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Authors
Heerspink, Hiddo J Lambers
Chertow, Glenn M
Akizawa, Tadao
et al.

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Baseline characteristics in the Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes mellitus: the Occurrence of renal eveNts (BEACON) trial

Hiddo J. Lambers Heerspink[1],
Glenn M. Chertow[2],
Tadao Akizawa[3],
Paul Audhya[4],
George L. Bakris[5],
Angie Goldsberry[4],
Melissa Krauth[4],
Peter Linde[6],
John J. McMurray[7],
Colin J. Meyer[4],
Hans-Henrik Parving[8],
Giuseppe Remuzzi[9],
Heidi Christ-Schmidt[10],
Robert D. Toto[11],
Nosratola D. Vaziri[12],
Christoph Wanner[13],
Janet Wittes[10],
Danielle Wrolstad[10]
and Dick de Zeeuw[1]

[1]Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands,
[2]Department of Medicine, Stanford University School of Medicine, Palo Alto, CA, USA,
[3]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan,
[4]Reata Pharmaceuticals, Irving, TX, USA,
[5]Department of Medicine, AHS Comprehensive Hypertension Center, The University of Chicago Medicine, Chicago, IL, USA,
[6]Abbvie Pharmaceuticals, Chicago, IL, USA,
[7]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK,
[8]Department of Medical Endocrinology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark,
[9]Unit of Nephrology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo and IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy,
[10]Statistics Collaborative, Inc., Washington, DC, USA,
[11]Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA,
[12]Department of Nephrology and Hypertension, University of California, Irvine, CA, USA and
[13]Division of Nephrology, Department of Medicine, University of Würzburg, Würzburg, Germany

Correspondence and offprint requests to:
Dick de Zeeuw; E-mail: d.de.zeeuw@umcg.nl

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ORIGINAL ARTICLE

ABSTRACT

Background. Type 2 diabetes mellitus (T2DM) is the most important contributing cause of end-stage renal disease (ESRD) worldwide. Bardoxolone methyl, a nuclear factor-erythroid-2-related factor 2 activator, augments estimated glomerular filtration. The Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes mellitus: the Occurrence of renal eveNts (BEACON) trial was designed to establish whether bardoxolone methyl slows or prevents progression to ESRD. Herein, we describe baseline characteristics of the BEACON population.

Methods. BEACON is a randomized double-blind placebo-controlled clinical trial in 2185 patients with T2DM and chronic kidney disease stage 4 (eGFR between 15 and 30 mL/min/1.73 m^2) designed to test the hypothesis that bardoxolone methyl added to guideline-recommended treatment including inhibitors

of the renin–angiotensin–aldosterone system slows or prevents progression to ESRD or cardiovascular death compared with placebo.

Results. Baseline characteristics (mean or percentage) of the population include age 68.5 years, female 43%, Caucasian 78%, eGFR 22.5 mL/min/1.73 m^2 and systolic/diastolic blood pressure 140/70 mmHg. The median urinary albumin:creatinine ratio was 320 mg/g and the frequency of micro- and macroalbuminuria was 30 and 51%, respectively. Anemia, abnormalities in markers of bone metabolism and elevations in cardiovascular biomarkers were frequently observed. A history of cardiovascular disease was present in 56%, neuropathy in 47% and retinopathy in 41% of patients.

Conclusions. The BEACON trial enrolled a population heretofore unstudied in an international randomized controlled trial. Enrolled patients suffered with numerous co-morbid conditions and exhibited multiple laboratory abnormalities, highlighting the critical need for new therapies to optimize management of these conditions.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to be the single most important contributing cause of end-stage renal disease (ESRD) worldwide. Novel drugs that slow or halt loss of function in diabetic (and other) causes of chronic kidney disease (CKD) are therefore highly desirable [1]. Bardoxolone methyl, a potent activator of nuclear factor-erythroid-2-related factor 2 (Nrf2) and suppressor of NF-κB, stimulates an antioxidant response and attenuates inflammatory processes [2]. These effects have been associated with an increase in estimated glomerular filtration rate (eGFR) which is sustained for at least 52 weeks [3]. This finding suggests that pharmacological Nrf2/NF-κB targeting might be an attractive approach to advance the management of diabetic kidney disease beyond conventional therapy with inhibitors of the renin–angiotensin–aldosterone system (RAAS).

Previous randomized controlled trials in diabetic kidney disease used death, ESRD (dialysis or transplantation) or doubling of serum creatinine as the primary composite endpoint [4, 5]. These trials generally enrolled patients with mild to moderately impaired kidney function (CKD stage 3, corresponding to an eGFR between 30 and 59 mL/min), in order that sufficient endpoints (including a doubling of serum creatinine) would occur within a realistic time period. Since the mechanism by which bardoxolone methyl decreases serum creatinine was previously not well described, the FDA recommended a renal composite endpoint that did not include a serum creatinine-based component. The Bardoxolone methyl EvAluation in patients with CKD and type 2 diabetes mellitus: the Occurrence of renal eveNts (BEACON) trial was therefore designed to assess the effect of bardoxolone methyl versus placebo on ESRD or cardiovascular death. Enrollment of a population with advanced (stage 4) CKD (corresponding to an eGFR between 15 and 30 mL/min/1.73 m^2) would be necessary in order for sufficient primary endpoints to occur and to mitigate the need for an extremely large trial of 5 or more years' duration. No randomized controlled trial in a stage 4 CKD population has been previously conducted.

