Improvement of Lipoprotein Lipid Composition in Type II Diabetic Patients With Concomitant Hyperlipoproteinemia by Acipimox Treatment

Results of a multicenter trial

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OBJECTIVE — To study the tolerability and efficacy of acipimox on hyperlipidemia and diabetes compensation in patients with NIDDM under conditions of a routine clinical practice.

RESEARCH DESIGN AND METHODS — We recruited 121 patients (60 men and 61 women) from 10 participating clinical centers. They were randomly divided into two groups and treated for 3 mo either with acipimox (250 mg three times a day) or placebo, using an open study design.

RESULTS — Acipimox treatment led to a significant drop in fasting serum total triglyceride levels (by 28%) after 1 mo of drug administration. This decrease prevailed up to the end of the 3-mo study. Serum total cholesterol levels declined by 14%, and high-density lipoprotein tended to rise in acipimox-treated patients. These changes in lipid metabolism were not accompanied by any adverse effects of acipimox on glucose metabolism as judged by HbA_{1c} measurements and the oral glucose tolerance test. Eight patients (out of 82 treated with acipimox) reported moderate adverse events of transient character, such as skin reactions and gastric disturbances.

CONCLUSIONS — Acipimox seems to be a useful agent for treatment of diabetic dyslipidemia and does not deteriorate glycemic control.

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NIDDM, non-insulin-dependent diabetes mellitus; VLDL, very-low-density lipoprotein; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACI, acipimox; FFA, free fatty acid; HMG-CoA, 3-hydroxy-3-methylglutaric acid-coenzyme A; CHO, carbohydrate; OGTT, oral glucose tolerance test; RIA, radioimmunoassay; FBG, fasting blood glucose; AUC, area under the curve; BMI, body mass index.

NIDDM is associated with alterations in serum lipoproteins (1,2), and these alterations are of interest because of their important role in the etiology of the increased cardiovascular disease associated with this disorder (3). One of the most consistent findings in NIDDM has been the elevation in the production of VLDL TG (4) accompanied by a clearance defect for them (5). In addition, higher LDL, and lower HDL cholesterol levels have been observed in NIDDM patients (2,6).

Recent guidelines for the treatment of diabetic dyslipidemia suggest a significant number of individuals require therapeutic intervention in addition to dietary measures and good diabetes compensation to achieve satisfactory control of their lipid metabolism (7). Administration of nicotinic acid or its recently introduced analogue—ACI—to nondiabetic individuals produces sustained and significant reductions (30–40%) in serum total and VLDL TG. Although the mechanism involved still is a matter of controversy, the effect is undoubtedly associated with a profound reduction in serum FFA levels, which is thought to diminish hepatic TG synthesis by limiting substrate availability (8).

The cholesterol-lowering action of ACI in serum seems to involve an inhibitory action of the drug on cholesterol synthesis at the level of liver HMG-CoA reductase. However, a large proportion of cholesterol leaving the liver does so in the form of VLDL cholesterol. If this pathway is substantially inhibited after down regulation of VLDL TG production, then the cholesterol that would have been secreted in the large TG-rich lipoprotein accumulates in the hepatocytes and may lead there in reduction of HMG-CoA reductase (9). ACI also suppresses LDL production and increases HDL serum concentration (9). Thus, the actions of ACI in aggregate may offer an overall cardioprotection to the recipient, including an NIDDM patient.

Nicotinic acid, an inhibitor of li-

Table 1—*Basal clinical characteristics of diabetic patients*

	Placebo group		ACI group		
	Mean	SE	Mean	SE	Significance
Age (yr)	55.5	1.47	55.6	0.75	NS
Sex (M/F)	18/24		42/37		
Height (cm)	165.8	1.5	167.7	0.92	NS
Weight (kg)	74.6	2.24	78.5	1.37	NS
BMI (kg/m^2)	26.83	0.56	27.5	0.32	NS

polysis, has been available for use in humans for many years. It has been contraindicated in NIDDM, however, because it was shown to worsen glucose tolerance (10). A closer analysis of similar data showed that nicotinic acid has a short duration of action with a significant rebound in FFA, which matches glucose levels closely. ACI, an analogue of nicotinic acid, has a longer duration of action (9). Thus, the latter should avoid worsening of glucose tolerance in NIDDM patients.

