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Article *in* Nephrology Dialysis Transplantation · April 2009

DOI: 10.1093/ndt/gfn721 · Source: PubMed

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Original Article

Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design

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Abstract

Background. Patients with type 2 diabetes are at increased risk of macro- and microvascular disease, and the presence of albuminuria and/or reduced kidney function further enhances macrovascular risk. Angiotensin-converting-enzyme inhibitors reduce both macro- and microvascular events, yet the residual renal and cardiovascular risk still remains high. Aliskiren a novel oral direct renin inhibitor that unlike ACEi and ARBs, lowers plasma renin activity, angiotensin I and angiotensin II levels, may thereby provide greater benefit compared to ACEi or ARB alone.

Methods. The primary objective of the ALTITUDE trial is to determine whether aliskiren 300 mg once daily, reduces cardiovascular and renal morbidity and mortality compared with placebo when added to conventional treatment (including ACEi or ARB). ALTITUDE is an international, randomized, double-blind, placebo-controlled, parallel-group study, which will include three categories of high-risk patients with type 2 diabetes (aged ≥35 years): those with either urinary albumin/creatinine ratio (UACR) ≥200 mg/g; microalbuminuria (UACR) ≥20 <200 mg/g and eGFR ≥30 <60 mL/min/1.73 m^2; and thirdly, those with a history of cardiovascular disease and eGFR ≥30 <60 mL/min/1.73 m^2 with or without microalbuminuria. ALTITUDE is an event driven trial that aims to randomize 8600 patients with a planned follow-up time of 48 months. The primary outcome measure is time to first event for the composite endpoint of cardiovascular death, resuscitated death, myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease or doubling of baseline serum creatinine concentration. Secondary endpoints include a composite CV endpoint and a composite renal endpoint.

Conclusion. ALTITUDE will determine whether dual RAAS blockade with the direct renin inhibitor aliskiren in combination with an ACEi or ARB will reduce major morbidity and mortality in a broad range of high-risk patients with type 2 diabetes.

Keywords: albuminuria; aliskiren; cardiovascular disease; diabetes; kidney disease

Introduction

Type 2 diabetes mellitus is a public health concern, and projections of its future effects are alarming. According to the World Health Organization [1], diabetes currently affects more than 240 million people worldwide, and the number is predicted to rise to more than 360 million by 2030. The diabetic epidemic is more pronounced in developing countries compared to developed countries. This global trend not only has profound medical implications but also economic and social consequences due to the cost of managing diabetes and its vascular, kidney and neuropathic complications. Furthermore, these complications are likely to occur even more frequently in the future, since earlier age at onset of type 2 diabetes is already more prevalent.

The pathogenesis of diabetic macro- and microangiopathy is multifactorial and the renin–angiotensin–aldosterone system plays an important role [2–5]. The overall global prevalence of micro- and macroalbuminuria is nearly 50%. Asian and Hispanic patients have the highest prevalence and Caucasians the lowest [6]. Persistent albuminuria is the hallmark of diabetic nephropathy, a condition that is characterized by progressive rise in systemic blood pressure, declining GFR and a high risk of end-stage renal disease (ESRD) and fatal or non-fatal cardiovascular events. Baseline albuminuria, treatment-induced changes in albuminuria

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and residual albuminuria despite renoprotective therapy are all closely associated with the risk of ESRD and CVD events in diabetes [7–9]. In addition, it is now well established that reduced GFR (<60 mL/min/1.73 m^2) is an independent CVD risk factor [10]. Previous studies have shown that CVD event rates in type 2 diabetes are equivalent to those in non-diabetic people with pre-existing CVD [11,12] and that type 2 diabetic patients are two to four times more likely to develop CVD than people without diabetes [13].

During the past 20 years, the outlook for type 2 diabetic patients with or without renal or CVD manifestations has improved, in part due to early aggressive lowering of blood pressure and blocking of the renin–angiotensin–aldosterone system [5,14–17], lipid lowering particularly with statins [18,19] and improved glycaemic control [20] (to an HbA1c level of ∼7%). However, more aggressive glycaemic therapy to an HbA1c level of <6.5% has not shown benefit in the ACCORD study [21] or the ADVANCE trial [22], suggesting that there may be limits to the benefit on macrovascular endpoints that can be achieved by very aggressive glycaemic intervention. In addition, treatment with low-dose aspirin has reduced CVD in diabetes [23]. Recently, the STENO 2 study has clearly demonstrated the beneficial effect of intensive multifactorial intervention with multiple drug combinations on both diabetic micro- and macroangiopathy including death [5]. However, there is still a large, unmet need for newer strategies for further reductions in cardiovascular and renal complications of diabetes.

