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Baseline characteristics in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE)

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Abstract

Introduction: Patients with type 2 diabetes are at enhanced risk for macro- and microvascular complications. Albuminuria and/or reduced kidney function further enhances the vascular risk. We initiated the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE). Aliskiren, a novel direct renin inhibitor, which lowers plasma renin activity, may thereby provide greater cardio-renal protection compared with angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) alone.
Materials and methods: ALTITUDE is a randomized, double-blind, placebo-controlled study in high risk type 2 diabetic patients receiving aliskiren 300 mg once daily or placebo added to recommended cardio-renal protective treatment including ACEi or ARB, but not both. The number of patients randomized was 8606.
Results: Baseline characteristics (median, IQR) are: age 65 (58, 72) years, male 68%, BMI 29.1 (25.7, 32.2) kg/m^2, cardiovascular disease 47.9%, blood pressure 134.7 (126, 150)/74.3 (67, 81) mmHg, HbA_{1c} 7.5 (6.6, 8.6)%, LDL-cholesterol 2.4 (1.9, 3.0) mmol/L, haemoglobin 130 (119, 143) g/L, serum creatinine 115 (91, 137) µmol/L, eGFR 51.7 (42, 65) ml/min per 1.73 m^2, geometric mean UACR 198.9 (52, 2886) mg/g and frequency of micro/macroalbuminuria 25.7% and 58.2%. ALTITUDE is an event-driven trial to continue until 1628 patients experience a primary cardiovascular-renal event.
Conclusions: ALTITUDE will determine the potential cardio-renal benefit and safety of aliskiren in combination with ACEi or ARB in high risk patients with type 2 diabetes.

Keywords

Albuminuria, aliskiren, cardiovascular disease, kidney disease

Introduction

Persistent albuminuria is the hallmark of diabetic nephropathy, a condition that is characterized by progressively rising arterial blood pressure, declining glomerular filtration (GFR) rate and a high risk of end-stage renal disease (ESRD) and fatal or non-fatal cardiovascular disease (CVD).[1] Next to blood pressure, baseline urinary albumin excretion, initial reduction in albumin excretion with therapy and residual albumin excretion, despite renoprotective treatment, are all closely associated with decline in GFR, risk of ESRD, CVD events and mortality in diabetes.[2–5] In addition, reduced GFR (<60 ml/min per 1.73m^2) is an independent risk factor for both ESRD and CVD.[6,7] Type 2 diabetes and chronic kidney disease (CKD) are both characterized by increased activity of the renin–angiotensin–aldosterone system (RAAS).[1] A novel renal metabolic receptor, GPR91, which binds succinate, is a direct link

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between glycaemic control and renin release.[8] Patients with poor glycaemic control have the highest renin release. Previous studies have demonstrated that the RAAS plays an important role in the development and progression of diabetic macro- and microangiopathy.[1] Consequently RAAS blockade and blood pressure (BP) lowering have been a cornerstone in the prevention and treatment of cardio-renal complications in diabetic patients.[9–12] Despite the improved outlook for type 2 diabetic patients there is still a large unmet need for new strategies to further reduce cardiovascular and renal complications.

In 2007 an orally active direct renin inhibitor, aliskiren, was approved for treatment of hypertension. Aliskiren inhibits the first and rate-limiting step in the RAAS cascade, the conversion of angiotensinogen to angiotensin I, thereby reducing synthesis of all subsequent components of the cascade, except plasma renin concentration.[13] Several small studies with aliskiren in diabetes have demonstrated an anti-proteinuric effect of monotherapy, enhanced albuminuria reduction with dual RAAS blockade and that the optimal dose for reno-protection is 300 mg once daily.[14–16] In a multinational, randomized, double-blind study (AVOID), in 599 patients with hypertension, type 2 diabetes and nephropathy, who are receiving the recommended renoprotective treatment, we showed that the anti-proteinuric effect of aliskiren was independent of its blood pressure-lowering action.[17]

The aim of the present trial is to determine the effectiveness and safety of direct renin inhibition with aliskiren compared with placebo in type 2 diabetic patients at high risk of fatal and non-fatal renal and CVD events. Aliskiren is added to optimal treatment with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), along with other evidence-based cardiovascular protective therapy, which is recommended in all patients.

