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Preventing Early Renal Loss in Diabetes (PERL) Study: A Randomized Double-Blinded Trial of Allopurinol—Rationale, Design, and Baseline Data

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PERL Study organization

The *Data Coordinating Center (DCC),* based at the University of Michigan, manages all the trial data, monitors enrollment, retention and compliance. DCC also performs regular site visits and collects, monitors, cleans and analyzes data, including adverse events, from all clinical sites.

The *Central Laboratory*, located at the University of Minnesota, is responsible for analyses of the blood and urine laboratory tests sent by each site.

The PERL *Steering Committee* is composed of the study PIs, Drs. Doria and Mauer, directors of all clinical sites, directors of the DCC and the Central Laboratory as well as the NIH and JDRF program officers. The Steering Committee is responsible for the design of the study and its execution.

The external *Data Safety and Monitoring Board (DSMB),* appointed by the NIH, convenes regularly to provide independent review of the study, assessing the risks to study subjects and monitoring study progress and integrity.

The *Drug Monitoring Committee (DMC),* consisting of the study PIs, the clinical site directors, the DCC Project Manager, the Lead Clinical Coordinator and a research pharmacist, is co-chaired by two site directors (Drs. Caramori and Rossing), responsible for the oversight of study drug administration as well as RAS blocking and antihypertensive therapy during the trial, convenes regularly to review adverse events and medication side-effects. Both the DSMB and the DMC receive regular reports from the Data Coordination Center and have access to all data relevant to committee needs.

PERL Study Group:

***Principal Investigators**:** Alessandro Doria (Joslin Diabetes Center), Michael Mauer (University of Minnesota)

***Steering Committee**:** Ronnie Aronson (LMC Diabetes), Maria Luiza Caramori (University of Minnesota), Jill P. Crandall (Albert Einstein College of Medicine), Ian H. de Boer (University of Washington), Alessandro Doria (Joslin Diabetes Center), John H. Eckfeldt (University of Minnesota), Thomas G. Elliott (BCDiabetes), Michael Flessner (NIDDK), Andrzej T. Galecki (University of Michigan), Allison B. Goldfine (Joslin Diabetes Center), Irl B. Hirsch (University of Washington), Amy B. Karger (University of Minnesota), Ildiko Lingvay (University of Texas Southwestern Medical Center), David M. Maahs (Stanford University), Michael Mauer (University of Minnesota), Janet B. McGill (Washington University), Mark E. Molitch (Northwestern University), Helen Nickerson (JDRF), Afshin Parsa (NIDDK), Bruce A. Perkins (University of Toronto), Sarit Polsky (Barbara Davis Center for Diabetes), Rodica Pop-Busui (University of Michigan), Marlon Pragnell (JDRF), Sylvia E. Rosas (Joslin Diabetes Center), Peter Rossing (Steno Diabetes Center), Peter Senior (University of Alberta), Ronald J. Sigal (University of Calgary), Catherine Spino (University of Michigan), Katherine R. Tuttle (Providence Health Care, University of Washington), Guillermo E. Umpierrez (Emory University)

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* Listed alphabetically by last name.

† Director of PERL central unit or clinical site

‡ Former Director of PERL central unit or clinical site

¶ Overall Study PI's

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Supplementary Table S1. Schedule of Events

