

Diastolic Dysfunction Prevalence Rises With Age

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The prevalence of diastolic dysfunction increases as people age, even among healthy adults, according to a longitudinal study.

Results of the study add to the findings of previous cross-sectional community studies that diastolic dysfunction is highly prevalent in older adults, demonstrat-

ing that during 10 years of follow-up, middle-aged and elderly people were nearly three times more likely to show deteriorating diastolic function than improving diastolic function.

“That diastolic dysfunction worsened even in healthy persons supports the concept that aging may be accompanied by progressive deterioration in diastolic function. This age-related progression of diastolic dysfunction in the population

contributes to the pathophysiologic substrate from which overt heart failure emerges,” said Dr. Garvan C. Kane of Mayo Clinic and Medical School, Rochester, Minn., and his associates.

Previously, the investigators had performed two cross-sectional analyses of diastolic function in community residents aged 45 and older participating in the Olmsted County Heart Function Study in 1997-2000 and again in 2001-

2004. They now report the results of 6 years of further follow-up of a subset of 1,402 of these subjects, which tracked within-patient changes in diastolic function over time.

In all, 90% of the study subjects were white, and 81% lived in urban settings.

Over time, 23% of subjects showed progression of diastolic dysfunction, compared with only 9% who showed improvement in diastolic dysfunction. The remaining 68% of subjects showed no change in diastolic dysfunction.

“A similar pattern of worsening diastolic function also was observed in a subset of [531] healthy participants” who

concomitant use of WELCHOL and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating WELCHOL and frequently enough during early WELCHOL therapy to ensure that no significant alteration in INR occurs. Once the INR is stable, continue to monitor the INR at intervals usually recommended for patients on warfarin. [See *Post-marketing Experience* (6.2)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of colessevelam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm. Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colessevelam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colessevelam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colessevelam hydrochloride is not expected to be excreted in human milk because colessevelam hydrochloride is not absorbed systemically from the gastrointestinal tract.

8.4 Pediatric Use

The safety and effectiveness of WELCHOL as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH [See *Clinical Studies* (14.1) in the full prescribing information]. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo [See *Adverse Reactions* (6.1)].

Due to tablet size, WELCHOL for Oral Suspension is recommended for use in the pediatric population. Dose adjustments are not required when WELCHOL is administered to children 10 to 17 years of age.

WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia: Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were ≥ 65 years old, and 58 (4%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Type 2 Diabetes Mellitus: Of the 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 onto 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.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] 50-80 mL/min), 53 (5%) had moderate renal insufficiency (CrCl 30-50 mL/min), and none had severe renal insufficiency (CrCl <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 CrCl <50 mL/min (n=53) and those with a CrCl ≥ 50 mL/min (n=1075).

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

Dosing: Patients should be advised to take WELCHOL Tablets with a meal and liquid. WELCHOL can be taken as 6 tablets once daily or 3 tablets twice daily. Patients should be advised to take WELCHOL for Oral Suspension as one 3.75 gram packet once daily or one 1.875 gram packet twice daily. To prepare, empty the entire contents of one packet into a glass or cup. Add $\frac{1}{2}$ to 1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. WELCHOL for Oral Suspension should be taken with meals. To avoid esophageal distress, WELCHOL for Oral Suspension should not be taken in its dry form. Always mix WELCHOL for Oral Suspension with water, fruit juice, or diet soft drinks before ingesting. [See *Dosage and Administration* (2) in the full prescribing information]

Drug interactions: Drugs with a known interaction with colessevelam (e.g., cyclosporine, glyburide, levothyroxine, oral contraceptives) should be administered at least 4 hours prior to WELCHOL. Drugs that have not been tested for interaction with colessevelam, especially those with a narrow therapeutic index (e.g., phenytoin), should also be administered at least 4 hours prior to WELCHOL. Alternatively the physician should monitor blood levels of the coadministered drug. [See *Drug Interactions* (7)]

Gastrointestinal: WELCHOL can cause constipation. WELCHOL is contraindicated in patients with a history of bowel obstruction. WELCHOL is not recommended in patients who may be at risk of bowel obstruction, including patients with gastroparesis, other gastrointestinal motility disorders, or a history of major gastrointestinal surgery. Patients should be instructed to consume a diet that promotes bowel regularity. Patients should be instructed to promptly discontinue WELCHOL and seek medical attention if severe abdominal pain or severe constipation occurs. Because of the tablet size, WELCHOL Tablets can cause dysphagia or esophageal obstruction and should be used with caution in patients with dysphagia or swallowing disorders. To avoid esophageal distress, WELCHOL for Oral Suspension should not be taken in its dry form. Always mix WELCHOL for Oral Suspension with water, fruit juice, or diet soft drinks before ingesting. [See *Warnings and Precautions* (5.4)]

Hypertriglyceridemia and pancreatitis: Patients should be instructed to discontinue WELCHOL and seek prompt medical attention if the hallmark symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting). [See *Warnings and Precautions* (5.2)]

17.1 Primary Hyperlipidemia

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet.

17.2 Type 2 Diabetes Mellitus

General: Patients should be advised that it is important to adhere to dietary instructions, a regular exercise program, and regular testing of blood glucose.

Hypertriglyceridemia and cardiovascular disease: Patients receiving a sulfonylurea or insulin should be informed that WELCHOL may increase serum triglyceride concentrations and that the long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. [See *Warnings and Precautions* (5.2)]

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VITALS

Major Finding: Over time, 23% of study subjects showed progression of diastolic dysfunction, compared with only 9% who showed improvement in diastolic dysfunction; in a subset of healthy subjects, 20% showed progression of diastolic dysfunction, compared with only 5% who showed improvement.

Data Source: A population-based cohort study involving 1,402 older adults whose heart function was followed for 4 years and again for an additional 6 years.

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had been free of hypertension, diabetes, coronary artery disease, and heart failure at baseline. About 20% showed worsening diastolic function, compared with 5% who showed improvement in diastolic dysfunction over time. The remaining 75% showed no change in diastolic dysfunction.

“However, to put diastolic dysfunction in context, it should be noted that only about 1 in 4 persons with moderate or severe diastolic dysfunction at examination 2 developed incident heart failure during follow-up. This suggests that superimposed clinical events play an important role in the transition from asymptomatic diastolic dysfunction to overt heart failure with preserved LVEF [left ventricular ejection fraction],” Dr. Kane and his colleagues said (JAMA 2011;306:856-63).

“Specifically, our findings are consistent with the hypothesis that a combination of cardiovascular aging and superimposed cardiovascular disease accelerates the deterioration in diastolic function, setting the stage for symptomatic heart failure with preserved LVEF in elderly persons,” they noted.

It follows that preventing such superimposed events by addressing risk factors, particularly hypertension, “might be fundamental to reducing heart failure with preserved LVEF,” they added. ■