# Eccentric Training Rivals Achilles Tendon Brace

### BY TIMOTHY F. KIRN Sacramento Bureau

pneumatic brace was as effective as eccentric training in resolving chronic Achilles tendon pain in a study that randomized 100 patients.

The investigators hypothesized that the brace, a device known as the AirHeel, probably does work to help resolve tendinopathy, and that perhaps combining the AirHeel brace with eccentric training-one of the more common treatments for chronic Achilles tendon paincould yield a synergistic effect.

Instead, they found that both the brace and the training were only moderately beneficial and that the combination was a only a little better than either the brace or training alone (Am. J. Sports Med. 2007;35:1659-67).

The investigators randomized 37 patients to eccentric, calf-muscle training, 35 patients to the brace, and 28 patients to both. Some patients had pain in both Achilles tendons.

Patients who were randomized to use the brace wore it for 12 weeks.

The AirHeel brace has two interconnected air bladders. One fits under the heel and the other just above the calcaneus. As a person walks in the brace, pressure alternates between the two bladders, applying pulsating compression to reduce swelling and discomfort, and massaging the areas to enhance circulation.

The massaging may help to move away metabolites, such as glutamate or lactate, or it may help break down adhesions between the tendon, the paratenon, and the surrounding tissue. But, the mechanism has never been studied, Dr. Wolf Petersen of the department of orthopedics at the University of Muenster (Germany) and his associates said.

Likewise, several mechanisms have been suggested for the effect of eccentric training. It may enhance collagen fibril alignment, or it may rid the aggravated area of neovascularization. Nevertheless, several studies have demonstrated that eccentric exercises improve pain and function, the authors noted.

Patients randomized to exercise were told to stand on the forefoot of the injured leg, with the ankle in plantar flexion, on a step or other elevation, and then lower down slowly. They were to exercise three times daily for 12 weeks, performing three sets of 15 repetitions, with the knee straight and the knee bent.

The patients in the brace-only treatment group were instructed not to perform strengthening exercises on their own.

The patient groups were all similar in age (a mean of 42 years), body mass index (a mean of about 25 kg/m<sup>2</sup>), and duration of symptoms (a mean of 7 months). A total of 92 of the 100 patients were active in sports, and 60 were men.

A total of 87 of the patients previously had been advised to rest the affected leg, and most had received other treatments as well, generally nonsteroidal anti-inflammatory drugs.

Of the 100 patients enrolled, 86 patients completed the active, treatment phase of the study, and 72 patients completed the 1-year follow-up. Patients dropped out of study for a variety of reasons, includpatients who found training painful patients who found the brace too unfortable. One patient in the brace ip and one patient in the training ip had surgery after completing their assigned treatment.

At 54 weeks, 90% of the remaining patients reported returning to their preinjury sports activity level.

Pain during daily activities, as measured by the visual analogue scale, was reduced from pretreatment by 20% in the eccentrictraining group at 6 weeks, by 41% in the brace-only group, and by 22% in the combination group. But, by week 12, there was no further reduction in pain in the AirHeel group, while the eccentric-training group had further improvement, to a 60% reduction, and the combination group had further improvement, to a 56% reduction.

At the 1-year follow-up, pain still was reduced by 30% in the eccentric-training group, 27% in the brace-only group, and 53% in the combination group.

Pain during sports at 1 year was reduced 51% in the training group, 47% in the brace-only group, and 74% in the combination group.

The braces were supplied for the study by the company (Aircast, Vista, Calif.). Dr. Petersen and his associates disclosed receiving funds for research from Aircast Europe. 

Pages 40a—40ft⟩

### **LOVAZA**<sup>™</sup>

### (omega-3-acid ethyl esters) Capsules

### Brief Summary of Prescribing Information

Brief Summary of Prescribing Information CLINICAL STUDIES Thigh Trigtycerides: 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-bind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high trigtycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with persistent high trigtycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with persistent with simvastatin on gre drag 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, patients were randomized to either Lovaza 4 g ber day or placebo for an additional 8 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 sim-rastatin groups are shown in Table 1.

