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The Diabetes Atherosclerosis Intervention Study (DAIS): a study conducted in cooperation with the World Health Organization

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Summary The incidence of coronary artery disease is greatly increased in those with diabetes mellitus. The largest number of those who have coronary artery disease have non-insulin-dependent diabetes (NIDDM). Lipoprotein abnormalities have been identified among the several risk factors that could account for this increase in atherosclerosis. There have been many studies demonstrating that correction of dyslipoproteinaemias will reduce the risk of coronary disease in non-diabetic populations. Current advice to those with diabetes is based on extrapolations from such studies. However, the justification for this, and the treatment targets are unclear as there has been no direct test of the lipid hypothesis in diabetes. This paper describes the protocol of the first intervention trial designed to examine directly whether correcting dyslipoproteinaemia in men and women with NIDDM will reduce their coronary artery disease. The Diabetes Atherosclerosis Intervention Study (DAIS), is a multinational angiographic study using the 200 mg micronized form of fenofibrate in a double-blind, placebo-controlled protocol. [Diabetologia (1996) 39: 1655–1661]

Keywords Diabetes mellitus, atherosclerosis, intervention trial, fenofibrate, lipoprotein, coronary angiography.

The frequency of coronary artery disease is greatly increased in diabetic patients [1–4]. This is true of both insulin-dependent diabetes mellitus [IDDM] and non-insulin-dependent diabetes [NIDDM] [4]. However, the burden of coronary artery disease is much greater in NIDDM. This is at least partly because the prevalence of NIDDM is greater than that of IDDM and because the average age of the NIDDM population is older than that of the IDDM population. The risk of coronary artery disease in diabetes increases as either plasma cholesterol levels or plasma triglyceride levels increase [2, 5]. There is debate about whether the risk effect of hypertriglyceridaemia is, or is not dependent on associated low levels of HDL-cholesterol [6]. The gender difference in coronary artery disease incidence is reduced in diabetic populations [3, 4, 7].

There have been many studies demonstrating, mainly in middle-aged men, that reducing elevated levels of plasma cholesterol decreases the risk of both clinical and angiographic coronary artery disease. Cholesterol reduction has now also been shown to reduce total mortality [8]. The Helsinki Heart Study [9] also showed that coronary artery disease risk could be reduced by increasing the level of HDL-cholesterol with a fibric acid derivative, gemfibrozil. In that study, almost all of the beneficial effect was seen in the population that had both a low level of HDL-cholesterol and a high level of plasma triglycerides [10]. Thus, its data does not allow the effects of correcting abnormalities in the plasma levels

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Abbreviations: DAIS, Diabetes Atherosclerosis Intervention Study; MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; NIDDM, Non-insulin-dependent-diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; MRFIT, Multiple Risk Factor Intervention Trial.

of HDL-cholesterol or of triglyceride to be separated. A subgroup analysis of the few subjects with diabetes in the Helsinki Heart Study was consistent with a beneficial effect of reducing triglyceride and increasing HDL-cholesterol levels in the plasma, but it was not statistically significant [11]. A second post-hoc subgroup analysis has recently been reported, on those in the 4S Study who had diabetes and serum cholesterol levels between 5.5 and 8.0 mmol/l [12]. It suggested that secondary intervention with simvastatin (i.e. treatment of those who had prior coronary disease) would be beneficial in terms of coronary disease. However, in addition to the criteria of post-hoc subgroup analyses, its applicability to diabetes in general is limited by the exclusion of individuals with triglyceride concentrations exceeding 2.5 mmol/l [8]. Most NIDDM subjects who are hyperlipidaemic have triglyceride concentrations in excess of this [13]. No studies have been reported to date that are specifically designed to examine the impact of correcting dyslipoproteinaemias in those with diabetes. Hence, present advice to diabetic patients is based on extrapolation.

