Effect of aspirin on renal disease progression in patients with type 2 diabetes: A multicenter, double-blind, placebo-controlled, randomized trial. The renaL disEase progression by aspirin in diabetic pAtients (LEDA) trial. Rationale and study design

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Background Type 2 diabetes mellitus (T2DM) is one of the most common causes of chronic kidney disease and kidney failure. It has been estimated that the annual decline of estimated glomerular filtration rate (eGFR) among patients with T2DM is approximately 2.0-2.5 mL min^{-1} y^{-1}. Cyclooxygenase-dependent eicosanoids, such as 11-dehydro-thromboxane (Tx)B_2, are increased in T2DM patients and are potentially involved in the regulation of renal blood flow. Animal models showed that cyclooxygenase inhibitors, such as aspirin, are associated with improvements in renal plasma flow and eGFR values.

Hypothesis The primary end point of the LEDA trial is to evaluate the 1-year decline of eGFR in T2DM patients treated or not with low-dose aspirin (100 mg/d). Secondary end points will be the rapid decline in renal function, defined as a reduction of eGFR ≥5 mL/min, and change of renal function class after 1-year follow-up. Furthermore, urinary excretion 11-dehydro-TxB_2 will be related to renal function modifications.

Study design A phase 3 no-profit, multicenter, double-blind, randomized intervention trial of aspirin 100 mg/dvs placebo (ClinicalTrials.gov Identifier: NCT02895113). All patients will be monitored at 6 and 12 months after randomization to assess drug adherence and eGFR changes.

Summary The LEDA trial is the first double-blind, placebo-controlled, randomized clinical trial aimed at examining whether aspirin treatment may beneficially affect kidney function in patients with T2DM by reducing the annual eGFR decline. The trial will also examine whether the potential renoprotective effects of aspirin might be partly due to its inhibition of TxB_2 production. (Am Heart J 2017;189:120-7.)

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Several epidemiologic data showed that the prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic proportions worldwide. The progressive increase in food intakes, the greater availability of refined grains, and sedentary lifestyles exert an adverse impact on the risk of new-onset T2DM. It is expected that the number of people suffering from T2DM will double in the period 2000-2030.[1] The most important increase in the incidence of T2DM is expected in developing countries, where the prevalence of obesity is also rapidly increasing. Unlike developing countries, in the United States and Europe, the higher prevalence of T2DM is mainly related to the increased life expectancy of the general adult population and patients with T2DM. In Italy, the Casale Monferrato Study reported an increased rate of T2DM of approximately 45% (2.6% vs 3.8%)

in the period 1988-2000.[2] This was particularly related to aging, as the prevalence of T2DM increased mainly in the age group >65 years; of note, a doubling of the prevalence at the age ≥80 years was recorded. The pathophysiology of T2DM is multifactorial as, beyond genetic background, several acquired risk factors contribute to the development of new-onset T2DM including prediabetic states (ie, impaired fasting glycemia and impaired glucose tolerance), overweight/obesity, dyslipidemia, and arterial hypertension.[3]

T2DM is associated with a high risk of long-term complications, which increase with the duration of hyperglycemia. They can be divided into nonvascular and vascular complications, the latter including microvascular (ie, nephropathy, retinopathy, and neuropathy) and macrovascular (ie, coronary, cerebrovascular and peripheral arterial diseases)[4] complications.

Renal dysfunction and T2DM

Worsening of kidney function is a peculiar feature of patients suffering from T2DM. It has been shown that the annual decline of estimated glomerular filtration rate (eGFR) in patients with T2DM is about 2.0-2.5 mL/min per year.[5] The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study showed that nonalbuminuric renal impairment is the predominant clinical phenotype in T2DM patients, particularly women with reduced eGFR, and that the nonalbuminuric form is associated with a significant prevalence of cardiovascular disease, especially at the level of the coronary vascular bed.[6,7] A recent prospective, observational study[8] showed that in a cohort of 1,682 T2DM patients with preserved renal function (ie, eGFR ≥60 mL/min per 1.73 m^2) who were followed up for 10 years, the decline of eGFR was -0.6 ± 0.1 mL min^{-1} y^{-1} in patients with normal albuminuria rising to -2.7 ± 0.4 mL min^{-1} y^{-1} in those with macroalbuminuria at baseline. The authors also found that together with abnormal albuminuria, older age, hypertension, insulin treatment, and lower baseline eGFR were the strongest predictors of annual eGFR decline in this population.[8]

