

DES Beats BMS for Saphenous Vein Graft Stenosis

BY ALICE GOODMAN

FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY

NEW ORLEANS – Drug-eluting stents outperformed bare-metal stents when placed in saphenous vein graft lesions that developed post-coronary artery bypass graft, in ISAR-CABG, the largest study ever performed to compare these two types of stents in this setting.

Specifically, DES significantly reduced the rate for the combined primary end point of death, MI, and repeat revascularization procedures.

“This study shows us that we don’t have to be afraid of DES in patients with these high-risk lesions, because use of DES cuts down the need for target vessel revascularization by 50% and does not increase myocardial infarction mortality and stent thrombosis formation

when compared with BMS [bare-metal stents],” Dr. Julinda Mehilli, director of clinical research and data coordinating ISAR (Intracoronary Stenting and Antithrombotic Regimen) at the German Heart Center in Munich, said at the meeting.

ISAR-CABG enrolled 610 patients who underwent a first CABG with a saphenous vein graft and developed at least one stenotic lesion of at least 50% in the

graft. Patients were randomized to receive either a DES or a BMS in a 1:1 ratio. In the DES group, patients were assigned 1:1:1 to three commonly used types of stents (sirolimus, paclitaxel, and biodegradable sirolimus) to mirror real-world use, Dr. Mehilli explained.

The primary end point was a composite of death, myocardial infarction, and target-vessel revascularization at 1 year of follow-up after percutaneous

NIASPAN® (niacin extended-release tablets)

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hyperlipidemia. Niaspan therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1. Niaspan is indicated to reduce elevated TC, LDL-C, Apo B and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.
2. Niaspan in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate.
3. In patients with a history of myocardial infarction and hyperlipidemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction.
4. In patients with a history of coronary artery disease (CAD) and hyperlipidemia, niacin, in combination with a bile acid binding resin, is indicated to slow progression or promote regression of atherosclerotic disease.

Limitations of Use No incremental benefit of Niaspan coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin, or lovastatin monotherapy has been established.

CONTRAINDICATIONS

Niaspan is contraindicated in the following conditions:

- Active liver disease or unexplained persistent elevations in hepatic transaminases [see Warnings and Precautions]
- Patients with active peptic ulcer disease
- Patients with arterial bleeding
- Hypersensitivity to niacin or any component of this medication [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

Niaspan preparations should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to Niaspan, therapy with Niaspan should be initiated with low doses (i.e., 500 mg at bedtime) and the Niaspan dose should then be titrated to the desired therapeutic response.

Caution should also be used when Niaspan is used in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs such as nitrates, calcium channel blockers, or adrenergic blocking agents.

Niacin is rapidly metabolized by the liver, and excreted through the kidneys. Niaspan is contraindicated in patients with significant or unexplained hepatic impairment [see Contraindications and Warnings and Precautions] and should be used with caution in patients with renal impairment. Patients with a past history of jaundice, hepatobiliary disease, or peptic ulcer should be observed closely during Niaspan therapy.

Skeletal Muscle Cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses (≥ 1 g/day) of niacin and statins. Physicians contemplating combined therapy with statins and Niaspan should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

The risk for myopathy and rhabdomyolysis are increased when lovastatin or simvastatin are coadministered with Niaspan, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism.

Liver Dysfunction Cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted sustained-release (modified-release, timed-release) niacin products for immediate-release (crystalline) niacin at equivalent doses.

Niaspan should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of Niaspan.

Niacin preparations have been associated with abnormal liver tests. In three placebo-controlled clinical trials involving titration to final daily Niaspan doses ranging from 500 to 3000 mg, 245 patients received Niaspan for a mean duration of 17 weeks. No patient with normal serum transaminase levels (AST, ALT) at baseline experienced elevations to more than 3 times the upper limit of normal (ULN) during treatment with Niaspan. In these studies, fewer than 1% (2/245) of Niaspan patients discontinued due to transaminase elevations greater than 2 times the ULN.