The aim of our study was to reduce the atherogenic risk among NIDDM patients by decreasing the serum lipid levels with ACI therapy over a period of 3 mo in an open, placebo-controlled parallel study. Moreover, we measured parameters of diabetes compensation.

RESEARCH DESIGN AND METHODS

— We treated 121 (60 men and 61 women) NIDDM patients, with known duration of diabetes >6 mo, treated with oral agents (glipizide, Minidiab, Farmitalia Carlo Erba, Milan, Italy). The participants were recruited into the study sequentially from patients' rosters at 10 participating clinical centers. Diabetes was defined according to the criteria of the National Diabetes Data Group (11).

Basal clinical characteristics of the two patient groups are shown in Table 1. Diabetic patients with severe diabetic complications (e.g., proliferative retinopathy, impaired renal function with values >20% above the normal range, painful diabetic neuropathy) were not enrolled in the study. All patients were instructed to eat a weight-maintaining diet consisting of ~45% CHO, 40% fat, and 15% protein, respecting the local dietary habits. All patients had baseline serum parameters of CHO and lipid metabolism measured on two occasions, at wk 0 and 4.

In an open study design (where patients were blinded and investigators not) diabetic patients were randomly allocated (2 to 1) to receive either one (Olbetam, Farmitalia Carlo Erba) 250-mg capsule of ACI three times a day or one placebo capsule three times a day. After starting treatment at wk 4, lipid and CHO parameters were measured at wk 8 and 16 (i.e., after 1 and 3 mo of treatment). Compliance was monitored by capsule count at each visit.

OGTT

Before beginning treatment (wk 0) and after 1 and 3 mo of treatment, all patients received an OGTT. Blood samples were collected for measurement of serum glucose and insulin at 0, 30, 60, 90, and 120 min after ingestion of 75 g glucose.

Assays

Total TG and cholesterol were measured enzymatically with commercially available kits from Boehringer Mannheim (Mannheim, Germany). The HDL cholesterol level was obtained by precipitation (12).

Serum glucose and insulin levels were measured with commercial glucoseoxidase and RIA kits, respectively. HbA_{1c} levels were determined with the aid of a monodisperse cation exchanger (13).

Statistical analysis

We calculated standard descriptive statistics (mean ± SE). Before statistical analyses, homogeneity of variances of compared parameters was tested using Cochran's C and Bartlett-Box tests (14). Parameters that did not pass the test (TG, CHO, HbA_{1c}, HDL cholesterol, FFA, and $AUC_{insulin}$), were log-transformed to obtain homogenous variances. To assess differences between the placebo and active group, we performed a multivariate comparison using the Bonferroni inequality (15) at the overall significance threshold of $\alpha_T = 0.05$. To comply with requirements of the Bonferroni inequality, the threshold of $\alpha = 0.005$ had to be reached for individual univariate tests (14,15).

RESULTS — Of the 82 patients treated with ACI, 8 suffered from minor side effects (skin reactions and gastric disturbances), which were overcome. Those patients remained in the study.

Table 2 compares the ACI and placebo groups, based on selected parameters of serum lipids and diabetes compensation at baseline. No statistically significant differences were found between the two groups in any of the parameters under investigation.

Tables 3 and 4 reflect serum lipid and lipoprotein responses (absolute differences from baseline) to 1- and 3-mo therapy, respectively. When expressed in terms of percentage change from baseline, treatment with ACI for 3 mo produced a 28% fall in serum TG and a 14% fall in total cholesterol (Fig. 1). Moreover, ACI treatment was associated with a tendency to increase serum HDL cholesterol (up to 24%) (Fig. 1). Unfortunately, this increase of HDL cholesterol did not reach the required threshold of $\alpha = 0.005$. No substantial changes in any of the above parameters were ob-