Materials and methods

The detailed rationale, study design and methods for ALTITUDE have been published elsewhere.[18]

Study population

We are studying type 2 diabetic patients at high risk for fatal and non-fatal cardiovascular and renal events. The patients are required to fulfil the following inclusion criteria: persistent albuminuria (urinary albumin/creatinine ratio, UACR $\geq$ 200 mg/g) in two out of three consecutive first morning void urine samples, or an eGFR $\geq 30 < 60$ ml/min per 1.73 m^2 calculated by the abbreviated MDRD study equation[19] and persistent microalbuminuria (UACR $\geq$ 20 mg/g) in two out of three consecutive first morning void urine samples or a history of CVD. In ALTITUDE microalbuminuria was defined as a UACR 20–200 mg/g, as compared with the standard definition of 30–300 mg/g, because all patients were already on therapy with an ACEi or ARB.

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 provided written informed consent. An external independent data monitoring committee (DMC) will monitor safety throughout this study. The trial has been registered on Clinicaltrials.gov, NCT00549757.

Medical management

It is recommended that all patients receive optimal doses of an ACEi or ARB, optimal antihypertensive therapy for renal and CVD protection and primary or secondary preventive therapy with a statin, anti-platelet therapy and a beta-blocker treatment, as indicated by local guidelines. Glycaemic control is also recommended to follow local guidelines.

Primary objective

The primary endpoint is the composite of cardiovascular (CV) death, resuscitated sudden death, non-fatal myocardial infarction (MI), non-fatal stroke, unplanned hospitalization for heart failure, ESRD or renal death or doubling of baseline serum creatinine concentration, sustained for at least a month, which will be analysed as time to the first event. 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). Renal death is defined as death attributable to kidney failure or due to lack of renal replacement therapy because dialysis or transplantation is unavailable, not provided or refused.

Results

Enrolment

From 10 October 2007 through 23 June 2010, a total of 21,152 patients from 36 countries were screened and 8606 (41%) of these were randomized. The geographical distribution of the randomized patients is shown in Table 1. The main reasons for screen failures were: patients had unacceptable laboratory values (47.3%), did not meet diagnostic/severity criteria (40.1%) or 7.3% withdrew their consent.

Overall cohort

Table 2 shows the baseline characteristics of the randomized population. At the time of randomization 56.6% were treated with insulin, and biguanides and sulphonylureas were used by 46.2% and 31.9%, respectively (Table 3). An ACEi was used by 44.2% and the remaining 55.9% of the patients used an ARB; 63.2% used loop/thiazide diuretics at baseline. The frequency of diuretic use at baseline

Table 1. ALTITUDE – study global status by geographic distribution

Region		Screened	Randomized	Screen failed	Randomization rate
US/Canada		3520	1217	2303	35%
Latin America	Argentina, Brazil, Colombia, Guatemala, Peru, Venezuela	3456	1075	2381	31%
Europe	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, Netherlands, Turkey, UK	8151	3574	4577	44%
Asia	Japan, Korea, Singapore, Taiwan, Thailand	1483	844	639	57%
China		2767	1228	1539	45%
India		1279	476	803	37%
S. Africa		496	192	304	39%
Total		21,152	8606	12478	41%

varied considerably from country to country (range: 26.1% to 89.8%, data not shown). The Asian countries had the lowest use of diuretics, while the European countries had the highest use. Statin treatment was used by 65.1% and aspirin or other anti-platelet agents were used by 62.5%.