While extrapolating from studies in non-diabetic subjects may seem reasonable to some, others could argue against it. For example, the Multiple Risk Factor Intervention Trial [MRFIT] [2] found that the coronary artery disease risk in diabetic subjects at any given plasma cholesterol level was approximately four times greater than in non-diabetic subjects. This would imply that other factors far exceed plasma cholesterol as a risk factor for coronary artery disease in diabetes. Hence, some might argue that even if correcting a dyslipoproteinaemia were to be beneficial in diabetes, its impact on the overall risk of coronary artery disease might be relatively minor. Others argue that it might be particularly important to correct any dyslipoproteinaemia in diabetes just because of the greatly increased risk of coronary disease in that population. Even if such an argument were true, there is no concrete information from which one could suggest target lipid values for the diabetic population.

Against this background, and at the request of the World Health Organization, a group drawn from medical faculties in a number of countries developed a protocol to test the effect of treating dyslipoproteinaemia on the course of angiographically evaluated coronary artery disease in a population of men and women with NIDDM. The dyslipoproteinaemia would be treated using a drug in a double-blind randomized, placebo controlled trial. The protocol planning group chose to use the micronized form of fenofibrate because it not only reduces plasma triglyceride and increases plasma HDL-cholesterol levels, but because it also reduces plasma cholesterol [14]. This allowed the drug to be used to examine the spectrum of dyslipoproteinaemias that can be found in diabetes.

The primary objective of the Diabetes Atherosclerosis Intervention Study (DAIS) is to determine by quantitative angiography, whether long-term correction of the dyslipoproteinaemia of diabetes with fenofibrate results in evidence of decreased progression or regression of pre-existing coronary atherosclerosis. In an angiographic study that seeks to examine regression as well as progression, the participants should have some evidence of coronary lesions. Thus, this may be considered by some to be secondary intervention. However, many have such lesions without any past clinical events or symptoms. This is particularly so in diabetes, a condition in which asymptomatic coronary disease frequently occurs [15]. Studies of such individuals in purely clinical event trials would be considered as primary intervention studies. Because of the vagueness of definition of primary compared to secondary intervention the study group decided to include a secondary objective, namely to determine the responses in patients who have undergone previous coronary intervention (either coronary artery bypass grafting [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) and those without such intervention. Another secondary objective of DAIS is to evaluate the long-term safety and tolerability of fenofibrate in NIDDM.

Subjects and methods

Eligibility criteria (Table 1). The study population consists of both men and women with NIDDM and is between the ages of 40 and 65 years at entry. The subjects have moderate dyslipoproteinaemia, and glycaemia which is at least moderately controlled; previous coronary intervention may have been performed, and a quantitative angiogram would have been conducted according to a specific study protocol within the 6 months prior to randomization. The subjects have demonstrated an ability to adhere to both diet and drug regimens and have given their voluntary informed consent.

The decision to conduct the study in subjects in this age range with NIDDM is because coronary disease is greatest in this population. The observation that in diabetes the gender difference in the incidence of coronary artery disease is greatly reduced [3, 4, 7] allows DAIS to examine both men and women. The criteria for glycaemic control are based on those found in community medical practices. Furthermore, this study is not a test of the impact of glycaemic control. In fact, glycaemic control and management should be the same in both the active and the placebo groups. Finally, individuals with moderate and not severe dyslipoproteinaemias are being studied because these are the most frequently observed lipoprotein abnormalities and because one of the groups will be treated with diet and placebo for the duration of DAIS.

Exclusion criteria (Table 2). An individual is excluded if he or she fails to meet the inclusion criteria, has had a major coronary event within the 6 months prior to randomization, has other major medical problems that could influence the risk of coronary disease or life prognosis, has a significant likelihood of becoming intolerant to the drug, consumes excessive alcohol, has inadequately treated hypothyroidism, or is pregnant.

Table 1. Eligibility criteria

Age	40–65 years
Gender	Male and female
Non-insulin-dependent diabetes	
Definition	Fasting hyperglycaemia: venous plasma glucose $\geq$ 7.8 mmol/l or venous whole blood > 6.7 mmol/l or Oral glucose tolerance test [75 g]: 2 h glucose: venous plasma $\geq$ 11.1 mmol/l or venous whole blood $\geq$ 10.1 mmol/l or treatment for previously diagnosed diabetes *plus* Age of onset $\geq$ 35 years; no history of ketoacidosis
Control	Haemoglobin $A_{1c} \leq$ 170 % of upper normal limit
Dyslipoproteinaemia (mean of last two baseline values while on study diet)	
LDL-Cholesterol	3.5–4.5 mmol/l and triglyceride $\leq$ 5.2 mmol/l or
Triglyceride	1.7–5.2 mmol/l and LDL-cholesterol $\leq$ 4.5 mmol/l *plus*
Total-/HDL-cholesterol $\geq$ 4	
Voluntary informed consent	