In three safety and efficacy studies with a combination tablet of Niaspan and lovastatin involving titration to final daily doses (expressed as mg of niacin/ mg of lovastatin) 500 mg/10 mg to 2500 mg/40 mg, ten of 1028 patients (1.0%) experienced reversible elevations in AST/ALT to more than 3 times the ULN. Three of ten elevations occurred at doses outside the recommended dosing limit of 2000 mg/40 mg; no patient receiving 1000 mg/20 mg had 3-fold elevations in AST/ALT.

Niacin extended-release and simvastatin can cause abnormal liver tests. In a simvastatin-controlled, 24 week study with a fixed dose combination of Niaspan and simvastatin in 641 patients, there were no persistent increases (more than 3x the ULN) in serum transaminases. In three placebo-controlled clinical studies of extended-release niacin there were no patients with normal serum transaminase levels at baseline who experienced elevations to more than 3x the ULN. Persistent increases (more than 3x the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the placebo-controlled clinical trials and the long-term extension study, elevations in transaminases did not appear to be related to treatment duration; elevations in AST levels did appear to be dose related. Transaminase elevations were reversible upon discontinuation of Niaspan.

Liver function tests should be performed on all patients during therapy with Niaspan. Serum transaminase levels, including AST and ALT (SGOT and SGPT), should be monitored before treatment begins, every 6 to 12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise, the drug should be discontinued.

Laboratory Abnormalities **Increase in Blood Glucose:** Niacin treatment can increase fasting blood glucose. Frequent monitoring of blood glucose should be performed to ascertain that the drug is producing no adverse effects. Diabetic patients may experience a dose-related increase in glucose intolerance. Diabetic or potentially diabetic patients should be observed closely during treatment with Niaspan, particularly during the first few months of use or dose adjustment; adjustment of diet and/or hypoglycemic therapy may be necessary.

Reduction in Platelet Count: Niaspan has been associated with small but statistically significant dose-related reductions in platelet count (mean of -11% with 2000 mg). Caution should be observed when Niaspan is administered concomitantly with anticoagulants; platelet counts should be monitored closely in such patients.

Increase in Prothrombin Time (PT): Niaspan has been associated with small but statistically significant increases in prothrombin time (mean of approximately +4%); accordingly, patients undergoing surgery should be carefully evaluated. Caution should be observed when Niaspan is administered concomitantly with anticoagulants; prothrombin time should be monitored closely in such patients.

Increase in Uric Acid: Elevated uric acid levels have occurred with niacin therapy, therefore use with caution in patients predisposed to gout.

Decrease in Phosphorus: In placebo-controlled trials, Niaspan has been associated with small but statistically significant, dose-related reductions in phosphorus levels (mean of -13% with 2000 mg). Although these reductions were transient, phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Clinical Studies Experience In the placebo-controlled clinical trials database of 402 patients (age range 21-75 years, 33% women, 89% Caucasians, 7% Blacks, 3% Hispanics, 1% Asians) with a median treatment duration of 16 weeks, 16% of patients on Niaspan and 4% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with Niaspan that led to treatment discontinuation and occurred at a rate greater than placebo were flushing (6% vs. 0%), rash (2% vs. 0%), diarrhea (2% vs. 0%), nausea (1% vs. 0%), and vomiting (1% vs. 0%). The most commonly reported adverse reactions (incidence >5% and greater than placebo) in the Niaspan controlled clinical trial database of 402 patients were flushing, diarrhea, nausea, vomiting, increased cough and pruritus.

