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Optimization of Albuminuria-Lowering Treatment in Diabetes by Crossover Rotation to Four Different Drug Classes: A Randomized Crossover Trial

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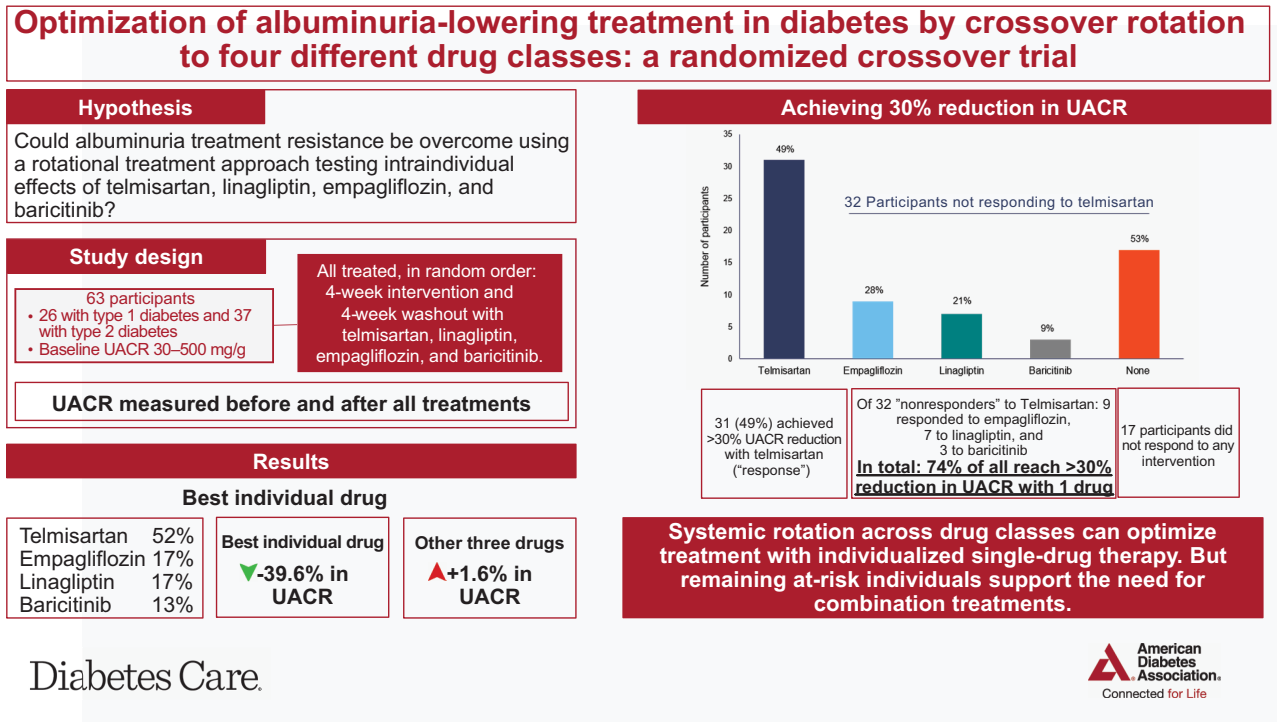

ARTICLE HIGHLIGHTS

- Renin–angiotensin system (RAS) blockade is first-line treatment in patients with diabetes and albuminuria, but up to 40% of patients do not respond satisfactorily.
- Can treatment resistance to RAS blockade be overcome through rotation of telmisartan, empagliflozin, linagliptin, and baricitinib, and selection of the best drug per individual?
- The mean reduction in albuminuria of an individual's best-performing drug was 39.6% (95% CI 33.8, 44.8; $P < 0.001$). A 30% reduction in albuminuria (as recommended by the American Diabetes Association 2022 Standards of Care) was achieved in 74% of participants, using the individual's best-performing drug versus 49% with telmisartan.
- Systemic rotation through different drug classes can optimize individual albuminuria-lowering treatment.

Optimization of Albuminuria-Lowering Treatment in Diabetes by Crossover Rotation to Four Different Drug Classes: A Randomized Crossover Trial

Viktor Rotbain Curovic,[1] Niels Jongs,[2] Marjolein Y.A.M. Kroonen,[2] Emilie H. Zobel,[1] Tine W. Hansen,[1] Taha Sen,[2] Gozewijn D. Laverman,[3] Adriaan Kooy,[4,5] Frederik Persson,[1] Peter Rossing,[1,6] and Hiddo J.L. Heerspink[2]

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OBJECTIVE

Renin–angiotensin system (RAS) inhibitors decrease the urinary albumin to creatinine ratio (UACR) but are ineffective in up to 40% of patients. We hypothesized that rotation through different drug classes overcomes RAS inhibitor resistance and tested this in a randomized crossover trial.

