms, including fungl. If the infection is not improved after one week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various

ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

nformation for Patients: Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or alleroic reaction.

Otitis Externa

Otitis Externa
Prior to administration of FLOXIN® Otic, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for five minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

Acute Otitis Media and Chronic Suppurative Otitis Media Prior to administration of FLOXIN® Otic, the solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Specific drug interaction studies have not been conducted with FLOXIN® Otic.

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Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies to determine the carcinogenic potential of
ofloxacin have not been conducted. Ofloxacin was not mutagenic
in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS)
assay using human fibroblasts, the dominant lethal assay, or the
mouse micronucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin
did not affect male or female reproductive performance at oral
doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area,
assuming total absorption of ofloxacin from the ear of a patient
treated with FLOXIN® Otic twice per day.

Prennancy

Pregnancy
Teratogenic effects: Pregnancy Category C. Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

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These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended

Nonteratogenic Effects: Additional studies in the rat demon-Nonceradgenic Errects: Additional studies in the Fat definition adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. FLOXIN® Otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- six months and older: otitis externa with intact tympanic mem-
- branes one year and older: acute otitis media with tympanostomy tubes twelve years and older: chronic suppurative otitis media with perforated tympanic membranes

Safety and efficacy in pediatric patients below these ages have not

Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.

Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

ADVERSE REACTIONS
Subjects with Otitis Externa
In the phase III clinical trials performed in support of once-daily dosing, 799 subjects with otitis externa and intact tympanic membranes were treated with ofloxacin otic solution. The studies, which served as the basis for approval, were 020 (pediatric, adolescents and adults), 016 (adolescents and adults) and 017 (pediatric). The following treatment-related adverse events occurred in two or following treatment-related adverse events occurred in two or more of the subjects.

	incidence kate		
	Studies 002/003 [†]	Studies 016/017 [†]	Study 020†
Adverse Event	BID (N=229)	QD (N=310)	QD (N=489)
Application Site			
Reaction	3%	16.8%	0.6%
Pruritus	4%	1.2%	1.0%
Earache	1%	0.6%	0.8%
Dizziness	1%	0.0%	0.6%
Headache	0%	0.3%	0.2%
Vertigo	1%	0.0%	0.0%

†Studies 002/003 (BID) and 016/017 (QD) were active-controlled and comparative. Study 020 (QD) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once daily dosing studies, there were also single reports of nau-sea, seborrhea, transient loss of hearing, tinnitus, otitis externa, oti-tis media, tremor, hypertension and fungal infection.

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) and Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes In phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution:

daciii otic solution.	
Incidence (N = 656)	
7%	
1%	
1%	
1%	
1%	
1%	

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), toorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

Post-Marketing Adverse Events
Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

Otitis Externa: The recommended dosage regimen for the treatment of otitis externa is:

For pediatric patients (from 6 months to 13 years old): Five drops (0.25 mL, 0.75 mg ofloxacin) instilled into the affected ear once

For patients 13 years and older: Ten drops (0.5 mL, 1.5 mg ofloxacin) instilled into the affected ear once daily for seven days.

The solution should be warmed by holding the bottle in the her solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for five minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

Acute Otitis Media in pediatric patients with tympanostomy tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from 1 to 12 years old) with tympanostomy tubes is:

mpanostomy tubes is:
Five drops (0.25 mL, 0.75 mg ofloxacin) instilled into the affected ear twice daily for ten days. The solution should be
warmed by holding the bottle in the hand for one or two minutes to avoid dizziness which may result from the instillation of
a cold solution. The patient should lie with the affected ear
upward, and then the drops should be instilled. The tragus
should then be pumped 4 times by pushing inward to facilitate
penetration of the drops into the middle ear. This position
should be maintained for five minutes. Repeat, if necessary, for
the opposite ear.

the opposite ear.

Chronic Suppurative Otitis Media with perforated tympanic membranes: The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is:

Ten drops (0.5 mL, 1.5 mg ofloxacin) instilled into the affected ear twice daily for fourteen days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizzines which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

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aceutical Corporation Daiichi Pharn Montvale, NJ 07645 Revised 4/05 Covered by U.S. Patent No. 5.401.741

DAIICHI

Preventable Diabetes-Related Hospitalizations Drop

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — The rate of diabetes-related, potentially preventable hospitalizations in the United States fell by 35% between 1994 and 2002, Michael M. Engelgau, M.D., reported at a press briefing during the annual scientific sessions of the American Diabetes Association.