Year	1	1	1	1	1	1	1	1	1	1	2	2	2	3	3	3	3	3
Week	-12	-9	-7	-3		0	4	16	32	48	64	80	96	112	128	142	156	164
Visit #	1	2	3	4	4a*	5	6	7	8	9	10	11	12	13	14	15	16	17
^Type of Visit: In-Person Visit Required (V); Phone Call (C) ; Other Visit (In-Person or Remote Visit, O)	O	V	O	V	V	C	O	O	O	O	O	V	O	O	O	O	V	V
EVENT						Allopurinol or placebo											Wash-out	
	Screen	Run-in				RANDO 100 mg	200-400 mg											EOS
Informed Consent	x	x																
Demographics	x																	
Initial Medical Hx		x																
Interval Medical Hx and BP Control Review			x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Meds	x	x	x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Blood Pressure and Measurements	x	x	(x)	x	(x)		(x)	(x)	(x)	(x)	(x)	x	(x)	(x)	(x)	(x)	x	x
ECG Report		x		x	(x)							x					x	
Physical Exam		x		(x)	(x)							x					x	
Skin Assessment				x	(x)							x					x	x
Eligibility	x			x	(x)	x												
Randomization						x												
Family History				x	(x)													
RAS and BP Med Log		x	x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
IGFR Procedure				x	(x)							x					x	x
PERL Study Drug Prescription						x	x	x	x	x	x	x	x	x	x	x		
Study Drug Compliance							x	x	x	x	x	x	x	x	x	x	x	
CENTRAL LAB																		
Serum uric acid, serum creat, cystatin C	x		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Urine ACR/AER	x		x	x	(x)		.	x		x		x		x		x	x	x
HbA1c	x			x	(x)			x	x	x	x	x	x	x	x	x	x	x
HLA B*58:01			x															
iGFR				x	(x)							x					x	x
NIDDK Repository: serum, plasma, urine				x								x					x	x
LOCAL LAB																		
Pregnancy test serum HCG	x		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test urine dipstick		x		x	(x)							x					x	x
ALT, K, CBC, serum creatinine, urine	x		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Protocol Deviation		x	x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events		x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x

*If normal blood pressure control is not achieved at Visit 4, the run-in period may be extended for two more weeks after which participants will be examined as in Visit 4 (Visit 4A). In this event, the GFR measurement scheduled for Visit 4 will be conducted at Visit 4A.

^ Study visits will be generally conducted at the Study Sites or their Satellites. "In-Person Visits" (V) are required for Visit 2 and all visits requiring iohexol-GFR measurements. If a participant lives far from a study site or satellite, or travel impediments are present, other (O) visits may be conducted remotely or in-person. For any given study visit to be conducted remotely, a Phone Visit and a Remote Biospecimen Collection will be both required; a Phone Visit is performed by the study coordinator using the telephone or other media such as Skype to collect results of study procedures that do not require physical interactions (e.g., collection of medical history), and a Remote Biospecimen Collection is performed at a clinical laboratory close to where participants live.

Note: (x) indicates an optional assessment.

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Supplementary Table S2. Rationale for exemptions to eligibility criteria

Eligibility criterion not met	N	Reason for granting exemption
Hemoglobin or platelet count below lower limit	10	Deemed safe through consultation with hematologist and/or primary care provider
Incomplete type 1 diabetes diagnostic criteria	6	Adjudicated as type 1 diabetes by experts in the committee
BP higher than upper limit	4	Blood pressure deemed controllable during the trial
Baseline eGFR outside limits	3	Less than 1 ml/min/1.73 m^2 outside eligible range
Time span of albuminuria shorter than 2 years	2	Minimal deviation from 2 years
Time span of eGFR slope shorter than 3 years	1	Minimal deviation from 3 years
History of prostate cancer	1	Problem considered resolved
History of multiple renal stones	1	Events in distant past

Abbreviation: eGFR, estimated glomerular filtration rate

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Supplemental Table S3. Medication use in PERL participants

Medication	**All (n=530)**	**Albuminuric (n=419)**	**Normoalbuminuric (n=94)**	**Indeterminate (n=17)**
Antihypertensive, N (%)				
Beta blocker	68 (12.8%)	62 (15.0%)	4 (4.3%)	2 (11.8%)
Calcium channel blocker	75 (14.2%)	70 (16.7%)	3 (3.2%)	2 (11.8%)
Loop diuretic	35 (6.6%)	34 (8.2%)	1 (1.1%)	0 (0%)
Thiazide diuretic	59 (11.1%)	49 (11.8%)	8 (8.5%)	2 (11.8%)
Potassium-sparing diuretic	3 (0.6%)	1 (0.2%)	2 (2.1%)	0 (0%)
RAAS inhibitor	477 (90%)	398 (95%)	70 (74.5%)	9 (52.9%)
Alpha1 blocker	3 (0.6%)	3 (0.7%)	0 (0%)	0 (0%)
Other	4 (0.8%)	4 (1%)	0 (0%)	0 (0%)
Affect SUA				
Losartan alone	119 (22.4%)	109 (26%)	9 (9.6%)	1 (5.9%)
Losartan and HCTZ	5 (0.9%)	5 (1.2%)	0	0
HCTZ alone	15 (2.8%)	15 (3.6%)	0	0
Oral glucose-lowering agent, N (%)	5 (0.9%)	3 (0.7%)	1 (1.0%)	1 (5.9%)
Metformin	5 (0.9%)	3 (0.7%)	2 (2.1%)	0
SGLT2 inhibitor	7 (1.3%)	4 (1.0%)	3 (3.2%)	0
Lipid lowering, N (%)				
HMG CoA reductase inhibitor	216 (46.2%)	185 (49.5%)	25 (31.6%)	6 (28.6%)