RESEARCH DESIGN AND METHODS

We assigned 26 adults with type 1 diabetes and 37 with type 2 diabetes and UACR between 30 and 500 mg/g and estimated glomerular filtration rate >45 mL/min/1.73 m^2 to 4-week treatment periods with telmisartan 80 mg, empagliflozin 10 mg, linagliptin 5 mg, and baricitinib 2 mg in random order, separated by 4-week washout periods. Each participant was then re-exposed for 4 weeks to the drug that induced that individual's largest UACR reduction. Primary outcome was the difference in UACR response to the best-performing drug during the confirmation period versus UACR response to the other three drugs.

RESULTS

There was substantial variation in the best-performing drug. Telmisartan was best performing for 33 participants (52%), empagliflozin and linagliptin in 11 (17%), and baricitinib in 8 participants (13%). The individuals' best-performing drug changed UACR from baseline during the first and confirmatory exposures by a mean of −39.6% (95% CI −44.8, −33.8; $P < 0.001$) and −22.4% (95% CI −29.7, −12.5; $P < 0.001$), respectively. The Pearson correlation for first versus confirmatory exposure was 0.39 ($P = 0.017$). The mean change in UACR with the other three drugs was +1.6% (95% CI −4.3%, 8.0%; $P = 0.593$ versus baseline; difference versus individuals' best-performing drug at confirmation, 30.9% [95% CI 18.0, 45.3]; $P < 0.001$).

CONCLUSIONS

We demonstrated a large and reproducible variation in participants' responses to different UACR-lowering drug classes. These data support systematic rotation through different drug classes to overcome therapy resistance to RAS inhibition.

Renin–angiotensin system (RAS) inhibitors are the cornerstone of treatment to slow progressive kidney function loss in patients with diabetes and chronic kidney disease

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(CKD) (1–3). RAS inhibitors reduce the risk of kidney failure and decrease albuminuria, an established surrogate outcome for progression of CKD in patients with and without diabetes (4–6). Accordingly, a reduction in albuminuria of at least 30% is recommended by clinical practice guidelines to slow the progression of CKD in patients with diabetes (7,8). However, although RAS inhibition is a guideline-recommended standard of care, a striking 40–50% of patients do not respond to RAS inhibitors and do not achieve a 30% reduction in albuminuria (9–11). These patients remain at high risk of kidney failure and cardiovascular complications (12). Alternative treatments to overcome individual therapy resistance to RAS inhibition are thus desired.

Novel drugs targeting other mechanisms and pathways than the RAS have emerged. Prior randomized controlled trials with patients with diabetes and CKD have demonstrated that sodium glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitor (DPP4i), endothelin receptor antagonists, and Janus kinase (JAK-STAT) inhibitors decrease albuminuria compared with placebo, on average, by 20–35% (13–18). However, there is also a marked variability in patients' albuminuria-lowering response to these newer classes of drugs. Whether systemic rotation through these alternative drug classes may overcome therapy resistance to RAS inhibitors and improve individual albuminuria-lowering efficacy is not prospectively investigated but may be expected, given the complex and variable pathogenesis of diabetes and large heterogeneity in drug response.

We performed a prospective rotation of four main albuminuria-lowering drug classes—RAS inhibition (telmisartan), SGLT2 inhibition (empagliflozin), DPP4 inhibition (linagliptin), and JAK-STAT inhibition (baricitinib)—to investigate patients' individual albuminuria-lowering responses in order to optimize treatment. After the rotation, patients were re-exposed to their best drug to confirm the consistency of each patient's response.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The Rotation for Optimal Targeting of Albuminuria and Treatment Evaluation (ROTATE) trials were two similarly designed, randomized, prospective, open-label, multicenter, crossover trials in participants with type 1 diabetes (ROTATE-1) and type 2 diabetes (ROTATE-2). The studies were conducted at 1 clinical site in Denmark (Steno Diabetes Center Copenhagen, Herlev) and two in the Netherlands (Ziekenhuis Groep Twente, Almelo; and Bethesda Diabetes Research Center, Hoogeveen). The central coordination center was located at the University Medical Center Groningen, the Netherlands. Adult participants with type 1 or type 2 diabetes with a urinary albumin to creatinine ratio (UACR) between 30 and 500 mg/g and estimated glomerular filtration rate (eGFR) $\geq$45 mL/min/1.73 m^2 were eligible. Individuals with a cardiovascular disease event within 6 months of study enrolment, using glucagon-like peptide-1 receptor agonists, or pregnant women were excluded. Renin-angiotensin-aldosterone system inhibitor, SGLT2i, and DPP4i medications were not allowed in the 4 weeks prior to randomization and during follow-up. Participants who tested positively for latent hepatitis B, hepatitis C, or tuberculosis infections did not receive baricitinib at the participating center in Denmark.