Chronic kidney disease (CKD) has also a negative prognostic impact in patients with T2DM. The FIELD study, which included 9,795 T2DM patients, showed that a reduced eGFR and the presence of albuminuria were independent predictors of renal and cardiovascular mortality.[9]

Aspirin, eicosanoids, and kidney (dys)function

Aspirin is an effective antithrombotic agent that inhibits the production of thromboxane (Tx) A_2 and other prostaglandins by blocking the enzyme cyclooxygenase (COX) 1. The antiplatelet action of acetylsalicylic acid (ASA) is via specific inhibition of COX-1 through an irreversible acetylation of serine-529 of COX-1. This enzyme exerts both COX(converting arachidonate into prostaglandin G2) and peroxidase activities (converting prostaglandin G2 into PGH2, the biochemical precursor of many other prostaglandins and Tx). Inhibition of COX-1 by aspirin results in complete inhibition of the proaggregating TxA_2. As platelets are anucleated, such aspirin-induced TxA_2 inhibition can be fully restored only through the synthesis of new platelets, that is, after approximately 7 days from aspirin administration. Previous randomized clinical trials have shown that aspirin is effective as an antithrombotic agent at a dosage ranging from 50 to 1500 mg/d. In patients treated with low-dose aspirin, serum TxB_2 levels are the most reliable marker of COX-1 inhibition. Patrono et al[10] have investigated the relationship between the aspirin dose and TxB_2 levels, showing that a single dose of 100 mg reduces by 98% the 1-hour concentration of serum TxB_2. Notably, serum TxB_2 returned to normal levels after a period compatible with the platelet half-life. Urinary levels of TxB_2 metabolites such as 11-dehydro-TxB_2 and 2.3-dinor-TxB_2 reflect the production of TxB_2 in whole body.[11]Because 11-dehydro-TxB_2 is excreted in higher amounts and has a longer half-life, its analysis in urine is largely used for clinical purpose.[12-14] Thromboxane binding to its receptor expressed by platelets, smooth muscle cells, endothelium, and vessels may exert vasoconstriction and platelet aggregation.[15]

It is noteworthy that urinary 11-dehydro-TxB_2 levels reflect platelet activation in T2DM patients and is largely dependent on glycemic control.[16]

In the kidney, COX enzymes exert their physiologic regulatory functions in the macula densa, medulla, and interstitium.[17] The products of COX enzymes, and in particular the balance between Tx and prostacyclin production, are crucial for kidney homeostasis.[18] Experimental studies showed that in the macula densa, COX enzymes favor renin production and are involved in the regulation of renal blood flow. In particular, in animal models, the administration of either aspirin or Tx receptor inhibitors was associated with improvements in renal plasma flow and eGFR values, suggesting a pathogenic role for Tx in the progression of renal damage.[19-22] A previous study in kidneys from diabetic rats has also demonstrated that an imbalance between TxA_2 and prostacyclin production could favor the onset of diabetic nephropathy.[19] Furthermore, a higher urinary Tx/prostacyclin ratio was also found in patients with T2DM as compared with healthy volunteers.[23]

Moreover, a recent cross-sectional study performed in 115 patients with stage 1-4 CKD showed that urinary levels of 11-dehydro-TxB_2 were significantly higher in stage 3-4 patients as compared with stage 1-2.[24]

To date, however, the data available in the literature on the long-term effects of low-dose aspirin (or other antiplatelet agents) on kidney function and progression of CKD in humans are scarce and inconclusive.

In a prospective cohort study of 4,494 US male physicians, aspirin intake significantly reduced the risk for decline in kidney function compared with those who never use it in the group of subjects without cardiovascular risk factors.[25]

In a study including 14 patients with severe congestive heart failure, the administration of picotamide, which is a TxA_2 synthase and TxA_2/prostaglandin H_2 receptor inhibitor, resulted in an improvement in effective renal plasma flow and eGFR.[26]

In a retrospective cohort study of 3,585 patients with CKD undergoing cardiac surgery, it has been reported that preoperative aspirin use was associated with a significant decrease in postoperative acute kidney injury.[27]

In a recent observational cohort study, involving 800 patients with nonvalvular atrial fibrillation,[29] we found that the use of aspirin (100 mg/d) was significantly associated with a reduced risk of CKD progression over 2 years of follow-up. In particular, patients who were not receiving aspirin had a 3-fold higher risk of progressing to an eGFR value <45 mL/min per 1.73 m^2 at the end of follow-up compared with those treated with aspirin. Furthermore, levels of urinary 11-dehydro-TxB_2 excretion were inversely associated with the aspirin use, and strongly predicted the annual eGFR decline during the 2-year follow-up period.