Aliskiren is an orally active renin inhibitor, which became the first drug in its class to receive regulatory approval for the treatment of hypertension in 2007. Aliskiren inhibits the first rate-limiting step in the RAAS cascade, the conversion of angiotensinogen to angiotensin I and thereby reducing synthesis of all subsequent components of the cascade [24]. In contrast, use of an ACE inhibitor or ARB leads to a compensatory rise in the upstream components of the RAAS cascade, including plasma renin activity [24]. Recently, addition of aliskiren to an ACE inhibitor or ARB and ß-blocker had favourable neurohumoral effects on heart failure [25]. Furthermore, the AVOID trial showed that aliskiren has renoprotective effects that are independent of its blood pressure lowering effect in hypertensive type 2 diabetic patients with nephropathy who are receiving the recommended maximal renoprotective treatment [26]. This study also demonstrated that side effects in the aliskiren-treated group were comparable to those seen in placebo-treated patients.

The aim of this trial is to determine the effectiveness and safety of direct renin inhibition with aliskiren on fatal and non-fatal renal and CVD events compared to placebo in type 2 diabetic patients at a high risk of these complications. All patients are recommended to receive optimal treatments with ACEi or ARB along with other evidence-based CVD protective therapy. This placebo-controlled trial will also evaluate the safety of this unique approach of dual blockade of the RAAS.

Trial design and methods

The members of the executive committee designed the trial and wrote the study protocol in collaboration with co-authors employed by Novartis. HHP led the drafting of the present report and the other authors contributed to the writing. All authors reviewed and approved the paper. Approximately 800 centres in 36 countries will participate in the study. The protocol has been approved by the Ethics Review Committee/Institutional Review Board affiliated with each centre. The study is being conducted in accordance with Good Clinical Practice, Declaration of Helsinki 2002. All participants will provide written informed consent. An external independent data monitoring committee (DMC) will monitor safety throughout the study. The trial has been registered on Clinicaltrials.gov, NCT00549757.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, two-arm study that comprises two study phases (Figure 1):

Pre-randomization phase (4–12 weeks). During the 4- to 12-week screening period, the patients' eligibility for randomization into the trial will be evaluated and the patient should be stabilized on conventional therapy according to local guidelines relevant to his/her medical history and concomitant conditions. The screening period should last no less than 4 weeks, and no more than 12 weeks if treatment adjustments are required. Prior to randomization, patients' treatment should be stable and without any adjustments for at least 4 weeks. All patients should receive an individually titrated optimal recommended dose of an ACEi or ARB, but not both. Aldosterone antagonists are not allowed.

Double-blind study phase. Patients who fulfil all eligibility criteria will be randomized to receive aliskiren 150 mg or placebo on top of their conventional treatment (visit 3). The randomization list will be generated by a validated system that automates the random assignment of treatment groups to randomization numbers. Four weeks after randomization (visit 5), forced up-titration of aliskiren to 300 mg once daily or placebo on top of their conventional treatment will occur. Patients can be down-titrated to 150 mg at any time of the study in case of severe adverse events. Scheduled follow-up visits will occur at 5, 8 and 12 weeks after randomization with subsequent visits planned every 3 months.

The duration of the double-blind treatment phase is expected to be 48 months, but the actual length of the study depends on the observed patient enrolment rate and primary endpoint rate. The closure of the double-blind treatment period will be decided upon by the executive committee based on the recommendation of the independent DMC.

Study population

We are studying type 2 diabetic patients at high risk for fatal and non-fatal cardiovascular and renal events. Type 2 diabetic patients are required to fulfil the following inclusion criteria: persistent albuminuria [urinary albumin/creatinine ratio (UACR) ≥200 mg/g] in two out of three consecutive first morning void urine samples; or an estimated GFR ≥30 <60 mL/min/1.73 m^2 calculated by the abbreviated MDRD study equation [27] and persistent microalbuminuria (UACR ≥20 mg/g <200 mg/g) in two out of three