Patients with and without history of CVD

Several of the below-mentioned differences were dictated by the inclusion criteria. Patients with CVD were older and more often White, obese, and male, compared with patients without a history of CVD (Table 2). In patients with CVD, the level of UACR and frequency of micro–macroalbuminuria was lower than in patients without a CVD history, whereas serum creatinine was higher. Mean blood pressure and HbA_{1c} were similar, while cholesterol and triglycerides were lower in patients with CVD compared with those without. Patients with CVD were more likely to report beta-blocker, diuretic, statin, aspirin or other anti-platelet agent use compared with those who did not have CVD (Table 3).

Patients with and without macroalbuminuria

Patients with macroalbuminuria were younger, more often non-White, less likely to have CVD and had a lower average creatinine concentration compared with those without macroalbuminuria (Table 2). Blood pressure, HbA_{1c} and LDL-cholesterol tended to be higher in patients with overt albuminuria. Use of CVD-protective therapy was less common in patients with macroalbuminuria, while insulin use was more frequent, compared with those without macroalbuminuria (Table 3).

Comparison with the ONTARGET study

Both ALTITUDE and ONTARGET[20] evaluate the impact of dual RAAS blockade on CVD events, but drug classes differ (ACEi and ARB used in ONTARGET). The primary composite endpoint is identical, but is expanded with ESRD or renal death or doubling of baseline serum creatinine concentration (sustained for at least one month) in ALTITUDE.[18] The ALTITUDE patients are characterized by higher frequency of arterial hypertension (94.4% *vs.* 69%), micro–macroalbuminuria (83.9% *vs*. 17.1%), CKD stage 3 (65% *vs*. 24%) and use of diuretics (63.2% *vs*. 28.0%) compared with the ONTARGET patients. All patients in ALTITUDE have type 2 diabetes, while this was present in 37.5% in the ONTARGET study. CVD history was more common in the ONTARGET patients (85.0% *vs*. 47.9%).

Conclusions

A key aim of treating type 2 diabetes is to prevent or reduce development of micro- or macrovascular complications, and to try to achieve as near normal quality and quantity of life as possible. Multifactorial intervention – with improved glycaemic regulation and the use of RAAS blockers, aspirin and lipid-lowering agents – has been shown to reduce the risk of fatal and non-fatal renal and cardiovascular events.[21] However, the impact on preventing CVD events by different interventions (per 1000 patient-years of treatment) varies considerably: 12 per 4 mmHg lower systolic blood pressure, 8 per 1 mmol/L lower LDL-cholesterol and 3 per 0.9% lower HbA_{1c}.[22] A recent meta-analysis of randomized controlled trials of glycaemic regulation concluded: 'when only high quality studies are considered, no benefit was associated with intensive treatment, and the risk of severe hypoglycaemia doubled'.[23] In the ADVANCE study severe hypoglycaemia was strongly associated with increased risk fatal and non-fatal CVD events.[24] However, no relationship was found between repeated episodes of severe hypoglycaemia, vascular outcomes or death in the ADVANCE study.

The primary objective of ALTITUDE is to evaluate the efficacy and safety of aliskiren 300 mg once daily added to full recommended conventional therapy (including a maximum dose of an ACEi or ARB) in patients with type 2 diabetes who are at high risk of cardiovascular and renal

Table 2. Baseline characteristics of the overall study cohort and by subgroup; randomized population