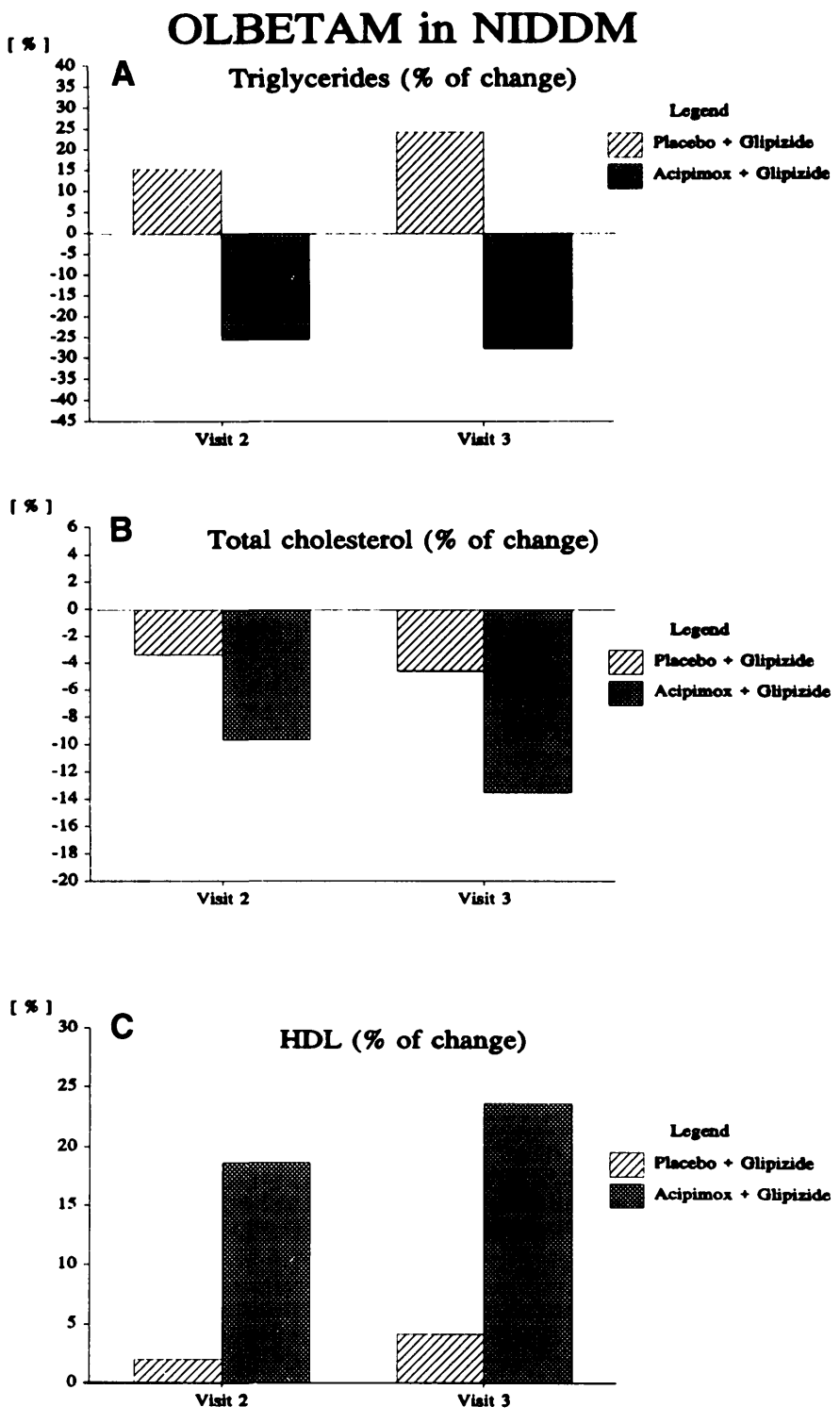

Figure 1—*Percentage of changes from baseline in concentrations of serum TG (A), total cholesterol (B), and HDL cholesterol (C) in NIDDM patients with hyperlipidemia treated for 1* (visit 2) *or 3 mo* (visit 3) *with either ACI or placebo.*

served in the placebo-treated group of patients.

Tables 3 and 4 also summarize the effect of ACI on serum parameters of diabetes compensation and the secretory response of pancreatic β-cells to oral glucose challenge. ACI treatment for 3 mo changed neither the FBG nor fasting insulinemia and HbA_{1c}. No improvements or deteriorations were reached in the AUC of glycemia or insulinemia during OGTT in both treatment groups when compared against basal values.