Herein, we describe the patient characteristics of the BEACON trial population.

MATERIALS AND METHODS

BEACON was a randomized, multicenter, double-blind, placebo-controlled, parallel group clinical trial designed to assess the safety and efficacy of bardoxolone methyl relative to placebo in patients with T2DM and stage 4 CKD. The study design, inclusion and exclusion criteria and outcome measures have been reported in detail elsewhere [6]. The study protocol was designed and implemented in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (as adapted by local health authorities), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki. The study is registered at http://www.clinicaltrials.gov (NCT01351675).

Patient population

We enrolled persons ≥18 years of age with T2DM and stage 4 CKD, defined as eGFR between 15 and 30 mL/min/1.73 m^2 with the abbreviated (4-variable) Modification of Diet in Renal Disease Study formula [7], on a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 6 weeks prior to the screening visit unless medically contraindicated. Patients not taking an ACEi or ARB because of a medical contraindication or taking an ACEi or ARB below guideline-recommended levels were not to comprise >12.5% of the total trial population. Inclusion criteria included systolic blood pressure between 105 and 160 mmHg (inclusive), diastolic blood pressure ≤90 mmHg and serum magnesium at least 1.3 mg/dL. Exclusion criteria included type 1 diabetes, known non-diabetic kidney disease, history of kidney transplantation, urinary albumin:creatinine ratio (UACR) >3500 mg/g, hemoglobin A1c ≥ 11.0%, acute dialysis or acute kidney injury within 12 weeks before screening, a cardiovascular event within 12 weeks before randomization and New York Heart Association Class III or IV heart failure. Women who were pregnant or nursing, or who were intending to become pregnant, were also excluded.

Study outcomes

The primary efficacy endpoint of BEACON was the time to the first occurrence of the composite endpoint of ESRD or cardiovascular death. ESRD was defined as the need for maintenance dialysis (peritoneal or hemodialysis) for 12 or more weeks, kidney transplantation or other 'renal death'. Renal death was defined as death attributable to kidney failure or due to lack of renal replacement therapy because dialysis or transplantation was unavailable, not provided or refused. The trial was designed as event driven with follow-up to continue until at least 300 primary endpoints occurred. An independent blinded event adjudication committee was to adjudicate all potential events.

Study design

Patients with T2DM and stage 4 CKD who met all inclusion criteria and none of the exclusion criteria after a 2-week screening period were randomly assigned to receive bardoxolone methyl 20 mg per day (amorphous spray-dried dispersion formulation) or matched placebo. Randomization was stratified by enrollment site. A maximum of 25% of all enrolled patients were to have had UACR <30 mg/g to ensure a balanced population at moderate-to-high risk for ESRD. After randomization, patients were seen every 4 weeks until Week 16 after which study visits alternated with telephone contact visits every 4 weeks. In keeping with current clinical practice guidelines, blood pressure was targeted throughout the trial to <140/90 mmHg in patients with UACR <300 mg/g and to <130/80 mmHg in patients with UACR ≥300 mg/g.

Statistical analyses

Descriptive statistics for baseline variables are presented with means and standard deviations or medians and 25 and 75th percentiles. Categorical variables are reported as counts and percentages. Analysis of variance or Fisher's exact tests were computed to test differences among subgroups defined by UACR, eGFR or presence of a cardiovascular disease history. A log-transformation was applied to non-normally distributed variables for the purpose of analysis. Only P-values <0.001 were considered statistically significant in the current analysis.

RESULTS

Enrollment

From June 2011 until August 2012, 4319 patients were screened at 319 enrollment sites. Of these, 2185 were randomly allocated to bardoxolone methyl or placebo. The main reasons for exclusion were out-of-range values for eGFR, transaminases, blood pressure as well as UACR >3500 mg/g, or HbA1c >11%. As visualized in Figure 1, enrollment proceeded rapidly with, on average, 146 patients randomized per month. Just over 70% of the BEACON population was enrolled in the USA (Figure 1) with representation from 13 other countries.

Overall cohort

Baseline characteristics of the BEACON population are shown in Table 1. The mean age of the population was 68.5 years and 43% were female. Seventy-eight percent of the population was Caucasian, 17% African-American and 3% Asian. The median eGFR was 22.5 mL/min/1.73 m^2. Baseline eGFR was equally distributed across the 15–30 mL/min/1.73 m^2 range (Figure 2). The median UACR was 320 mg/g (Table 1). Approximately 19% of the patients had normoalbuminuria, 30% had microalbuminuria and 51% had macroalbuminuria. The eGFR was inversely correlated with UACR ($r = -0.23$) so that patients with higher eGFR were more likely to have normoalbuminuria, whereas those with lower eGFR were more likely to have macroalbuminuria (Figure 2). The mean systolic/diastolic blood pressure was 140/70 mmHg (Table 1). The Kidney Disease Improving Global Outcomes (KDIGO) blood pressure clinical practice guideline recommends a blood pressure target of 140/90 mmHg for persons with UACR <300 mg/g and 130/80 mmHg for persons with UACR ≥300 mg/g [8]. The KDIGO systolic blood pressure target was met by 35%; the diastolic blood pressure target was met by 89%. Markers of bone and mineral metabolism, electrolytes, markers reflecting acid/base balance and cardiovascular disease markers were above the population reference range in many patients (Table 1).