Variable	Total (*N* = 8606)	Cardiovascular disease history[a]		Urinary albumin to creatinine ratio ≥ 200 mg/g[b]	
		Yes (*N* = 4118)	No (*N* = 4488)	Yes (*N* = 5023)	No (*N* = 3583)
Age, years	65.0 (58, 72)	68.0 (62, 74)	62.0 (55, 69)	62.0 (55, 69)	69.0 (63, 75)
Male, *n* (%)	5851 (68.0)	2991 (72.6)	2860 (63.7)	3437 (68.4)	2414 (67.4)
Race, *n* (%)					
White	4873 (56.6)	2902 (70.5)	1971 (43.9)	2332 (46.4)	2541 (70.9)
African American	280 (3.3)	126 (3.1)	154 (3.4)	164 (3.3)	116 (3.2)
Asian	2726 (31.7)	809 (19.6)	1917 (42.7)	2048 (40.8)	678 (18.9)
Native American	10 (0.1)	9 (0.2)	1 (0.0)	7 (0.1)	3 (0.1)
Other	703 (8.2)	265 (6.4)	438 (9.8)	463 (9.2)	240 (6.7)
Pacific island	14 (0.2)	7 (0.2)	7 (0.2)	9 (0.2)	5 (0.1)
Body mass index (kg/m^2)	29.1 (25.7, 33.2)	30.0 (26.5, 34.0)	28.2 (25.1, 32.3)	28.5 (25.2, 32.8)	29.8 (26.4, 33.6)
Known duration of diabetes, *n* (%)					
≤ 1 year	288 (3.3)	140 (3.4)	148 (3.3)	139 (2.8)	149 (4.2)
> 1–5 years	1229 (14.3)	556 (13.5)	673 (15.0)	669 (13.3)	561 (15.7)
≥ 5 years	7086 (82.3)	3422 (83.1)	3664 (81.6)	4214 (83.9)	2871 (80.1)
Retinopathy, %	36.8	31.3	41.8	43.2	27.7
Laser treatment, n (%)	1457 (16.9)	618 (15.0)	839 (18.7)	1009 (20.1)	448 (12.5)
Peripheral Neuropathy - *n* (%)	2397 (27.9)	1072 (26.0)	1325 (29.5)	1583 (31.5)	814 (22.7)
Any of the following cardiovascular diseases, *n* (%)	4118 (47.9)	4118 (100.0)	0 (0.0)	1715 (34.1)	2403 (67.1)
Congestive heart failure or hospitalization for congestive heart failure	960 (11.2)	960 (23.3)	0 (0.0)	355 (7.1)	605 (16.9)
Unstable angina pectoris	830 (9.6)	830 (20.2)	0 (0.0)	278 (5.5)	552 (15.4)
Myocardial infarction	1434 (16.7)	1434 (34.8)	0 (0.0)	484 (9.6)	950 (26.5)
Prior percutaneous coronary intervention	1224 (14.2)	1224 (29.7)	0 (0.0)	437 (8.7)	787 (22.0)
Prior coronary artery bypass graft	1067 (12.4)	1067 (25.9)	0 (0.0)	326 (6.5)	741 (20.7)
Stroke	852 (9.9)	852 (20.7)	0 (0.0)	378 (7.5)	474 (13.2)
Transient ischaemic attack	353 (4.1)	353 (8.6)	0 (0.0)	153 (3.0)	200 (5.6)
Amputation of toe/foot/leg	341 (4.0)	341 (8.3)	0 (0.0)	226 (4.5)	115 (3.2)
Atrial fibrillation	736 (8.6)	736 (17.9)	0 (0.0)	270 (5.4)	466 (13.0)
Pacemaker implanted	209 (2.4)	209 (5.1)	0 (0.0)	72 (1.4)	137 (3.8)
Smoking history, %					
Current	13.1	9.6	16.4	17.4	7.2
Ex-smoker	36.4	44.8	28.7	32.9	41.3
Diastolic blood pressure, mmHg	74.3 (67.3, 80.7)	73.0 (66.3, 79.7)	75.0 (68.3, 81.3)	75.3 (69.0, 81.7)	72.0 (65.7, 79.0)
Systolic blood pressure, mmHg	134.7 (126.0, 149.7)	136.3 (126.7, 150.3)	133.7 (125.7, 148.7)	135.7 (126.7, 151.3)	133.7 (125.0, 147.3)
Pulse pressure, mmHg	62.0 (52.0, 73.3)	63.7 (53.3, 75.3)	60.3 (50.7, 71.3)	61.3 (51.3, 73.3)	62.3 (52.7, 73.3)
Serum creatinine, µmol/L	115.0 (91.0, 137.0)	119.0 (99.0, 139.0)	109.6 (83.0, 134.0)	105.0 (80.0, 134.0)	121.0 (106.0, 139.0)
eGFR, ml/min per 1.73 m^2	51.7 (41.9, 64.9)	49.2 (41.4, 59.3)	54.1 (42.3, 73.4)	57.4 (43.3, 78.1)	48.0 (40.8, 54.6)
eGFR, ml/min per 1.73 m^2 category, *n* (%)					
< 30	220 (2.6)	108 (2.6)	112 (2.5)	153 (3.0)	67 (1.9)
≥ 30 to < 45	2574 (29.9)	1352 (32.8)	1222 (27.2)	1249 (24.9)	1325 (37.0)
≥ 45 to < 60	3024 (35.1)	1667 (40.5)	1357 (30.2)	1287 (25.6)	1737 (48.5)
≥ 60	2781 (32.3)	985 (23.9)	1796 (40.0)	2331 (46.4)	450 (12.6)

