

New Stent Showed Good Long-Term Safety

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Presuming that the Resolute zotarolimus-eluting coronary stent enters the U.S. market within the next year, interventionalists likely will rely on data from two key studies to weigh how it matches up against its main competition, the Xience V/Promus

everolimus-eluting coronary stent.

Two features seemed to especially capture the attention of the cardiologists who reported the data at the meeting and those who heard it: the impressive performance of the zotarolimus-eluting stent (ZES) in patients with diabetes, and the long-term safety of the ZES compared with the everolimus-eluting stent (EES) for stent thrombosis.

One of the two studies was the

RESOLUTE All Comers trial, which compared the ZES against the EES in a randomized trial of 2,292 European patients for whom follow-up now extends to 2 years.

The second study, RESOLUTE US, evaluated the new ZES in a series of 1,402 U.S. patients with a high, 34% prevalence of diabetes; this study had a special focus on the stent's performance in the 150 narrow, 2.25-mm-diameter ar-

teries included in the series.

The roughly 2,500 ZES recipients included in these two studies form about half of the 5,227 total-patient worldwide experience with the stent to date, and constituted what Medtronic, the company developing the Resolute ZES, submitted to the Food and Drug Administration for marketing approval and labeling.

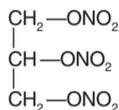
One major take on these data by experts was that the ZES showed good overall performance that matched well with the performance of the EES.

The two stents "seemed to be fairly equivalent for most of the important safety and efficacy metrics. They are

Nitrolingual® Pumpspray

(nitroglycerin lingual spray)
400 mcg per spray, 60 or 200 Metered Sprays

DESCRIPTION: Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate (C₃H₅N₃O₉). The compound has a molecular weight of 227.09. The chemical structure is:



Nitrolingual® Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.

CLINICAL PHARMACOLOGY: The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilatation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arterial relaxation reduces systemic vascular resistance and arterial pressure (after-load).

The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved.

While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of exertional angina is unclear.

Nitroglycerin is rapidly metabolized *in vivo*, with a liver reductase enzyme having primary importance in the formation of glyceryl nitrate metabolites and inorganic nitrate. Two active major metabolites, 1,2- and 1,3-dinitroglycerols, the products of hydrolysis, although less potent as vasodilators, have longer plasma half-lives than the parent compound. The dinitrates are further metabolized to mononitrates (considered biologically inactive with respect to cardiovascular effects) and ultimately glycerol and carbon dioxide.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Patients with elevated left ventricular filling pressure and systemic vascular resistance values in conjunction with a depressed cardiac index are likely to experience an improvement in cardiac index. On the other hand, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced.

In a pharmacokinetic study when a single 0.8 mg dose of Nitrolingual® Pumpspray was administered to healthy volunteers (n = 24), the mean C_{max} and T_{max} were 1,041 pg/mL · min and 7.5 minutes, respectively. Additionally, in these subjects the mean area-under-the-curve (AUC) was 12,769 pg/mL · min.

In a randomized, double-blind single-dose, 5-period cross-over study in 51 patients with exertional angina pectoris significant dose-related increases in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo.

Additionally the drug was well tolerated as evidenced by a profile of generally mild to moderate adverse events.

INDICATIONS AND USAGE: Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

CONTRAINDICATIONS: Allergic reactions to organic nitrates are rare. Nitroglycerin is contraindicated in patients who are allergic to it. Nitrolingual® Pumpspray is contraindicated in patients taking certain drugs for erectile dysfunction (phosphodiesterase inhibitors), as their concomitant use can cause severe hypotension. The time course and dose-dependency of this interaction are not known.

WARNINGS: Amplification of the vasodilatory effects of Nitrolingual® Pumpspray by certain drugs (phosphodiesterase inhibitors) used to treat erectile dysfunction can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion. The use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

PRECAUTIONS: (General) Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug, therefore, should be used with caution in subjects who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g., below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and anti-anginal effects of nitrates has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory.