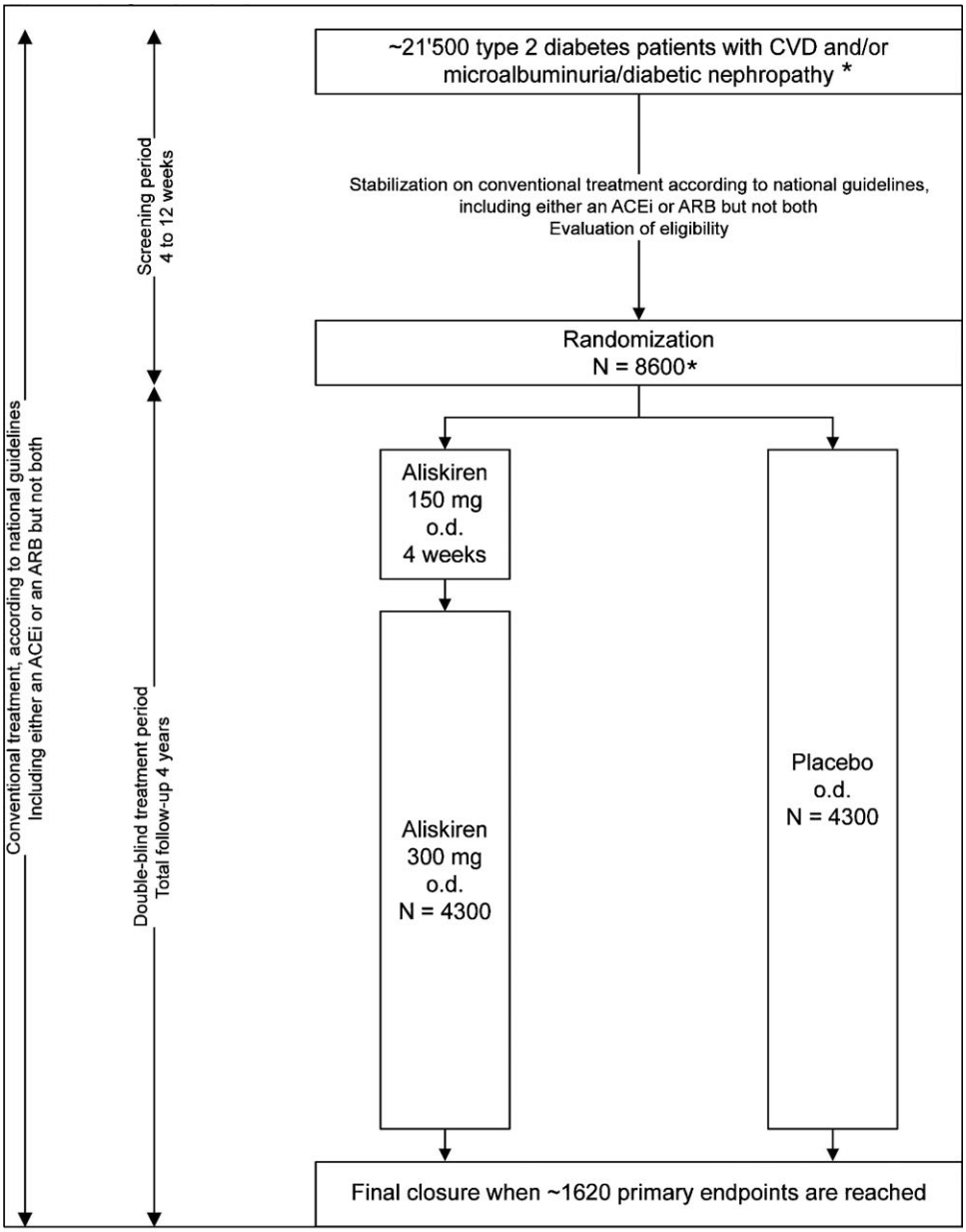

Fig. 1. Study design. *Assuming a screening failure rate of 60%

consecutive first morning void urine samples or a history of cardiovascular disease. This definition using 20–200 mg/g for microalbuminuria as compared to the textbook one (30–300 mg/g) has been developed for this study because all patients are already on therapy ACEi/ARB. All patients should be on optimal recommended treatment with an ACEi or ARB according to local guidelines. Specific inclusion and exclusion criteria are listed in Table 1.

