The Effect of Metformin on the Metabolic Abnormalities Associated With Upper-Body Fat Distribution

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OBJECTIVE — The constellation of anomalies associated with insulin resistance is a plausible additional cause of ischemic cardiovascular disease and of NIDDM. To test this hypothesis in a primary prevention trial, the effects of metformin as a potential candidate for intervention in the insulin resistance syndrome (IRS) were evaluated in 324 middle-aged subjects with upper-body obesity.

RESEARCH DESIGN AND METHODS — Trial patients were selected on the basis of a high waist-to-hip ratio. They were randomly allocated to receive either metformin or placebo, following a double-blind procedure. After 1 year of treatment, the main clinical and biological parameters of the IRS were assessed and their evolution compared between treatment groups.

RESULTS — Compared with placebo, metformin induced a significant weight loss, a better maintenance of fasting blood glucose, total and LDL cholesterol levels, and a greater decrease of fasting plasma insulin concentration. Moreover, tissue-type plasminogen activator antigen, a marker of fibrinolytic impairment, showed a significant decrease under metformin. By contrast, metformin treatment had no significant effect on blood pressure or serum triglyceride and HDL cholesterol concentrations. The main side effect of metformin was diarrhea.

CONCLUSIONS — The BIGuanides and Prevention of Risks in Obesity (BIGPRO1) results suggest that metformin would be a suitable candidate for long-term intervention for the prevention of diabetes but that its use in a trial of primary prevention of cardiovascular diseases requires either a reevaluation of its properties toward the most potentially atherogenic anomalies of the IRS or a better definition of the target population.

Over the past 10 years, there has been increasing evidence of the existence of an additional cardiovascular risk factor (apart from blood pressure, cholesterol levels, and smoking); Reaven (1) gave a first tentative description in 1988 under the name syndrome X (1). This syndrome, also called the insulin resistance syndrome (IRS), includes a constellation of clinical and biological anomalies, clustering in subjects with upper-body fat distribution who often exhibit insulin resistance at the cell level (2–5). Among these anomalies are hyperinsulinemia, glucose intolerance, dyslipidemic profile of high triglyceride and low HDL cholesterol, elevated blood pressure, and impaired fibrinolytic activity (1,6).

Considering that many of the elements of the insulin resistance syndrome have at least a potential for precipitating cardiovascular complications (7–9), it appears relevant to address the question of whether the insulin resistance syndrome is a cause of cardiovascular diseases. This can be achieved through an intervention trial comparing incidence of cardiovascular diseases in two comparable groups of subjects with the insulin resistance syndrome who differ only by the randomized allocation or nonallocation to an "insulin-sensitizing" intervention. This primary intervention trial was the ultimate objective of the BIGuanides and Prevention of the Risks in Obesity (BIGPRO) trial. We report here the results of its preliminary phase (named BIGPRO1), which was used to evaluate the effect of a candidate "insulin sensitizer," metformin (10), on the main anomalies of the IRS in a population characterized by an upper-body fat distribution.

RESEARCH DESIGN AND METHODS

BIGPRO1 was designed as a multicenter (see appendix) randomized double-blind controlled clinical trial of 1 year duration. Nondiabetic subjects, free of cardiovascular diseases, but with a high waist-to-hip circumference ratio—an indicator of upper-body fat distribution—were treated either by metformin or by indistinguishable placebo tablets.

The trial was conducted in accordance with French regulations (11) and the protocol approved by the Ethics Committee of Marseille's Hospitals. All subjects gave written informed consent, specifying the freedom to leave the trial at will, at any time.

Entry criteria

In the absence of a definition for the IRS, the main inclusion criterion was a high waist-to-hip ratio (men: ≥0.95; women: ≥0.80). This was supposed to recruit a study population with insulin resistance

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ECG, electrocardiogram; BIGPRO, BIGuanides and Prevention of the Risks in Obesity; IRS, insulin resistance syndrome; PAI-1, plasminogen activator inhibitor 1; t-PA, tissue-type plasminogen activator.

(2,3). The other entry criterion was age (men: 35–60 years; women: 40–65 years).