Of note, in the First United Kingdom Heart and Renal Protection (UK-HARP-I) study, which randomized 448 CKD patients to receive treatment with simvastatin 20 mg or aspirin 100 mg, allocation to treatment with 100 mg of aspirin daily was not associated with an excess of major bleeds, suggesting that the use of low-dose aspirin may be safe in CKD patients.[28]

Aspirin and renal function in T2DM

The efficacy and safety of aspirin as an antithrombotic agent has been assessed both in apparently healthy people at low risk for cardiovascular complications (primary prevention) and in patients at high risk, such as those with a prior myocardial infarction or ischemic stroke (secondary prevention). Patients with T2DM represent an important group of patients in whom treatment with aspirin should be carefully considered. The evidence that T2DM patients without previous cardiovascular events have similar cardiovascular risk compared with nondiabetic individuals with prior myocardial infarction could make the use of aspirin as primary prevention strategy for cardiovascular diseases in this clinical setting reasonable. However, although there is consolidated evidence about the use of aspirin for secondary prevention in patients with T2DM, there is no evidence of an effective use for primary cardiovascular prevention[30,31]; thus, currently, the use of aspirin in this specific group of T2DM patients remains largely at physician discretion.[4]

However, aspirin may exert effects beyond cardiovascular prevention in T2DM[32]; for instance, some authors investigated the relationship between aspirin administration and renal function in T2DM providing conflicting evidence.

A randomized trial including 76 patients with diabetic nephropathy showed that short-term use of high-dose aspirin (1000 mg) was able to reduce the rate of proteinuria by the 15.9% as compared with control group, with no adverse effects related to the use of aspirin.[33]

A Swedish cohort study[34] that investigated the decline of renal function at 5-7 years in 801 patients with CKD showed that chronic administration of aspirin was associated with a slower decline of renal function compared with untreated patients (mean difference of 0.8 mL/min per 1.73 m^2). The authors reported that this beneficial effect of aspirin was maintained also in the group of patients with diabetic nephropathy.

Conversely, the JPAD2 cohort study showed no effect of aspirin on kidney function in 2,536 Japanese patients, but the allocation of patients to aspirin (81 mg or 100 mg daily) or not was at physician discretion.[35]

Primary end point

The aim of the study is to evaluate the decline of renal function, as assessed by absolute change in eGFR, calculated as the difference between eGFR at 12 months and baseline eGFR, in T2DM patients receiving low-dose aspirin (100 mg/d) or placebo.

Secondary end points

The following will be considered as secondary end points:

- The rapid decline in renal function, defined as a reduction of eGFR $\geq$5 mL/min at 1 year
- Change of renal function class (from G1 to G2, from G2 to G3a, and so on) at 12 months, dialysis, or transplantation
- Urinary 11-dehydro-TxB_2 levels at the end of the follow-up to be correlated with renal function modifications

Study design

This is a phase 3, no-profit, multicenter, double-blind, placebo-controlled, randomized, intervention trial of 1-year treatment with aspirin 100 mg/dvs placebo in patients with T2DM. The inclusion and exclusion criteria are specified in Table I. Table II reports the timeline of events and assessments. In all participants, the following data will be collected:

- anthropometric/clinical data (at each visit): age, gender, height, weight, body mass index, waist circumference, systolic and diastolic blood pressure, heart rate;

Table I. Inclusion and exclusion criteria of the LEDA trial

Inclusion criteria
Diagnosis of type 2 diabetes[43,44]: - Random blood glucose ≥200 mg/dL (≥11.1 mmol/L) - Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.* - Blood glucose 2 h after oral glucose tolerance test (75 g OGTT) ≥200 mg/dL. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* - Hemoglobin A1c ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* - Treatment with any glucose-lowering agent
Exclusion criteria
(1) History of cardiovascular or cerebrovascular events (defined on history and/or instrumental findings provided by the patient) (2) Presence of inadequate glycemic control (ie, hemoglobin A1c ≥8%) (3) Presence of uncontrolled blood pressure despite antihypertensive treatment (≥140/≥85 mm Hg) (4) Previous major bleeding (ie, intracranial) (5) Previous gastrointestinal ulcer (6) Clinical diagnosis of type 1 diabetes (diagnosis of diabetes and insulin use before age 35 y) (7) Patients with CKD G4 or G5 stage (ie, eGFR <30 mL/min per 1.73 m^2 or dialysis) (8) Chronic active infections or (9) Evidence of malignancy in the last 5 y. Patients with in situ neoplastic disease successfully treated only with local excision can be included in the study (including in situ nonmelanoma skin cancer). (10) Autoimmune systemic diseases (11) Sustained cardiac arrhythmias requiring anticoagulant treatment (ie, atrial fibrillation). In this category, isolated ventricular/supraventricular extrasystoles are not included. (12) Use of nonsteroidal anti-inflammatory drugs, or other antiplatelet agents in the previous 30 days (13) Cirrhosis of any etiology (14) Use of anticoagulants (15) Life expectancy <1 y (16) Known allergy to aspirin (17) Known pregnancy (18) Severe psychiatric illness