Table 2. Exclusion criteria

Major coronary event
(Infarct, CABG, or PTCA) in the 6 months prior to randomization [entry into baseline study cannot occur for 4 months after an infarct or CABG or 3 months after PTCA]

Angiogram
No adequate quantitative angiogram conducted according to protocol within the 6 months prior to randomization

Congestive heart failure
Ejection fraction < 30 % or active treatment (defined as an increase or change in drug within the preceding 90 days) for congestive heart failure

Surgical intervention
Individuals expected to require surgical intervention [PTCA or CABG] within 6 months

Lipid lowering medication
Individuals who received a lipid lowering medication within the prior 4 weeks (or 1 year in the case of probucol)

Body mass index
< 18 kg/m^2 or $\geq$ 35 kg/m^2

Renal disease
Proteinuria $\geq$ 500 mg/24 h or albuminuria $\geq$ 200 μg/min and/or creatinine for men $\geq$ 150 μmol/l or for women $\geq$ 140 μmol/l

Other illnesses or medical conditions
Pregnancy; known liver disease (including transaminase > 2 × upper limits of normal); excess alcohol (> 14 drinks per week); symptomatic cholelithiasis without cholecystectomy; malignancy that would limit prognosis for life; uncontrollable hypertension; inadequately treated hypothyroidism; immunosuppressive therapy; corticosteroid therapy (except topical or inhaled); lactose intolerance; other life limiting conditions

Failure to meet inclusion criteria

Failure to adhere during baseline period

Baseline period. DAIS is divided into two stages, a 2-month baseline period followed by randomization and the treatment period. The purpose of the baseline period is to ensure that each participant fulfils the study entry criteria while off lipid-lowering medications, while adhering to the study diet and while glycaemic control is within the study limits. He or she is also given a placebo in a single blind protocol to determine the participant's compliance, one of the criteria determining eligibility for randomization.

During the baseline period, the participant undergoes a quantitative coronary angiogram according to a specific protocol, which will be the subject of a later report. As mentioned previously, the entry angiogram need not be performed during the baseline period if a quantitative angiogram has been conducted according to protocol not more than 6 months prior to the date of randomization. Such prior angiograms might have been performed if the participant had undergone investigation for suspected coronary disease, or had undergone a PTCA.

In the case of previous myocardial infarct, a coronary artery bypass graft (CABG) or a PTCA randomization cannot be done until 6 months after the coronary event. However, the participant is considered to be sufficiently stable metabolically to enter into the baseline period 3 months after a PTCA, or 4 months after a myocardial infarct or CABG.

Randomization. When the participant is declared eligible to enter the treatment period, he or she is randomized to receive either the 200 mg micronized form of fenofibrate or a placebo that does not contain fenofibrate; this occurs at visit 4. Randomization is stratified by three factors: gender, previous coronary intervention (PTCA or CABG) and clinical centre. After this point DAIS is conducted as a double-blind study.

Treatment period. The study medication, supplied in coded boxes, is to be taken with the morning meal. At each scheduled visit, the participant is to return any unused capsules and further supplies of medication are issued. To verify the packaging, capsules are randomly sampled and assayed for fenofibrate.

On scheduled return visits participants are assessed with respect to clinical status, laboratory status and compliance with medication, with protocol and with diet. Medication compliance is evaluated both by capsule counting and by periodic testing of the plasma for fenofibric acid levels. The treatment period will continue until 3 years after the final entrant has been randomized. At the end of the treatment period a second quantitative angiogram will be conducted according to the protocol used for the initial angiogram. This second angiogram may be performed during the 1-year interval before the treatment period for the entire study is concluded. However, in no case will it be done before an individual has completed at least 36 months of treatment, and treatment will not be stopped until this second angiogram has been completed.