The study population had to be free of ischemic cardiovascular disease (whether recognized before inclusion or detected by the electrocardiogram [ECG] required for inclusion) and diabetes (whether diagnosed before inclusion or by the oral glucose tolerance test at inclusion using World Health Organization criteria [12]). Heavy chronic medical treatment, serious life-threatening medical conditions, or psychiatric disorders were additional exclusion criteria. Subjects with impaired renal function (plasma creatinine ≥15 mg/l [130 μmol/l]), the major purveyor of the most serious adverse effect of metformin, lactic acidosis (10,13), were not included.

Treatments

Treatment was either one 850-mg tablet of metformin chlorhydrate or a matching placebo tablet, taken twice daily for 1 year. The allocation of treatment was stratified by center and by sex.

All patients included were given lifestyle (diet and exercise) advice to reduce insulin resistance (14). The only treatments not authorized during the course of the trial were metformin and lipid-lowering drugs.

Enrollment and follow-up

A clinical examination was scheduled for each patient at entry to the trial and every 3 months for 1 year. The main recorded data were age, sex, smoking habits, menopausal status for women, weight, height, waist and hip circumferences, blood pressure, clinical cardiovascular condition, diagnosis of diabetes, and medical treatments in use. An ECG was performed at entry and at 1 year after entry.

Fasting blood samples were collected at entry and at 6 months and 1 year after entry for centralized measurements of lipoprotein fractions and particles, plasma glucose and insulin levels, and fibrinolysis parameters. At entry and 1 year after entry, a 75-g oral glucose tolerance test was scheduled for additional measures of 2-h postload glucose and plasma insulin levels. Creatinine levels were checked locally at 6 months after entry for drug safety purposes.

Table 1—*Comparison of entry characteristics of subjects present and absent at 12 months*

Parameter	Present at 12 months	Absent at 12 months
n	324	133
Age (years)	49.5 ± 6.6	48.3 ± 6.7
Men (%)	33	32
With familial history of diabetes (%)	22	24
Smokers (%)	18	23
BMI (kg/m^2)	33.1 (24.2–45.3)	32.5 (22.4–47.1)
Waist-to-hip ratio	0.94 ± 0.08	0.94 ± 0.08
Systolic blood pressure (mmHg)	134 ± 16	132 ± 16
Diastolic blood pressure (mmHg)	81 ± 11	81 ± 10
With antihypertensive treatment (%)	33	15
Fasting blood glucose (mmol/l)	5.3 ± 0.8	5.3 ± 0.8
2-h blood glucose (mmol/l)	6.4 ± 1.7	6.4 ± 1.8
With abnormal glucose tolerance (%)	21	23
Fasting insulin (pmol/l)	96 (42–222)	90 (36–240)
2-h insulin (pmol/l)	396 (126–1,260)	360 (90–1,470)
Total cholesterol (mmol/l)	5.5 ± 1.1	5.4 ± 1.0
LDL cholesterol (mmol/l)	3.5 ± 1.0	3.5 ± 0.9
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.2 ± 0.4
Triglyceride (mmol/l)	1.6 (0.7–3.4)	1.5 (0.7–3.1)
PAI-1 activity (IU/ml)	12 (3–54)	12 (2–57)
PAI-1 antigen (ng/ml)	39 (7–225)	35 (6–201)
t-PA antigen (ng/ml)	9.1 (4.5–18.3)	8.8 (4.1–19.1)

Quantitative variables are expressed as arithmetic means ± SD or geometric mean (95% tolerance limit). For antihypertensive treatment and HDL cholesterol, $P < 0.01$, present vs. absent at last visit.

Biochemical assays

Aliquots of blood samples drawn during the trial were immediately centrifuged and frozen and sent to the central laboratories in Lille (INSERM U325) for glucose, creatinine, and lipid measurements, and in Marseille (Endocrinology and Hematology Departments of La Timone Hospital) for insulin, blood coagulation, and fibrinolysis measurements.

Blood was drawn on fluoride Vacutainer tubes for glucose, EDTA Vacutainer tubes for lipids, and dry Vacutainer tubes for creatinine measurements. Plasma and serum were obtained after a 10-min centrifugation at 3,000*g*. Glucose, creatinine, cholesterol, and triglyceride were measured by enzymatic methods (Boehringer Mannheim, Germany) adapted to an automatic analyzer (Hitachi 717), and HDL cholesterol was measured by cholesterol quantification after precipitation of very-low- and low-density lipoproteins by a mixture of sodium phosphotungstate and magnesium chloride (Boehringer Mannheim, Germany).