A full list of inclusion and exclusion criteria can be found in Supplementary Table 1. All participants gave written informed consent before any study-specific procedure commenced. The studies were approved by the national competent authorities and institutional ethics committees of the participating centers and complied with the declaration of Helsinki and Good Clinical Practice. The ROTATE-1 and ROTATE-2 trials are both registered at trialregister.nl (registration no. NTR5602 and NTR5603).

Intervention and Randomization

Participants received, in random order, 4 weeks of treatment with an angiotensin-receptor blocker (ARB; telmisartan 80 mg daily), an SGLT2i (empagliflozin 10 mg daily), a DPP4i (linagliptin 5 mg daily), and a JAK-STAT inhibitor (baricitinib 2 mg daily) with 4-week washout periods in between. At the end of the four-way rotation schedule, participants were re-exposed to a 4-week treatment period with the drug that induced the strongest albuminuria-lowering response for each participant.

Treatment sequence was randomized. A computer-generated randomized code was supplied to the conducting centers by the coordinating sponsor. Participants and investigators were not masked because this study was primarily concerned with individual responses to each drug and, therefore, there was no systemic bias to be avoided.

Procedures and Measurements

After a screening visit to assess eligibility, participants using RAS inhibitors, SGLT2i, or DPP4i had to discontinue these drugs and enter a run-in period during which blood pressure and glycated hemoglobin (HbA_{1c}) was regularly monitored. If blood pressure increased more than 10 mmHg or HbA_{1c} more than 5 mmol/mol, blood pressure–lowering agents (calcium channel blockers, clonidine, or β-blockers) or diabetes medication (metformin or sulfonylurea derivatives) could be initiated at the discretion of the treating physician. Additionally, insulin doses could be adjusted at the discretion of the treating physician. The visit schedule during the run-in period was left to the discretion of the investigator to allow for flexibility of visits to optimize blood pressure and HbA_{1c} control. Participants could not proceed to randomization if blood pressure or HbA_{1c} could not be stabilized during the maximum 16-week run-in period. After run-in, eligible participants proceeded to the randomized, open-label treatment phase.

The study comprised four consecutive crossover treatment periods of 4 weeks each with 4-week washout periods in between. A 4-week interval was chosen because previous studies have demonstrated that the effect of the chosen interventions were fully present after 4 weeks (13–18). Specifically, ARBs and SGLT2i, including telmisartan and empagliflozin, reduced albuminuria after 4 weeks' treatment in participants with type 1 and type 2 diabetes (19–28). A pooled analysis of linagliptin trials reported that linagliptin compared with placebo significantly reduced albuminuria after 24 weeks' treatment, with clinically relevant reductions observed early after treatment initiation (29). Another study demonstrated that linagliptin response varied widely among participants, with treatment effects observed at the first on-treatment visit after 6 weeks (18). Clinical studies reported the safety of linagliptin in participants with type 1 diabetes (30,31). In experimental models of type 1 diabetes, linagliptin

reduced oxidative stress and ameliorated kidney fibrosis, suggesting that possible benefits observed in participants with type 2 diabetes may extend to those with type 1 diabetes (32,33). Finally, baricitinib reduced albuminuria after 4 weeks in individuals with type 2 diabetes (Supplementary Fig. 1) (16). Ongoing studies are assessing the efficacy and safety of baricitinib in participants with type 1 diabetes (ClinicalTrial.gov identifier NCT04774224).

At the end of the 4-week rotation schedule, participants proceeded to a 4-week confirmatory treatment period during which they were treated with their individual best UACR-lowering drug. At all study visits, three consecutive first-morning-void urine samples were collected for quantification of urinary albumin and creatinine levels. At the start and end of each treatment period, vital signs data and blood samples were collected for biochemistry assessment.