Table 2. (Continued)

Variable	Total (*N* = 8606)	Cardiovascular disease history[a]		Urinary albumin to creatinine ratio ≥ 200 mg/g[b]	
		Yes (*N* = 4118)	No (*N* = 4488)	Yes (*N* = 5023)	No (*N* = 3583)
Urinary albumin to creatinine ratio, mg/g[c]	198.9 (56.2, 886.0)	88.3 (13.1, 513.7)	410.4 (184.5, 1205.7)	772.5 (353.7, 1502.6)	27.7 (8.8, 90.3)
Urinary albumin to creatinine ratio, mg/g, category, *n* (%)[d]					
< 20	1240 (14.4)	1162 (28.2)	78 (1.7)	0 (0.0)	1240 (34.6)
≥ 20 to < 200	2210 (25.7)	1120 (27.2)	1090 (24.3)	0 (0.0)	2210 (61.7)
≥ 200	5012 (58.2)	1707 (41.5)	3305 (73.6)	5012 (99.8)	0 (0.0)
Albumin (g/L)	43.0 (41.0, 45.0)	43.0 (41.0, 45.0)	43.0 (40.0, 45.0)	42.0 (39.0,44.0)	44.0 (42.0, 46.0)
Haemoglobin A_{1C}, %	7.5 (6.6, 8.6)	7.4 (6.6, 8.4)	7.6 (6.7, 8.7)	7.6 (6.8, 8.9)	7.3(6.5, 8.2)
Haemoglobin (g/L)	130.0 (119, 143)	132.0 (121.0, 144.0)	130.0 (118.0, 142.0)	130.0 (119, 143)	131.0 (121, 143)
Total cholesterol, mmol/L	4.4 (3.7, 5.1)	4.1 (3.5, 4.8)	4.6 (3.9, 5.3)	4.6 (3.9, 5.4)	4.1 (3.5, 4.8)
LDL cholesterol, mmol/L	2.4 (1.9, 3.0)	2.2 (1.7, 2.8)	2.6 (2.0, 3.2)	2.5 (2.0, 3.2)	2.2 (1.7, 2.7)
HDL cholesterol, mmol/L	1.1 (1.0, 1.4)	1.1 (0.9, 1.3)	1.2 (1.0, 1.4)	1.1 (1.0, 1.4)	1.1 (0.9, 1.3)
Triglycerides, mmol/L	1.80 (1.30, 2.53)	1.70 (1.20, 2.50)	1.80 (1.30, 2.60)	1.80 (1.30, 2.70)	1.70 (1.20, 2.40)
Serum potassium, mmol/L	4.5 (4.2, 4.8)	4.5 (4.2, 4.8)	4.5 (4.2, 4.8)	4.5 (4.2, 4.8)	4.5 (4.2, 4.8)

Median with first and third quartiles indicated except for urinary albumin to creatinine ratio (UACR). Denominator is the total number of patients in each column.