Plasma insulin was determined by radioimmunoassay using a commercially available kit (CIS, Bio Industrie Gif-sur-Yvette, France) with a coefficient of variation of 4.8% in the range 2–50 μU/ml. In this assay, the cross-reactivity of proinsulin is 1:4 on a molar basis.

For determination of fibrinolytic parameters, blood was collected on trisodium citrate (0.011 mol/l final concentration) in the presence of platelet inhibitors (Diatube, Diagnostica Stago, Asnières, France) and immediately cooled on ice. Plasminogen activator inhibitor 1 (PAI-1) activity was determined using a commercially available kit (Biopool, Umea, Sweden), according to Ericksson et al. (15). PAI-1 antigen and tissue-type plasminogen activator (t-PA) antigen were evaluated with an enzyme-linked immunosorbent assay with kits from Diagnostica Stago (Asnières, France), according to Declerck et al. (16) for PAI-1 antigen and Holvoet et al. (17) for t-PA antigen.

Endpoints and statistical analysis

Characteristics between groups were compared with *t* tests and χ^2 tests. All the variables described, as pertaining to the IRS, were considered as endpoints. Statistical comparison of treatments was on an intent-to-treat basis of the absolute changes over 1 year for each endpoint. The required sample size was estimated

Table 2—*Reasons for absence at last visit*

Reason	Metformin	Placebo
n	63	70
Side effect of allocated treatment	11 (17.5)	3 (4.3)
Death	1 (1.6)	0
Diabetes	0	2 (2.9)
Other health problem	5 (7.9)	4 (5.7)
Specified personal reason unrelated to trial	4 (6.4)	12 (17.1)
Demotivation	5 (7.9)	9 (12.9)
Unspecified personal reason	16 (25.4)	15 (21.4)
No information	21 (33.3)	25 (35.7)

Data are count (% within treatment group).

for each variable under consideration (two-tailed Student's t test, $\alpha = \beta = 0.05$). The minimum sample size required for fasting insulin levels, blood pressure, and triglyceride was calculated to be 200 per group.

The independence of the changes in related variables induced by metformin was tested by analysis of covariance. All analyses were performed with the SAS package (SAS Institute, Cary, NC) on a Vax computer.

RESULTS— Enrollment of patients started in January 1991 and was stopped 1 year later when 457 subjects had been included. However, there were 133 subjects (28% of the 227 allocated to metformin and 30% of the 230 allocated to placebo) who did not attend the 12-month visit.

Main characteristics of subjects with complete follow-up are indicated in Table 1. To check whether initial comparability of the treatment groups could be affected by the high drop-out rate, characteristics at entry were compared between patients absent at the last visit and the remaining subjects (Table 1). The only differences were that patients remaining in the trial were slightly more dyslipidemic than the dropouts and more often treated for hypertension.

Reasons for absence at 12 months were compared between the two treatment groups (Table 2) and appeared to be similar, whatever the actual treatment received, apart from a slight overrepresentation of side effects in the metformin group and demotivation in the placebo group. Two patients, both of them in the placebo group, left the trial after diabetes was diagnosed.

Trial results

Of the subjects, 324 were available for analysis at 1 year. The main clinical and biological entry characteristics of the 324 patients seen at 12 months (Table 3) were similar in the metformin and placebo groups, except for the proportion of patients with a family history of diabetes in first relatives. The selected population was mostly female, obese, and with mean values for the insulin resistance syndrome parameters in the normal range, except for insulin levels and markers of fibrinolytic activity impairment, which were relatively high.

The 1-year effects of metformin on the clinical and biological variables of the IRS are shown in Table 4. Metformin had a beneficial effect on weight loss ($P < 0.06$), fasting blood glucose ($P < 0.05$), and LDL cholesterol ($P < 0.07$) maintenance and fasting insulin level decrease ($P < 0.06$), compared with placebo. However, no effect was detectable on 2-h glucose and insulin levels, nor on blood pressure, triglyceride, and HDL cholesterol values. The differential evolution of fasting blood glucose between the two treatment groups was found to be of borderline significance ($P < 0.08$) after adjustment for weight loss (12 months minus entry) by analysis of covariance.