Co-morbidity

The median reported time since diagnosis of diabetes was 18 [25–75th percentile: 11–25] years. Nearly, all the patients (99%) had a diagnosis of hypertension; the median reported time since diagnosis of hypertension was 15 (8–22) years. At baseline, 47% of the population had neuropathy, 56% had a history of cardiovascular disease and 41% had a diagnosis of retinopathy (Tables 2 and 3). Myocardial infarction and coronary angioplasty were the most frequent indicators of cardiovascular disease (Table 3).

Concomitant medication

At baseline, 90% of patients used either ACEi or ARBs; 10% of those patients used a combination of both an ACEi and ARB. Eighty-four percent of the population used ACEi or ARBs at the guideline-recommended doses at baseline. Sixty-two percent of the population used insulin, 31% used sulfonylureas, 81% used statins, 16% used erythropoiesis-stimulating agents (ESAs) and 58% used oral-activated vitamin D preparations (Table 4).

Baseline characteristics according to eGFR and albuminuria categories

Patients with lower eGFR were younger and had higher UACR, blood urea nitrogen, phosphate, parathyroid hormone and B-type natriuretic peptide (BNP) concentrations as well as lower hemoglobin and bicarbonate concentrations (Table 1). Patients in the lowest eGFR category were more likely to have a diagnosis of retinopathy (Table 2), and were less likely to be treated with ACEi or ARBs, whereas ESA and phosphate binders were more frequently used, as expected (Table 4).

Patients with more severe albuminuria were younger, less likely female, had higher systolic and diastolic blood pressure, higher phosphate, parathyroid hormone and BNP as well as lower BMI and eGFR (Table 1). Patients in the highest UACR category were more likely to have a diagnosis of retinopathy (Table 2). The use of ACEi or ARB therapy did not differ across UACR categories (Table 4).

Baseline characteristics of patients with or without a history of cardiovascular disease

Patients with cardiovascular disease were more often Caucasian, less likely female, had lower LDL and HDL cholesterol and higher BNP concentrations, and were more likely to be diagnosed with neuropathy (Tables 1 and 2). Patients with cardiovascular disease were less likely to be treated with ACEi or

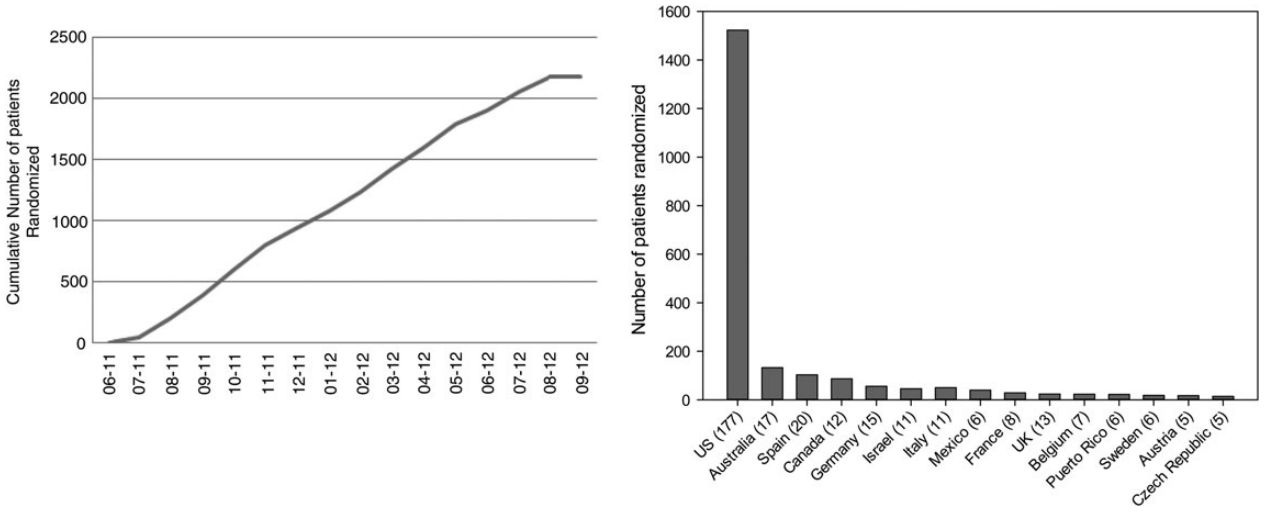

FIGURE 1: Randomizing in BEACON. The left graph shows the total number of patients randomized over time. The right graph shows the number of patients randomized in each country. The number between brackets on the *x*-axis reflects the number of recruiting sites in each country.

ARB but β-blockers, statins and loop diuretics were more frequently prescribed (Table 4).

DISCUSSION

The BEACON trial enrolled a population (T2DM and CKD stage 4) never before assembled in a large multinational randomized controlled trial. Among randomized patients, >80% had either microalbuminuria or macroalbuminuria despite the use of ACEi or ARB therapy in 90% of the population. As expected, electrolyte and hormone disturbances, as well as signs of fluid overload, were common. In addition, many patients suffered from co-morbidities: more than half of the population had cardiovascular disease, and nearly half had neuropathy and retinopathy. Patients used multiple drugs to manage symptoms and complications of impaired kidney function and related co-morbidities.