The data represents number of participants (percentage) taking each medication.
Abbreviations: HCTZ, hydrochlorothiazide; RAAS, renin-angiotensin-aldosterone-system

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Supplementary Table S4. Baseline clinical characteristics according to albuminuria and rapid GFR decline.

Variable	Albuminuric DKD (No eGFR decline) N=205	Albuminuric DKD (With eGFR decline) N=174	P value*	Normo-albuminuric DKF N=94	P value†
Age, years	53 (47, 60)	50 (39, 57)	0.0008	56 (49, 62)	<0.0001
Male, N (%)	199 (69.8%)	116 (66.7%)	0.51	54 (57.4%)	0.13
Race, N (%)			0.22		0.20
White	177 (86.3%)	137 (78.7%)		83 (88.3%)	
Black	20 (9.8%)	26 (15.0%)		6 (6.4%)	
Asian	1 (0.5%)	3 (1.7%)		1 (1.1%)	
Other	7 (3.4%)	8 (4.6%)		4 (4.3%)	
Ethnicity, N (%)			0.23		0.06
Non-Hispanic	196 (95.6%)	159 (91.4%)		92 (97.9%)	
Hispanic	8 (3.9%)	14 (8.0%)		1 (1.1%)	
Unknown	1 (0.5%)	1 (0.6%)		1 (1.1%)	
Diabetes duration, years	39 (29, 47)	30 (21, 40)	<0.0001	33 (25, 42)	0.26
Age at diabetes diagnosis, years	13 (8, 20)	15 (9, 26)	0.03	20 (11, 32)	0.005
Hypertension, N (%)	201 (98.0%)	169 (97.1%)	0.56	72 (76.6%)	<0.0001
Prior self-reported CVD, N (%)	47 (24.6%)	29 (17.4%)	0.12	13 (14.9%)	0.57
Self-reported diabetic retinopathy, N (%)	150 (77.3%)	121 (72.9%)	0.51	35 (43.8%)	<0.0001
Smoking, N (%)			0.28		0.06
Never	128 (62.4%)	99 (56.9%)		67 (71.3%)	
Current	25 (12.2%)	18 (10.3%)		5 (5.3%)	
Past	52 (25.4%)	57 (32.8%)		22 (23.4%)	
RAS inhibitor use, N (%)‡			0.72		<0.0001
Full dose	158 (77.1%)	135 (77.6%)		49 (52.1%)	
Reduced dose	36 (17.5%)	32 (18.4%)		21 (22.3%)	
Contra-indicated/Not indicated	9 (4.4%)	6 (3.4%)		23 (24.5%)	
No RAS inhibitor	2 (1.0%)	1 (0.6%)		1 (1.1%)	
HMG-CoA reductase inhibitors, N (%)	99 (54.4%)	74 (46.5%)	0.15	25 (31.6%)	0.03
BMI, kg/m^2					
Median (IQR)	29 (26, 33)	29 (25, 34)	0.98	30 (25, 34)	0.62
25-29.9 kg/m^2 (overweight), N (%)	77 (38)	58 (33)	0.63	28 (30)	0.50
≥30 kg/m^2 (obese), N (%)	84 (41)	71(41)		42 (45)	
Blood pressure – mmHg‡					
Systolic	127 (118, 138)	129 (113, 139)	0.92	121 (113, 131)	0.02
Diastolic	71 (66, 79)	72 (63, 80)	0.80	69 (63, 76)	0.03
HbA1c	7.9 (7.3, 8.7)	8.5 (7.6, 9.2)	0.0008	7.7 (7.0, 8.5)	<0.0001
Serum uric acid, mg/dL‡	5.9 (5.1, 7.0)	6.0 (5.1, 7.0)	0.98	5.4 (4.7, 6.2)	0.0002
Urine AER (mg/min)§					
Median (IQR)	65 (21, 222)	103 (32, 380)	0.01	3 (2, 5)	By design
≤20, N (%)	50 (25%)	24 (14%)		94 (100%)	
20-199, N (%)	94 (46%)	91 (52%)	0.03	0	By design
>200, N (%)	59 (29%)	59 (34%)		0	
Historical eGFR slope, mL/min/1.73m^2/year‖	0.2 (-0.7, 2.4)	-6.0 (-10, -4)	By design	-4.7 (-6.5, -3.6)	0.0009
Baseline eGFR, mL/min/1.73m^2‡	73 (56, 88)	76 (60, 89)	0.25	82 (67, 90)	0.06
iGFR, mL/min/1.73m^2 ‡	65 (52, 79)	67 (55, 78)	0.43	76 (59, 87)	0.0025