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

	LOVAZA + Simvastatin		Placebo + Simvastatin					
Parameter	N=122		N=132			Difference	P-Value	
	BL	EOT	Median	BL	EOT	Median		
			% Change			% 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
Аро-В	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 4 g per day significantly reduced on-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

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 whoss baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 week 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 Par Very High TG Levels (≥500 mg/dL) neters in Patients with

Parameter		/AZA = 42	Plac N=	Difference		
	BL	% Change	BL	% Change	1	
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						

The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been evaluated.

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.

mg/dL) triglyceride levels. Usage Considerations: In indivduals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important con-tributing 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 Iherapy, thiazide diuretics, and beta blockers are sometimes associ-ated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if med-ically 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 PRECAU-TIONS).

CONTRAINDICATIONS Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medicat 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 appropri-ate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes melli-tus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacer-bate 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.

months of treaument. 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.

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 dur-ing 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 triatment.

HMG-CoA reductase inhibitors: In a 14-day study of 24 healthy adult subjects, daily co-administration of simvas tatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C<sub>max</sub>) of exposure to simvastatin or the majo active metabolitic heta-hydroxy simvastatin at teach verter.

## Carcinogenesis, Mutagenesis, Impairment of Fertilitis: In a rat carcinogenicity study with oral gavage doese of 100, 600, 2000 mg/kg/day by oral gavage, males were treat-ed 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 does of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice. Omena-3-acid ethyl esters were not mutagenic or clas openic with or without metabolic activation in the bacteria mutagenesis (Ames) test with Salmonella lyphimurium and Escherichia coli or in the chromosomal aberration assay in Chinese hamster 179 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo*

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Induse inicidinuceus 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).

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.

**LOVAZA**<sup>™</sup>

g/day based unit a budy surface and 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 con-tinuing 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 a body surface area comparison). In neronant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no systemic exposure following doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no

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

ADVERSE REACTIONS Treatment-emergent adverse events during 8 randomized, placebo-contr events led to discontinuation of treat

Table 3: Adverse Events in Rando

High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day						
BODY SYSTEM		AZA 226)	Placebo* (N = 228)			
Adverse Event	n	%	n	%		
Subjects with at least 1 adverse event	80	35.4	63	27.6		
Body as a whole Back pain Flu syndrome Infection Pain	5 8 10 4	2.2 3.5 4.4 1.8	3 3 5 3	1.3 1.3 2.2 1.3		
Cardiovascular Angina pectoris	3	1.3	2	0.9		
Digestive Dyspepsia Eructation	7 11	3.1 4.9	65	2.6 2.2		
Skin Rash	4	1.8	1	0.4		
Special senses	6	27	0	0.0		

Revised: June 2007

Distributed by: Reliant Pharmaceuticals, Inc. Liberty Corner, NJ 07938

RESTINGTION FOR THE ASSUME UNDERING INFORMATION AND ADDRESS CONTROL FOR THE ADDRESS CONTROL FOR THE ADDRESS CONTROL 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

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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).

uouy suriace area comparison). In pregnant rats 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)

comparison). In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no find-ings 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 tox-icitly 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.

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.

s reported in at least 1% of patients treated with Lovaza 4 g per day or placebo rolled, double-blind, parallel-group studies for HTG are listed in Table 3. Adverse timent in 3.5% of patients treated with Lovaza and 2.6% of patients treated with lomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very Levels (> 500 mg/dL) that Used LOVAZA 4 g per Day						
		LOVAZA (N = 226)		Placebo* (N = 228)		grou
	n	%	n	%		grou
se event	80	35.4	63	27.6		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, fun-gal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death. CARDIOVASCULARS SYSTEM: Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, perpheral vascular disorder, syncope, and tachycardia. DIGESTIVE SYSTEM: Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroinettis, gastroinetsinal disorder, increased appetite, intestinal obstruction. HEMATOLOGIC-LYMPHATIC SYSTEM: Lymphadenopathy. INFECTIONS AND INTRITIONAL DISORDERS: Edema, hyperglycemia, increased ALT, and increased AST. MUSCULOSKELETAL SYSTEM: Arthraigia, arthritis, myalgia, pathological fracture, and tendon disorder. NERVOUS SYSTEM: Marthraigia, arthritis, myalgia, pathological fractures, emotional lability, facial paralysis, insomna, vasodilatation, and vertigo. RESPIRATORY SYSTEM: Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, minitis, and sinusitis.