The BEACON trial recruited 2185 patients within 14 months. The rapid enrollment reflects the enthusiasm of clinicians and patients to participate in this trial, the paucity of competing trials in this specific patient population and the desperate lack of novel therapeutic options for this high risk population. Recruitment in other clinical trials in nephrology has taken substantially longer. For example, recruitment of 1513 and 1715 patients with T2DM and nephropathy in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study and Irbesartan in Diabetic Nephropathy Trial trials took 28 and 36 months, respectively.

Micro- and macroalbuminuria were frequently observed despite maximum tolerated RAAS blockade in 90% of the population. The high prevalence of micro- and macroalbuminuria in the BEACON population contrasts with other studies reporting that most patients with T2DM and nephropathy have urinary albumin excretion in the normal range [9]. Although these cross-sectional data do not establish whether the high albuminuria is a cause or consequence of kidney disease, they do suggest that management and treatment of albuminuria has room for improvement.

Patients with established CKD face a high risk of cardiovascular disease events as observed in the BEACON population. The high prevalence of cardiovascular disease and other T2DM-related co-morbidities, such as neuropathy and retinopathy, indicates that BEACON did not enroll a 'healthy' clinical trial population. Patients with severe CKD have been systematically excluded from cardiovascular disease prevention or intervention trials. The exceptionally high cardiovascular disease burden in patients with T2DM and advanced CKD emphasizes the need for dedicated cardiovascular disease trials in this population.

Optimal blood pressure control is an important management goal in patients with diabetic kidney disease but is difficult to achieve when kidney function declines. At randomization, only 35% of the population met the KDIGO systolic blood pressure target, highlighting the complexity of controlling blood pressure in stage 4 CKD. Dual RAAS blockade with ACE inhibitors and ARBs was allowed and 10% of patients were on dual RAAS blockade despite evidence (part of which was obtained after the trial inception) that this treatment strategy does not confer renal or cardiovascular protection [10, 11]. Ten percent of the population did not use either an ACEi or an ARB and these patients were somewhat more likely to have had an eGFR <20 mL/min/1.73 m^2. Hyperkalemia was the most frequently reported contraindication to the use of RAAS inhibitors distantly followed by (acute) impaired kidney function. We cannot exclude the possibility that investigators had withdrawn ACEi/ARB therapy in patients with the lowest eGFR in order to induce a rise in eGFR hoping to forestall the initiation of dialysis [12]. Next to ACEi and ARB, diuretic therapy is indicated in almost all patients with T2DM and CKD to decrease extracellular volume [13]; however, in BEACON, only 70% of patients were treated with loop diuretics, and 10% with thiazide or thiazide-type diuretics. As expected, loop diuretics were more frequently prescribed in patients with the lowest eGFR.

Table 1. Baseline characteristics of the overall BEACON population and stratified by categories of baseline eGFR, baseline albuminuria and previous cardiovascular disease history