Fibrinolytic activity significantly improved in both groups over the course of the trial, with a decrease over 1 year of all three parameters ($P < 0.001$, two-tailed paired t test). Metformin yielded a greater decrease of t-PA antigen com-

Table 3—*Comparison between treatment groups at entry visit for subjects present at 12 months*

Parameter	Metformin	Placebo
n	164	160
Age (year)	49.7 ± 6.3	49.2 ± 6.9
Men (%)	35	32
With familial history of diabetes (%)	19	29
Smokers (%)	21	15
BMI (kg/m^2)	33.3 (24.6–45.1)	33.0 (24.0–45.4)
Waist-to-hip ratio	0.94 ± 0.09	0.94 ± 0.08
Systolic blood pressure (mmHg)	134 ± 16	133 ± 17
Diastolic blood pressure (mmHg)	81 ± 10	82 ± 11
With antihypertensive treatment (%)	34	32
Fasting blood glucose (mmol/l)	5.3 ± 0.8	5.2 ± 0.6
2-h blood glucose (mmol/l)	6.4 ± 1.8	6.4 ± 1.7
With abnormal glucose tolerance (%)	21	22
Fasting insulin (pmol/l)	96 (42–246)	96 (48–198)
2-h insulin (pmol/l)	396 (126–1,242)	396 (126–1,254)
Total cholesterol (mmol/l)	5.7 ± 1.0	5.4 ± 1.1
LDL cholesterol (mmol/l)	3.6 ± 0.8	3.4 ± 1.0
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.1 ± 0.3
Triglyceride (mmol/l)	1.6 (0.7–3.4)	1.6 (0.7–3.5)
PAI-1 activity (IU/ml)	12 (3–56)	12 (3–53)
PAI-1 antigen (ng/ml)	40 (7–225)	39 (7–227)
tPA antigen (ng/ml)	9.2 (4.6–18.3)	8.9 (4.3–18.4)

Quantitative variables are expressed as arithmetic means ± SD or geometric mean (95% tolerance limit). For familial history of diabetes, $P < 0.03$, metformin vs. placebo groups.

Table 4—*Comparison between treatment groups of the change in trial endpoints over 1 year*

Parameter	Metformin	Placebo
n	164	160
Weight (kg)	−2.0 (−3.0 to −1.1)	−0.8 (−1.6 to 0.1)
Waist-to-hip ratio	−0.009 (−0.016 to −0.002)	−0.017 (−0.024 to −0.009)
Systolic blood pressure (mmHg)	−0.88 (−3.63 to 1.88)	−1.88 (−4.56 to 0.79)
Diastolic blood pressure (mmHg)	−0.89 (−2.66 to 0.89)	−1.50 (−3.59 to 0.66)
Fasting blood glucose (mmol/l)	0.2 (0.05 to 0.4)	0.4 (0.3 to 0.6)
2-h blood glucose (mmol/l)	0.5 (0.1 to 0.9)	0.3 (−0.2 to 0.7)
Fasting insulin (pmol/l)	−29 (−37 to −21)	−20 (−25 to −14)
2-h insulin (pmol/l)	−47 (−91 to −4)	−103 (−163 to −43)
Total cholesterol (mmol/l)	0.05 (−0.08 to 0.18)	0.21 (0.08 to 0.33)
LDL cholesterol (mmol/l)	−0.02 (−0.15 to 0.08)	0.10 (0 to 0.21)
HDL cholesterol (mmol/l)	0.05 (−0.02 to 0.10)	0.10 (0.05 to 0.16)
Triglyceride (mmol/l)	0.10 (−0.01 to 0.22)	−0.02 (−0.15 to 0.11)
PAI-1 activity (IU/ml)	−3.6 (−5.7 to −1.5)	−3.5 (−5.4 to −1.5)
PAI-1 antigen (ng/ml)	−18.4 (−26.0 to −10.8)	−15.2 (−23.2 to −7.2)
t-PA antigen (ng/ml)	−1.1 (−1.6 to −0.6)	−0.2 (−0.8 to 0.3)

Data are the mean differences between values at 12 months and entry (95% CI for the mean). Two-tailed *t* test, metformin vs. placebo: for total cholesterol, $P < 0.09$; LDL cholesterol, $P < 0.07$; fasting insulin, $P < 0.06$; fasting blood glucose, $P < 0.05$; and t-PA antigen, $P < 0.02$.

pared with placebo ($P < 0.02$) but had no significant effect on PAI-1 activity and PAI-1 antigen.