The rate of hospitalizations refers to the number of admissions per total number of people with diabetes in the United States.

Although the exact cause of the reduction was not studied, the declines in hospitalizations "are representative of good care," said Dr. Engelgau, associate director for prevention policy in the division of diabetes translation at the Centers for Disease Control and Prevention.

"This could be [because] the diabetic population is growing very quickly in the United States," he suggested. "Maybe it's a slightly healthier population [with diabetes that] doesn't need hospitalization quite as much. Or there could be changes in some of the hospitalization practices in the various health care systems in the United States. Some of these factors are coming into play. We can't say exactly how important those are, but the bottom line is that this does seem to be a very positive trend in these types of potentially preventable hospitalizations."

To study the number of preventable

Continued from previous page

procedure-related MI, and 3.1% vs. 2.3% for fatal or nonfatal stroke.

In the diabetic participants, similar patterns were also seen for secondary event rates and clearly illustrated that having diabetes increases vascular disease risks across the board: The proportions experiencing any cardiovascular event, for example, were 44.1% of the diabetics with 10-mg atorvastatin and 39.8% of those taking 80 mg, compared with 33.5% and 28.1%, respectively, for the nondiabetics.

Peripheral arterial disease occurred in 8.9% vs. 9.1% of the diabetics, compared with 5.6% and 5.5% of the nondiabetics.

Current guidelines from the National Cholesterol Education Program, which consider diabetes a coronary risk equivalent, advise an LDL cholesterol level below 100 mg/dL for all diabetic patients.

An NCEP update published last year suggested that in patients at very high risk, including those with "multiple major risk factors (especially diabetes)," an LDL target of less than 70 mg/dL might be considered as a therapeutic option (Circulation 2004;110:227-39).

There were no differences in treatmentrelated side effects between the 10-mg and 80-mg diabetic groups.

Treatment-related myalgia occurred in 3.6% of the 10-mg group and 2.4% of those taking 80 mg, while persistent liverenzyme elevations three times the upper limit of normal occurred in 0.4% vs. 0.8%, respectively. No cases of rhabdomyolysis occurred in any patient throughout the 5 study years.

hospitalizations, Dr. Engelgau and his associates used the Healthcare Cost and Utilization Project National Inpatient Sample from 1994-2002. This sample consists of about 80% of hospitalizations in 35 states and is weighted to represent the nation.

The researchers zeroed in on four conditions that can be avoided with high-quality outpatient care, or can be less severe if treated early and correctly: uncontrolled diabetes, short-term complications such as diabetic ketoacidosis, long-term com-

plications such as chronic kidney disease, and lower extremity amputations.

Between 1994 and 2002, the number of diabetes-related preventable hospitalizations in the United States increased from 439,000 in 1994 to 473,000 in 2002. Total costs for the hospitalizations increased from \$4 billion in 1994 to \$9.5 billion in 2002.

During the same time, people diagnosed with diabetes increased from 8.1 million in 1994 to 13.3 million in 2002. As a result, the rate of diabetes-related preventable hospi-

tal admissions decreased from 55 per 1,000 people with diabetes to 36 per 1,000 people with diabetes, a decline of 35%.

Of the four diabetes-related conditions studied, admission rates for uncontrolled diabetes had the largest decline, from 10 per 1,000 people with diabetes in 1994 to 4 per 1,000 in 2002. The hospital admission rate for long-term complications also had a large decline, from 28 per 1,000 people with diabetes in 1994 to 20 per 1,000 in 2002.

The starting and maintenance dose for MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily. Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore, the daily dose of MOBIC should not exceed 15 mg.

Indications: MOBIC is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

Contraindications: MOBIC is contraindicated in patients with known hypersensitivity to meloxicam. It should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Important NSAID risk

information: Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Serious GI bleeding can occur without warning.

Please see following pages for Brief Summary of Prescribing Information.

MOBIC: A TREATMENT OPTION FOR OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

- Improvement in pain, stiffness, and physical function in OA studies
- Significant improvement in ACR20 responder rate in an RA study
- Low incidence of serious GI adverse events²
- Low incidence of hypertension and edema in OA studies³
- No sulfonamide contraindication
- Once-daily 7.5 mg and 15 mg tablets for OA and RA



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References: 1. Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. *Arch Intern Med.* 2000;160:2947-2954. 2. Singh G, Lanes S, Triadafilopoulos G. Risk of serious upper gastrointestinal and cardiovascular thromboembolic complications with meloxicam. *Am J Med.* 2004;117:100-106. 3. Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.