

Elderly HF Patients Get Same Benefits From CRT

BY BRUCE JANCIN

SNOWMASS, COLO. — Advanced age is not a valid reason to exclude otherwise qualified patients from cardiac resynchronization therapy, a study indicates.

Dr. Jamie B. Conti often hears colleagues say, “I think that patient is too old for CRT.” But the 2008 American College of Cardiology/American Heart Association/Heart Rhythm Society CRT guide-

lines make no mention of an age cutoff. And Dr. Conti and coworkers recently conducted a study that concluded CRT is as effective—and safe—in heart failure patients above age 75 as in those who are younger, she noted at a conference sponsored by the ACC.

There has never been a randomized trial looking at the effects of CRT specifically in the elderly. So the researchers performed a subanalysis of 839 partici-

pants in two major randomized trials of CRT: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync-ICD Randomized Clinical Evaluation (MIRACLE-ICD).

The over-75 cohort in the subanalysis comprised 174 patients. Another 297 patients were aged 65-75, and 368 were aged under 65 years. All received a CRT device, then were randomized to 6 months with the device activated or turned off.

All three age groups had significant improvements in New York Heart Association functional class and left ventricular ejection fraction (LVEF) with CRT activated compared with patients in whom the device was turned off, said Dr. Conti, professor of medicine and chief of the division of cardiovascular medicine at the University of Florida, Gainesville.

The improvement in NYHA class after 6 months with the CRT device turned on compared with CRT off amounted to a net 1.32 class units in the under-65 cohort, 1.27 units in the 65-75 age group, and 1.22 units in the oldest group. LVEF improved by 3.45% more with CRT on than off in the under-65 group, by 2.23% more in the 65- to 75-year-olds, and by 3.45% more in the over-75 group (J. Interv. Card. Electrophysiol. 2009;25:91-6).

In addition, there was a strong albeit nonsignificant trend for improvement in

Pharmacodynamic interactions can be expected with beta-blockers; calcium antagonists and digoxin [see Drug Interactions (7.1)]. In clinical trials, patients treated with dronedarone received concomitant medications including beta-blockers, digoxin, calcium antagonists (including those with heart rate-lowering effects), statins and oral anticoagulants.

7.1 Pharmacodynamic Interactions

Drugs prolonging the QT interval (inducing Torsade de Pointes)

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

Digoxin

Digoxin can potentiate the electrophysiologic 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. Gastrointestinal disorders were also increased.

Because of the pharmacokinetic interaction [see Drug Interaction (7.3)] and possible pharmacodynamic interaction, reconsider the need for digoxin therapy. If digoxin treatment is continued, halve the dose of digoxin, monitor serum levels closely, and observe for toxicity.

Calcium channel blockers

Calcium channel blockers with depressant effects on the sinus and AV nodes could potentiate dronedarone's effects on conduction.

Give low doses of calcium channel blockers initially and increase only after ECG verification of good tolerability [see Drug Interactions (7.3)].

Beta-blockers

In clinical trials, bradycardia was more frequently observed when dronedarone was given in combination with beta-blockers.

Give low dose of beta-blockers initially, and increase only after ECG verification of good tolerability [see Drug Interactions (7.3)].

7.2 Effects of Other Drugs on Dronedarone

Ketoconazole and other potent CYP 3A inhibitors

Repeated doses of ketoconazole, a strong CYP 3A inhibitor, resulted in a 17-fold increase in dronedarone exposure and a 9-fold increase in C_{max} . Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, voriconazole, ritonavir, clarithromycin, and nefazodone is contraindicated [see Contraindications (4)].

Grapefruit juice

Grapefruit juice, a moderate inhibitor of CYP 3A, resulted in a 3-fold increase in dronedarone exposure and a 2.5-fold increase in C_{max} . Therefore, patients should avoid grapefruit juice beverages while taking MULTAQ.

Rifampin and other CYP 3A inducers

Rifampin decreased dronedarone exposure by 80%. Avoid rifampin or other CYP 3A inducers such as phenobarbital, carbamazepine, phenytoin, and St John's wort with dronedarone because they decrease its exposure significantly.

Calcium channel blockers

Verapamil and diltiazem are moderate CYP 3A inhibitors and increase dronedarone exposure by approximately 1.4- to 1.7-fold [see Drug Interactions (7.1, 7.3)].

Pantoprazole

Pantoprazole, a drug that increases gastric pH, did not have a significant effect on dronedarone pharmacokinetics.

7.3 Effects of Dronedarone on Other Drugs

Statins

Dronedarone increased simvastatin/simvastatin acid exposure by 4- and 2-fold, respectively.

Because of multiple mechanisms of interaction with statins (CYPs and transporters), follow statin label recommendations for use with CYP 3A and P-gP inhibitors such as dronedarone.

