

ON THE BEAT

Obituary

Dr. Helmut Drexler, an expert in chronic heart failure and clinical stem cell research, died suddenly on Sept. 13 of cardiac arrest. He was 58.

Dr. Drexler, who was director of the department of cardiology and angiology at Hannover



DR. HELMUT DREXLER

(Germany) Medical School (MHH), had collapsed while riding his bicycle.

"We [have lost] a role model as a physician, researcher, university professor, and human being," MHH President Dieter Bitter-Suermann said in a statement.

A member of the European Society of Cardiology and the Heart Failure Association, Dr. Drexler was principal investigator in the BOOST study, a randomized trial of bone marrow-derived cell therapy post MI, and CADs, a comparison of captopril and digoxin in patients with

post-MI left ventricular dysfunction.

His colleagues at the ESC remembered him not only as a scientist who pioneered translational research in cardiovascular medicine, but also as a friend with a sense of humor and a passion for skiing.

Born in 1951 in Karlsruhe, Germany, Dr. Drexler received his medical degree in 1976 from the University of Freiburg. He was a fellow at the university's Institute of Pathology (1978-1979), a research fellow at Pennsylvania State University, Hershey (1982-1983), and a visiting professor of cardiology at Stanford (Calif.) University (1991-1992).

He became associate professor at the University of Freiburg in 1993 before joining MHH in 1996. MHH's cardiology and angiology department specializes in the treatment of heart failure, atherosclerosis, cardiac arrhythmias, and congenital heart defects, as well as regenerative therapies. Its cardiac catheterization laboratory opened in 2008, and a new intensive care unit was added this year.

Dr. Drexler's research interests included the pathophysiology of heart failure, endothelial function, the renin-angiotensin system, and vascular inflammation. At the time of his death, Dr. Drexler

One-Fifth of Presenters Mum On Disclosures

Despite explicit requirements, a number of speakers at medical meetings do not disclose financial conflicts of interest, a study has found.

"Currently, disclosures by physicians are largely self-reported, but there is reason to suspect that this may change in the near future" pending legislation, wrote Dr. Kanu Okike of Brigham and Women's Hospital and Massachusetts General Hospital Boston, and colleagues.

The authors analyzed payments made to physicians in 2007 by five makers of total hip and knee prostheses that together account for nearly 95% of the market (N. Engl. J. Med. 2009;361:1466-74). They compared payments with conflict-of-interest disclosures by physicians who presented or served as board/committee members at the 2008 annual meeting of the American Academy of Orthopaedic Surgeons.

In all, 1,347 payments were made to 1,162 physicians. Overall, 166 physicians received payments from multiple companies, and 282 payments exceeded \$100,000. Nearly one-fourth of the payments (344) were made to presenters or board/committee members at the AAOS meeting. Payment was directly related to the presentation topic in 70% of cases.

The overall disclosure rate for the payments was 71%, including 79% for directly related, 50% for indirectly related, and 49% for unrelated payments. Thirty-six respondents who did not disclose payments cited unrelated topics among their reasons.

The authors cited the high nondisclosure rate as most notable "despite instructions directing each participant to make a disclosure 'if he or she has received something of value from a commercial company or institution, which relates directly or indirectly to the subject of their presentation.'" The 43 nondisclosed payments relating directly to the presentations totaled \$4.3 million.

As for their own disclosures, coauthors Dr. Mininder Kocher, Dr. Charles Mehlman, and Dr. Mohit Bhandari have received grants from or consulted for a number of medical device firms, including several of those mentioned in the study. No other conflicts were reported.

—Joyce Frieden

MULTAQ (dronedarone) Tablets

Rx Only

Brief Summary of Prescribing Information

WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic [see Contraindications (4)].

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone [see Clinical Studies (14.3) in the full prescribing information].

1 INDICATIONS AND USAGE

MULTAQ[®] is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted [see Clinical Studies (14) in the full prescribing information].

2 DOSAGE AND ADMINISTRATION

The only recommended dosage of MULTAQ is 400 mg twice daily in adults. MULTAQ should be taken as one tablet with the morning meal and one tablet with the evening meal.