At the end of the treatment period participants will be discontinued from the study medication. In order to avoid unblinding, participants will not have any lipid determinations performed until 6 to 8 weeks after the last dose of study medication has been taken.

Other medical management. There will be no active attempt to intervene on either smoking or obesity. However, if the participant requests advice for either of these it will be given according to usual medical practice.

It is expected that some participants may exceed the study guidelines for glycaemic control (HbA_{1c} < 170 % of the upper normal limit). Under such circumstances the participant may require changes in his or her hypoglycaemic regimen. This

will be done according to the following algorithm. Adherence to the study diet would first be validated and, if necessary reinforced. If the control is inadequate espite this and the participant is on diet alone, a sulphonylurea or metformin would be introduced. Those already taking either or both of these groups of oral hypoglycaemic drugs would have insulin added either alone or in combination with the oral hypoglycaemic agents. The dose of any of these agents would be adjusted to attain the study's acceptable level of glycaemic control. If insulin therapy is initiated the blood sample that was obtained during the Sustacal test in the baseline period, and kept frozen, would be thawed and assayed for C-peptide. In the Sustacal test, the participant is fasting and does not take any hypoglycaemic medication in the morning. Blood samples (9.5 ml) are drawn at 0, 10 and 90 min after consuming a standard amount of Sustacal (Mead Johnson Division, Bristol-Myers Squibb Canada Inc., Belleville, Ont., Canada). The standard amount is the amount that supplies 30 kcal/kg up to a maximum of a 360 ml volume drink. The serum separated from this blood is frozen at –70°C until analysis. This procedure is followed in order to minimize the chance of including individuals with IDDM in the study population.

If a participant develops hypertension requiring medication, the first drug to be tried would be an angiotensin converting enzyme inhibitor. Should that be contraindicated or ineffective, then a calcium channel blocker would be tried. Should additional or other antihypertensive medication be indicated then alpha blockers, cardioselective beta blockers with intrinsic sympathomimetic activity and/or diuretics may be tried in that order of preference.

Angina, should it develop, will be treated with nitrates and/or cardioselective beta blockers. Nifedipine, if used, should not be used above conventional doses.

Any other illnesses developing during the study will be treated according to accepted medical procedures and the treatment regimens documented.

Early discontinuation of an individual from the study. If a participant develops a medical condition, a drug-related adverse event, or a toxic laboratory value (including lipoprotein values in the toxic range) that would necessitate withdrawal from the study medication, every effort will be made to document the participant's status at the end of the study. Furthermore, if the participant has been in treatment for more than 1 year, an attempt will be made to obtain a final quantitative angiogram. Even if the medication has been discontinued, the statistical analysis will be conducted by intention to treat.

Study diet. After a pre-baseline evaluation, the study diet is explained at the start of the baseline period taking into account the fact that the participants have both diabetes and moderate dyslipoproteinaemia. Therefore, it is close to the step 1 diet as described by the National Cholesterol Education Program [16]. However, it is slightly modified to allow for carbohydrate control needed for diabetic subjects. It is designed to be nutritionally adequate, to contain 30 % of its total energy as fat, 10 % as saturated fat, a maximum of 10 % as polyunsaturated fat, 10 to 15 % as monounsaturated fat, 300 mg/day of cholesterol, 50 to 60 % from carbohydrate (the type and distribution being designed to optimize glycaemic control) and not more than 14 drinks containing 15 g of ethanol per week. Reinforcement of the diet is given at scheduled visits during the treatment period. The diet is evaluated at the end of the baseline period (visit 4), annually during the treatment period and at the end of the study. The nutrient composition of the diets is computed by local dietitians who use software with nutrient databases that reflect the foods for each of the nations participating in the DAIS.

Standardization of procedures. Clinic procedures have been standardized by centralized training of dietitians and nurses, completion of certification programs and regularly scheduled conference calls, mailings and meetings. Study monitors review in detail the procedures in each clinic at approximately monthly intervals and report regularly to the project office.