Urine samples collected at the end of the treatment periods were shipped at −80°C to the laboratory of the University Hospital of Leicester NHS Trust to determine presence of urinary telmisartan, empagliflozin, and linagliptin. Urine samples were analyzed by liquid chromatography–tandem mass spectrometry using an Agilent 6490 triple quadrupole mass spectrometer (Santa Clara, CA). The liquid chromatography–tandem mass spectrometry assay is a validated qualitative method to detect the presence and absence of medications. The assay is accredited by the United Kingdom Accreditation Service. The sensitivity of the assay is high, with limits of detection between 10 and 110 ng/mL (P. Gupta, P. Patel, unpublished data).

End Points

The primary end point of the pooled ROTATE-1 and ROTATE-2 trials was the difference in UACR response between the confirmatory exposure of the participants' best-performing drug compared with the mean UACR response of the other three drugs during the rotation schedule. The secondary end point of the pooled ROTATE-1 and ROTATE-2 trials was the correlation in UACR response of the participants' individual best-performing drug during the first and confirmatory treatment period. The number of participants who achieved a 30% reduction from baseline in UACR at the end of each treatment period was an additional end point.

Statistical Analyses

A sample size of 68 participants in the pooled ROTATE-1 and ROTATE-2 trials provided 88% statistical power assuming that the difference in UACR response for a participant's best-performing drug during the confirmatory treatment period compared with the mean UACR response of the other three drugs during the rotation schedule was 25% (−0.2877 natural log scale). The sample-size calculation assumed an SD in natural log–transformed UACR of 0.75 and a type I error of 5% (α = 0.05). Under these assumptions, 80% statistical power would be achieved when 56 participants completed the study. Sixty-eight participants completing the trials provided 80% statistical power to detect a Pearson correlation of 0.33 (α = 0.05).

Baseline characteristics were defined by measurements obtained at the randomization visit and summarized for all randomized participants. Normally distributed variables are presented as mean and SD. Variables with a skewed distribution are presented as median (25th–75th percentile) and compared using nonparametric tests (Mann-Whitney *U* test for continuous and χ^2 test for categorical variables). The geometric mean UACR from three first-morning-void urine samples were determined at each visit.

Analyses were performed in the modified intention-to-treat (mITT) population, which included all randomized participants who did not have major protocol violations and excluded participants with prespecified criteria known to influence UACR, including symptomatic urinary tract infections. The primary efficacy analysis was based on the geometric mean UACR obtained at the start of each treatment period. UACR response was defined as the difference between the end and start of each treatment period on the natural log scale. A repeated measures linear mixed-effects model (RMMM) was used to estimate the difference in UACR response between the confirmatory exposure of the patients' best-performing drug and the three other drugs. The model included a single fixed effect for confirmation period (yes/no) and random slopes and intercept for each subject and an unstructured covariance matrix. The same model was used to determine the UACR difference between the first exposure of the patients' best-performing drug compared with the three other drugs. We confirmed the absence of carryover effects by adding a treatment by period-interaction term to the relevant linear mixed effects models (*P* for interaction = 0.975).

The secondary correlation outcome was assessed by Pearson correlation. Subgroup analyses of the primary and secondary outcomes were performed in subgroups defined by baseline age, sex, UACR, eGFR, HbA_{1c}, diabetes status (type 1 or type 2), BMI, and systolic blood pressure values. Subgroup variables were added to the RMMM used for the main analysis as a fixed effect with an interaction term between subgroup and treatment. The effect of the four drugs on the mean change from baseline in UACR was also assessed using the RMMM. All statistical analyses were performed using R, version 4.1.2 (R Core Team, Vienna, Austria).

RESULTS

Participants and Follow-up

Between 3 February 2017 and 22 October 2019, a total of 118 participants were assessed for eligibility in the ROTATE-1 (*n* = 48 individuals) and ROTATE-2 (*n* = 70 individuals) trials, of whom 29 and 54, respectively, entered run-in. During run-in, a total of six participants discontinued because of withdrawal of consent (*n* = 5 participants) or unstable glycemic control (*n* = 1 participant). Overall, 76 participants were randomized, of whom six discontinued during follow-up in ROTATE-2 (*n* = 4 because of adverse events, *n* = 2 who withdrew consent). None of the ROTATE-1 participants discontinued the study. Seventy participants completed the trial. Of these 70, 63 participants were included in the mITT population at the end of the trial; seven were excluded because of major protocol violations or prespecified exclusion criteria known to influence UACR: five participants were excluded because of symptomatic urinary tract infections, one participant because of discontinuation of diuretic treatment during the confirmatory treatment period, and another because of a telmisartan dose reduction (Supplementary Fig. 2). Two participants did not receive baricitinib, because of a positive hepatitis B test.

