

Zotarolimus Noninferior to Everolimus Stent

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One year after implantation, the zotarolimus-eluting coronary stent was found to be noninferior to the everolimus-eluting stent in preventing target-lesion failure.

This “new-generation” stent was tested in a large population with a mix of traits usually excluded from randomized

clinical trials of stents, including multi-vessel intervention, small-vessel disease, long lesions, bifurcations, or trifurcations. “Therefore, we consider that our findings are highly generalizable to patients in everyday clinical practice,” said Dr. Patrick W. Serruys of Erasmus University Medical Center, Rotterdam, the Netherlands, and his associates.

In the multicenter open-label study, sponsored by Medtronic CardioVascular,

maker of the zotarolimus-eluting stent, patients were randomly assigned to undergo percutaneous coronary intervention (PCI) with placement of either zotarolimus-eluting (1,140 patients with 1,661 lesions) or everolimus-eluting stents (1,152 patients with 1,705 lesions). Patients were followed by telephone or hospital visit at 1, 6, and 12 months, and will be followed annually for 5 years.

The primary end point was target-le-

sion failure at 1 year, defined as a composite of death from cardiac causes, MI, or target-lesion revascularization. This occurred in 8.2% of patients who received zotarolimus-eluting stents and 8.3% of those who received everolimus-eluting stents, a nonsignificant difference.

The zotarolimus-stent group had significantly reduced rates of death from any cause while they were hospitalized (0.1% vs. 0.8%) and at 30 days (0.2% vs.

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/m^2 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/m^2 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/m^2 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 overdose, 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.

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VITALS

Major Finding: Target-lesion failure at 1 year occurred in 8.2% of zotarolimus-eluting stent patients and 8.3% of everolimus-eluting stent patients; 1-year mortality from any cause was 1.6% (zotarolimus group) vs. 2.8% (everolimus group), nonsignificant differences. Significant differences in in-hospital and 30-day mortality favored the zotarolimus stent. The rate of definite stent thrombosis was significantly higher in the zotarolimus group (1.2%) than the everolimus group (0.3%).

Data Source: Multicenter open-label, randomized study comparing zotarolimus-eluting stents (1,140 patients with 1,661 lesions) with everolimus-eluting stents (1,152 patients with 1,705 lesions).

Disclosures: Dr. Serruys and some associates reported ties to Medtronic Inc., Boston Scientific Corp., and Abbott Labs, maker of the everolimus-eluting stent. The study was sponsored by Medtronic CardioVascular, maker of the zotarolimus-eluting stent.

0.9%), compared with the everolimus-stent group. However, the 1-year mortality from any cause was 1.6% in the zotarolimus group and 2.8% in the everolimus group, a nonsignificant difference, the investigators said (N. Engl. J. Med. 2010 [10.1056/NEJMoa1004130]).

These results remained consistent across all subgroups of patients. At least one off-label criterion was present in the majority (66.3%) of the patients.

The rate of definite stent thrombosis was significantly higher in the zotarolimus group (1.2%) than the everolimus group (0.3%).

A smaller percentage of patients than expected underwent angiographic assessment of in-stent stenosis. In-stent stenosis was worse in the zotarolimus group but still met the criterion for non-inferiority, Dr. Serruys and his colleagues said.

The rates of adverse events were low and compared favorably with those in previous studies, with no significant between-group differences, they added.

“Although our findings are hypothesis generating and require additional investigation, definitive conclusions will be obtained only from longer-term follow-up in large patient populations in studies that have sufficient statistical power to detect differences in rates of stent thrombosis,” the researchers said. ■