RA, Diabetes Confer Same Cardiovascular Risk

BY DIANA MAHONEY

FROM ANNALS OF THE RHEUMATIC DISEASE

The cardiovascular risk in rheumatoid arthritis is comparable to that of diabetes, a large Danish study has shown.

Further, the risk of myocardial infarction (MI) in rheumatoid arthritis patients corresponds to that observed in the general population of individuals without the musculoskeletal condition who are, on average, 10 years older and does not appear to be affected by the duration of drug treatment for the disease, Dr. Jesper Lindhardsen of Gentofte University Hospital in Copenhagen, and colleagues reported.

Using nationwide registers encompassing the entire Danish population older than 16 years, the investigators identified individuals with new-onset rheumatoid arthritis (RA), new-onset diabetes, and new MI during a 10-year period, excluding individuals with prior disease and incomplete data entries from the full cohort of 4,311,022 subjects, they wrote.

During the 10-year study period, 9,921 individuals developed RA and 129,659 developed diabetes. Compared with the diabetes patients, "RA patients were more often women, used less cardioprotective medications, and had less comorbidity, whereas age was similar in the two groups," they reported.

Regarding cardiovascular outcomes, 265 of the RA patients and 3,948 of the diabetes patients had new MI, representing in both cohorts a 1.7 increased incidence rate ratio (IRR) of MI in a fully adjusted model compared with the general population in which 75,870 individ-

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VITALS

Major Finding: The RA and diabetes cohorts both had a 1.7 increased incidence rate ratio (IRR) of MI, compared with the general population.

Data Source: A large, population-based study of the incidence of new-onset rheumatoid arthritis, diabetes, and myocardial infarction using Danish patient registry information covering a 10-year period.

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uals had new myocardial infarctions. The IRR among patients with both RA and diabetes was 2.6, "which roughly equaled the predicted additive risk for the two separate diseases, they wrote (Ann. Rheum. Dis. 2011;70:929-34).

The investigators conducted a nested case-control study that corroborated the comparable risk of MI in the RA and diabetes patients. The findings demonstrated that the increased risk in these groups was independent of treatment duration within the time frame of the current study, they wrote.

Stratified by gender, the MI risk estimates did not differ between women and men in the RA group. In the diabetes patients, however, women were at significantly higher risk than men for the adverse cardiovascular outcome, the authors wrote. An age-dependent pattern of MI risk was also observed. Specifically, among women with RA and diabetes, respectively, the risk of MI in those younger than 50 years old was 5.5 and 5.9 times that observed in the age-matched reference group, they reported. Additionally, for women between 50 and 65 years of age, the IRRs were 1.7 and 2.6 for RA and diabetes patients, respectively.

The age-stratified patterns observed in men were different, the authors stated, noting that "the IRRs in the two oldest age groups were comparable, and even tended to be slightly higher in the 50-65 years age group of RA patients compared to the same-aged [diabetes] patients." And while the youngest men with RA had a markedly raised IRR, diabetes patients in the same age stratum had a significantly higher risk, with an

Continued on following page

with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration]*.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta

CYP1A2 Inhibitors—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs

Drugs Metabolized by CYP2D6—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines, and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

Other Clinically Important Drug Interactions

Alcohol—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta group and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In postmarketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2489), GAD (N=910), OA (N=239), CLBP (N=600), DPNP (N=906), and FM (N=876). The population studied was 17 to 91 years of age; 65.5%, 62.5%, 61.5%, 42.9%, and 94.9% female; and 86.5%, 81.2%, 86.2%, 74.0%, and 88% Caucasian for MDD, GAD, OA and CLBP, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day *[see Clinical Studies (14)]*.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

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IRR of 4.9 compared with 2.1, they said.

In a fully adjusted regression model in which the IRRs for MI in RA patients were calculated according to 10-year subject age intervals, "RA patients had the same, or higher, risk of MI as control subjects who were, on average, 10 years older," the authors reported.

Although the study has several limitations, including the identification of RA patients based on dispensed prescriptions and diagnosis versus the 1987 American College of Rheumatology criteria, the reliance on the use of glucose-lowering drugs as a proxy for diabetes, and the lack of information about classic cardiovascular risk factors, "the results corroborate and expand previous findings in this area of research and indicate that patients with RA should be considered for more aggressive primary [cardiovascular disease] prevention," the authors stressed.

'RA patients had the same, or higher, risk of MI as control subjects who were, on average, 10 years older.'

DR. LINDHARDSEN

In an accompanying editorial, Dr. Michael T. Nurmohamed and Dr. George Kitas of VU University Medical Centre in Amsterdam wrote that the findings of the current study should put to bed any doubt or debate about an enhanced cardiovascular risk in RA. "Importantly, they also provide further evidence that the cardiovascular risk in RA is broadly similar to that of contemporarily managed diabetes," they stated. The results of the study, as well as the success of cardiovascular risk management in diabetes provides a clear incentive to identify and actively manage, if necessary, cardiovascular risk in all RA patients as part of quality routine rheumatological practice" (Ann. Rheum. Dis. 2011;70:881-3).

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