

# Metformin Cut Deaths in Patients With CVD Risk

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FROM THE ANNUAL MEETING OF  
THE AMERICAN DIABETES ASSOCIATION

ORLANDO — Metformin use was associated with a significant decrease in the risk of all-cause death among diabetic patients at risk for cardiovascular events.

The subanalysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry found that subjects

with type 2 diabetes who took metformin were 24% less likely to die of all-cause mortality over a 2-year period than were those who did not take the drug. The association remained significant even after researchers controlled for age and sex, and after factoring in several baseline characteristics that varied significantly between the groups.

“Given the diversity of the 44 countries and widely different practice settings

involved in the registry, we think these data are highly relevant,” Dr. Ronan Roussel said at the meeting. While perhaps not sufficient to make practice recommendations, he did say the results are strong enough to prompt clinical trials, especially when viewed in the context of the growing body of evidence about metformin’s cardioprotective effects.

The REACH Registry was established to track outcomes in patients with

atherothrombosis or atherothrombotic risk factors. Almost 70,000 patients were enrolled. They were either symptomatic, with documented cardiovascular, coronary artery, or peripheral artery disease; or asymptomatic with at least three risk factors for atherothrombosis.

Of this group, 19,699 had type 2 diabetes and 2-year outcomes data. Dr. Roussel of the Groupe Hospitalier Bichat-Claude Bernard, Paris, and his colleagues compared those who were taking metformin at baseline with those who were not. Metformin was taken by 40% of the patients.

There were some significant baseline differences between the groups, Dr. Roussel noted. Patients taking metformin were significantly younger (67 vs.

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69 years), had a higher average fasting blood glucose (138 mg/dL vs. 131 mg/dL), and higher systolic blood pressure (138 mm Hg vs. 136 mm Hg).

Prior arterial disease was present in 80% of those taking metformin and 75% of those not. Metformin users were also taking significantly more cardiovascular drugs, including aspirin (74% vs. 69%), statins (75% vs. 67%), and angiotensin-converting enzyme inhibitors (54% vs. 49%).

Over the 2-year follow-up period, there were 1,270 deaths. After researchers adjusted for sex and age only, metformin was associated with a 33% reduction in the risk of all-cause death.

After adjustment for the other factors, the mortality difference still remained significant in favor of metformin use, with a 24% risk reduction in all-cause death. When the researchers examined the sexes separately, they found no statistically significant differences.

In an age analysis, with subjects split into groups 40-65 years, 65-80 years, and older than 80 years, the risk reductions were significant for the youngest group (37%) and the middle group (23%). The oldest subjects did not have a survival advantage with the drug.

Metformin also improved the odds of survival in patients with existing heart failure, conferring a significant 31% reduction in the risk of death.

Subjects who were taking insulin as well as metformin benefited more than did those who were taking metformin alone (hazard ratio, 0.64 vs. 0.80).

The REACH Registry is sponsored by Sanofi-Aventis, Bristol-Myers Squibb, and the Waksman Foundation, Tokyo. Dr. Roussel disclosed that he has received research support or consulting fees from Sanofi-Aventis, Servier Laboratories, Roche, Eli Lilly & Co., Novo Nordisk Inc., Medtronic Inc., and LifeScan Inc. ■



## LIDODERM® (Lidocaine Patch 5%)

**Brief Summary** (For full Prescribing Information refer to package insert.)

### INDICATIONS AND USAGE

LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin**.

### CONTRAINDICATIONS

LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

### WARNINGS

#### Accidental Exposure in Children

Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to **store and dispose of LIDODERM out of the reach of children, pets, and others**. (See HANDLING AND DISPOSAL)

#### Excessive Dosing

Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

### PRECAUTIONS

#### General

**Hepatic Disease:** Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

**Allergic Reactions:** Patients allergic to para aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

**Non-intact Skin:** Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. LIDODERM is only recommended for use on intact skin.

**External Heat Sources:** Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

**Eye Exposure:** The contact of LIDODERM with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

#### Drug Interactions

**Antiarrhythmic Drugs:** LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

**Local Anesthetics:** When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis:** A minor metabolite, 2, 6-xylylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

**Mutagenesis:** Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

**Impairment of Fertility:** The effect of LIDODERM on fertility has not been studied.

#### Pregnancy

**Teratogenic Effects: Pregnancy Category B.** LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LIDODERM should be used during pregnancy only if clearly needed.

#### Labor and Delivery

LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

#### Nursing Mothers

LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk: plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

#### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### ADVERSE REACTIONS

##### Application Site Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

##### Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

##### Other Adverse Events

Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

##### Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of LIDODERM are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

##### OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdose from other sources of lidocaine or other local anesthetics.

The oral LD<sub>50</sub> of lidocaine HCl is 459 (346-773) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

##### DOSEAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See HANDLING AND DISPOSAL) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

##### HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. LIDODERM should be kept out of the reach of children.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Manufactured for:

Endo Pharmaceuticals Inc.  
Chadds Ford, Pennsylvania 19317



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