

# Second MIs Are Becoming Rarer, Less Deadly

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STOCKHOLM — The marked decline in the incidence of first MI and the improved rate of survival after its occurrence constitute one of the great medical success stories of recent decades. But what about second MIs? Are they also decreasing in incidence and lethality?

The answer is a resounding yes, based on the findings of two studies presented

at the annual congress of the European Society of Cardiology. The studies captured highly favorable trends in first and second MIs in Scotland and Denmark, two places with comprehensive national medical record-keeping.

Dr. Niamh Murphy used the Scottish Linked Record Database to analyze all 110,226 hospitalizations for a first MI and 9,664 admissions for a second MI in Scotland during 1990-2000. She found that the hospitalization rate for a first MI declined

by 29% over the decade. The reduction in the hospitalization rate for a second MI was even more impressive—it was down by 59%, which is testimony to the great strides made in secondary prevention.

The median time between a first and second MI was 2.3 years in men and 4.8 years in women. Overall survival after a first MI was 8.8 years in men and 4.3 years in women. Survival after a second MI was considerably shorter—an average of 3.6 years in men and 1.8 years in

women, said Dr. Murphy of the Western Infirmary, Glasgow.

During the same period, overall mortality after a first MI was 20.1% at 1 month, 28.4% at 1 year, and 44.7% at 5 years. Mortality was substantially worse after a second MI: 24.5% at 1 month, 38.3% at 1 year, and 60.2% at 5 years.

Advanced age was a powerful risk factor for mortality. For example, men older than 84 years at their first MI were more than 15-fold more likely to die within 30 days than were those with a first MI before the age of 55 years. Age also affected mortality after a second MI, but to a lesser extent.

After adjustment for age, gender, comorbid illnesses, and other potential confounders, the 30-day case fatality rate after a first MI fell by 38% in men and by 24% in women. The decline in 30-day mortality after a second MI was smaller and not statistically significant. However, the decline in adjusted 5-year mortality after a second MI was more robust: 29% in men and 17% in women. During the same period, adjusted 5-year mortality after a first MI fell by 27% in men and 23% in women, Dr. Murphy continued.

However, despite the dramatic decline in recent years in the rate of second MIs and the substantial drop in the associated fatality rate, the prognosis after a second MI remains considerably worse than it does after the first. "This last finding underscores the importance of using all available evidence-based therapies to prevent recurrent events in patients who've experienced a first MI," Dr. Murphy stressed.

In a separate presentation, Dr. Pernille Buch reported on all 167,260 patients diagnosed with a first MI in Denmark during 1985-2002. One-year mortality after hospitalization for a first MI declined steadily throughout the study period, from 39% in the first 5 years of the study, during 1985-1989, to 25% in during 2000-2002, the last three years of the study. (The researchers used the 3-year period because the change in 2003 of the definition of acute MI disrupted longitudinal epidemiologic studies.)

There was an even more pronounced reduction in mortality among the 5,363 patients who experienced recurrent MI within 30 days of their first MI. During the 1985-1989 period, the 1-year mortality following such an event was 49%; by the 2000-2002 period, it had dropped to 18%, according to Dr. Buch of Bispebjerg University Hospital, Copenhagen.

Most of the improved prognosis after recurrent MI during the 17-year study period came from a marked decline in mortality during the first week after the event. During 1985-1989, patients who had a recurrent MI within 30 days of a first MI were 14-fold more likely to die within the next 7 days, compared with patients who didn't have a second MI. By the 2000-2002 period, they were only fivefold more likely to die within a week.

Likewise, patients with recurrent MI during 1985-1989 were 5-fold more likely to die during days 8-60 than were those who did not have a second MI, but by 2000-2002, they were at only 1.8-fold increased risk of death during the same time period.

Van Kerrebroeck et al: A 12-week, double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and tolerability of tolterodine tartrate capsules (4 mg qd) compared with tolterodine tartrate tablets (2 mg bid) and placebo in 1529 patients with overactive bladder (published data from the Registration Study). The primary efficacy variable was the change in the number of incontinence episodes per week from baseline to Week 12.