Variable	Total	eGFR category (mL/min/1.73 m^2)			UACR category (mg/g)			CV disease history	
		<20	20–25	>25	0–30	30–300	>300	No	Yes
N	2185	707	765	713	411	656	1118	957	1228
Age, years	68.5 (9.6)	67.4 (9.8)	68.3 (9.2)	69.9 (9.5)[a]	70.8 (8.6)	70.7 (8.5)	66.4 (10)[a]	66.7 (9.9)	69.9 (9)[a]
Female, *n* (%)	934 (42.8)	315 (44.6)	307 (40.1)	312 (43.8)	261 (63.5)	305 (46.5)	368 (32.9)[a]	463 (48.4)	471 (38.4)[a]
Race, *n* (%)									
Caucasian	1694 (77.5)	542 (76.7)	593 (77.5)	559 (78.4)	343 (83.5)	517 (78.8)	834 (74.6)[a]	724 (75.7)	970 (79.0)
Afro-American	361 (16.5)	127 (18.0)	128 (16.7)	106 (14.9)	56 (13.6)	105 (16.0)	200 (17.9)	172 (18.0)	189 (15.4)
Asian	69 (3.2)	20 (2.8)	25 (3.3)	24 (3.4)	2 (0.5)	21 (3.2)	46 (4.1)	35 (3.7)	34 (2.8)
Native American	13 (0.6)	3 (0.4)	6 (0.8)	4 (0.6)	6 (1.5)	2 (0.3)	5 (0.5)	2 (0.2)	11 (0.9)
Pacific Island	13 (0.6)	5 (0.7)	1 (0.1)	7 (1.0)	2 (0.5)	5 (0.8)	6 (0.5)	4 (0.4)	9 (0.7)
Other	35 (1.6)	10 (1.4)	12 (1.6)	13 (1.8)	2 (0.5)	6 (0.9)	27 (2.4)	20 (2.1)	15 (1.2)
BMI, kg/m^2	33.8 (7.1)	34.1 (7.6)	33.5 (6.9)	33.9 (7)	35.5 (7.3)	34.2 (7.5)	33.0 (6.7)[a]	33.9 (7.3)	33.8 (7)
Systolic BP, mmHg	139.6 (12)	140.4 (12)	139.8 (12)	138.7 (12)	132.7 (12)	138.9 (12)	142.7 (11)[a]	140.1 (11)	139.3 (12)
Diastolic BP, mmHg	70.4 (9)	70.3 (9)	70.8 (9)	70.1 (9)	66.2 (8)	69.1 (8)	72.7 (9)[a]	72 (9)	69.2 (9)[a]
Laboratory measurements									
Hemoglobin A_{1c}	7.1 (1.2)	7.1 (1.2)	7.1 (1.2)	7.2 (1.2)	6.9 (1.1)	7.1 (1.2)	7.2 (1.3)	7.1 (1.3)	7.1 (1.2)
Serum creatinine, mg/dL	2.7 (0.6)	3.3 (0.5)	2.7 (0.4)	2.2 (0.3)[a]	2.4 (0.5)	2.6 (0.5)	2.9 (0.6)[a]	2.7 (0.6)	2.7 (0.6)
eGFR, mL/min/1.73 m^2	22.5 (4.5)	17.4 (1.6)	22.4 (1.4)	27.6 (2.2)[a]	24.1 (4.3)	22.9 (4.3)	21.7 (4.5)[a]	22.2 (4.4)	22.7 (4.5)
UACR, mg/g (median; 25–75th percentile)	320 (57–1140)	579 (139–1521)	313 (63–1090)	146[a] (23–768)	10 (4–18)	109 (64–179)	1106 (604–1836)	339 (57–1189)	312 (57–1094)
Blood urea nitrogen, mg/dL	53.3 (16)	61.4 (16)	52.7 (15)	45.9 (13)[a]	50.8 (17)	54.1 (16)	53.8 (15)	52.6 (15)	53.9 (17)
Hemoglobin, g/dL	11.5 (1.4)	11.1 (1.3)	11.6 (1.4)	11.8 (1.4)[a]	11.6 (1.3)	11.5 (1.4)	11.4 (1.5)	11.4 (1.4)	11.5 (1.5)
HDL cholesterol, mg/dL	45.5 (15)	44.7 (14)	45.6 (14)	46.2 (15)	47.8 (15)	45.5 (15)	44.6 (14)	47 (15)	44.3 (14)[a]
LDL cholesterol, mg/dL	79.4 (34)	79.0 (36)	80.9 (33)	78 (33)	78.8 (29.5)	76.3 (32)	81.4 (35.7)	81.7 (35)	77.5 (32)
Total cholesterol, mg/dL	161.6 (43)	160.7 (48)	163.3 (40)	160.8 (40)	162.4 (37)	157.1 (41)	164 (46)	165 (43)	159 (42)
Triglycerides, mg/dL (median; 25–75th percentile)	156 (110–230)	150 (109–220)	158 (108–229)	159 (113–238)	162 (113–222)	149 (107–214)	158 (112–239)	153 (109–223)	157 (111–233)
Magnesium, mmol/L	1.7 (0.2)	1.7 (0.3)	1.7 (0.2)	1.7 (0.2)[a]	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)
Potassium, mmol/L	4.7 (0.5)	4.8 (0.6)	4.7 (0.5)	4.7 (0.5)	4.5 (0.5)	4.7 (0.5)	4.8 (0.6)[a]	4.8 (0.5)	4.7 (0.5)[a]
Urate, mg/dL	8.2 (2)	8.3 (2.1)	8.2 (2)	8.1 (2)	8.5 (2.1)	8.3 (2.2)	8.1 (1.9)	8.1 (2)	8.3 (2)

Bicarbonate, mmol/L	23.7 (3)	23.2 (3.2)	23.8 (2.9)	24.2 (3)[a]	24.7 (2.8)	23.9 (3.1)	23.3 (2.9)[a]	23.3 (2.9)	24 (3.1)[a]
Albumin, mg/dL	4.2 (0.3)	4.1 (0.3)	4.2 (0.3)	4.2 (0.3)	4.3 (0.3)	4.2 (0.3)	4.1 (0.3)	4.2 (0.3)	4.2 (0.3)
Calcium, mmol/L	9.4 (0.6)	9.4 (0.6)	9.4 (0.5)	9.5 (0.5)	9.7 (0.5)	9.5 (0.6)	9.3 (0.6)[a]	9.5 (0.6)	9.4 (0.6)
Phosphate, mmol/L	4.1 (0.6)	4.3 (0.7)	4 (0.6)	3.8 (0.5)[a]	3.9 (0.6)	4.0 (0.6)	4.2 (0.7)[a]	4.1 (0.6)	4 (0.6)
PTH, pg/mL (median; 25–75th percentile)	98 (58–161)	129 (76–211)	97 (59–158)	76[a] (47–124)	74 (44–117)	98 (55–163)	107[a] (67–176)	96 (55–155)	102 (59–167)
BNP, pg/mL (median; 25–75th percentile)	149 (71–293)	159 (79–328)	152 (73–293)	135[a] (65–271)	119 (60–242)	155 (71–298)	158[a] (79–313)	107 (56–215)	193[a] (95–367)

Mean and standard deviations are reported unless otherwise indicated.
Patients were selected for the trial based on their eGFR value during the screening period. At randomization eGFR of 35 patients was <20 mL/min/1.73 m^2 and in 84 patients it was >30 mL/min/1.73 m^2.
BMI, body mass index; BNP, B-type natriuretic peptide; IQR, inter-quartile range; PTH, parathyroid hormone; UACR, urinary albumin:creatinine ratio.
[a]Statistical significance ($P < 0.001$) among three eGFR groups, three UACR groups or two CV disease history groups.