Data are presented median (IQR) unless otherwise defined, as in Table 2. All other variables are as defined in Table 2.

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Abbreviations: DKD, diabetic kidney disease; DKF, declining kidney function. In the albuminuric DKD group with no eGFR decline, data is missing for 14 participants for prior self-reported CVD, 11 for self-reported diabetic retinopathy, 23 for HMC-CoA reductase inhibitor use, 1 for BMI, 2 for urine AER, and 1 for iGFR. In the albuminuric DKD group with eGFR decline, data is missing for 7 participants in prior self-reported CVD, 8 for self-reported diabetic retinopathy, 15 for HMG-CoA reductase inhibitor use, and 2 for BMI and HbA1c. In the normoalbuminuric DKF group, data is missing for 7 participants for prior self-reported CVD, 14 for self-reported diabetic retinopathy, 15 for HMG-CoA reductase inhibitor use, and 2 for BMI.

P-values relate to the comparison between albuminuric DKD with eGFR decline vs. albuminuric DKD without eGFR decline (*) or normoalbuminuric DKF vs albuminuric DKD with eGFR decline (†). ‡Obtained during visit 4. §Geometric mean of AERs for visits 3 and 4. ‖Obtained during visit 1.

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Supplementary Table S5. Association between baseline clinical characteristics in the albuminuric and non-albuminuric participants