Blinding

Patients, investigator staff, persons performing the assessments and data analysts will remain blinded to the identity of the treatment from time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by any one else involved in the study with the exception of the members of the independent DMC and the independent biostatistician who will perform the interim analyses.
2. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance and odour. Unblinding will only occur in the case of an individual patient emergency, at the time of interim analysis and at the conclusion of the study.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	
For visit 1	• Patients with type 2 diabetes mellitus who are on oral antidiabetics and/or insulin or documented fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L • Male or female patients ≥35 years of age • Patients who provide written informed consent
Additional criteria for visit 3	• Patient on conventional therapy (national guidelines) and on concomitant ACEI or an ARB without any adjustments to the antihypertensive therapy for at least 4 weeks prior to randomization • At least one of the following Persistent macroalbuminuria (UACR ≥200 mg/g[a]) and eGFR ≥30 mL/min/1.73 m^2 Persistent microalbuminuria (UACR ≥20 mg/g and <200 mg/g[a]) and a mean eGFR ≥30 and <60 mL/min/1.73 m^2 A history of cardiovascular disease (e.g. myocardial infarction, stroke, heart failure or coronary artery disease) and a mean eGFR ≥ 30 and <60 mL/min/1.73 m^2
Exclusion criteria	For patients with any of the following at visit 1 through visit 3
General criteria	• Serum potassium >5.0 mmol/L directly preceding visit 3 • Type 1 diabetes mellitus • Unstable serum creatinine[b]
Cardiovascular history	• Congestive heart failure NYHA class III or IV • Stroke, transient ischaemic cerebral attack, MI, unstable angina, CABG, PCI, hospitalization due to HF, 3 months prior to visit 1 • Hypertension at visit 3 with msSBP ≥170 mmHg or msDBP ≥110 mmHg • Hypertension at visit 3 with msSBP ≥135 and <170 mmHg or msDBP ≥85 and <110 mmHg unless treated with at least three antihypertensives • Second or 3rd degree heart block without a pacemaker or life threatening or uncontrolled arrhythmia or clinically significant valvular heart disease • Renal artery stenosis
Surgical or medical condition	• History of malignancy within the past 5 years • Concurrent life-threatening condition with a life expectancy <2 years • Patients with previous renal transplant or under immunosuppressive therapy. • Any surgical or medical condition that alters the pharmacokinetic parameters of the study drug, or jeopardizes the evaluation of efficacy or safety of the study drug or affects patient's compliance • A history or evidence of drug or alcohol abuse within the last 12 months • Hypersensitivity or allergy or suspected/known contraindications to the study drugs • Pregnant (confirmed by a positive hCG test), lactating women or women of child-bearing potential
Others	• Concomitant treatment with ≥ 2 agents blocking the renin–angiotensin–aldosterone system. Potassium-sparing diuretics • Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment, whichever is longer • Persons directly involved in the execution of this protocol • Patients enrolled in the CSPP100AC2201 trial • Noncompliance to medical regimens or unwillingness to comply with the study protocol

[a]In at least 2 out of 3 morning-voided urine samples.
[b]Defined as ≥20% difference between two consecutive serum creatinine measurements before visit 3 msSBP = mean sitting systolic blood pressure, msDBP = mean sitting diastolic blood pressure, MI = myocardial infarction, CAD = coronary arterial disease, HF = heart failure, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, hCG = human chorionic gonadotropin, UACR = urinary albumin-to-creatinine ratio, eGFR = estimated glomerular filtration rate.

Medical management

It is recommended that all patients receive optimal doses of ACEi and ARB and optimal antihypertensive therapy for renal and CVD protection, according to local guidelines. Statin, anti-platelet and beta-blocker treatment is also recommended according to local guidelines. It is advised that other guideline recommendations for management of cardiovascular disease are also followed. Glycaemic control should be dealt with according to local guidelines.

Primary objective

The primary analysis will be time to the first event of the following composite primary endpoint: cardiovascular (CV) death, resuscitated sudden death, non-fatal myocardial infarction (MI), non-fatal stroke, unplanned hospitalization for heart failure, ESRD or renal death (death attributable to kidney failure, need for renal replacement therapy with no dialysis or transplantation available or applied) or doubling of baseline serum creatinine concentration, sustained for at least a month.

The onset of ESRD is defined as initiation of persistent dialysis, renal transplantation or a serum creatinine concentration >6.0 mg/dL (530 μmol/L).

Secondary objectives

The secondary objectives are as follows:

1. To determine whether aliskiren, compared to placebo, will delay the occurrence of cardiovascular complications, defined as the first occurrence of CV death, resuscitated sudden death, non-fatal MI, non-fatal stroke or unplanned hospitalization for heart failure.