In industrial workers continuously exposed to nitroglycerin, tolerance clearly occurs. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In various clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of nitroglycerin is not known.

PRECAUTIONS: (INFORMATION FOR PATIENTS) Physicians should discuss with patients that Nitrolingual® Pumpspray should not be used with certain drugs taken for erectile dysfunction (phosphodiesterase inhibitors) because of the risk of lowering their blood pressure dangerously.

DRUG INTERACTIONS: Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Nitroglycerin acts directly on vascular muscle. Therefore, any other agents that depend on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending upon the agent.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and oral controlled-release nitroglycerin were used in combination. Dose adjustments of either class of agents may be necessary.

Concomitant use of nitric oxide donors (like Nitrolingual® Pumpspray) and certain drugs for the treatment of erectile dysfunction (phosphodiesterase inhibitors) can amplify their vasodilatory effects, resulting in severe hypotension. The concomitant use of these drugs is contraindicated (see **CONTRAINDICATIONS**) and alternative therapies should be used to treat acute angina episodes.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Animal carcinogenesis studies with sublingual nitroglycerin have not been performed. Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At high dose, the incidences of hepatocellular carcinomas in both sexes were 52% vs. 0% in controls, and incidences of testicular tumors were 52% vs. 8% in controls. Lifetime dietary administration of up to 1058 mg/kg/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was weakly mutagenic in Ames tests performed in two different laboratories. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats treated with doses up to about 363 mg/kg/day, p.o., or in *in vitro* cytogenetic tests in rat and dog tissues.

In a three-generation reproduction study, rats received dietary nitroglycerin at doses up to about 434 mg/kg/day for six months prior to mating of the F₂ generation with treatment continuing through successive F₁ and F₂ generations. The high dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F₂ generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males. In this three-generation study there was no clear evidence of teratogenicity.

PREGNANCY: Pregnancy Category C – Animal teratology studies have not been conducted with nitroglycerin-pumpspray. Teratology studies in rats and rabbits, however, were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. There are no adequate and well-controlled studies in pregnant women. Nitroglycerin should be given to pregnant women only if clearly needed.

NURSING MOTHERS: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nitrolingual® Pumpspray is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of nitroglycerin in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reactions to oral nitroglycerin dosage forms, particularly headache and hypotension, are generally dose-related. In clinical trials at various doses of nitroglycerin, the following adverse effects have been observed: Headache, which may be severe and persistent, is the most commonly reported side effect of nitroglycerin with an incidence on the order of about 50% in some studies. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop. Occasionally, an individual may exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) may occur even with therapeutic doses. Drug rash and/or exfoliative dermatitis have been reported in patients receiving nitrate therapy. Nausea and vomiting appear to be uncommon.

Nitrolingual® Pumpspray given to 51 chronic stable angina patients in single doses of 0.4, 0.8 and 1.6 mg as part of a double-blind, 5-period cross-over study exhibited an adverse event profile that was generally mild to moderate. Adverse events occurring at a frequency greater than 2% included: headache, dizziness, and paresthesia. Less frequently reported events in this trial included (≤2%): dyspnea, pharyngitis, rhinitis, vasodilation, peripheral edema, asthenia, and abdominal pain.

OVERDOSAGE: Signs and Symptoms: Nitrate overdosage may result in: severe hypotension, persistent throbbing headache, vertigo, palpitation, visual disturbance, flushing and perspiring skin (later becoming cold and cyanotic), nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), methemoglobinemia with cyanosis and anorexia, initial hyperpnea, dyspnea and slow breathing, slow pulse (dicrotic and intermittent), heart block, increased intracranial pressure with cerebral symptoms of confusion and moderate fever, paralysis and coma followed by clonic convulsions, and possibly death due to circulatory collapse.

Methemoglobinemia: Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrates could produce harmful concentrations of methemoglobin.