Calcium channel blockers

Dronedarone increases calcium channel blocker (verapamil, diltiazem or nifedipine) exposure by 1.4- to 1.5-fold [see Drug Interactions (7.1)].

Sirolimus, tacrolimus, and other CYP3A substrates with narrow therapeutic range Dronedarone can increase plasma concentrations of tacrolimus, sirolimus, and other CYP 3A substrates with a 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. Dronedarone increased metoprolol exposure by 1.6-fold following multiple dose administration [see Drug Interaction (7.1)]. Other CYP 2D6 substrates, including other beta-blockers, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may have increased exposure upon co-administration with dronedarone.

Digoxin and P-glycoprotein substrates

Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter [see Drug Interactions (7.1)]. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone.

Warfarin and losartan (CYP 2C9 substrates)

In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR. In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. Monitor INR per the warfarin label.

No interaction was observed between dronedarone and losartan.

Theophylline (CYP 1A2 substrate)

Dronedarone does not increase steady state theophylline exposure.

Oral contraceptives

No decreases in ethinylestradiol and levonorgestrel concentrations were observed in healthy subjects receiving dronedarone concomitantly with oral contraceptives.

MULTAQ (dronedarone) Tablets

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4)]

MULTAQ may cause fetal harm when administered to a pregnant woman. In animal studies, dronedarone was teratogenic in rats at the maximum recommended human dose (MRHD), and in rabbits at half the MRHD. 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 the fetus.

When pregnant rats received dronedarone at oral doses greater than or equal to the MRHD (on a mg/m² basis), fetuses had increased rates of external, visceral and skeletal malformations (cranioschisis, cleft palate, incomplete evagination of pineal body, brachygnathia, partially fused carotid arteries, truncus arteriosus, abnormal lobation of the liver, partially duplicated inferior vena cava, brachydactyly, ectrodactyly, syndactyly, and anterior and/or posterior club feet). When pregnant rabbits received dronedarone, at a dose approximately half the MRHD (on a mg/m² basis), fetuses had an increased rate of skeletal abnormalities (anomalous ribcage and vertebrae, pelvic asymmetry) at doses ≥ 20 mg/kg (the lowest dose tested and approximately half the MRHD on a mg/m² basis).

Actual animal doses: rat (≥ 80 mg/kg/day); rabbit (≥ 20 mg/kg)

8.3 Nursing Mothers

It is not known whether MULTAQ is excreted in human milk. Dronedarone and its metabolites are excreted in rat milk. During a pre- and post-natal study in rats, maternal dronedarone administration was associated with minor reduced body-weight gain in the offspring. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MULTAQ, 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 [see Contraindications (4)].

8.4 Pediatric Use

Safety and efficacy in children below the age of 18 years have not been established.

8.5 Geriatric Use

More than 4500 patients with AF or AFL aged 65 years or above were included in the MULTAQ clinical program (of whom more than 2000 patients were 75 years or older). Efficacy and safety were similar in elderly and younger patients.

8.6 Renal Impairment

Patients with renal impairment were included in clinical studies. Because renal excretion of dronedarone is minimal [see Clinical Pharmacology (12.3) in the full prescribing information], no dosing alteration is needed.

8.7 Hepatic Impairment

Dronedarone is extensively metabolized by the liver. There is little clinical experience with moderate hepatic impairment and none with severe impairment. No dosage adjustment is recommended for moderate hepatic impairment [see Contraindications (4) and Clinical Pharmacology (12.3) in the full prescribing information].

10 OVERDOSAGE

In the event of overdosage, monitor the patient's cardiac rhythm and blood pressure. Treatment should be supportive and based on symptoms.

It is not known whether dronedarone or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

There is no specific antidote available.

Manufactured by Sanofi Winthrop Industrie

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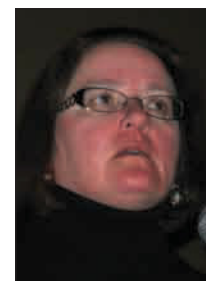
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left ventricular end systolic volume with CRT turned on in patients over age 75. The LV end systolic volume fell by a mean of 17.68 mL from baseline with CRT on in the oldest cohort, compared with a 0.86-mL decrease with CRT off. LV end systolic volume fell by a mean of 35.1 mL more with CRT on than off in the under-65 group. The difference between CRT on and off in the 65-75 age group was a net 26.51-mL decrease.

Complication rates were no different in the three age groups, Dr. Conti said.

The ACC/AHA/HRS guidelines recommend CRT for patients with an LVEF of 35% or less, a QRS duration of at least 120 msec, and NYHA functional class III or ambulatory class IV despite optimal medical therapy. However, it seems likely that the indications will broaden to include patients in class I/II on the strength of the positive results of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, predicted Dr. Conti, who had no relevant financial interests. ■

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