Variable	Univariate, β (p-value)				Multivariate, β (p-value)			
	All	Albuminuric DKD		NDKF	All	Albuminuric DKD		NDKF
		All	Slope<-3			All	Slope<-3	
N	530	419		94	530	419		94
iGFR with								
Age	**-0.3 (<0.0001)**	**-0.2 (0.002)**	-0.2 (0.11)	**-0.7 (0.0002)**	**-0.2 (0.002)**	**-0.2 (0.02)**	-0.2 (0.2)	**-0.4 (0.01)**
Female	**-7.6 (<0.0001)**	**-6.7 (<0.0001)**	**-6.1 (0.01)**	**-11.0 (0.002)**	**-9.9 (<0.0001)**	**-8.8 (<0.0001)**	**-7.4 (0.002)**	**-12.0 (0.0002)**
DM Dur	**-0.3 (<0.0001)**	**0.2 (0.001)**	**-0.1 (0.2)**	**-0.6 (0.0001)**	-0.1 (0.09)	-0.1 (0.1)	-0.1 (0.3)	-0.2 (0.2)
Race	-1.8 (0.4)	-2.2 (0.3)	-6.2 (0.03)	1.0 (0.9)	-1.6 (0.4)	-1.3 (0.5)	-3.7 (0.2)	-5.9 (0.2)
AER	-1.8 (0.07)	-1.8 (0.08)	-3.4 (0.02)	-1.7 (0.7)	**-2.7 (0.006)**	**-2.7 (0.02)**	**-4.2 (0.009)**	0.3 (0.9)
SUA	**-4.6 (<0.0001)**	**-4.4 (<0.0001)**	**-4.9 (<0.0001)**	**-5.4 (<0.0001)**	**-4.7 (<0.0001)**	**-4.6 (<0.0001)**	**-4.6 (<0.0001)**	**-4.6 (<0.0001)**
HbA1c	**-1.5 (0.01)**	**-1.2 (0.05)**	**-1.9 (0.02)**	-2.8 (0.07)	**-2.0 (0.0003)**	**-1.9 (0.003)**	**-2.0 (0.02)**	**-2.9 (0.02)**
SBP	0.06 (0.3)	0.04 (0. 5)	0.07 (0.4)	0.1 (0.3)	0.05 (0.4)	0.1 (0.2)	0. 2(0.1)	-0.1 (0.3)
DBP	**0.3 (<0.0001)**	**0.2 (0.002)**	**0.2 (0.03)**	**0.8 (<0.0001)**	0.1 (0.2)	0.06 (0.6)	0.05 (0.8)	0.5 (0.02)
SUA with								
Age	0.005 (0.4)	0.002 (0.8)	0.002 (0.9)	0.02 (0.12)	-0.01 (0.1)	-0.01 (0.2)	-0.01 (0.4)	-0.004 (0.8)
Female	**-0.5 (0.0001)**	**-0.5 (0.0007)**	**-0.5 (0.02)**	-0.5 (0.07)	**-0.9 (<0.0001)**	**-0.8 (<0.0001)**	**-0.9 (<0.0001)**	**-1.1 (0.0002)**
DM Dur	0.006 (0.2)	0.0 (0.9)	0.1 (0.8)	0.04 (0.004)	0.003 (0.6)	-0.003 (0.7)	-0.009 (0.4)	0.02 (0.06)
Race	0.3 (0.1)	0.3 (0.1)	0.5 (0.05)	0.08 (0.9)	0.2 (0.3)	0.2 (0.3)	0.4 (0.1)	-0.2 (0.7)