Landis et al: A post hoc analysis of a 12-week, multinational, randomized, double-blind, placebo-controlled study that compared the efficacy of tolterodine tartrate capsules (4 mg qd) with placebo for overactive bladder in 986 patients with severe urgency incontinence. Severe urgency incontinence was defined as 21 to 168 urgency incontinence episodes/week.

References: 1. Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, for the Tolterodine Study Group. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology*. 2001;57:414-421. 2. Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *J Urol*. 2004;171:752-756.

## Detrol LA<sup>®</sup>

tolterodine tartrate  
extended release capsules

PHARMACIA

Brief Summary of Prescribing Information

### INDICATIONS AND USAGE

DETROL LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

### CONTRAINDICATIONS

DETROL LA Capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

### PRECAUTIONS

#### General

**Risk of Urinary Retention and Gastric Retention:** DETROL LA Capsules should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

**Controlled Narrow-Angle Glaucoma:** DETROL LA should be used with caution in patients being treated for narrow-angle glaucoma.

**Reduced Hepatic and Renal Function:** For patients with significantly reduced hepatic function or renal function, the recommended dose for DETROL LA is 2 mg daily. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

#### Patients with Congenital or Acquired QT Prolongation:

In a study of the effect of tolterodine immediate release tablets on the QT interval (See **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology** in full prescribing information), the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PMs) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped. These observations should be considered in clinical decisions to prescribe DETROL LA for patients with a known history of QT prolongation or patients who are taking Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol) antiarrhythmic medications (See **PRECAUTIONS, Drug Interactions**). There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA.

#### Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness.

#### Drug Interactions

**CYP3A4 Inhibitors:** Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see **CLINICAL PHARMACOLOGY, Variability in Metabolism and Drug-Drug Interactions** in full prescribing information). For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (eg, itraconazole, miconazole) or macrolide antibiotics (eg, erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of DETROL LA is 2 mg daily (see **DOSAGE AND ADMINISTRATION**).

#### Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine immediate release were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 µg·h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 µg·h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14-fold higher than expected in humans. No increase in tumors was found in either mice or rats. No mutagenic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* in the bone marrow micronucleus test in the mouse. In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 µg·h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

#### Pregnancy

Pregnancy Category C. At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 µg·h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

#### Nursing Mothers

Tolterodine immediate release is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced bodyweight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

#### Pediatric Use

Efficacy in the pediatric population has not been demonstrated. A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two Phase 3 randomized, placebo-controlled, double-blind, 12-week studies.

The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

#### Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** in full prescribing information).

#### ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for DETROL LA Capsules included 1073 patients who were treated with DETROL LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. The data described below reflect exposure to DETROL LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with DETROL LA and in 1.2% (n=6) of patients treated with placebo.

Table 4 lists the adverse events reported in 1% or more of patients treated with DETROL LA 4 mg once daily in the 12-week study. The adverse events were reported regardless of causality.

Table 4. Incidence\* (% of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
	headache	6	4
General	fatigue	2	1
	dizziness	2	1
Central/Peripheral Nervous	constipation	6	4
	abdominal pain	4	2
	dysepsia	3	1
Gastrointestinal	xerophthalmia	3	2
	vision abnormal	1	0
Vision	somnolence	3	2
	anxiety	1	0
Psychiatric	sinusitis	2	1
	dysuria	1	0

\* in nearest integer.

#### Postmarketing Surveillance

The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, including angioedema; tachycardia; palpitations; peripheral edema; and hallucinations. Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

#### OVERDOSAGE

A 27-month-old child who ingested 5 to 7 tolterodine immediate release tablets 2 mg was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

#### Management of Overdosage

Overdosage with DETROL LA Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly. ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated. (see **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

#### DOSAGE AND ADMINISTRATION

The recommended dose of DETROL LA Capsules are 4 mg daily. DETROL LA should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETROL LA 2 mg (see **CLINICAL STUDIES** in full prescribing information). For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY AND PRECAUTIONS, Drug Interactions** in full prescribing information).

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