Abbreviations: *OGTT*, Oral glucose tolerance test; *WHO*, World Health Organization; *NGSP*, National Glycohemoglobin Standardization Program; *DCCT*, Diabetes Control and Complications Trial.
* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing

- medical history (at baseline visit): diabetes duration, cardiovascular risk factors such as smoking, alcohol intake, dyslipidemia, arterial hypertension,[36] heart failure,[37] metabolic syndrome,[38] chronic obstructive pulmonary disease[39];

Table II. LEDA trial—timeline of visits and events

Event/Assessment(s)	Baseline visit	6-mo visit	12-mo visit
Informed consent	X		
Inclusion/exclusion	X		
Anthropometric/clinical data	X	X	X
Medical history and concomitant treatments	X		
Randomization	X		
Laboratory analysis	X	X	X
Assessment of kidney function	X	X	X
Urine sample collection and TxB_2 assessment	X	X	X
Study drug administration	X	X	
Withdrawal of the medication package and compliance monitoring		X	X
Adverse event monitoring		X	X

- use of all concomitant medications (at each visit): name and daily dosage of all medications taken by patients; and
- blood analysis (at each visit): serum creatinine (measured using a Jaffe´ rate–blanked and compensated assay), urea nitrogen, complete blood count, fasting glucose, insulin (only for patients not treated with insulin), hemoglobin A1c, serum liver enzymes (aminotransferases and γ-glutamyltransferase), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid, C-reactive protein (high-sensitivity C-reactive protein), albuminuria on a morning urine sample (at each visit).

According to albuminuria levels, patients will be classified into 3 groups: (1) <30, (2) 30-299, and (3) ≥300 mg/g. Measurements of urine and blood parameters ratio will be made with standard laboratory methods in each single center.

Estimation of kidney function

To estimate kidney function, eGFR will be calculated by the CKD–Epidemiology Collaboration formula.[40] Patients will be classified into 4 categories based on eGFR according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines: normal eGFR (> 90 mL/min per 1.73 m^2, stage G1), mild decrease in eGFR (89-60 mL/min per 1.73 m^2, stage G2), mild-moderate decrease in eGFR (59-45 mL/min per 1.73 m^2, stage G3a), moderate to severe decrease in eGFR (44-30 mL/min per 1.73 m^2, G3b stage), and severe decrease of eGFR (<30 mL/min per 1.73 m^2, stage G4).

Data collection

Each investigator will collect the data and fill them in a certified electronic platform. Each center will be provided with personal login procedures for direct entry of individual patient data. Investigators will be

also asked to fill all data in a paper form, which must be held until the end of the trial. Each investigator will be provided with a sequential numerical code (01, 02, etc), which will be used to identify the participating center at the time of filling in the electronic platform. Patients enrolled will be enumerated according to the order of enrollment. For example, the first patient from the center 01 will be identified with code "01-01," the second with the code "01-02," and so on. The promoter center (Sapienza University of Rome) will require further clarification of the data entered (eg, in the case of incorrect insertion), but will not require any information enabling the identification of the patient enrolled.

Collection of biological samples and measurement of urinary 11-dehydro-TxB_2

Urine samples (10 mL each visit for each patient) will be collected in all participants in the morning between 8:00 and 9:00 AM after an overnight fast. The urine samples will be stored at −80 °C until use. The levels of urinary 11-dehydro-TxB_2 will be measured centrally (at the promoter center) using a commercial ELISA kit (Cayman Chemical, Ann Arbor, MI).[41] The data will be expressed as ng/mg urinary creatinine. Urinary creatinine will be also centrally measured using a commercial enzyme immunoassay kit.