Treatment with Class I or III antiarrhythmics (e.g., amiodarone, flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol) or drugs that are strong inhibitors of CYP3A (e.g., ketoconazole) must be stopped before starting MULTAQ [see Contraindications (4)].

4 CONTRAINDICATIONS

MULTAQ is contraindicated in patients with:

- NYHA Class IV heart failure or NYHA Class II – III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic [see Boxed Warning and Clinical Studies (14.3) in the full prescribing information]
- Second- or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 bpm
- Concomitant use of strong CYP 3A inhibitors, such as ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazodone, and ritonavir [see Drug Interactions (7.2)]
- Concomitant use of drugs or herbal products that prolong the QT interval and might increase the risk of Torsade de Pointes, such as phenothiazine antipsychotics, tricyclic antidepressants, certain oral macrolide antibiotics, and Class I and III antiarrhythmics
- QTc Bazett interval ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy (Category X): MULTAQ may cause fetal harm when administered to a pregnant woman. MULTAQ is contraindicated in women who are or may become pregnant. 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 a fetus [see Use in Specific Populations (8.1)].
- Nursing mothers [see Use in Specific Populations (8.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Patients with New or Worsening Heart Failure during Treatment

Advise patients to consult a physician if they develop signs or symptoms of heart failure, such as weight gain, dependent edema, or increasing shortness of breath. There are limited data available for AF/AFL patients who develop worsening heart failure during treatment with MULTAQ. If heart failure develops or worsens, consider the suspension or discontinuation of MULTAQ.

5.2 Hypokalemia and Hypomagnesemia with Potassium-Depleting Diuretics

Hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics. Potassium levels should be within the normal range prior to administration of MULTAQ and maintained in the normal range during administration of MULTAQ.

5.3 QT Interval Prolongation

Dronedarone induces a moderate (average of about 10 ms but much greater effects have been observed) QTc (Bazett) prolongation [see Clinical Pharmacology (12.2) in the full prescribing information and Clinical Studies (14.1) in the full prescribing information]. If the QTc Bazett interval is ≥500 ms, MULTAQ should be stopped [see Contraindications (4)].

5.4 Increase in Creatinine after Treatment Initiation

Serum creatinine levels increase by about 0.1 mg/dL following dronedarone treatment initiation.

The elevation has a rapid onset, reaches a plateau after 7 days and is reversible after discontinuation. If an increase in serum creatinine occurs and plateaus, this increased value should be used as the patient's new baseline. The change in creatinine levels has been shown to be the result of an inhibition of creatinine's tubular secretion, with no effect upon the glomerular filtration rate.

5.5 Women of Childbearing Potential

Pre-menopausal women who have not undergone a hysterectomy or oophorectomy must use effective contraception while using MULTAQ. Dronedarone caused fetal harm in animal studies at doses equivalent to recommended human doses. Women of childbearing potential should be counseled regarding appropriate contraceptive

choices taking into consideration their underlying medical conditions and lifestyle preferences [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following safety concerns are described elsewhere in the label:

- New or worsening heart failure [see Warnings and Precautions (5.1)]
- Hypokalemia and hypomagnesemia with potassium-depleting diuretics [see Warnings and Precautions (5.2)]
- QT prolongation [see Warnings and Precautions (5.3)]

The safety evaluation of dronedarone 400 mg twice daily in patients with AF or AFL is based on 5 placebo controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated, 3282 patients with MULTAQ 400 mg twice daily, and 2875 with placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

In clinical trials, premature discontinuation because of adverse reactions occurred in 11.8% of the dronedarone-treated patients and in 7.7% of the placebo-treated group. The most common reasons for discontinuation of therapy with MULTAQ were gastrointestinal disorders (3.2 % versus 1.8% in the placebo group) and QT prolongation (1.5% versus 0.5% in the placebo group).

The most frequent adverse reactions observed with MULTAQ 400 mg twice daily in the 5 studies were diarrhea, nausea, abdominal pain, vomiting, and asthenia.