Because of the relatively high percentage of drop-outs, an endpoint analysis of the trial was also performed, using for each subject the last known value of his or her clinical or biological parameters during the trial. This analysis yielded results in concordance with those of the 1-year analysis.

During the course of the trial, no patient developed ischemic cardiovascular disease but five were diagnosed with diabetes by local investigators, all in the placebo group. For only one of these patients, the biological test was motivated by a clinical suspicion of diabetes (weight loss and polyuro-polydypsia). The fasting blood glucose concentration of this patient was 14.3 mmol/l. Three diagnoses were biological diagnoses: fasting blood glucose concentrations of 7.5, 8.1, and 8.7 mmol/l with subsequent confirmation by a second fasting blood glucose concentration 7.8 mmol/l for the two latter patients. The fifth diagnosis was made by telephoning a patient who had dropped out of the trial. No biological confirmation could be obtained for this subject. Two of these newly diagnosed diabetic patients left the trial (cf. Table 1). The three diabetic subjects who were present at the last visit were included in the trial analysis at 12 months in their randomly allocated treatment group (i.e., placebo). Two of them had stopped the trial treatment and were subsequently treated by metformin.

Because impaired glucose tolerance subjects may be targeted for preventive interventions for NIDDM or cardiovascular diseases, a subgroup analysis was secondarily performed by glucose tolerance status at entry into the trial (Table 5). The effect of metformin on fasting blood glucose was seen only in subjects with ab-

Table 5—*Comparison between treatment groups of the evolution of blood glucose concentrations over 1 year according to glucose tolerance at entry*

	Metformin	Placebo
Fasting blood glucose (mmol/l)		
Normal glucose tolerance		
n	171	175
Inclusion	5.2 ± 0.7	5.1 ± 0.6
Δ	0.3 (0.2–0.4)	0.3 (0.2–0.5)
Abnormal glucose tolerance		
n	49	47
Inclusion	6.0 ± 0.9	5.6 ± 0.8
Δ	−0.3 (−0.9–0.2)	0.8 (0.1–1.5)
2-h blood glucose (mmol/l)		
Normal glucose tolerance		
Inclusion	5.9 ± 1.1	5.7 ± 1.1
Δ	0.7 (0.3–1.1)	0.4 (0.1–0.8)
Abnormal glucose tolerance		
Inclusion	9.1 ± 1.2	7.5 ± 1.1
Δ	0.05 (−1.1–1.3)	−0.2 (−2.1–1.6)

Normal glucose tolerance: 2-h glucose concentration < 7.8 mmol/l. Abnormal glucose tolerance: 2-h glucose concentration ≥ 7.8 mmol/l. Inclusion: mean blood glucose value at entry ± SD. Δ: mean difference between values at 12 months and entry (95% CI for the mean). For fasting blood glucose, in normal and abnormal glucose tolerance, inclusion and Δ, $P < 0.02$, metformin vs. placebo, two-tailed *t* test.

Table 6—*Notified side effects of trial treatment*

Side effect	Metformin	Placebo
n	92	42
Diarrhea		
Severe	12	5
Moderate	33	5
Nausea/vomiting		
Severe	5	2
Moderate	9	4
Abdominal pain		
Severe	4	4
Moderate	3	7
Association of the above		
Severe	9	1
Moderate	5	2
Constipation	2	0
Cramps	1	1
Headache/fatigue	3	2
Mood shifts	2	1
Cutaneous rash	1	4
Hunger	3	2
Bad taste in mouth	0	2

n values are for 88 subjects in the metformin group and 40 subjects in the placebo group. Patients who suffered several digestive side effects are counted only once, under the type of the most severe episode.

normal glucose tolerance (i.e., 2-h glucose 7.8 mmol/l), with a significant increase in the placebo group ($P < 0.03$) and no significant change in the metformin group. There was no significant difference in 2-h glucose concentration changes between the metformin and placebo groups, whatever the initial glucose tolerance status.

Side effects

Of the 324 subjects present at the last visit, 42 (13%) had stopped the treatment during follow-up. The main reasons were side effects, especially in the metformin group (11 subjects vs. 5 in the placebo group), or the patient's decision (7 in the metformin group, 11 in the placebo group).

Side effects were evaluated on all 457 subjects included, regardless of whether the patients had left the trial or abandoned treatment (Table 6). Except for diarrhea and, to a much lesser degree, nausea and vomiting, all other reported side effects occurred with a similar frequency in both treatment groups.