CONCLUSIONS— We studied the effects of ACI, a new nicotinic acid derivative, on serum lipids and their lipoprotein distribution in hyperlipidemic NIDDM patients. We also evaluated selected parameters of diabetes compensation and insulin secretion in ACI-treated patients. At a dosage of 750 mg/day of ACI, side effects of flushing and nausea were minimal and the drug well tolerated, with good compliance. In our multicenter study, ACI produced a striking improvement, with a 28% fall in serum TG and a 14% fall in total cholesterol. We also noted a tendency toward an increase of HDL cholesterol.

In controlled trials conducted in several countries with a large number of hyperlipidemic patients, ACI caused a statistically significant decrease (25–45%), compared with baseline, in serum TG concentrations (16). On average, it decreased serum cholesterol levels by ~10%. These findings were confirmed by long-term postmarketing surveillance studies that showed similar changes in serum lipid levels during ACI treatment (17–19). Indeed, other research has shown these percentage ranges of serum lipid decrements under ACI treatment as well (9).

In our study, the patients were blinded but the investigators were not. This approach has been adopted by the members of the Central and Eastern Europe Study Group of Metabolic Diseases to which the investigators and authors of this study belong. This Group was con-

Table 2—*Serum lipids and parameters of diabetes compensation of the active and placebo groups at baseline*

	Placebo group		ACI group		
	Mean	SE	Mean	SE	Significance
TG (mM)	2.64	0.173	3.33	0.212	NS
Total cholesterol (mM)	6.65	0.174	7.23	0.150	NS
HDL cholesterol (mM)	1.17	0.063	1.11	0.036	NS
FFA (mM)	0.743	0.087	0.942	0.098	NS
FBG (mM)	7.8	0.47	8.23	0.31	NS
HbA_{1c} (%)	6.89	0.413	6.99	0.195	NS
Fasting insulinemia (μU/ml)	23.58	2.73	24.80	2.06	NS
$AUC_{glucose}$ ($mmol \cdot min^{-1} \cdot L^{-1}$)	1833	105.5	1649	65.3	NS
$AUC_{insulin}$ ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	5888	1042.5	6731	672.0	NS

Overall significance threshold $\alpha_T = 0.05$.

cerned, to a certain degree, about running a double blind trial of a nicotinic acid derivative in diabetic patients: particularly because of the possible negative action of ACI on diabetes compensation.

Moreover, the patients were randomized 2 to 1 (ACI to placebo). Such unequal randomization is recommended if patients are expected to have to be withdrawn from the study because of side effects (20). Nevertheless, both of these precautionary measures were superfluous. Even with the use of conservative statistical methods, we found a significant effect of ACI on serum TG and cholesterol in patients from 10 participating centers, negating concerns about the open nature of the study design.

The TG- and cholesterol-lowering action of ACI were expressed in our study despite unfavorable dietary habits and accessibility of a suitable diet in the given geographical area. Our patients were instructed to eat a certain diet (see METHODS), but the dietary intake was not verified during the study, and local dietary distinctions had to be anticipated and accepted. Nevertheless, patients were reinforced at each hospital visit to watch their body weight throughout the study. Thus, we believe that the above facts act in favor of a good hypolipidemic action of ACI.

Note that although baseline differences between the two groups were not statistically significant, the TG and cholesterol serum levels were somewhat higher in the ACI group. This should be kept in mind when evaluating the finding that, after treatment with ACI, serum cholesterol levels in the active group were not in fact lower than the baseline values in the placebo group.