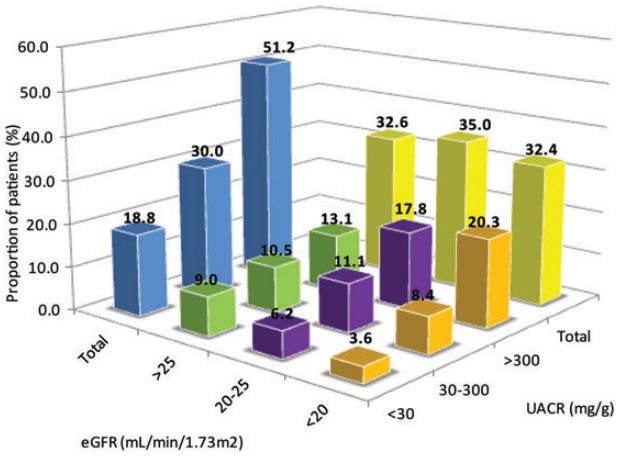

FIGURE 2: Distribution of eGFR and albuminuria. The number on top of each bar is the percentage of the BEACON population.

Apart from blood pressure-lowering agents, other drugs were frequently used to manage co-morbidities. Statins were used by 81% of patients. Studies have shown that the relative cardiovascular protective effects of statins appear to attenuate at lower levels of kidney function but the absolute risk reduction appears to be similar owing to the higher CV risk of patients with low eGFR [14, 15]. The proportion of patients receiving statins was similar to the type 2 diabetic population at cardio-renal risk enrolled in the ALTITUDE trial [16]. With respect to glucose-lowering agents, only 2% of the population used biguanides, which are contraindicated in CKD stage 4 owing to the risk of inducing severe lactic acidosis.

The BEACON population is not representative of all the patients with type 2 diabetes and stage 4 CKD. We excluded patients with the albumin:creatinine ratio >3500 mg/g, HbA1c >11% and systolic blood pressure above or below 160 mmHg or 105 mmHg. To what extent could the exclusion of these patients have influenced the interpretation of our findings? First, we concluded that few people in the BEACON population had normoalbuminuria. The percentage we observed likely overestimates the proportion in the general type 2 diabetes population with stage 4 CKD as we excluded patients at the high end of the albuminuria range. Second, many patients suffered from co-morbidities. The exclusion of patients with indicators of more severe disease could have led to a lower frequency of co-morbidities than in the population seen in clinical practice. Third, the population required multiple drugs. Again, the degree of polypharmacy is likely lower than in the population at large because we excluded more severely diseased patients who would very likely require more medications. Thus, the BEACON may represent a somewhat 'healthier' type 2 diabetes population with stage 4 CKD than seen in clinical practice so that the frequently observed laboratory abnormalities and co-morbidities in BEACON may underestimate what is seen in clinical practice.

In conclusion, the BEACON trial population is unique among nephrology clinical trials in its inclusion of patients with T2DM and stage 4 CKD. In this population, distinct laboratory abnormalities and numerous cardiovascular and other co-morbid conditions were frequently observed. These

Table 2. Diabetic complications in the overall population and stratified by categories of baseline eGFR, baseline albuminuria and cardiovascular disease history

Variable	Total	eGFR category			UACR category			CV disease history	
		<20	20–25	>25	0–30	30–300	>300	No	Yes
N	2185	707	765	713	411	656	1118	957	1228
Retinopathy, *n* (%)	891 (40.8)	320 (45.3)	309 (40.4)	262 (36.7)	119 (29)	264 (40.2)	508 (45.4)[a]	380 (39.7)	511 (41.6)
Neuropathy, *n* (%)	1017 (46.5)	319 (45.1)	355 (46.4)	343 (48.1)	189 (46)	301 (45.9)	527 (47.1)	403 (42.1)	614 (50.0)[a]
Amputation, *n* (%)	106 (4.9)	38 (5.4)	37 (4.8)	31 (4.4)	9 (2.2)	46 (7.0)	51 (4.6)	37 (3.9)	69 (5.6)
Foot ulcers, *n* (%)[b]	73 (8.5)	27 (9.2)	18 (5.7)	28 (11.1)	3 (2.9)	29 (11.2)	41 (8.2)	24 (6.3)	49 (10.1)

[a]Statistical significance ($P < 0.001$) among three eGFR groups, three UACR groups or two CV disease history groups.
[b]Foot ulcer data were collected in a subpopulation of 861 subjects.

findings emphasize the need for novel therapeutic agents in this population and renders BEACON trial results relevant to the broad population of patients with T2DM and stage 4 CKD.