Table 2. Exploratory objectives

To explore the effects of aliskiren compared with placebo on
• Delaying occurrence of the following composite endpoint
CV death
Resuscitated sudden death
Non-fatal myocardial infarction
Unplanned hospitalization for heart failure
Unplanned hospitalization for acute coronary syndrome
Any arterial revascularization
• Delaying occurrence of new diagnosis of atrial fibrillation
• Delaying all-cause mortality
• Delaying occurrence of all-cause mortality/all hospitalizations
• Delaying progression of albuminuria[a]
• Inducing regression of albuminuria[a]
• Change in albuminuria from baseline[a]
• Change and slope of eGFR[a]
• Selected biomarkers for CV and renal risk

[a]Change in albuminuria category, accompanied by a ≥30% increase or decrease from baseline.
eGFR = estimated glomerular filtration rate, CV = cardiovascular.

2. To determine whether aliskiren, compared to placebo, will delay the occurrence of renal complications, defined as the first occurrence of doubling of baseline serum creatinine concentration for at least 1 month or ESRD or renal death.

Exploratory objectives

Table 2 shows the exploratory objectives of this study.

The progression of albuminuria is defined as a change in albuminuria from normoalbuminuria (UACR <20 mg/g) to microalbuminuria (UACR ≥20 mg/g and <200 mg/g) or from microalbuminuria to macroalbuminuria (UACR ≥200 mg/g), in all cases accompanied by a ≥30% change from baseline.

The objective is to determine whether aliskiren, compared to placebo, will reduce the time to regression of persistent albuminuria, defined as a change in albuminuria from macroalbuminuria (UACR ≥200 mg/g) to persistent microalbuminuria (UACR ≥20 mg/g and <200 mg/g) or microalbuminuria (UACR ≥20 mg/g and <200 mg/g) to persistent normoalbuminuria (UACR <20 mg/g), in all cases accompanied by a ≥30% change from baseline.

All assessments of urine and blood will be performed by the same company in a central laboratory in Europe or the United States. The urinary albumin concentration will be determined by immunoturbidimetry, and serum creatinine concentration by means of the Jaffe reaction with the use of a Roche kit. The Modification of Diet in Renal Disease (MDRD) formula will be used to estimate the glomerular filtration rate. Glycosylated haemoglobin will be measured by means of high performance liquid chromatography (Bio-Rad, Hercules, CA, United States). All the other laboratory variables will also be measured centrally with the use of conventional laboratory techniques.

Sample size

Based on the RENAAL [16] and IDNT [17] trials in hypertensive, type 2 diabetic patients with nephropathy, as well as the diabetic (sub)populations in the HOPE [4], TNT [28], HPS [18], PROACTIVE [29] and FIELD [30] studies, the annual event rate of the primary composite endpoint is estimated to be 8% for the placebo arm on top of conventional treatment. In addition, the enhancing impact of micro- and macroalbuminuria and stage 3 kidney disease on the primary endpoint was taken into account [31]. Using a two-sided test at a 0.05 significance level, a total of 1620 patients reaching the primary composite endpoint will provide 90% statistical power for detecting 15% risk reduction in the aliskiren arm compared to the placebo arm. In the calculation, adjustment has been made for two equally spaced interim analyses using O'Brien–Fleming stopping boundaries. Assuming a 24-month enrolment period and total trial duration of 48 months with ∼8.0% inflation due to dropouts, ∼8600 patients (∼4300 per treatment arm) will need to be randomized for the trial.

Statistical analysis

The primary analysis will be in the intent-to-treat (ITT) population that comprises all randomized patients.

The primary efficacy variable is the time to the first event of the primary composite endpoint. The Cox proportional hazards model with treatment assignment and two stratifying factors [cardiovascular disease history (yes/no) and baseline albuminuria level UACR ≥ 200mg/g (yes/no)] will be used to estimate the hazard ratio and to obtain the confidence limits and the two-sided *P*-value. The overall statistical significance level for the interim and final analyses together is 0.05 for the two-sided test. A supplemental log-rank test will also be performed, and the survival function for each treatment arm will be estimated by the Kaplan–Meier method. Additionally, the Cox proportional hazards model with treatment assignment, two stratifying factors and change from baseline in blood pressure at each visit as covariates will be used to evaluate whether the effect of aliskiren on endpoints can be accounted for by changes in blood pressure over time, or not.