BMI	**0.04 (0.0003)**	**0.04 (0.001)**	**0.04 (0.01)**	0.04 (0.1)	**0.03 (0.001)**	**0.03 (0.01)**	**0.03 (0.05)**	**0.04 (0.03)**
iGFR	**-0.04 (<0.0001)**	**-0.04 (<0.0001)**	**-0.04 (<0.0001)**	**-0.03 (<0.0001)**	**-0.04 (<0.0001)**	**-0.05 (<0.0001)**	**-0.04 (<0.0001)**	**-0.04 (<0.0001)**
AER	**0.2 (0.005)**	**0.3 (0.005)**	0.1 (0.4)	0.1 (0.8)	0.1 (0.6)	0.1 (0.5)	-0.2 (0.2)	-0.3 (0.3)
HbA1c	-0.1 (0.2)	-0.1 (0.1)	-0.04 (0.6)	0.1 (0.6)	**-0.1 (0.03)**	**0.1 (0.01)**	-0.1 (0.5)	-0.03 (0.8)
SBP	0.001 (0.9)	0.003 (0.6)	-0.004 (0.5)	-0.01 (0.4)	0.003 (0.6)	0.01 (0.3)	0.01 (0.6)	-0.01 (0.3)
DBP	-0.01 (0.3)	0.005 (0.5)	-0.01 (0.2)	-0.02 (0.1)	-0.002 (0.8)	-0.01 (0.3)	-0.01 (0.4)	0.02 (0.2)
AER with								
Age	**-0.02 (<0.0001)**	**-0.03 (<0.0001)**	**-0.02 (<0.0001)**	**-0.02 (0.003)**	**-0.01 (0.002)**	**-0.02 (0.0001)**	-0.01 (0.1)	**-0.01 (0.02)**
Female	**-0.3 (<0.0001)**	**-0.3 (<0.0001)**	-0.2 (0.07)	-0.2 (0.06)	**-0.4 (<0.0001)**	**-0.4 (<0.0001)**	**-0.4 (0.002)**	-0.2 (0.1)
DM Dur	**-0.01 (<0.0001)**	**-0.02 (<0.0001)**	**-0.02 (<0.0001)**	0.01 (0.2)	-0.004 (0.2)	-0.005 (0.3)	-0.01 (0.1)	-0.006 (0.2)
Race	**0.3 (0.001)**	**0.4 (0.0006)**	**0.3 (0.03)**	-0.06 (0.7)	0.07 (0.4)	0.07 (0.5)	0.002 (0.99)	0.0 (0.99)
iGFR	-0.004 (0.07)	-0.004 (0.08)	**-0.008 (0.02)**	-0.001 (0.7)	**-0.006 (0.006)**	**-0.006 (0.02)**	**-0.01 (0.01)**	-0.001 (0.9)
SUA	**0.06 (0.005)**	**0.08 (0.005)**	0.03 (0.4)	0.01 (0.8)	0.02 (0.6)	0.02 (0.5)	-0.06 (0.2)	-0.05 (0.3)
HbA1c	**0.2 (<0.0001)**	**0.2 (<0.0001)**	**0.2 (<0.0001)**	0.04 (0.3)	**0.1 (<0.0001)**	**0.2 (<0.0001)**	**0.2 (<0.0001)**	0.07 (0.2)
SBP	**0.01 (<0.0001)**	**0.01 (<0.0001)**	**0.01 (0.005)**	0.0 (0.7)	**0.01 (0.0004)**	**0.01 (0.0002)**	**0.02 (0.0006)**	-0.0 (0.8)
DBP	**0.02 (<0.0001)**	**0.02 (<0.0001)**	**0.02 (<0.0001)**	0.0 (0.7)	0.03 (0.5)	0.002 (0.8)	-0.01 (0.4)	0.004 (0.6)

