

Longer Duration of Type 2 Doubles CHD Risk

BY MARY ANN MOON

FROM ARCHIVES OF INTERNAL MEDICINE

Among older white men, coronary heart disease risk is approximately twice as high in those who developed type 2 diabetes relatively early in adulthood and have had the disease for more than 8 years, compared with those who developed it later and have had it for fewer than 8 years, a study has shown.

In older white men with an earlier onset and a longer duration of type 2 diabetes, the risk of CHD events is equivalent to that of nondiabetic men who had already had prior myocardial infarction,

The risks for vascular events and mortality in men with early onset of diabetes 'were comparable to those in men with prior MI.'

said S. Goya Wannamethee, Ph.D., of the department of primary care and population health, University College London, and associates.

"Although diabetes is a well-established risk factor for CHD, whether diabetes alone is a CHD equivalent in assessing the risk of future cardiovascular events [has been] controversial. ... Our observations plus prior research [suggest] that CHD risk in patients with diabetes escalates significantly with disease duration and approaches CHD risk equivalence only when disease duration is beyond 8 years," they noted.

Dr. Wannamethee and colleagues ex-

amined the relationship among age of diabetes onset, duration of disease, and cardiovascular risk using data from the British Regional Heart Study (BRHS), a prospective assessment of cardiovascular disease in 7,735 white men aged 40-59 years at enrollment in 1978-1980 who were recruited from general practices in 24 British towns. For this analysis, data were

assessed on 4,045 of these subjects who were 60-79 years of age at the 20-year mark of the BRHS and were followed for all-cause mortality and CHD morbidity for a mean of 9 more years.

During that time there were 372 major CHD events, including 263 CHD deaths.

Men with an early onset of type 2 diabetes, with a diagnosis at or before age

60, had a mean duration of disease of 16.7 years. Their CHD risk was approximately twice that of men who had a later onset, with a diagnosis after age 60 and a mean duration of disease of 4.9 years.

"Moreover, the [relative risk] for vascular events and mortality in [men] with early onset of diabetes were comparable to those in men with prior MI, suggesting that a longer duration of diabetes may be necessary to raise risks toward a

See related commentary on page 16.

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References: 1. Fuchs GS, Mikkelsen S, Knudsen TK, Kappelgaard A-M. Ease of use and acceptability of a new pen device for the administration of growth hormone therapy in pediatric patients: an open-label, uncontrolled usability test. *Clin Ther.* 2009;31:2906-2914. 2. Norditropin® FlexPro® [Instructions for Use]. Princeton, NJ: Novo Nordisk Inc; 2010. 3. Data on file. PDS290 pen-injector for Norditropin® SimpleXx® container closure system: comparison to Norditropin NordiFlex®. Princeton, NJ: Novo Nordisk Inc; 2009.

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VITALS

Major Finding: Men who developed diabetes at or before age 60 and had the disease for at least 8 years had nearly twice the risk of a major cardiovascular event (relative risk 1.95) than did men who developed diabetes at a later age and had it for fewer than 8 years.

Data Source: Analysis of data on 4,045 subjects participating in a prospective study of cardiovascular disease in older, white British men.

Disclosures: The British Regional Heart Study is supported by the British Heart Foundation. No financial conflicts of interest were reported.

CHD risk equivalent,” the investigators said (*Arch. Intern. Med.* 2011;171:404-10).

These findings should go a long way toward resolving the confusion and de-

bate over the issue, and explain why previous studies that did not specifically address age of onset or disease duration have yielded conflicting results, the researchers noted.

“The clinical implication is that, although 10-year CHD risk for newly diagnosed diabetes may not be very high, CHD risk beyond 10 years or indeed lifetime risk will be much higher. This pattern ... emphasizes the need to be aggressive with CHD risk reduction [that is, statin use and blood pressure modification] in patients with type 2 diabetes diagnosed at a relatively young age,” Dr. Wannamethee and associates said.

“Finally, neither adjustment for traditional risk factors nor a range of novel risk factors (including markers of inflammation, endothelial dysfunction,

and renal dysfunction) explained the excess CHD risk in patients with known diabetes, particularly in those with early onset. These men still showed an almost threefold increase in risk after adjustment,” compared with men who did not have diabetes.

Future studies of this issue must examine whether the findings hold true in women and people of nonwhite ethnicities, they added.

The British Regional Heart Study is supported by the British Heart Foundation. No financial conflicts of interest were reported. ■



Indications and Usage

Norditropin® (somatropin [rDNA origin] injection) is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone, the treatment of children with short stature associated with Noonan syndrome or Turner syndrome, the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2-4 years, and for the replacement of endogenous growth hormone in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: 1. Adult Onset: Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or 2. Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Important Safety Information

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure as increased mortality may occur.

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment. There have been reports of sudden death when somatropin was used in such patients. Norditropin® is not indicated for the treatment of patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Somatropin should not be used or should be discontinued with any evidence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence. In childhood cancer survivors, an increased risk of a second neoplasm, particularly meningiomas in patients treated with radiation to the head for their first neoplasm, has been reported in patients treated with somatropin.

Somatropin should not be used in patients with active proliferative or severe non-proliferative diabetic retinopathy, for growth promotion in pediatric patients with closed epiphyses, or in patients with known hypersensitivity to somatropin or any of its excipients.

Somatropin may decrease insulin sensitivity particularly at higher doses in susceptible patients. Glucose levels should be monitored periodically, including close monitoring of patients with preexisting diabetes or glucose intolerance. Doses of anti-hyperglycemic drugs (insulin or oral agents) may require adjustment for patients with diabetes on somatropin therapy.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting, usually occurring within the first eight (8) weeks after initiation of somatropin therapy, has been reported in a small number of patients. In all reported cases, rapid resolution has occurred after therapy cessation or a reduction of dose. Funduscopic examination should be performed routinely before and during somatropin therapy. If papilledema is observed, somatropin treatment should be discontinued.

Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent.

In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Periodic thyroid function tests are recommended and thyroid hormone replacement therapy should be initiated or adjusted as needed.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or with rapid growth. Onset of a limp or complaints of hip or knee pain in somatropin patients should be carefully evaluated. Rapid growth may also result in progression of preexisting scoliosis. Patients with a history of scoliosis or skeletal abnormalities, which may be present in untreated Noonan, Turner or Prader-Willi syndrome, should be monitored.

Patients with Turner Syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. Somatropin may also increase the risk of IH in Turner patients. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions.

Congenital heart disease is an inherent component of Noonan syndrome. Though a clinical study in Noonan syndrome reported no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography), the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known.

Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain.

Other somatropin-related adverse reactions include injection site reactions/rashes, lipoatrophy and headaches. Subcutaneous injection of somatropin at the same site repeatedly may result in tissue atrophy and can be avoided by rotating the injection site.

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue, and may significantly impact the metabolism of cortisol and cortisone. In patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy, especially with cortisone acetate and prednisone, for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses.

Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine) as limited published data suggest somatropin may alter clearance of these compounds.

In adult women on oral estrogen replacement, a larger dose of somatropin may be required to achieve the defined treatment goal.

The safety and effectiveness of Norditropin® in patients age 65 years and older has not been evaluated in clinical studies. Elderly patients may be more sensitive to the actions of somatropin and may be more prone to develop adverse reactions.

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