Informative sheet and informed consent

At enrollment, an investigator will explain to each patient the modalities and the aim of the trial. Each patient will then be asked to provide written informed consent before the inclusion in the study. It will be also specified that each participant is allowed to withdraw at any time and to be informed about results at the end of the study. The trial will be conducted in accordance with the Standards of Good Clinical Practice (ICH-GCP), as expected by current regulations concerning clinical trials and the protection of personal data (Administrative Order; June 30, 2003; No. 196), and according to what established by the Declaration of Helsinki (version of the 59nd WMA General Assembly, Seoul, October 2008). In addition, an informative letter for the general practitioner will be delivered to each patient. The study protocol has been approved by the coordinating center's ethic committee (Ref. 4338/2017) and, thereafter, by the ethics committee of each center outside the Policlinico Umberto I "Sapienza" University Hospital. Moreover, the study protocol has been approved by the Italian Medicine Agency (AIFA). The study protocol has been registered at the ClinicalTrials.gov (NCT02895113) and at the European Clinical Trials Database (EudraCT number 2015-005231-40).

Treatment delivery

All patients will be randomly assigned to either aspirin 100 mg/d or placebo (Figure) to be taken after lunch (in nonfasting conditions) according to the randomization list. At baseline (T0 visit), an amount of tablets for 6 months will be delivered; then, patients will be reevaluated by an investigator (T6 visit) who will assess the presence of any adverse effect occurred during treatment or contraindication to continue the study. The investigator will also verify the adherence to the assigned treatment by the withdrawal of drug bottle/empty placebo. Any error in the assumption of the drug by the patient (ie, a reported early depletion of tablets or the presence of residual tablets in the container) must be promptly notified by the investigator at the promoter center, which will assess in each case whether such errors compromise the continuation of the study for the patient. At T6, the investigator will give the patient the vial containing pills necessary for the rest of the study, until the 12-month visit (T12 visit).

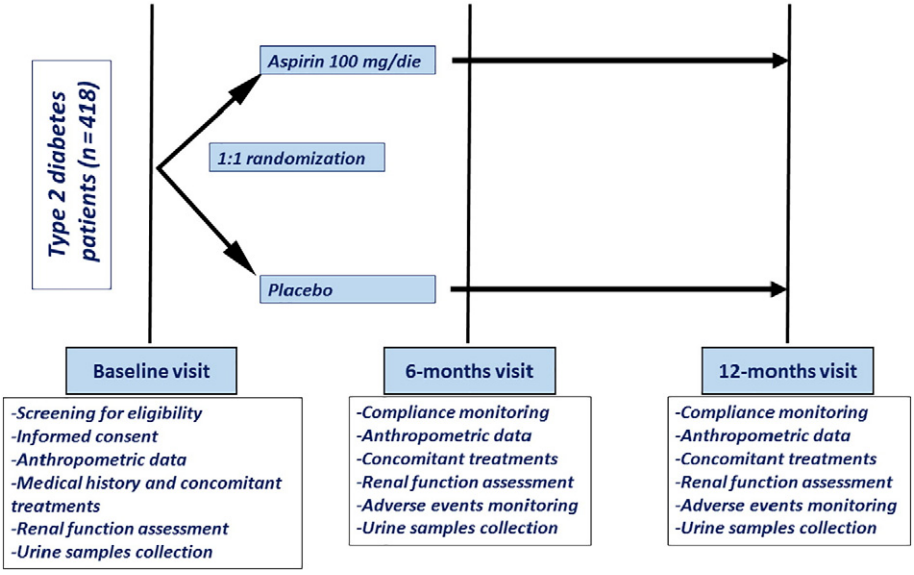
Randomization list

The randomization list will be generated by software and will be managed by the promoter center that will assign the codes for all patients at each participating center in order of enrollment. An operator who will not be involved in patients' recruitment, or in data analysis will be in charge of code assignment and maintenance of randomization list in a safe place not accessible to other investigators.

Management and monitoring of participating centers

Each participating center will receive all study materials, including the study protocol and synopsis, the case report forms (T0, T6, T12), the information sheet, and informed consent for the patient, as well as the approval of the ethics committee of the promoter center, a letter of intent to the local ethics committees, and a letter for the general practitioners. Two investigator meetings are being planned; the first meeting will be held before the start of enrolments to explain the scientific rationale and the modalities of the study and the second to assess the state of enrollment. We will also plan to carry out in each center, after its activation, a site visit to check (1) the ability to conduct the study (approval if it will be obtained a copy of the local ethics committee and viewed the informed consent of the patients enrolled), (2) proper data collection, and (3) the adequate storage of the biological samples. A form of relating to each center the evaluation after the visit will then be filled in. The participating centers will be required to retain all documentation relating to the study for the entire duration of the study, and thereafter for at least 10 years, and send it to the promoter center if needed.