CONCLUSIONS— In diabetic patients, metformin is considered more of an antihyperglycemic agent than a glucose-lowering agent: its effect on glycemia is not obtained at the expense of increased insulin secretion (10). The BIGPRO1 trial conducted on upper-body obese nondiabetic subjects, assumed to have insulin resistance, indeed supports this. Metformin maintained fasting blood glucose levels (which increased over 1 year in the placebo group) independently of weight loss, at the same time the fasting plasma insulin decreased. The effect on fasting blood glucose concentration was actually restricted to subjects with abnormal glucose tolerance. The natural tendency toward an increase of fasting glucose concentration in these subjects in the placebo group was prevented by metformin. In spite of a mismatch in fasting glucose concentration between the metformin and placebo groups in subjects with abnormal glucose tolerance, the regression to the mean effect is unlikely to have confounded this result because it should have yielded a decrease of fasting blood glucose in the placebo group as well as in the metformin group. It is likely that the observed effects can be attributed to metformin, despite the relatively high drop-out rate. Indeed, the drop-outs did not differ notably from those who remained in the trial. Moreover, the coherence of the BIGPRO1 trial results and other randomized controlled trials of metformin in diabetic (18–20) as well as in nondiabetic (21,22) subjects suggests an action of metformin on glucose metabolism. An improvement of insulin action at the cell level is likely, although up to now, evidence of whether or how metformin alleviates insulin resistance remains contradictory (18,23–25). The observed effect of metformin on both glucose and insulin may be of marginal importance. It may be because the subjects included were mainly obese and normoglycemic, whereas the subgroup analysis suggests that metformin may have a greater role in subjects with abnormal glucose tolerance. This latter result is of potential importance for the prevention of NIDDM.

Apart from the insulin glucose metabolism, another significant effect of metformin was detected for t-PA antigen, the level of which is inversely correlated with overall fibrinolytic activity (26). Metformin induced a greater reduction of t-PA antigen compared with placebo. No effect of metformin was seen for the two other well-known markers of fibrinolytic activity impairment, PAI-1 antigen, and PAI-1 activity. However, it is to be noted that a similar dissociation between t-PA and PAI-1 under metformin treatment has already been found in another trial (27). Besides, PAI-1 concentrations have been shown to decrease in other randomized trials of metformin (21,28), and it is also known that there is a strong positive correlation between markers of fibrinolytic impairment and insulin plasma levels (6), which metformin decreased in the BIGPRO1 trial. If the result is confirmed, it will be of great relevance for the prevention of cardiovascular ischemic complications (29).

An effect of metformin on total and LDL cholesterol has been found before (28,30,31), although not in all studies (19,22,32).

Although the effect of metformin on glucose and insulin is supposedly directed at the root of the vicious cycle that gives rise to the insulin resistance syndrome (1,33), metformin did not significantly modify triglyceride and HDL cholesterol concentrations or blood pressure in the BIGPRO1 trial. The absence of an effect on triglyceride concentrations is difficult to account for, since several other randomized trials have shown a decrease of triglyceride under metformin in diabetic as well as in nondiabetic subjects (19,21,22,32,34). A lack of power in the BIGPRO1 trial is unlikely, in view of the mean changes in lipid values over 1 year. An alternative explanation could be the absence of frank perturbations of triglyceride concentrations in BIGPRO1 subjects.

Overall, the BIGPRO1 trial results suggest that metformin is a suitable candidate for a primary prevention trial of NIDDM given its effects on glucose and plasma insulin levels in subjects "at risk" of getting the disease. The observed side effects, consisting mostly of gastrointestinal discomfort, do not preclude the long-term use of metformin; as in most patients, they reverted spontaneously or after dose reduction.

On the other hand, the absence of observed effect of metformin on the major potentially atherogenic abnormalities of the insulin resistance syndrome, namely high triglyceride, low HDL cholesterol, and elevated blood pressure, makes the implementation of a trial with the objective of testing whether metformin reduces the incidence of cardiovascular diseases hazardous. Considering the fact that the BIGPRO1 trial population was perhaps too "normal" in terms of lipid profile and given the observed effect of metformin on t-PA, further investigation of this drug as a potential candidate to test whether the insulin resistance syndrome is causally related to cardiovascular complications is required.

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APPENDIX

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