For the secondary endpoints, the same Cox proportional hazards model will be used to estimate the hazard ratio with the confidence limits and the *P*-value for treatment comparison. Holm's multiple comparison procedure will be used to control the overall type I error rate for the two secondary variables. The significance level used for the final analysis of the primary efficacy variable will be used as the overall significance level for the analysis of two secondary efficacy variables. For example, if the significance level for final analysis is 0.046, then this 0.046 will be used as the overall significance level for secondary analysis.

All exploratory endpoints will be analysed using appropriate statistical methods, and all tests will be two-sided at a significance level of 0.05.

Two efficacy interim analyses have been planned and the results of the interim analyses will be reviewed by the independent DMC. The Lan-DeMets alpha spending function approximating an O'Brien–Fleming boundary will be used to ensure the overall type I error of 0.025 based on a one-sided test. The trial may be concluded early for efficacy if a significant difference between two treatment arms for the primary endpoint is achieved by crossing the pre-specified boundary at interim analysis. This boundary will be

calculated based on alpha spending function at each analysis time point. If interim analysis is done at an equally spaced timepoint, then the boundary will be the O'Brien–Fleming boundary.

Central event adjudication

All potential study endpoints will be adjudicated by a central adjudication committee. Investigators will complete endpoint adjudication forms and submit these along with endpoint-specific source documentation. All potential endpoints are independently reviewed and adjudicated by two physician reviewers. When there is disagreement regarding the appropriate adjudication amongst the two reviewers, events are brought and discussed before the full endpoint committee comprising all the other physician reviewers and the committee chair and/or co-chair, who serve as the final arbiter of the appropriate adjudication in the event of inability to achieve consensus. All deaths will be classified as cardiovascular or non-cardiovascular, and cardiovascular death will be subclassified as fatal myocardial infarction, pump failure, sudden death, presumed sudden death, fatal stroke, fatal pulmonary embolism, procedure-related death or presumed cardiovascular death. Non-cardiovascular deaths will also be subclassified.

Sudden death is defined as death occurring unexpectedly in an otherwise stable subject and will be further subclassified as follows:

1. death witnessed or subject last seen alive <1 h previously or
2. subject last seen alive between 1 h and <24 h previously.

Presumed sudden death is defined as death occurring unexpectedly in an otherwise stable subject last seen alive 24 h previously, with circumstances suggestive of sudden death. Deaths within 14 days of a cardiovascular procedure due to procedure-related complications will be classified as cardiovascular deaths. The following non-fatal endpoints will be adjudicated: (a) Unplanned hospitalization for heart failure, (b) resuscitated sudden death, (c) stroke, (d) ESRD, (e) doubling of baseline serum creatinine concentration, (f) myocardial infarction and (g) unplanned hospitalization for myocardial ischaemia. A complete list of endpoint definitions are listed in Table 3.

Program management and committees

Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) is an investigator-initiated study, conducted and funded by Novartis. As the investigators, led by HHP, conceived the original idea, designed the trial and wrote the protocol, we have termed this an investigator-initiated trial.

Members of the executive committee are H.-H. Parving, Chairman, Denmark; M. Pfeffer, Co-chairman, USA; B.M. Brenner, USA; J.J.V. McMurray, Scotland; D. de Zeeuw, the Netherlands; S.M. Haffner, USA; S.D. Solomon, USA; N. Chaturvedi, England; M. Ghadanfar, Switzerland.

Members of the independent DMC are G.C. Viberti, Chairman, England; B. Zinman, Canada; T.R. Pedersen, Norway; J.M. Lachin, USA.

Members of the Endpoint Adjudication Committee are S.D. Solomon, Chairman, USA; Akshay Desai, MD, MPH, Co-Chair; Peter Finn, MD; Lawrence Weinrauch, MD; Olga Vasylyeva, MD; Julie Lin, MD, MPH.

Discussion

The primary objective of ALTITUDE is to evaluate the efficacy and safety of the optimal recommended dose of aliskiren (300 mg daily) added to full recommended conventional therapy (including maximum dose of ACEi or ARB) in preventing and treating cardiovascular and renal events in patients with type 2 diabetes who are at a high risk of developing such events; i.e. patients with either persistent albuminuria, or persistent microalbuminuria with eGFR ≥30 and <60 mL/min/1.73 m^2, or history of cardiovascular disease with eGFR ≥30 and <60 mL/min/1.73 m^2.