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CONFLICT OF INTEREST STATEMENT

Members of the BEACON Steering Committee received consulting fees for activities related to the trial. H.J.L.H. has consultancy agreements with the following companies: AbbVie, Astellas, Johnson & Johnson, Reata and Vitae. All honoraria are paid to his employer/institution University of Groningen. G.M.C. serves on the Board of Directors of Satellite Healthcare and the Scientific Advisory Board of DaVita Clinical Research. He has received research support from NIDDK and NHLBI, Amgen and Reata and serves as an advisor to Allocure, Ardelyx, Gilead, Home Dialysis Plus, Keryx, PuraCath, Theravance and Thrasos Innovations. T.A. is consultant and received grants and honoraria from Kyowa Kirin, Chugai, Abbott/Abbvie, Astellas, Otsuka, Bayer, Baxter, Daiichisankyo and Retea. P.A., A.G., M.K. and C.J.M. are employed by Reata (P.A. and M.K. at the time of study). G.L.B. Consultant for Takeda, AbbVie, Diachi-Sankyo, Boeringher-Ingelheim, Lilly, Janssen, Mesoblast. Reata. Principal Investigator-Medtronic, Relypsa. J.J.M. is consultant and received honoraria (to employer/institution Glasgow University) from Reata for his time working as a member of the BEACON steering committee. H.-H.P. has reported having equity in Merck and NovoNordisk, receiving consulting and lecture fees from Novartis, Abbott and Reata. G.R. has consultancy agreements with Alexion Pharmaceuticals, Abbvie, Bayer Healthcare, Novartis Pharma and is member of the BEACON Steering Committee (Reata). G.R. does not accept personal remuneration, compensations are paid to his institution for research and educational activities. P.L. is employed by Abbvie. R.D.T. is a consultant for and received honoraria from Amgen, Boehringer-Ingelheim, Abbvie, Hoffman-La Roche, Merck. He has received research support from Novartis and Reata. N.D.V. has received research funding from Reata. C.W. is consultant and received grants (to employer/institution) and honoraria from Abbott/Abbvie, Amgen, Boehringer-Ingelheim, Genzyme-Sanofi and Reata. H.C.-S., D.W., J. W., all of Statistics Collaborative, have a consulting agreement with Reata for statistical work on other trials that Reata is planning. Statistics Collaborative also has consulting agreements with many companies developing drugs, biologics and medical devices. D.d.Z. is consultant for and received honoraria (to employer) from AbVie, Astellas, AstraZeneca, Chemocentryx, J&J, Hemocue, Novartis, Reata, Takeda and Vitae.

Table 3. Cardiovascular disease history in the overall population and stratified by categories of baseline eGFR and albuminuria

Variable	Total	eGFR category			UACR category		
		<20	20–25	>25	<30	30–300	>300
Any CV disease history, *n* (%)	1228 (56.2)	386 (54.6)	411 (53.7)	431 (60.5)	229 (55.7)	379 (57.8)	620 (55.5)
Myocardial infarction	428 (19.6)	136 (19.2)	145 (19)	147 (20.6)	64 (15.6)	137 (20.9)	227 (20.3)
Coronary angioplasty	425 (19.5)	137 (19.4)	147 (19.2)	141 (19.8)	71 (17.3)	136 (20.7)	218 (19.5)
Hospitalization for unstable angina pectoris	157 (7.2)	44 (6.2)	59 (7.7)	54 (7.6)	26 (6.3)	43 (6.6)	88 (7.9)
Coronary artery bypass graft	308 (14.1)	94 (13.3)	110 (14.4)	104 (14.6)	64 (15.6)	93 (14.2)	151 (13.5)
Hospitalization for heart failure	238 (10.9)	88 (12.4)	84 (11)	66 (9.3)	44 (10.7)	77 (11.7)	117 (10.5)
Stroke	224 (10.3)	75 (10.6)	69 (9.0)	80 (11.2)	41 (10)	59 (9.0)	124 (11.1)
Transient ischemic attack	161 (7.4)	46 (6.5)	46 (6.0)	69 (9.7)	33 (8.0)	54 (8.2)	74 (6.6)
Hospitalization for arrhythmias	143 (6.5)	35 (5.0)	52 (6.8)	56 (7.9)	30 (7.3)	52 (7.9)	61 (5.5)
Valve replacement	39 (1.8)	12 (1.7)	12 (1.6)	15 (2.1)	11 (2.7)	11 (1.7)	17 (1.5)
Subpopulation ($N = 861$)[a]							
Congestive heart failure	157 (18.2)	48 (16.4)	59 (18.7)	50 (19.8)	25 (23.8)	45 (17.4)	87 (17.5)
Peripheral artery disease	120 (13.9)	38 (13)	34 (10.8)	48 (19)	10 (9.5)	43 (16.7)	67 (13.5)
Stable angina pectoris	96 (11.1)	31 (10.6)	39 (12.3)	26 (10.3)	9 (8.6)	33 (12.8)	54 (10.8)
Atrial fibrillation/flutter	93 (10.8)	26 (8.9)	36 (11.4)	31 (12.3)	18 (17.1)	31 (12)	44 (8.8)
Pacemaker	58 (6.7)	12 (4.1)	20 (6.3)	26 (10.3)	12 (11.4)	20 (7.8)	26 (5.2)
Carotid artery surgery	26 (3.0)	7 (2.4)	7 (2.2)	12 (4.7)	1 (1.0)	12 (4.7)	13 (2.6)
Lower limb revascularization	32 (3.7)	12 (4.1)	8 (2.5)	12 (4.7)	3 (2.9)	8 (3.1)	21 (4.2)
Implantable cardioverter defibrillator	12 (1.4)	1 (0.3)	3 (0.9)	8 (3.2)	4 (3.8)	3 (1.2)	5 (1.0)

None of the P-values across eGFR and UACR subgroups was >0.001.