[a]The subgrouping of cardiovascular disease history is based on the cardiovascular diseases listed in this table.

[b]If baseline UACR is missing, then subgrouping of UACR ≥200 mg/g (Yes/No) is taken from randomization stratification.

[c]UACR is calculated by using the geometric mean of last three measurements prior to randomization visit date. Geometric mean with first and third quartiles indicated.

[d]UACR category definition is based on the median of last three measurements prior to randomization visit date.

Table 3. Baseline medication of the overall study cohort and by subgroup; randomized population

Medication, *n* (%)	Total (*N* =8606)	Cardiovascular disease history[a]		Urinary albumin to creatinine ratio ≥ 200 mg/g[b]	
		Yes (*N* =4118)	No (*N* =4488)	Yes (*N* =5023)	No (*N* =3583)
Insulin of any kind	4871 (56.6)	2254 (54.7)	2617 (58.3)	3124 (62.2)	1747 (48.8)
Biguanides	3982 (46.3)	1859 (45.1)	2123 (47.3)	2367 (47.1)	1615 (45.1)
Sulphonylureas	2742 (31.9)	1309 (31.8)	1433 (31.9)	1526 (30.4)	1216 (33.9)
Thiazolidinediones	725 (8.4)	282 (6.8)	443 (9.9)	411 (8.2)	314 (8.8)
Angiotensin-converting-enzyme inhibitor	3807 (44.2)	2089 (50.7)	1718 (38.3)	2038 (40.6)	1769 (49.4)
Angiotensin-II-receptor blocker	4814 (55.9)	2041 (49.6)	2773 (61.8)	2997 (59.7)	1817 (50.7)
Beta-blocker	4312 (50.1)	2716 (66.0)	1596 (35.6)	2184 (43.5)	2128 (59.4)
Calcium channel blocker	5265 (61.2)	2366 (57.5)	2899 (64.6)	3341 (66.5)	1924 (53.7)
Loop/thiazide diuretics	5438 (63.2)	2907 (70.6)	2531 (56.4)	2910 (57.9)	2528 (70.6)
Aldosterone receptor blocker	30 (0.3)	23 (0.6)	7 (0.2)	6 (0.1)	24 (0.7)
Statin	5600 (65.1)	3169 (77.0)	2431 (54.2)	2971 (59.1)	2629 (73.4)
Other lipid lowering agent	1392 (16.2)	799 (19.4)	593 (13.2)	713 (14.2)	679 (19.0)
Aspirin only	4183 (48.6)	2270 (55.1)	1913 (42.6)	2258 (45.0)	1925 (53.7)
Aspirin or other anti-platelet agent	5381 (62.5)	3209 (77.9)	2172 (48.4)	2803 (55.8)	2578 (72.0)

Denominator is the total number of patients in each column. Baseline medications are defined as the medications taken at baseline visit (randomization visit). Indapamide (classified as other diuretics) is not included in loop/thiazide diuretics.

[a]The subgrouping of cardiovascular disease history is based on the cardiovascular diseases listed in Table 2.

[b]If baseline urinary albumin to creatinine ratio (UACR) is missing, then subgrouping of UACR ≥ 200 mg/g (Yes/No) is taken from randomization stratification.

events. At baseline, the majority of patients had micro- or macroalbuminuria and stage 3 CKD, i.e. are at high risk for both renal events and CVD. In addition, nearly half already had a history of CVD. Indeed, this may be an underestimate as a recent study suggested that more than 50% of asymptomatic patients with type 2 diabetes and an UACR above 30 mg/g had significant coronary arterial disease.[25]

At randomization 220 patients had stage 4 CKD, except 12 patients with pre-randomized determination of eGFR below 30 ml/min per 1.73m^2, the remaining 208 had pre-randomized determination above 30 ml/min per 1.73m^2. It should be mentioned that the enrolment criteria led to a lower eGFR in CVD patients as compared with patients with macroalbuminuria, since reduced eGFR was not a requirement in the latter group.