In the placebo-controlled clinical trials, flushing episodes (i.e., warmth, redness, itching and/or tingling) were the most common treatment-emergent adverse reactions (reported by as many as 88% of patients) for Niaspan. Spontaneous reports suggest that flushing may also be accompanied by symptoms of dizziness, tachycardia, palpitations, shortness of breath, sweating, burning sensation/skin burning sensation, chills, and/or edema, which in rare cases may lead to syncope. In pivotal studies, 6% (14/245) of Niaspan patients discontinued due to flushing. In comparisons of immediate-release (IR) niacin and Niaspan, although the proportion of patients who flushed was similar, fewer flushing episodes were reported by patients who received Niaspan. Following 4 weeks of maintenance therapy at daily doses of 1500 mg, the incidence of flushing over the 4-week period averaged 8.6 events per patient for IR niacin versus 1.9 following Niaspan.

Other adverse reactions occurring in $\geq 5\%$ of patients treated with Niaspan and at an incidence greater than placebo are shown in 1 below.

Table 1. Treatment-Emergent Adverse Reactions by Dose Level in $\geq 5\%$ of Patients and at an Incidence Greater than Placebo; Regardless of Causality Assessment in Placebo-Controlled Clinical Trials

	Placebo-Controlled Studies Niaspan Treatment ^a				
	Placebo (n = 157) %	500 mg ^b (n = 87) %	1000 mg (n = 110) %	1500 mg (n = 136) %	2000 mg (n = 95) %
Gastrointestinal Disorders					
Diarrhea	13	7	10	10	14
Nausea	7	5	6	4	11
Vomiting	4	0	2	4	9
Respiratory					
Cough, increased	6	3	2	< 2	8
Skin and Subcutaneous Tissue Disorders					
Pruritus	2	8	0	3	0
Rash	0	5	5	5	0
Vascular Disorders					
Flushing ^c	19	68	69	63	55

Note: Percentages are calculated from the total number of patients in each column.

^a Adverse reactions are reported at the initial dose where they occur.

^b Pooled results from placebo-controlled studies; for Niaspan, n = 245 and median treatment duration = 16 weeks.

^c Number of Niaspan patients (n) are not additive across doses.

^d The 500 mg/day dose is outside the recommended daily maintenance dosing range.

^e 10 patients discontinued before receiving 500 mg, therefore they were not included.

In general, the incidence of adverse events was higher in women compared to men.

Postmarketing Experience Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of Niaspan:

Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, flushing, dyspnea, tongue edema, larynx edema, face edema, peripheral edema, laryngismus, and vesiculobullous rash; maculopapular rash; dry skin; tachycardia; palpitations; atrial fibrillation; other cardiac arrhythmias; syncope; hypotension; postural hypotension; blurred vision; macular edema; peptic ulcers; eruption; flatulence; hepatitis; jaundice; decreased glucose tolerance; gout; myalgia; myopathy; dizziness; insomnia; asthenia; nervousness; paresthesia; dyspnea; sweating; burning sensation/skin burning sensation; skin discoloration, and migraine.

Clinical Laboratory Abnormalities **Chemistry:** Elevations in serum transaminases [see Warnings and Precautions], LDH, fasting glucose, uric acid, total bilirubin, amylase and creatine kinase, and reduction in phosphorus.

Hematology: Slight reductions in platelet counts and prolongation in prothrombin time [see Warnings and Precautions].

DRUG INTERACTIONS

Statins Caution should be used when prescribing niacin (≥ 1 gm/day) with statins as these drugs can increase risk of myopathy/rhabdomyolysis. Combination therapy with Niaspan and lovastatin or Niaspan and simvastatin should not exceed doses of 2000 mg Niaspan and 40 mg lovastatin or simvastatin daily. [see Warnings and Precautions].

Bile Acid Sequestrants An *in vitro* study results suggest that the bile acid-binding resins have high niacin binding capacity. Therefore, 4 to 6 hours, or as great an interval as possible, should elapse between the ingestion of bile acid-binding resins and the administration of Niaspan.

Aspirin Concomitant aspirin may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear.

Antihypertensive Therapy Niacin may potentiate the effects of ganglionic blocking agents and vasoactive drugs resulting in postural hypotension.