Treatment of Overdosage: Keep the patient recumbent in a shock position and comfortably warm. Passive movement of the extremities may aid venous return. Administer oxygen and artificial ventilation, if necessary. If methemoglobinemia is present, administration of methylene blue (1% solution), 1-2 mg per kilogram of body weight intravenously, may be required. If an excessive quantity of Nitrolingual® Pumpspray has been recently swallowed gastric lavage may be of use.

WARNING: Epinephrine is ineffective in reversing the severe hypotensive events associated with overdosage. It and related compounds are contraindicated in this situation.

DOSE AND ADMINISTRATION: At the onset of an attack, one or two metered sprays should be administered onto or under the tongue. No more than three metered sprays are recommended within a 15-minute period. If the chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

Each metered spray of Nitrolingual® Pumpspray delivers 48 mg of solution containing 400 mcg of nitroglycerin after an initial priming of 5 sprays. It will remain adequately primed for 6 weeks. If the product is not used within 6 weeks it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming sprays. There are 60 or 200 metered sprays per bottle. The total number of available doses is dependent, however, on the number of sprays per use (1 or 2 sprays), and the frequency of repriming.

The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level.** Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used.

During application the patient should rest, ideally in the sitting position. The container should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should preferably be sprayed onto the tongue by pressing the button firmly and the mouth should be closed immediately after each dose. **THE SPRAY SHOULD NOT BE INHALED.** The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. Patients should be instructed to familiarize themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation for administration at night.

HOW SUPPLIED: Each box of Nitrolingual® Pumpspray contains one glass bottle coated with red transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each bottle contains 4.9 g or 12 g (Net Content) of nitroglycerin lingual spray which will deliver 60 or 200 metered sprays containing 400 mcg of nitroglycerin per spray after priming.

Nitrolingual® Pumpspray is available as:
• 60-dose (4.9 g) single bottle NDC 24338-300-65
• 200-dose (12 g) single bottle NDC 24338-300-20

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

Note: Nitrolingual® Pumpspray contains 20% alcohol. Do not forcefully open or burn container after use. Do not spray toward flames. Rx Only.

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‘The results were quite substantial,’ with a 3.0% rate of target-lesion revascularization among diabetes patients.

DR. LEON

both superb,” said Dr. Martin B. Leon, director of the center for interventional vascular therapy at Columbia University in New York, and lead investigator for the RESOLUTE US study.

But other interventionalists hearing the data from both studies weren’t as completely convinced.

“My initial take on the data is that [the ZES] doesn’t seem to be better than the Xience stent, which is a very good stent and the dominant stent we use [in the United States] at this time,” Dr. Abhiram Prasad, an interventional cardiologist and professor of medicine at the Mayo Clinic in Rochester, Minn., said in an interview.

Safety concerns with the ZES date back to the initial, 12-month follow-up report, the first indication that the ZES fell short compared with the EES on the rate of stent thrombosis in the RESOLUTE All Comers trial. The New England Journal of Medicine report last year (2010;363:136-46) documented 18 patients (1.6%) with definite or probable stent thrombosis in the ZES arm, compared with 8 cases (0.7%) of definite or probable stent thrombosis in the EES group, a significant difference.

The new, 24-month follow-up data provided some reassurance on safety, in that the stent thrombosis gap between the two stents stayed stable. During an extra year of follow-up, three new cases of definite or probable stent thrombosis occurred in each of the two treatment arms, said Dr. Patrick W. Serruys, professor of interventional cardiology at Erasmus University and the Thoraxcentrum, Rotterdam, and lead investigator for the RESOLUTE All Comers trial. Aside from this one early safety deviation, the ZES and EES continued to show virtually identical efficacy performance through the 2 years of study, he showed in the updated data. Concurrently with his report at the meeting, the results appeared in an article pub-

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lished in the Lancet (2011 [doi:10.1016/S0140-6736(11)60404-2]).