A recent systemic review of event rates in clinical trials in diabetes mellitus concluded:[26] 'Trials including diabetic subjects without cardiovascular disease or proteinuria generate few events, and require substantial participant numbers to achieve adequate power. However, presence of coexisting cardiovascular disease or proteinuria increases event rate multiple-fold'. The enrolment criteria in ALTITUDE reflect that knowledge.

At randomization the patients were already fairly well treated, regarding important cardiovascular and renal risk factors, such as blood pressure, lipid levels, glycaemic regulation, haemoglobin and low frequency of smoking. Approximately 80% of the patients were treated with a lipid lowering agent and 63% with anti-platelet therapy, with even higher rates of use of these drugs in patients with CVD. Insulin, as expected, was the most commonly prescribed hypoglycaemic drug, followed by metformin. The common use of metformin is notable in relation to the reduced renal function in the patients, but reflects the much wider indication for biguanides nowadays. The main concern for lactic acidosis is in patients with an eGFR <30 ml/min per 1.73 m^2.

CKD and the diabetic state are characterized by enhanced tissue RAAS activity[27] and sodium and fluid retention. Consequently, diuretic treatment should be considered in nearly all of our patients. The benefits from diuretics are numerous: reduced sodium and fluid retention, improved effect of RAAS blockade, improved blood pressure control and reduced frequency of hyperkalaemia. However, only 63% of the patients in ALTITUDE are prescribed diuretics at baseline.

Aliskiren differs from an ACEi and ARB in blocking the first and rate-limiting step in the RAAS, leading to suppression of all RAAS hormones including plasma renin activity, but not plasma renin concentration. In addition, the drug has a half-life of approximately 40 hours, with a trough-to-peak ratio of 0.9 for the 300 mg dose. Enhanced and more complete blockade of the intrarenal RAAS has also been demonstrated.[28] Animal studies suggest that aliskiren reduces the number of (pro)renin receptors in the kidney.[29] Since non-dipping of night-time blood pressure and enhanced diurnal blood pressure variability are frequently present in patients with CKD and long standing diabetes,[30–32] long lasting stable blood pressure reduction as obtained with aliskiren might prove beneficial.

What is key, however, to the hypothesis tested in ALTITUDE is that aliskiren has additional potentially beneficial actions when added to an ACEi or ARB and that these might translate into improved clinical outcomes. In AVOID, when combined with an ARB, aliskiren lowered urinary albumin excretion in patients with diabetic nephropathy.[17] Numerous studies[2–4] have documented that the initial treatment-induced reduction in albuminuria is highly predictive of reduction of fatal and non-fatal renal and cardiovascular events including the most recent analysis of the ONTARGET and TRANSCEND studies. When added to an ACEi or an ARB in patients with chronic heart failure, aliskiren reduced brain natriuretic peptide (BNP), a change also predictive of improved outcome in this condition[31]. Although adding aliskiren to an ACEi or ARB did not lead to greater regression of left ventricular mass in hypertensive patients with left ventricular hypertrophy[33] or reduce left ventricular remodelling after MI[34] overall in ALLAY and ASPIRE, there was a trend to more regression and less remodelling with aliskiren in the subgroup of patients with diabetes, possibly because these patients have enhanced RAAS activity. More regression of left ventricular hypertrophy in hypertension and left ventricular remodelling after MI are both predictive of better clinical outcomes.

In conclusion, the ALTITUDE study will determine the potential cardio-renal benefit and safety of the direct renin inhibitor aliskiren in combination with ACEi or ARB in a broad range of high risk patients with type 2 diabetes.

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Conflict of interest

All authors have received consultancy/lecture fees from Novartis. MN, AR, ZX and JA are employed by Novartis.

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