Other Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of Niaspan.

Laboratory Test Interactions Niacin may produce false elevations in some fluorometric determinations of plasma or urinary catecholamines. Niacin may also give false-positive reactions with cupric sulfate solution (Benedict's reagent) in urine glucose tests.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C.

Animal reproduction studies have not been conducted with niacin or with Niaspan. It is also not known whether niacin at doses typically used for lipid disorders can cause fetal harm when administered to pregnant women or whether it can affect reproductive capacity. If a woman receiving niacin for primary hyperlipidemia becomes pregnant, the drug should be discontinued. If a woman being treated with niacin for hypertriglyceridemia conceives, the benefits and risks of continued therapy should be assessed on an individual basis.

All statins are contraindicated in pregnant and nursing women. When Niaspan is administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin.

Nursing Mothers Niacin is excreted into human milk but the actual infant dose or infant dose as a percent of the maternal dose is not known. Because of the potential for serious adverse reactions in nursing infants from lipid-altering doses of nicotinic acid, 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. No studies have been conducted with Niaspan in nursing mothers.

Pediatric Use Safety and effectiveness of niacin therapy in pediatric patients (≤ 16 years) have not been established.

PROFESSIONAL BRIEF SUMMARY

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Geriatric Use Of 979 patients in clinical studies of Niaspan, 21% of the patients were age 65 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment No studies have been performed in this population. Niaspan should be used with caution in patients with renal impairment [see Warnings and Precautions].

Hepatic Impairment No studies have been performed in this population. Niaspan should be used with caution in patients with a past history of liver disease and/or who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations and significant or unexplained hepatic dysfunction are contraindications to the use of Niaspan [see Contraindications and Warnings and Precautions].

Gender Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of Niaspan.

OVERDOSAGE

Supportive measures should be undertaken in the event of an overdose.

PATIENT COUNSELING INFORMATION

Patient Counseling Patients should be advised to adhere to their National Cholesterol Education Program (NCEP) recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised to inform their healthcare professionals prescribing a new medication that they are taking Niaspan.

The patient should be informed of the following:

Dosing Time Niaspan tablets should be taken at bedtime, after a low-fat snack. Administration on an empty stomach is not recommended.

Tablet Integrity Niaspan tablets should not be broken, crushed or chewed, but should be swallowed whole.

Dosing Interruption If dosing is interrupted for any length of time, their physician should be contacted prior to restarting therapy; re-titration is recommended.

Muscle Pain Notify their physician if any unexplained muscle pain, tenderness, or weakness promptly. They should discuss all medication, both prescription and over the counter, with their physician.

Flushing Flushing (warmth, redness, itching and/or tingling of the skin) is a common side effect of niacin therapy that may subside after several weeks of consistent Niaspan use. Flushing may vary in severity and is more likely to occur with initiation of therapy, or during dose increases. By dosing at bedtime, flushing will most likely occur during sleep. However, if awakened by flushing at night, the patient should get up slowly, especially if feeling dizzy, feeling faint, or taking blood pressure medications. Advise patients of the symptoms of flushing and how they differ from the symptoms of a myocardial infarction.

Use of Aspirin Medication Taking aspirin (up to the recommended dose of 325 mg) approximately 30 minutes before dosing can minimize flushing.

Diet Avoid ingestion of alcohol, hot beverages and spicy foods around the time of taking Niaspan to minimize flushing.

Supplements Notify their physician if they are taking vitamins or other nutritional supplements containing niacin or nicotinamide.

Dizziness Notify their physician if symptoms of dizziness occur.

Diabetics If diabetic, to notify their physician of changes in blood glucose.

Pregnancy Discuss future pregnancy plans with your patients, and discuss when to stop Niaspan if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking Niaspan and call their healthcare professional.

Breastfeeding Women who are breastfeeding should be advised to not use Niaspan. Patients, who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

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coronary intervention for stent placement. Secondary end points were each of those events separately, as well as ARC (Academic Research Consortium)-definite stent thrombosis.