Dr. Serruys, as well as others, chalked up the early difference in stent thrombosis rates to chance, and to some isolated poor performance in certain sites undertaking the coronary interventions.

"Numerically, the stent thrombosis is very small, a difference of 21 vs. 11 patients in more than 2,000 total patients. It could be the play of chance," Dr. Serruys said.

The RESOLUTE US results seemed to add to the safety assurance. In those 1,402 patients, two cases (0.1%) of stent thrombosis occurred during 12 months of tracking. Concurrently with Dr. Leon's report, the RESOLUTE US results appeared in the Journal of the American College of Cardiology (2011 April 4 [doi:10.1016/j.jacc.2011.03.005]).

"This is one of the lowest 1-year stent thrombosis rates ever reported," noted Dr. Leon. "I take from this that it's a safe stent."

The pattern of some of the earliest cases of stent thrombosis in RESOLUTE All Comers suggested that it may have been caused more by operator failings and less by problems with the stent itself. During the study's first 30 days, stent thrombosis occurred in nine ZES patients and one

Comers diabetes subgroup, you have a robust enough population to justify consideration for approval, I think," he said.

"The results were quite substantial," with a 3.0% rate of target-lesion revascularization among the patients with diabetes, compared with a 2.0% rate for the entire main cohort of the study."

But even if the diabetes indication works out, will interventionalists be swayed by that, or by the data?

"An issue is, to what extent can a single trial address a subgroup?" said Dr. Krucoff. "To what degree is there statistical guidance that in the real world [the

ZES] would live up to this measure?"

"I don't think I'd put a lot of emphasis in my decision making on the [RESOLUTE US] data, because a problem with all [stenting] studies is that the rates are constantly improving, so the new device can appear to be better. ... Even if [the ZES] was approved for use in patients with diabetes, I don't think in my practice I'd pick it to use in those patients. They'd need to do a randomized study in patients with diabetes to convince me" that it was better than the EES, Dr. Prasad said.

Dr. Serruys and Dr. Prasad had no rel-

evant financial disclosures. Dr. Leon serves as an unpaid consultant to Abbott, Boston Scientific, and Medtronic. Dr. Yeung serves on the scientific advisory board of Medtronic; he is also a consultant for Abbott Vascular, Boston Scientific, and Cordis, and has received research grants from Boston Scientific, Edwards, and Medtronic. Dr. Fontana is an employee of Medtronic. Dr. Krucoff has been a consultant to or has received honoraria from Abbott, Biosensors, Cardiomind, Cordis Johnson & Johnson, Medtronic, Merck, Micelle, OrbusNeich, Prescient, Sanofi-Aventis, and Terumo. ■

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The ZES and EES continued to show virtually identical efficacy performance through the 2 years of study.

DR. SERRUYS

EES patient, making up most of the differential that wound up haunting the ZES arm through the next 2 years. "Stent thrombosis during the first 30 days is procedure related," and generally the stent itself plays no role, said Dr. Alan C. Yeung, professor of medicine and director of cardiac catheterization at Stanford (Calif.) University.

"Whether it's a real difference or a play of chance remains undetermined," commented Dr. Mitchell W. Krucoff, a professor of medicine and interventional cardiologist at Duke University in Durham, N.C. "These types of differences [21 patients vs. 11 patients] are not certain at a statistical level."

So if the ZES hopes to wrest any market share from the EES when it hits the U.S. market, it may need to have something to distinguish it, and that something may be an FDA-approved indication for treatment of coronary stenoses in patients with diabetes. At least that's what Medtronic is hoping for. The company included that application in its submission to the FDA, Jason Fontana, Ph.D., senior director for clinical communication at Medtronic, said in an interview.

"The diabetes subgroup was large enough, and the diabetes analysis was prespecified" in RESOLUTE US, Dr. Leon said in an interview. "If you include this subgroup, and the RESOLUTE All