TABLE I Characteristics of Four Patients Developing Atrioventricular Block During Intravenous Adenosine Infusion (140 μg/kg/min)

Patient	Age (yr)	Sex	Years from HTX	Medication*	SPECT Scintigraphy	Degree of AV Block
1	16	F	2	0	Normal	2
2	36	M	3	Felodipine	Reversible defect	2
3	45	M	8	Nifedipine + furosemide	Normal	3
4	53	M	2	Amlodipine	Normal	3

*All patients received immunosuppressive drugs.
HTX = heart transplantation; SPECT = single-photon emission computed tomography.

adenosine at the AV node may be responsible for the observed differences in inducing block. The actions of dipyridamole may be more complex than merely causing decreased cellular reuptake of adenosine.

Our findings suggest that adenosine stress testing, with or without submaximal exercise, should be used with caution in heart transplant recipients. Dipyridamole can be used as an acceptable alternative.

Pharmacologic stress testing with adenosine in heart transplant recipients implies a high risk of AV block. Dipyridamole is preferable as a coronary vasodilator.

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Effect of *Niacin* Supplementation on Fibrinogen Levels in Patients With Peripheral Vascular Disease

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Elevated fibrinogen levels and lipid abnormalities are established risk factors for peripheral vascular disease.[1–3] The predictive value of fibrinogen and lipid levels for vascular disease suggests that therapeutic lowering of these variables may be useful in slowing or reducing the progression of atherosclerosis. Recently, hypobetalipoproteinemia has been associated with low fibrinogen levels.[4] These observations suggest the possibility that lipid-lowering therapy also may result in modification of fibrinogen levels. Niacin is a highly effective agent for increasing high-density lipoprotein (HDL) cholesterol and decreasing low-density lipoprotein (LDL) cholesterol and triglyceride levels.[5,6] The aim of the present study was to evaluate the effects of niacin, antioxidants, and warfarin on hemostatic function and lipid levels in subjects with peripheral vascular disease enrolled in 1 clinical center of the Arterial Disease Multiple Intervention Trial.

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The study population consisted of 46 subjects ≥30 years old with asymptomatic or symptomatic peripheral vascular disease who had an ankle brachial index <0.85, averaged from 2 screening visits, or documented previous surgery, angioplasty, or amputation because of peripheral arterial disease.[2] Medical history, including symptoms of intermittent claudication, past cardiovascular events, and smoking history, was obtained upon entry. Subjects were excluded if there was a history of unstable angina, congestive heart failure, poorly controlled diabetes, uncontrolled blood pressure, active cancer, or a history within 6 months of myocardial infarction, stroke, or vascular surgery. Subjects with liver disease or alcohol consumption

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TABLE I Effects of Niacin on Fibrinogen, LDL, and HDL

	Fibrinogen (mg/dl)		LDL (mg/dl)		HDL (mg/dl)	
	+ Niacin (n = 18)	− Niacin (n = 17)	+ Niacin (n = 17)	− Niacin (n = 15)	+ Niacin (n = 18)	− Niacin (n = 16)
Baseline	323 ± 56	351 ± 53	141 ± 22	143 ± 19	45 ± 13	39 ± 11
48 wks	304 ± 72	387 ± 97	112 ± 25	135 ± 26	54 ± 21	41 ± 12
Difference	−19 ± 85*	36 ± 87	−29 ± 25†	−8.5 ± 30	10 ± 12†	2 ± 6

Data were analyzed by analysis of variance.
Values are reported as mean ± SD.
*p = 0.04; †p = 0.03.

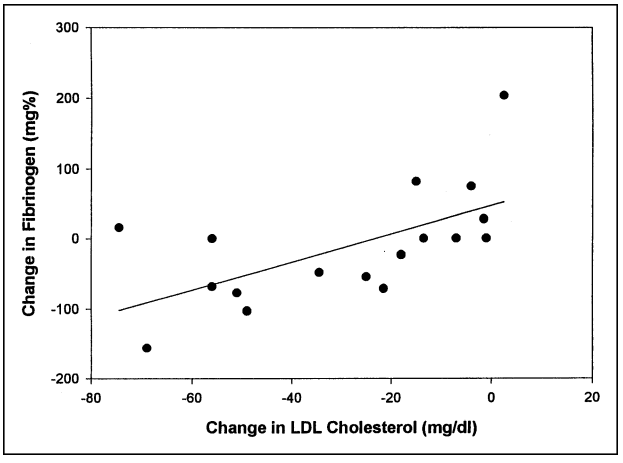

FIGURE 1. Change in LDL (mg/dl) versus change in fibrinogen (mg/dl) in subjects taking niacin (r = 0.61, p <0.009).

TABLE II Fibrinogen (mg/dl) in Subjects Given Warfarin and Antioxidants

	Warfarin		Antioxidants	
	+ Warfarin (n = 17)	− Warfarin (n = 18)	+ Antioxidants (n = 18)	− Antioxidants (n = 17)
Baseline	348 ± 56	325 ± 54	343 ± 56	329 ± 55
48 wks	362 ± 112	327 ± 71	345 ± 112	343 ± 73
Difference	14 ± 104	36 ± 87	2 ± 102	14 ± 75

Data were analyzed by analysis of variance.
Values are expressed as mean ± SD.
None of the differences were statistically significant.