The biochemical determinations are standardized through the Canadian Reference Laboratory (Vancouver, BC, Canada). This is, in turn, standardized against the Centres for Disease Control (Atlanta, GA, USA) The actual methods used for biochemical determinations will be the subject of future reports. Quality control challenge samples for cholesterol and triglyceride are sent to the two core biochemistry laboratories at 2-month intervals. In addition, semiannually nine samples of human plasma are sent to each laboratory to assess the performance and comparability of the values obtained for total cholesterol, HDL-cholesterol, calculated LDL-cholesterol, VLDL cholesterol/triglycerides, IDL cholesterol/triglycerides, total triglycerides, endogenous glycerol, apo A-I, apo B, Lp(a), LpAI and LpAI:AII. The quality of routine safety determinations is the responsibility of each laboratory.

Each centre conducts its angiograms according to a common standardized protocol (to be described in a later publication). Before the first coronary contrast injection, 0.1–0.3 mg of intracoronary nitroglycerine is given into each coronary artery. All films plus the catheter tips, which will be used for calibration, are sent to the Core Angiography Laboratory, Toronto Hospital (General Division). Before a participant can be randomized the angiogram must be confirmed to demonstrate good visualization of the coronary artery segments in multiple projections. In the case of no previous intervention, there must be at least one 15 % narrowing in a coronary artery by visual inspection or by quantitative analysis of the angiogram. Furthermore, proper documentation of all parameters is recorded in order to permit identical views and magnifications to be obtained on the re-angiogram. All angiograms are interpreted and submitted for quantitative analysis at the Core Angiography Laboratory. Before becoming a participating centre, the angiographic equipment at each site was surveyed (MEDIS Medical Imaging Systems B.V., Nuenen, The Netherlands). Scores of 1 (unacceptable) to 10 (excellent) were assigned by comparison to their normal ranges for each of the following parameters: signal to noise ratio; contrast; detail; geometric distortion; reproducibility geometry of the X-ray system; film-development process. An average of these scores had to be at least 7 for the machine to be acceptable. During the treatment period, the equipment at each site is surveyed annually or additionally on special request or if any equipment or component is changed. During the periods of recruitment and final angiograms, more frequent equipment surveys may be requested.

Statistical analysis

Sample size. The sample size is calculated based on the assumption that the coronary angiographic progression (mean segment diameter and standard deviation) over 3 years in the placebo group will be the same as that seen in the conventional therapy group of the St. Thomas' Atherosclerosis Regression Study (STARS) [17]. This may be conservative in view of the accelerated atherosclerosis seen in diabetes. It is also assumed that 20 % of patients might have poor medication adherence,

or drop out of the study without a second angiogram. As discussed below, a "worst case scenario" will be applied to attribute scores to individuals for whom a second angiogram is not available. If there is a difference between the active and the placebo treatment groups, this approach would reduce the difference, leading to the need for a larger sample size. For a 2.5 % one-sided test of the hypothesis that active treatment with fenofibrate will be beneficial in terms of coronary artery disease, using a standard sample size formula [18] and adjusting for 20 % non-compliance [19], 260 individuals would give a 90 % power to detect a difference as small as 0.15 mm. Randomization will be stratified by previous coronary intervention and by gender.

Data analysis. The primary analysis will test the one-sided null hypothesis that treatment with fenofibrate will be the same or worse than treatment with placebo in terms of angiographic changes. The primary angiographic outcome parameter will be the average segment diameter per patient. The primary hypothesis will be tested by analysis of covariance, on a per patient basis, using the intention to treat rule, and a one-tailed significance level of 0.025. Baseline average segment diameter, centre, gender, and previous intervention will be used as covariates. Other angiographic parameters will also be assessed, as outlined in the forthcoming publication on the angiographic methods. This study is not designed to detect an effect on clinical events such as death, myocardial infarction, angina, need for intervention (PTCA or CABG) or stroke. However, obviously, these will be periodically analysed and presented to the Safety and Data Monitoring Committee during the study. At the end of the study, they will also be examined by the investigators.

As noted, it is our intent to test the effect of treatment in relation to gender and in relation to previous coronary intervention. In addition, we will look at subjects with an elevated triglyceride but normal LDL-cholesterol, with and without decreased HDL-cholesterol, and with and without elevated total cholesterol/HDL-cholesterol ratios.