[a]In a subpopulation of 861 subjects an expanded set of cardiovascular disease indicators was collected.

Table 4. Baseline medication in the overall randomized population and stratified by categories of baseline eGFR, baseline albuminuria and cardiovascular disease history

Variable	Total	eGFR category			UACR category			CV disease history	
		<20	20–25	>25	<30	30–300	>300	No	Yes
N	2185	707	765	713	411	656	1118	957	1228
Insulin of any kind	1344 (61.5)	462 (65.3)	450 (58.8)	432 (60.6)	212 (51.6)	421 (64.2)	711 (63.6)[a]	546 (57.1)	798 (65.0)[a]
Biguanides	50 (2.3)	7 (1.0)	20 (2.6)	23 (3.2)	12 (2.9)	14 (2.1)	24 (2.1)	25 (2.6)	25 (2.0)
Sulphonyureas	668 (30.6)	200 (28.3)	231 (30.2)	237 (33.2)	177 (43.1)	186 (28.4)	305 (27.3)[a]	304 (31.8)	364 (29.6)
ACE inhibitor	934 (42.7)	280 (39.6)	335 (43.8)	319 (44.7)	201 (48.9)	254 (38.7)	479 (42.8)	414 (43.3)	520 (42.3)
ARB	1233 (56.4)	406 (57.4)	435 (56.9)	392 (55.0)	205 (49.9)	369 (56.3)	659 (58.9)	577 (60.3)	656 (53.4)
ACE inhibitor or ARB	1958 (89.6)	618 (87.4)	685 (89.5)	655 (91.9)	381 (92.7)	581 (88.6)	996 (89.1)	883 (92.3)	1075 (87.5)[a]
ACE inhibitor and ARB	209 (9.6)	68 (9.6)	85 (11.1)	56 (7.9)	25 (6.1)	42 (6.4)	142 (12.7)[a]	108 (11.3)	101 (8.2)
Direct renin inhibitors	49 (2.2)	13 (1.8)	21 (2.7)	15 (2.1)	6 (1.5)	16 (2.4)	27 (2.4)	25 (2.6)	24 (2.0)
Beta -blocker	1404 (64.3)	471 (66.6)	490 (64.1)	443 (62.1)	238 (57.9)	419 (63.9)	747 (66.8)	502 (52.5)	902 (73.5)[a]
Calcium channel blocker	1315 (60.2)	447 (63.2)	471 (61.6)	397 (55.7)	184 (44.8)	394 (60.1)	737 (65.9)[a]	604 (63.1)	711 (57.9)
Loop diuretics	1519 (69.5)	538 (76.1)	523 (68.4)	458 (64.2)[a]	297 (72.3)	472 (72.0)	750 (67.1)	588 (61.4)	931 (75.8)[a]
Thiazide diuretics	217 (9.9)	54 (7.6)	78 (10.2)	85 (11.9)	51 (12.4)	54 (8.2)	112 (10.0)	114 (11.9)	103 (8.4)
Mineralocorticoid receptor antagonist	117 (5.4)	27 (3.8)	46 (6)	44 (6.2)	38 (9.2)	35 (5.3)	44 (3.9)[a]	41 (4.3)	76 (6.2)
Statins	1774 (81.2)	571 (80.8)	612 (80.0)	591 (82.9)	330 (80.3)	544 (82.9)	900 (80.5)	745 (77.8)	1029 (83.8)[a]
Iron supplement	572 (26.2)	219 (31.0)	197 (25.8)	156 (21.9)[a]	113 (27.5)	157 (23.9)	302 (27.0)	255 (26.6)	317 (25.8)
Erythropoiesis-stimulating agents	343 (15.7)	157 (22.2)	106 (13.9)	80 (11.2)[a]	52 (12.7)	104 (15.9)	187 (16.7)	167 (17.5)	176 (14.3)
Vitamin D analogs	1258 (57.6)	436 (61.7)	447 (58.4)	375 (52.6)	256 (62.3)	379 (57.8)	623 (55.7)	549 (57.4)	709 (57.7)
Phosphate binders	302 (13.8)	154 (21.8)	88 (11.5)	60 (8.4)	44 (10.7)	100 (15.2)	158 (14.1)	125 (13.1)	177 (14.4)
Potassium binders	115 (5.3)	45 (6.4)	35 (4.6)	35 (4.9)	8 (1.9)	38 (5.8)	69 (6.2)	49 (5.1)	66 (5.4)

After the database was locked, we discovered that Caduet (amlodinpine/atorvastatine) was not included in the analysis data sets as a Calcium Channel Blocker. Since there were only 24 people involved, we have not rerun the analyses.
[a]Statistical significance ($P < 0.001$) among three eGFR groups, three UACR groups or two CV disease history groups.

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