

Subintimal Angioplasty Highly Efficacious in Legs

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BALTIMORE — Subintimal angioplasty is effective for revascularizing chronic, total occlusions in legs, based on experience with more than 600 procedures in more than 500 patients at one center.

Subintimal angioplasty "is successful in most patients regardless of where the occlusion is located, it produces acceptable secondary patency after 3 years, and it pro-

vides excellent limb salvage and relief of claudication," Dr. Eric C. Scott said at the Vascular Annual Meeting.

"Subintimal angioplasty is an appropriate first-line therapy that obviates the need for bypass in most patients," said Dr. Scott, a vascular surgeon at Eastern Virginia Medical School, Norfolk. It's a particularly attractive option in patients for whom bypass is a problem, such as those with multiple comorbidities and patients who lack a good vein for bypass.

From December 2002 to July 2006, subintimal angioplasty was used to treat 639 lower extremity occlusions in 591 patients at the school. The median age of the patients was 69 (range 35-99 years old), and the average follow-up was slightly more than 1 year. About half the patients had coronary artery disease, about half had diabetes, and 14% had end-stage renal disease. About two-thirds of the patients had critical limb ischemia, and the remaining third had claudication.

The 639 affected limbs had 1,006 occlusions, with 515 in the superficial femoral artery, 314 in the popliteal artery, 124 in the tibial artery, and 53 in the iliac artery. Technical success of subintimal angioplasty was achieved in 80%-87% of patients, varying slightly depending on the location of the occlusions.

Only a very small percent of patients were treated using a reentry device. Stents were placed only when angioplasty produced suboptimal results; about 20% of the patients in the series received stents, with an average of 1.6 stents per patient receiving stents. Following angioplasty, patients received clopidogrel (Plavix) for 1 month, and they also started aspirin treatment, which continued indefinitely.

Occlusions of the superficial femoral artery were treated in 79% of the patients in the series. For simplicity, Dr. Scott focused the remainder of his review on this subgroup. The overall complication rate (in the subgroup) was 6%; three patients required an operative intervention because of a complication. The 30-day mortality rate was 1%. Before the intervention, the average ankle-brachial index in the subgroup was 0.5. After subintimal angioplasty, the average index was 0.78.

Primary patency was 45% after 1 year and 25% after 3 years of follow-up. In a multivariate analysis, two factors were significantly linked with an increased risk of poor primary patency: tibial artery reentry, which increased the risk of failed primary patency by 57%, and critical limb ischemia, which made failed primary patency 39% more likely.

Secondary patency rates were much higher: 76% after 1 year and 50% after 3 years. A second procedure to improve blood flow to the original extremity was required in 28% of patients in the subgroup.

The limb salvage rate in the patients in the subgroup who began with critical limb ischemia was 87% after 1 year and 75% after 3 years, Dr. Scott said. In the patients with disabling claudication, 90% had improvement after 1 year, and 67% were still improved after 3 years.

The survival rate after 3 years was 43% in the patients with critical limb ischemia, and 81% in the claudicants. Bypass surgery was avoided in 89% of the patients during the first year after angioplasty, and 77% continued to avoid bypass by 3 years after their procedure.

"The critical limb ischemia patients are quite sick, and they are probably best served by a low impact, minimally invasive procedure such as subintimal angioplasty," Dr. Scott said. Given the high technical success rate that he and his associates have had with subintimal angioplasty, they have not used a transluminal approach for most patients.

"In our experience with subintimal angioplasty, we have survival rates, limb salvage rates, reintervention rates, and secondary patency rates that are very similar" to the Eastern Virginia Medical School data, commented Dr. Richard P. Cambria, chief of vascular and endovascular surgery at Massachusetts General Hospital in Boston. "We agree that the survival rates argue for using the subintimal angioplasty approach over bypass."

LOVAZA™ (omega-3-acid ethyl esters) Capsules

Brief Summary of Prescribing Information

CLINICAL STUDIES

High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

Table 1: Response to the Addition of LOVAZA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

Parameter	LOVAZA + Simvastatin N=122			Placebo + Simvastatin N=132			Difference	P-Value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non-HDL-C	137	123	-9.0	141	134	-2.2	-6.8	<0.0001
TG	268	182	-29.5	271	260	-6.3	-23.2	<0.0001
TC	184	172	-4.8	184	178	-1.7	-3.1	<0.05
VLDL-C	52	37	-27.5	52	49	-7.2	-20.3	<0.05
Apo-B	86	80	-4.2	87	85	-1.9	-2.3	<0.05
HDL-C	46	48	+3.4	43	44	-1.2	+4.6	<0.05
LDL-C	91	88	+0.7	88	85	-2.8	+3.5	=0.05

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL); Median % Change = Median Percent Change from Baseline; Difference = LOVAZA Median % Change - Placebo Median % Change

Lovaza 4 g per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

Very High Triglycerides: Monotherapy

The effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

The changes in the major lipoprotein lipid parameters for the Lovaza and placebo groups are shown in Table 2.

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL)

Parameter	LOVAZA N=42		Placebo N=42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline; Difference = Lovaza Median % change - Placebo Median % Change

Lovaza 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Lovaza on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been determined.

INDICATIONS AND USAGE

Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels.

Usage Considerations:

In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General:

Initial Therapy: Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy: Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests:

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.

In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy.

Drug Interactions:

Anticoagulants: Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with both Lovaza and anticoagulants should be monitored periodically.

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

LOVAZA™ (omega-3-acid ethyl esters) Capsules

Cytochrome P450-Dependent Monooxygenase Activities: Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Lovaza can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Lovaza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison. In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers:

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza is administered to a woman who is breastfeeding.

Pediatric Use:

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use:

A limited number of patients over 65 years of age were enrolled in the clinical studies. Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Lovaza 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 3. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza and 2.6% of patients treated with placebo.

Table 3: Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day

BODY SYSTEM Adverse Event	LOVAZA (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Erectation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

*Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: Enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death.
CARDIOVASCULAR SYSTEM: Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.
DIGESTIVE SYSTEM: Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.
HEMATOLOGIC-LYMPHATIC SYSTEM: Lymphadenopathy.
INFECTIONS AND INFESTATIONS: Viral infection.
METABOLIC AND NUTRITIONAL DISORDERS: Edema, hyperglycemia, increased ALT, and increased AST.
MUSCULOSKELETAL SYSTEM: Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.
NERVOUS SYSTEM: Central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.
RESPIRATORY SYSTEM: Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.
SKIN: Alopecia, eczema, pruritus, and sweating.
SPECIAL SENSES: Cataract.
UROGENITAL SYSTEM: Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Lovaza does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

Rx only

Revised: June 2007

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