In addition, we will examine the efficacy of the active drug on plasma lipids and lipoproteins, as well as on coagulation factors. Changes in these parameters will be related to the angiographic observations, taking into account other patient characteristics such as smoking and diabetes control. Clearly, the Safety and Data Monitoring Committee will have laboratory and clinical assessments available that are necessary to maintain the safety of the trial. In addition, a health perception questionnaire will be given to all participants and changes at the end, as opposed to the initiation, will be examined.

Failure to obtain a second angiogram or loss to follow-up. If a participant, despite all efforts is lost to follow-up, the most recent available information will be used for the analysis. If a participant fails to undergo a repeat coronary angiogram, the "worst case scenario" will be followed, as it was in the Familial Atherosclerosis Treatment Study, (FATS) trial [20]. In this situation, the assumption will be made, regardless of treatment group, that the angiographic changes would have been the same as those in the placebo group. In order to estimate what this would have been, a regression analysis of the final angiographic data as opposed to the initial angiographic data would be conducted for all individuals in the placebo group. The initial angiographic data of the participant would then be taken and an estimate of the final angiographic data would be made from the regression calculated above. In this way, even if the participant is in the active treatment group the angiogram would be presumed to change in a manner identical to that of the placebo group. This will lead to a conservative estimate of the effect of treatment.

Organization

The study group consists of clinical sites located in Canada, Finland, Sweden and France. Specific institutions are listed at the end of the paper. At each clinical site, in addition to nursing, secretarial and dietary staff, there are physicians whose primary responsibility is for the metabolic aspects of the participant; and cardiologists who are responsible for conducting the coronary angiograms and for making local evaluations of any clinical cardiovascular events. The blood samples from the European centres are analysed at the National Public Health Institute in Helsinki. Those from Canada are analysed in the laboratory at St. Paul's Hospital in Vancouver. The angiograms are all stored and read at the core angiography laboratory in Toronto. Dietary procedures are co-ordinated by the Project Dietitian, whose office is at The Toronto Hospital (General Division). The data are transmitted to the statistical co-ordinating centre at the University of North Carolina, where they are encoded and stored in secure computer files until they are required for analysis. The group at the statistical co-ordinating centre is also responsible for statistical analyses connected with DAIS. The overall co-ordination of DAIS is conducted by the project office which is situated at the World Health Organization Collaborating Centre for the Study of Atherosclerosis in Diabetes. That centre is housed at The Toronto Hospital (General Division) and the University of Toronto. Study medication is supplied from Laboratoires Fournier (Daix, France).

In addition DAIS has several committees to oversee and advise on various aspects of the study. The main committee, to which all others are subsidiary is the steering committee which is chaired by the project director and its voting members are the study's associate director, the clinic director and chief cardiologist from each site, the director of each biochemical core laboratory, the director of the core angiography laboratory, the director of the statistical coordinating centre, and the project dietitian. As noted earlier, DAIS is an investigator-initiated study. In order to ensure that it conforms to the highest academic standards and is not subject to any non-academic influences the steering committee has a representative from the World Health Organization. The steering committee convenes annually unless circumstances make an extraordinary meeting necessary. In order to permit rapid decisions in the interval between steering committee meetings, DAIS also has an executive which meets semiannually and communicates by conference calls on a quarterly basis. DAIS also has an advisory board consisting of academic experts

in lipoproteins, in diabetes and in cardiology. This group not only is able to advise on matters that concern the investigators, but it also serves as another monitor to prevent the study from deviating from its academic principles. An endpoints committee has also been established in order to verify and classify any clinical endpoints occurring during DAIS. Finally, as for any clinical trial, a safety and data monitoring committee has been established. It has three members; an expert in clinical trials; an expert in metabolic disorders; and an expert in cardiology. That committee meets quarterly to review data supplied to it by the statistical co-ordinating centre and to recommend on the advisability of continuing DAIS as it was initially planned.

Current status

The recruitment period has just finished and 418 individuals have been randomized. Of these 305 are men and 113 are women. Of the study population 285 have not had any prior coronary intervention (PTCA or CABG). At least 6 months prior to randomization 133 have had either a PTCA or a CABG. A full description of the baseline characteristics of the population will be prepared shortly.

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