Plasma renin activity, known to be inhibited by aliskiren, has been associated with increased cardiovascular risk [32]. If the profound inhibition of plasma renin activity by aliskiren leads to a beneficial effect in CVD, it will be evident in ALTITUDE. In addition, our study will evaluate the effect of direct renin inhibition in diabetic patients who have experienced the compensatory rise in plasma renin and other downstream RAAS components, including aldosterone, induced by ACE inhibition or ARBs. The damaging impact of aldosterone escape is well established in CVD and renal disease during ACE inhibition or ARB treatment [33–36]. Aliskiren is expected to block the compensatory rise in RAAS activity, and offer a novel approach to dual blockade of the RAAS. Although recent results of both VALIANT [37] and ONTARGET [38] showed no clinical benefits of the combination of effective doses of an ACEi and ARB, combining with aliskiren may offset potential deleterious effects of compensating renin activation.

Differences between the ONTARGET [39] and ALTITUDE studies regarding patient characteristics, drug intervention, impact of intervention on the RAAS, primary composite endpoint and annual event rate are presented in Table 4. Recently, data from the ONTARGET study, dealing with their renal outcome, revealed an overall rate of decline in estimated GFR of ∼1 mL/min/1.73 m^2, equal to the loss in kidney function due to ageing. In contrast to several previous renal studies using RAAS blockade [14,16,17,26], a rise in urinary albumin excretion rate of 20–30% was observed during the ONTARGET trial (RENAL). Discarding acute dialysis from the renal endpoint led to insignificant differences between the three groups. An editorial [40] dealing with the study stated:

> Data collection on kidney function was scant: specifically, urine albumin excretion was not assessed annually and the need for dialysis was established arbitrarily with no predetermined protocol and data assessed post hoc. A properly done prospective trial of patients with advanced proteinuric chronic kidney disease is still needed to answer

Table 3. Endpoint definitions

Death	Cardiovascular	Death due to cardiovascular cause, subclassified as myocardial infarction, heart failure, death during a cardiovascular procedure or as a result of procedure-related complications, sudden or presumed sudden death, stroke, pulmonary embolism, or death resulting from a documented cardiovascular cause other than those listed above. Death likely due to a cardiovascular cause in which the available clinical data are insufficient to support a more specific cause of death will also be adjudicated in this category
	Non-cardiovascular	With an unequivocal and documented non-cardiovascular primary cause of death, these will be further classified as infection, malignancy, pulmonary, gastrointestinal, renal, accidental, suicide, diabetes or other (which will be specified)
	Unknown	Insufficient data are available to make a reasonable differentiation of cardiovascular or non-cardiovascular cause of death
Myocardial infarction	Non-procedural	Troponin or CKMB > 2 × URL and either ischaemic symptoms or new ischaemic ECG changes
	Post-PCI/post-cardiac surgery	Troponin or CKMB > 3 × URL/troponin or CKMB > 5 × URL
Unplanned hospitalization for heart failure	Presentation to an acute care facility requiring an overnight hospitalization with an unexpected exacerbation of heart failure (1 or more symptoms and 2 or more signs), required treatment with either IV diuretics, vasodilators, inotropes, mechanical fluid removal or insertion of an intra-aortic balloon pump for haemodynamic compromise, initiation of standing oral diuretics or intensification of the maintenance diuretic	
End-stage renal disease	Initiation of dialysis, renal transplantation or a serum creatinine concentration >6.0 mg/dL	
Doubling of baseline serum creatinine concentration	A doubling of baseline serum creatinine to a value greater than the upper limit of normal as determined by two central laboratory measurements separated by ≥ 30 days	
Resuscitated sudden death	Subject experiences sudden death or cardiac arrest and is successfully resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation with a meaningful recovery of consciousness. Transient losses of consciousness such as seizures or vasovagal episodes that do not reflect significant cardiac dysfunction are excluded	
Non-fatal stroke	Event meeting one of the following criteria (1) A focal neurological deficit of central origin lasting >24 h, with or without imaging confirmation of cerebral infarction or intracerebral haemorrhage (2) Focal neurological deficit of central origin lasting <24 h with corresponding imaging evidence of cerebral infarction or intracerebral haemorrhage (3) A focal neurological deficit of central origin lasting <24 h that was treated with thrombolytic therapy or directed percutaneous intervention (4) A non-focal encephalopathy lasting >24 h with imaging evidence of cerebral infarction or haemorrhage adequate to account for the clinical state (5) Retinal artery ischaemia or haemorrhage. Further classified as: ischaemic, ischaemic with haemorrhagic conversion, primary intracranial haemorrhage, unknown	

URL = upper reference limit.