Table 1 displays adverse reactions more common with dronedarone 400 mg twice daily than with placebo in AF or AFL patients, presented by system organ class and by decreasing order of frequency. Adverse laboratory and ECG effects are presented separately in Table 2.

Table 1: Adverse Drug Reactions that Occurred in at Least 1% of Patients and Were More Frequent than Placebo

	Placebo (N=2875)	Dronedarone 400 mg twice daily (N=3282)
Gastrointestinal		
Diarrhea	6%	9%
Nausea	3%	5%
Abdominal pain	3%	4%
Vomiting	1%	2%
Dyspeptic signs and symptoms	1%	2%
General		
Asthenic conditions	5%	7%
Cardiac		
Bradycardia	1%	3%
Skin and subcutaneous tissue		
Including rashes (generalized, macular, maculo-papular, erythematous), pruritus, eczema, dermatitis, dermatitis allergic	3%	5%

Photosensitivity reaction and dysgeusia have also been reported at an incidence less than 1% in patients treated with MULTAQ.

The following laboratory data/ECG parameters were reported with MULTAQ 400 mg twice daily.

Table 2: Laboratory data/ECG parameters not necessarily reported as adverse events

	Placebo (N=2875)	MULTAQ 400 mg twice daily (N=3282)
Serum creatinine increased ≥10% five days after treatment initiation	21%	51%
	(N=2237)	(N=2701)
QTc Bazett prolonged (>450 ms in males >470 ms in females)	19%	28%

Assessment of demographic factors such as gender or age on the incidence of treatment-emergent adverse events did not suggest an excess of adverse events in any particular sub-group.

7 DRUG INTERACTIONS

Dronedarone is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6 [see Clinical Pharmacology (12.3) in the full prescribing information]. Dronedarone's blood levels can therefore be affected by inhibitors and inducers of CYP 3A, and dronedarone can interact with drugs that are substrates of CYP 3A and CYP 2D6.

Dronedarone has no significant potential to inhibit CYP 1A2, CYP 2C9, CYP 2C19, CYP 2C8 and CYP 2B6. It has the potential to inhibit P-glycoprotein (P-gp) transport.

was running a trial on a new treatment for postpartum cardiomyopathy. MHH announced plans to continue the trial in his memory. Dr. Bernhard Schieffer, has taken over as acting director of the cardiology and angiology department.

Dr. Drexler is survived by his wife, Christa, and daughter, Beatrice. A memorial service is planned for Nov. 28.

Cardiologists on the Move

Dr. Jonathan S. Stamler, formerly of Duke University, Durham, N.C., is director of the newly established Institute for Transformative Molecular Medicine

at Case Western Reserve University, Cleveland. He also holds the new Robert S. and Sylvia K. Reitman Family Foundation Distinguished Chair in Cardiovascular Innovation at Case Western University's Cardiovascular Center and University Hospitals Harrington-McLaughlin Heart & Vascular Institute. According to



DR. JOHNATHAN S. STAMLER

a statement from Case Western, the chair, funded by a \$1.5 million gift from the Reitman Family Foundation, is slated to be held by a preeminent physician scientist dedicated to advancing cardiovascular medicine through compassionate patient care, clinical research, and training of residents and fellows.

Recognized for his scientific studies advancing new therapies for cardiovascular, pulmonary, musculoskeletal, neurologic, an oncologic diseases, Dr. Stamler is credited with the discovery of a protein modification, S-nitrosylation, that helped clarify the role of nitric oxide in the con-

trol of complex physiological responses.

He earned his medical degree from Mount Sinai School of Medicine in New York, and completed his medical residency and fellowship training in cardiology and pulmonary medicine at Harvard Medical School and Brigham and Women's Hospital, Boston.

In 1993, he joined the faculty at Duke, where he went on to become the George Barth Geller Professor of Research in Cardiovascular Disease and professor of medicine and biochemistry, before accepting the position at Case Western.

—Jane Locastro

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 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.

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