Besides lowering serum TG and cholesterol concentrations, ACI increases serum HDL cholesterol levels (16–19). In this study with NIDDM patients, we were unable to prove a statistically significant increase in serum HDL cholesterol after 3 mo of treatment with ACI,

Table 3—*Serum lipids and parameters of diabetes compensation (absolute differences from baseline) 1 mo after commencing treatment with ACI or placebo*

	Placebo group		ACI group		
	Mean	SE	Mean	SE	*P* value
TG (mM)	0.10	0.153	−1.06	0.153	<0.001
Total cholesterol (mM)	−0.25	0.136	−0.69	0.107	0.014
HDL cholesterol (mM)	−0.016	0.046	0.13	0.038	0.025
FFA (mM)	0.012	0.063	−0.15	0.101	0.540
FBG (mM)	0.66	0.369	−0.37	0.222	0.02
HbA_{1c} (%)	−0.07	0.327	−0.20	0.149	0.79
Fasting insulinemia (μU/ml)	−3.47	2.48	0.15	2.833	0.340
$AUC_{glucose}$ ($mmol \cdot min^{-1} \cdot l^{-1}$)	−73.01	90.76	17.01	62.228	0.418
$AUC_{insulin}$ ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	−876.2	413.8	−138.3	603.4	0.163

Overall significance threshold $\alpha_T = 0.05$.

Table 4—*Serum lipids and parameters of diabetes compensation (absolute differences from baseline) 3 mo after commencing treatment with ACI or placebo*

	Placebo group		ACI group		
	Mean	SE	Mean	SE	*P* value
TG (mM)	0.30	0.156	−1.23	0.195	<0.001
Total cholesterol (mM)	−0.37	0.155	−1.00	0.096	<0.001
HDL cholesterol (mM)	0.018	0.034	0.193	0.037	0.105
FFA (mM)	0.025	0.044	−0.005	0.09	0.009
FBG (mM)	0.027	0.388	−0.70	0.225	0.11
HbA_{1c} (%)	−0.31	0.26	0.04	0.166	0.774
Fasting insulinemia (μU/ml)	5.37	2.910	1.66	2.087	0.306
$AUC_{glucose}$ ($mmol \cdot min^{-1} \cdot L^{-1}$)	5.78	83.25	−95.24	57.528	0.324
$AUC_{insulin}$ ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	383.6	426.9	−643.8	422.0	0.167

Overall significance threshold $\alpha_T = 0.05$.

although we noted a trend toward an increase in HDL cholesterol. However, a simple univariate comparison of the ACI versus the placebo group yielded a significant difference in serum HDL levels after 3 mo. This was not confirmed with multivariate analysis (14,15). Moreover, a logarithmic transformation of the data had to be performed to obtain homogeneous variances. In addition, the multivariate statistical methods used to assess the differences were rather conservative.

Longer persistence of ACI in serum allows a conventional (three times a day) dose regimen and avoids the major adverse metabolic complications of glucose intolerance (16). This was proven in our multicentric study: during the 3-mo treatment period, all indicators of diabetes compensation (e.g., fasting serum glucose and insulin, HbA_{1c}) remained unaltered. Moreover, prolonged ACI treatment was not associated with any deterioration of the response of pancreatic β-cell to an oral glucose challenge. The significance of this finding is underlined by the fact that during the study period no changes in BMI in both active and placebo groups were observed.

ACI on a three-times-a-day basis cannot give a 24-h suppression of lipolysis (16). In addition, administration of the drug results in periods of suppression interspersed with rebounds in FFA levels. This rebound is particularly relevant in the overnight period (21) and is responsible for an insignificant decrease in fasting serum FFA levels in NIDDM patients treated with ACI for 1 and 3 mo, respectively. On the other hand, in contrast with nicotinic acid, control of diabetes did not worsen.

In summary, ACI improved lipid levels in a multicentric open study of NIDDM patients with secondary hyperlipidemia, causing a fall of TG and total cholesterol, accompanied by a tendency to raise serum HDL cholesterol. For glycemic control, there was no effect toward worsening detected. ACI was well tolerated by the diabetic patients, who in the absolute majority of cases remained free of adverse effects.