The univariate linear regression models were run with iGFR (mL/min/1.73m^2), SUA (mg/dL) or AER (□g/min) as outcome variables and each of the other variables (age and diabetes duration in years, HbA1c in %, SBP and DBP in mmHg) singly added to the model as exposures. Multivariate linear regression models were run with AER, iGFR, or SUA as outcome and all other listed variables as exposures. Each regression analysis was run in the entire randomized group, as well as the subgroups with albuminuric DKD (n=419) and NDKF (n=94). Race was included as a binary variable (white vs. non-white), with the effect estimates referring to non-white vs. white. Albuminuria (AER) values were log transformed to render them more normally distributed. Abbreviations: AER, albumin excretion ratio; DM Dur, type 1 diabetes duration; HbA1c, glycated hemoglobin; iGFR, iohexol glomerular filtration rate; SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure.

SUPPLEMENTARY DATA

Supplementary Table S6. Baseline characteristics of randomized subjects according to sex

Variable	Total Cohort (N=530)	Albuminuria status					
		Albuminuric DKD (N=419)			Normoalbuminuric DKD (N=94)		
		Female (n=132)	Male (n=287)	P-value	Female (n=40)	Male (n=54)	P value‖
Age, years	52 (44, 59)	53 (42, 59)	52 (43, 59)	0.77	56 (49, 61)	56 (49, 63)	0.65
Race, N (%)							
White	446 (84.2)	108 (81.8)	241 (84.0)	0.71	37 (92.5)	46 (85.2)	0.30
Black	58 (10.9)	19 (14.4)	31 (10.8)		1 (2.5)	5 (9.3)	
Asian	6 (1.1)	1 (0.8)	4 (1.4)		1 (2.5)	0	
Other*	20 (3.8)	4 (3.0)	11 (3.8)		1 (2.5)	3 (5.6)	
Ethnicity, N (%)							
Non-Hispanic	504 (95.1)	125 (94.7)	270 (94.1)	0.75	40 (100.0)	52 (96.3)	0.47
Hispanic	23 (4.3)	7 (5.3)	15 (5.2)		0	1 (1.9)	
Unknown	3 (0.6)	0	2 (0.7)		0	1 (1.9)	
Diabetes duration, years	35 (25, 44)	**38 (27, 47)**	**33 (24, 44)**	**0.043**	36 (27, 42)	32 (21, 43)	0.47
Age at diabetes diagnosis, years	14 (9, 24)	**11 (7, 18)**	**14 (9, 23)**	**0.035**	18 (11, 32)	22 (12, 31)	0.32
Hypertension, N (%)	491 (92.6)	128 (97.0)	281 (97.9)	0.51	31 (77.5)	41 (75.9)	0.96
Prior self-reported CVD, N (%)	103 (20.6)	23 (17.4)	62 (21.6)	0.54	6 (15.0)	7 (13.0)	0.77
Self-reported diabetic retinopathy, N (%)	337 (67.5)	87 (65.9)	207 (72.1)	0.83	19 (47.5)	16 (29.6)	0.078
Smoking, N (%)							
Never	322 (60.8)	85 (64.4)	161 (56.1)	0.17	29 (72.5)	38 (70.4)	0.98
Current	58 (10.9)	11 (8.3)	40 (13.9)		2 (5.0)	3 (5.6)	
Past	150 (28.3)	36 (27.3)	86 (30.0)		9 (22.5)	13 (24.1)	
RAS inhibitor use, N (%)†							
Full dose	375 (70.8)	100 (75.8)	220 (76.7)	0.91	20 (50.0)	29 (53.7)	0.97
Reduced dose	102 (19.3)	24 (18.2)	54 (18.8)		10 (25.0)	11 (20.4)	
Contra-indicated/Not indicated	48 (9.1)	7 (5.3)	10 (3.5)		10 (25.0)	13 (24.1)	
No RAS inhibitor	5 (0.9)	1 (0.8)	3 (1.0)		0	1 (1.9)	
HMG-CoA reductase inhibitors, N (%)	216 (46.2)	61 (46.2)	124 (43.2)	0.83	9 (22.5)	16 (29.6)	0.33
BMI, kg/m^2	29 (25, 33)	29 (25, 34)	29 (26, 33)	0.24	**32 (26, 36)**	**28 (25, 33)**	**0.043**
Blood pressure, mmHg†							
Systolic	127(116, 137)	126 (113, 138)	129 (118, 138)	0.16	117 (110, 129)	125 (117, 134)	0.47
Diastolic	71 (65, 79)	**69 (63, 78)**	**72 (66, 81)**	**0.017**	67 (63, 73)	71 (63, 77)	0.14
HbA1c,%	8.0 (7.3, 8.8)	8.1 (7.5, 9.1)	8.1 (7.4, 9.0)	0.26	8.0 (7.1, 8.7)	7.6 (7.0, 8.3)	0.51
Serum uric acid, mg/dL†	5.9 (5.1, 6.9)	5.6 (4.9, 6.6)	6.2 (5.3, 7.3)	.0007	5.0 (4.4, 5.9)	5.5 (5.1, 6.3)	0.070
Urine AER, μg/min‡							
Median (IQR)	42 (9, 207)	**45 (17, 174)**	**112 (31, 430)**	**<0.0001**	3 (1, 4)	3 (2, 5)	0.17
<20, N (%)	189 (36)	**37 (28.0)**	**44 (15.3)**		40 (100.0)	54 (100.0)	NA
20-199, N (%)	203 (38)	**65 (49.2)**	**135 (47.0)**	**0.0014**			
≥200, N (%)	136 (26)	**30 (22.7)**	**106 (36.9)**				
Historical eGFR slope, mL/min/1.73m^2/year§	-3.5 (-5.8, 0)	-2 (-7, 1)	-2 (-5, 0)	0.30	-5 (-8, -4)	-5 (-6, -4)	0.096
Baseline eGFR, mL/min/1.73m^2†	76 (59, 90)	**69 (53, 84)**	**75 (59, 91)**	**0.025**	**72 (62, 88)**	**85 (78, 92)**	**0.012**
iGFR, mL/min/1.73m^2†	68 (55, 80)	**61 (51, 72)**	**70 (55, 80)**	**<0.0001**	**64 (53, 81)**	**79 (71, 89)**	**0.0024**

SUPPLEMENTARY DATA

Continuous variables are presented as median (interquartile range, IQR). Categorical variables are presented as count (percent). Missing data is as detailed in supplemental Table S3. *In race, 'other' is a combination of American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, multi-race, unknown or unreported. †Obtained during visit 4. ‡Geometric mean of AERs for visits 3 and 4Obtained during visit 4. §Obtained during visit 1. ||P-values refer to the comparison between men and women in each category.