Both groups had comparable characteristics at baseline. Their mean age was about 71.5 years, and the age of their stents averaged 13.5 years; about 15% were female, about 72% had hypertension, about 36% had diabetes, about 7% were current smokers, about 87% had hyperlipidemia, and about 55% had a previous MI. Also, disease characteristics were similar between the two groups.

About 50% of patients had diffuse disease. More than 60% had unstable angina, and 99% had multivessel disease. Lesions were evenly distributed in the saphenous vein graft. The degeneration score for saphenous vein grafts and the distribution of lesions within the graft were similar between groups, with about 40% of patients having moderate or severely degenerative grafts.

At 1 year, the primary end point was reduced by a significant 35% with DES, compared with BMS, with rates of 15.4% and 22.1%, respectively. The reduction in the DES group was driven pri-

marily by a significant 52% reduction in target vessel revascularizations, which occurred in 7.2% of the DES patients, compared with 13.1% of the BMS recipients.

Both types of stent were comparable in safety, with a similar rate of stent thrombosis, death, or myocardial infarction, said Dr. Mehilli. The rates of all-cause death or MI were similar between the two groups, at 8.5% and 10.9% of patients in the DES and BMS groups, respectively. One patient and zero patients, respectively, experienced ARC-definite stent thrombosis.

“Although saphenous vein graft lesions remain a challenging disease subset for angioplasty, this study demonstrates that DES can be safely used to reduce adverse events in this high-risk subset of patients,” Dr. Mehilli said.

She noted that, in Germany, the overwhelming majority of stents used in saphenous vein graft lesions are DES, and that the current study supports this practice.

The study was funded by the German Heart Center in Munich and by Cordis. Dr. Mehilli has received lecture fees from Abbott. ■

Keep Antiplatelet Interruptions as Brief as Possible

EXPERT ANALYSIS FROM THE ANNUAL ACADEMIC SURGICAL CONGRESS

HUNTINGTON BEACH, CALIF. – Patients with recently placed coronary stents who are on clopidogrel may need to discontinue the drug to prevent excessive bleeding during surgery, but it should be restarted as soon as possible, according to Dr. Alan Dardik.

Continuing antiplatelet therapy during the perioperative period is crucial, he noted, because “the risk of surgical bleeding, if dual-antiplatelet therapy is continued, is actually lower than the risk of coronary thrombosis due to agent withdrawal.”

Antiplatelet drugs pose a considerable bleeding risk: Aspirin can increase surgical blood loss up to 20%, and dual therapy up to 50%. According to Dr. Dardik, however, although “many studies show a small increase in complications from this bleeding, particularly increased transfusions, no study has actually shown an increase in mortality.”

Meanwhile, the risk of a fatal myocardial infarction is high when antiplatelet therapy is withdrawn, especially within 6 weeks of stent placement. The risk is especially high in patients with cancer, diabetes, and other hypercoagulable states, and in those with long, multiple, or overlapping stents, Dr. Dardik said.

“Keep the nontherapeutic window short, from about 3 days before the surgery to 1-2 days afterward, [and] re-load [patients] at high risk for thrombosis with 300 mg of clopidogrel,” Dr. Dardik said at the meeting.

Since dual-antiplatelet therapy is standard for 6 months following stent placement, patients on clopidogrel (Plavix) will almost certainly also be on aspirin. To offset the temporary loss of clopidogrel, he recommended increasing the aspirin dose, said Dr. Dardik, a vascular surgeon at Yale University, New Haven, Conn.

The best option for recently stented patients is to postpone surgery for at least 6 months – the point at which dual-antiplatelet therapy can be stopped – or even a year, when aspirin can also cease. When that’s not possible, Dr. Dardik recommends performing a less invasive procedure, with easier hemostasis.

He said he has no relevant disclosures.

–M. Alexander Otto

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