>14 drinks per week or who were taking ticlopidine, lipid-lowering drugs, cyclosporine, or corticosteroids were excluded from study. Subjects with LDL >190 mg/dl, triglycerides >400 mg/dl, alanine aminotransferase (ALT) >1.5 times the upper limit of normal, and/or bilirubin >2.5 mg/dl also were excluded. Subjects intolerant of niacin, warfarin, or antioxidants or with evidence of increasing ALT or prothrombin time during a 12-week test-dosing period were excluded. Informed consent was obtained from all study patients. This study was approved by the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School Institutional Review board.

During a test-dosing period, potential subjects received niacin ranging from 100 to 1,000 mg/day and warfarin 1 to 2 mg/day. Following test dosing, subjects were randomized to receive niacin (1.5 to 3.0 g/day), warfarin (2 to 4 mg/day), antioxidants (vitamins C 1 g/day, E 800 IU/day, and β carotene 24 mg/day), or placebo in a 2 × 2 × 2 factorial design for 48 weeks. Thirty-five subjects were randomized and completed the study.

Blood for hemostatic assays was collected in 0.109-M sodium citrate at baseline before the test-dosing period and at 48 weeks following randomization. Blood for lipid analysis was collected in ethylenediaminetetraacetic acid dipotassium salt. Fibrinogen was assayed by the Clauss method[7] using the same standardized fibrinogen (Organon-Teknika, Durham, North Carolina) preparation for all samples; factor VII coagulant activity was measured with a 1-stage clotting assay; von Willebrand factor antigen was assayed by enzyme immunoassay (Diagnostico Stago, Greenwich, Connecticut); and plasminogen activator inhibitor-1 (PAI-1) activity was determined with a chromogenic assay (American Diagnostica, Greenwich, Connecticut).[2] Because time of draw has been shown to affect PAI-1 levels with higher PAI-1 levels found in the morning,[8] the analysis for PAI-1 was performed on 27 subjects whose samples were drawn at or before 11 A.M. Plasma cholesterol and triglycerides were determined using conventional enzymatic methods. Plasma HDL was measured after heparin-manganese precipitation. LDL was calculated with the Friedewald equation in all cases with triglyceride levels <400 mg/dl.[9] All assays were performed in duplicate.

Data were analyzed using analysis of variance. Bivariate correlations were calculated according to Pearson.

As shown in Table I, subjects taking niacin exhibited significant decreases in fibrinogen and LDL levels and an increase in HDL levels after 48 weeks compared with subjects not taking niacin. In the niacin group, the changes in fibrinogen highly correlated with changes in LDL (r = 0.61; p <0.009) (Figure 1). Niacin, however, had no effect on PAI-1 activity, factor VII coagulant activity, or von Willebrand factor antigen (data not shown). Fibrinogen levels did not change in subjects taking warfarin or antioxidants (Table II). As expected, warfarin decreased factor VII activity (warfarin: 99% vs 75%; placebo: 94% vs 91%; p <0.007).

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Epidemiologic studies have shown fibrinogen to be a major risk factor for peripheral vascular disease.[1–3,10] However, longitudinal studies examining the effects of therapeutic agents on fibrinogen and other hemostatic variables in peripheral vascular disease are limited, and none have been reported using niacin or antioxidants. Our data demonstrate a significant de-

crease in plasma fibrinogen in subjects with lower limb atherosclerosis taking niacin but not in those taking warfarin or antioxidants.

It is well established that niacin induces a significant reduction in LDL and an increase in HDL by inhibiting hepatic synthesis.[5,6] Niacin has also previously been reported to decrease fibrinogen levels in subjects with primary hypercholesterolemia.[11] The present study demonstrates a correlation between changes in LDL and changes in fibrinogen in the group of subjects taking niacin. The mechanism of this association is unknown, but may be related to the hepatic effects of niacin. Thus, niacin may influence hepatic fibrinogen synthesis directly or secondarily via its hypolipedemic effects. Lifestyle interventions including exercise, weight reduction, and smoking cessation have been shown to lower fibrinogen, as have certain medications including ticlopidine and fibrates.[12–16] Our study identified niacin as a potential interventional agent that, in addition to its effects on lipids, resulted in a significant reduction in plasma fibrinogen in subjects with peripheral vascular disease.

In summary, this study demonstrates that niacin supplementation lowers fibrinogen in subjects with peripheral vascular disease.

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Hemodynamic Effects of *Arbutamine*

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Dobutamine, a synthetic intravenous catecholamine, was approved for the treatment of cardiac failure in 1978.[1,2] Arbutamine was designed to simulate the cardiac effects of exercise by increasing both heart rate and contractility, together with systolic blood pressure.[3] In 1997, the Food and Drug Administration approved arbutamine for clinical use as an adjunct to echocardiography and radionuclide myocardial perfusion imaging for detecting coronary artery disease (CAD).[4,5] The inotropic and chronotropic effects of arbutamine have not previously been studied in humans using invasive techniques. This study was therefore designed to examine the effects of arbutamine on central hemodynamics in patients with chest pain syndromes undergoing cardiac catheterization. The relations of hemodynamic changes to myocardial ischemia detected by ST-segment changes and single-photon emission computed tomography (SPECT) imaging with technetium (TC)-99m-sestamibi were also examined.

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The patients included in this study had chest pains suggestive of CAD and were scheduled to undergo cardiac catheterization and coronary angiography. Hemodynamic measurements were obtained before infusion of arbutamine, at a low infusion level, at the peak infusion level, and at 5 and 15 minutes after termination of the infusion (each was obtained using the heart rate hold feature). Low infusion rate was defined as the dose of arbutamine that increased heart rate by

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