Figure



The LEDA trial design.

Adverse events

In the case of any adverse event occurring during the trial, it is mandatory for the investigator to report it promptly to the promoter center. The major adverse events that should be reported include the following:

A. Adverse effects associated with the drug treatment:
   a. any occurrence of allergic reactions after taking the tablet;
   b. any gastrointestinal symptoms (eg, nausea, heartburn);
   c. any major or minor bleeding (clinically significant); and
   d. others.
B. Intercurrent disease/conditions that may be a contraindication to the continuation of the trial by the patient:
   a. any ischemic heart disease event (angina pectoris, acute myocardial infarction, cardiac revascularization procedures);
   b. any acute erebrovascular event (ischemic stroke, transient ischemic attack);
   c. any need to take anti-inflammatory drugs or antiplatelet drugs for more than 1 week; and
   d. other (eg, pregnancy, immobilization from accident traumas).

Each investigator is requested to contact the promoter center in the case of any doubt about the evaluation of the adverse event. In addition, each investigator will be required to complete and sign a prespecified form and to send it to the promoter center, along with any available clinical documentation to certify the adverse event.

Patients will be advised to contact the investigator immediately after the occurrence of any adverse event, without waiting for the next scheduled visit and before stopping the assigned treatment.

Statistical analyses

Categorical variables will be reported as percentages, whereas continuous variables expressed as means ± SD or medians and interquartile ranges according to their distribution, which will be tested with the Kolmogorov-Smirnov test. Differences between the percentages will be assessed by using the χ^2 test or by Fisher exact test. The Student t test and Pearson correlation analyses will be used for normally distributed continuous variables. Appropriate nonparametric tests will be used for all other variables. Multiple linear regression analysis will be used to assess independent predictors of the absolute annual changes in eGFR, whereas the multiple logistic regression analysis will be used to identify factors associated with the rapid decline in kidney function. To evaluate the changes in eGFR stages over the trial, ordinal logistic regression models will be used. The outcomes will be assessed at 2 follow-up times (at 6 and 12 months) simultaneously via regression models for longitudinal data, using a random subject-dependent intercept to take account of the dependence of replicate measurements on the same subjects.

An interim analysis will be performed on the primary end point when 33% of patients will have been randomized and completed the 12-month follow-up.

The Haybittle-Peto approach will be used: the trial will be ended using symmetric stopping boundaries at if $P < .001$ at interim.

Statistical significance will be determined at a value of $P < .05$. The analyses will be performed with the SPSS software version 20 for Windows (SPSS, Chicago, IL) and R v. 3.0.2 for Linux (© The R Foundation, Vienna, Austria).

Calculation of the sample size of the trial

The minimum sample size of the trial is estimated on data from previous studies that have estimated an annual reduction of GFR in patients with T2DM of about 2.5 mL/min per 1.73 m^2.[42] On this basis and assuming a protective effect of aspirin of about 20% on the progression of eGFR with a standard deviation (DS) of 1.5, it is estimated to include a minimum of 380 patients (190 treated with aspirin and 190 placebo) to have a 90% chance with a probability of error of type I $\alpha = .05$ to identify a significant reduction in the primary end point. With an expected 10% dropout rate at follow-up, the final sample to be included in the trial will be of 418 patients (209 for each arm of treatment).

The planned sample size will allow us to achieve an 80% power for a correlation (in absolute value) of 0.14 or more between urinary 11-dehydro-TxB_2 and renal function modifications.

Funding

The trial will be supported by an unrestricted grant from Bayer SpA for the production of aspirin and placebo. Bayer SpA will not be involved in any phase of patients' recruitment or data analysis and interpretation. Thus, the authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Summary

The LEDA trial will be the first multicenter, double-blind, placebo-controlled trial to examine whether treatment with aspirin (100 mg daily) may beneficially affect kidney function in adult patients with T2DM by lowering the annual decline of eGFR. The trial will also examine whether the potential renoprotective effects of aspirin might be partly due to its inhibition of TxB_2 production.

Disclosures

The authors have no conflict of interest to declare related to this study.

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