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References

1. Goldberg LB: Lipid disorders in diabetes. *Diabetes Care* 4:561–72, 1981
2. Howard BV, Abbott WGH, Beltz WF, Harper IT, Fields RM, Grundy SM, Taskinen MR: Integrated study of low-density lipoprotein metabolism and very-low-density lipoprotein metabolism in non-insulin-dependent diabetes. *Metabolism* 36:870–77, 1987
3. Middeke M, Holzgreve H: Review of major intervention studies in hypertension and hyperlipidemia: focus on coronary heart disease. *Am Heart J* 116:1708–12, 1988
4. Taskinen MR, Beltz WF, Harper IT, Fields RM, Schonfeld G, Grundy SM, Howard BV: Dissociation of the effects of type II diabetes on VLDL triglyceride and VLDL apoB metabolism: studies before and after sulfonylurea therapy. *Diabetes* 35:1268–77, 1986
5. Howard BV, Reitman, JS, Vasquez B, Zech L: Very-low-density lipoprotein triglyceride metabolism in non-insulin-dependent diabetes mellitus. *Diabetes* 32: 271–76, 1983
6. Fuh MMT, Shieh SM: Association of low plasma high-density lipoprotein (HDL) cholesterol concentration with documented coronary artery disease in males with non-insulin-dependent diabetes mellitus. *Horm Metab Res* 19:267–70, 1987

7. Study Group, European Atherosclerosis Society: Strategies for the prevention of coronary heart disease: a policy statement of the European Atherosclerosis Society. *Eur Heart J* 8:77–88, 1987
8. Carlson LA, Oro L: The effect of nicotinic acid on plasma free fatty acids: demonstration of a metabolic type of sympatholytics. *Acta Med Scand* 172:641–45, 1962
9. Shepherd J: The action of nicotinic acid and its analogues on lipoprotein metabolism. In *Atherosclerosis Reviews*. Vol. 22. Gotto AM Jr, Paoletti R, Eds. New York, Raven, 1991, p. 207–12
10. Walldius G, Wahlberg G: Effects of nicotinic acid and its derivatives on lipid metabolism and other metabolic factors related to atherosclerosis. In *Drugs Affecting Lipid Metabolism VIII*. Kritchensky D, Holmes WL, Paoletti R, Eds. New York, Plenum, 1985, p. 281–93
11. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–57, 1979
12. Gidez LI, Miller GJ, Burstein M.: Separation and quantification of subclasses of human high-density lipoproteins by a simple precipitation procedure. *J Lipid Res* 23:1206–23, 1982
13. Jeppson JO, Englund H, Nylund V, Wahlstrom L: Determination of HbA_{1c} using a monodisperse cation exchanger. In *5th European Congress Clinical Chemistry, Budapest, Hungary, 1983* Hungarian Clinical Chemistry Society, p. 289
14. Sachs L: *Applied Statistics*. New York, Springer Verlag, 1982
15. Afifi AA, Azen SP: *Statistical Analysis: A Computer-Oriented Approach*. New York and London, Academic, 1972
16. Buckley BM: Long-term safety profile of acipimox. Pharmacological basis and clinical evidence. In *Atherosclerosis Reviews*. Vol. 22. Gotto AM Jr, Paoletti R, Eds. New York, Raven, 1991, p. 217–24
17. Muggeo M, Lavezzari M, Montoro C: Long-term multicentre trial with acipimox in diabetic patients with hyperlipoproteinemia. In *Atherosclerosis and Cardiovascular Diseases*. Lenzi S, Descovich GC, Eds. Lancaster, U.K., MTP, 1987, p.459–72
18. Lavezzari M, Milanesi E, Oggioni E, Pamparana F: Results of a phase IV study carried out with acipimox in type II diabetic patients with concomitant hyperlipidemia. *J Int Med Res* 17:373–80, 1989
19. Luley C, Krueger KJ, Schumacher M, Reider HP, Kaplan E, Kloer HU: Plasma lipids in 6255 hyperlipidemic patients upon treatment with acipimox (Olbemox) for two years. In *Advances in Lipoprotein and Atherosclerosis Research, Diagnostics and Treatment*. Hanefeld M, Jaross W, Dude H, Eds. Stuttgart and New York, Gustav Fischer Verlag Jena, 1991, p. 113–22
20. Pocock SJ: Unequal randomization. In *Clinical Trials: A Practical Approach*. New York, Wiley, 1989, p. 87–89
21. Alberti KGMM, Fulcher G, Walker M: Metabolic effects of acipimox in non-insulin-dependent diabetes mellitus. In *Atherosclerosis Reviews*. Vol. 22. Gotto AM Jr, Paoletti R, Eds. New York, Raven, 1991, p. 193–96