Table 4. Differences between the ONTARGET and ALTITUDE studies

	ONTARGET	ALTITUDE
Characteristics		
No. of patients	25 620 (37.5% with diabetes)	8600 type 2 diabetes
Micro- and macroalbuminuria	17.1%	∼50%
eGFR ≥30<60 mL/min/1.73 m^2	24.0%	∼75%
eGFR <30 mL/min/1.73 m^2	263	excluded
Intervention		
Dual blockade with ACEi + ARB	+	−
Dual blockade with aliskiren and ACEi or ARB	−	+
Impact of dual RAAS blockade on components of the RAAS	Elevation of Ang I, Ang II, PRA	Reduction of Ang I, Ang II, PRA, aldosterone
Impact of dual RAAS blockade on urinary-albumin excretion	Increase	Decrease (based on AVOID data [26])
Outcome		
Primary composite endpoint	Cardiovascular death Myocardial infarction Non-fatal stroke Unplanned hospitalization for heart failure	Cardiovascular death Myocardial infarction Non-fatal stroke Unplanned hospitalization for heart failure ESRD or renal death or doubling of baseline serum creatinine concentration sustained for at least 1 month
Annual event rate of primary composite endpoint	4%	8%

Ang = angiotensin, PRA = plasma renin activity.

definitely the question about the efficacy of combination therapy to block the renin–angiotensin system on progression of chronic kidney progression.

Recently, a study of healthy people on a low-sodium diet has shown that renal vasodilation with aliskiren far exceeds that seen with ACE inhibition and ARBs [41]. These results indicate that aliskiren may provide greater and thus more effective blockade of the RAAS in the kidney. Since the renin–angiotensin system is upregulated in type 2 diabetic patients as compared with controls [42], the difference in renal vasodilation with aliskiren could be even more pronounced. Most recently, a synergistic effect of aliskiren and irbesartan on the degree of RAAS blockade, as indicated by the rise in plasma renin concentration, has been demonstrated in hypertensive type 2 diabetic patients with albuminuria [43]. Furthermore, the same study demonstrated a rather close inverse correlation ($r^2 = 0.6$, $P = 0.001$), between the rise in plasma renin concentration and albuminuria reduction, suggesting that a more pronounced intrarenal RAAS blockade induced a bigger renoprotective effect (Persson *et al*., JASN submitted). In addition, the rise in plasma renin concentration may reflect a longer half-life of renin bound to aliskiren [44] and/or detection of prorenin as renin [45]. The clinical importance of (pro)renin receptor activation independently of the conversion of angiotensinogen to angiotensin I is presently unknown.

Aliskiren has a plasma half-life of 24 h or more, and a trough-to-peak ratio of close to 1 for the 300 mg dose. Consequently, effective 24 h blood pressure control generally is obtainable with aliskiren [24]. This may be an advantage in long-standing diabetic patients with or without chronic kidney disease, since such patients frequently suffer from the so-called non-dipping of their night-time blood pressure [46]. Previous studies have demonstrated that night time blood pressure, compared to daytime, has a more damaging effect on the vasculature [47]. Several studies have documented the blood pressure lowering capacity of aliskiren either alone or in combination with other classes of blood pressure lowering drugs [48,49]. The dramatic increase in the global incidence of type 2 diabetes has a major adverse impact on public health. In addition to improved implementation of evidence-based therapies [5], novel approaches are needed. The recent disappointing results of studies of more intensive glycaemic control [21,22] underscore the need for properly powered morbidity and mortality randomized clinical trials to evaluate patients with diabetes. Unfortunately, less than 20% of the registered randomized clinical trials of interventions for diabetes are designed to determine whether patient important outcomes (rather than laboratory-based values) are altered by the intervention [50].

ALTITUDE seeks to determine whether an optimally treated cohort of at risk patients with type 2 diabetes will experience a clinically important reduction in cardiovascular and renal major events with the addition of aliskiren.

Conflict of interest statement. All authors have received consultancy/lecture fees from Novartis. M.G., N.W., Z.X. and J.A. are employed by Novartis.

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Received for publication: 29.9.08
Accepted in revised form: 1.12.08