Baseline demographic, physical, and biochemical characteristics, including concomitant medication, are listed in Table 1. The mean (SD) data are as follows: age was 64 (10) years, mean eGFR was 79 (19) mL/min/1.73 m^2, and HbA_{1c} was 60 (S11) mmol/mol; median UACR was 115 (25th–75th percentile, 66 to 285) mg/g. Baseline characteristics were generally similar between participants with type 1 and type 2 diabetes except that participants with type 2 diabetes were older and had a higher UACR (Table 1). Baseline characteristics were balanced among groups when stratified by their first assigned treatment (Supplementary Table 1). Adherence to intervention was high in all groups. The proportion of participants who adhered to study medication was 98% (SD 5), as measured by pill count. At the end of the treatment period, nearly all participants had detectable urinary drug concentrations: telmisartan was present in 61 participants (96.8%), empagliflozin in 62 (98.4%), and linagliptin in 61 (96.8%) (Supplementary Fig. 3).

Variability of UACR Responses

The UACR change from baseline for each participant during the four-way rotation schedule showed a marked variation in participants' responses (Fig. 1). Specifically, mean UACR change from baseline during telmisartan treatment was −31.0%, with a large between-patient variation (95% CI −36.7%, −24.8%). Similarly, the mean UACR change from baseline varied among participants during empagliflozin, linagliptin, and baricitinib treatment, with respective mean changes of −2.4% (95% CI −11.3%, 7.4%), −8.5% (95% CI −16.9%, 0.7%), and −1.1% (95% CI −10.9%, 9.7%). At the end of each 4-week washout period, UACR values returned to baseline (Fig. 1). Changes in UACR during each treatment period correlated with UACR changes during washout, such that participants with a more pronounced UACR reduction during treatment had a larger increase during wash-out (Fig. 2*A*).

There was substantial between-patient variation in the best-performing drug: telmisartan was best performing in 33 participants (52%), followed by empagliflozin in 11 participants (17%), linagliptin in 11 (17%), and baricitinib in 8 (13%). Telmisartan was the best-performing drug for most participants with type 2 diabetes (n = 24; 65%). In participants with type 1 diabetes, telmisartan also performed best for most participants (n = 9; 35%), followed by baricitinib and linagliptin (n = 6; 23% for both) and empagliflozin (n = 5; 19%) (Supplementary Table 2). Overall, in 24 participants (38.1%), the first assigned drug during the rotation schedule was the best-performing drug.

The mean change from baseline in UACR for the participants' individual best-performing drug was −39.6% (95% CI −44.8, −33.8; $P < 0.001$) during the first exposure and −22.4% (95% CI −29.7, −12.5; $P < 0.001$) during the confirmation period (Fig. 3). In contrast, the mean UACR change from baseline for the three other drugs was 1.6% (95% CI −4.3%, 8.0%; P = 0.593) (Fig. 3). The difference between the participants' individual best-performing drug at confirmation and the three other drugs was 30.9% (95% CI 18.0, 45.3; $P < 0.001$). A >30% reduction in UACR was achieved in 31 (49.2%), 16 (25.4%), 13 (20.6%), and 6 (9.5%) participants during treatment with telmisartan, empagliflozin, linagliptin, and baricitinib, respectively. In contrast, 45 participants (74.1%) achieved >30% UACR reduction with their individual best-performing drug. Of the participants who did not achieve a >30% reduction in UACR during treatment with telmisartan, nine showed a response (i.e., >30% reduction in UACR) to empagliflozin, seven to linagliptin, and three to baricitinib. Seventeen participants responded to none of the drugs.

A statistically significant correlation was observed between the UACR change during the first and confirmatory treatments of the individual participants' best-performing drug (Pearson r = 0.39; 95% CI 0.16, 0.66; P = 0.017) (Fig. 2*B*). The correlation was

Table 1—Baseline characteristics of participants in the ROTATE-1 and ROTATE-2 studies

	Overall (N = 63)	ROTATE-1 (n = 26)	ROTATE-2 (n = 37)
Age, years	64 (10)	60 (12)	67 (8)
Male sex, *n* (%)	52 (83)	19 (73)	33 (89)
Race, *n* (%)			
White	52 (83)	19 (73)	33 (89)
Non-White	11 (17)	7 (27)	4 (11)
Current smoker, *n* (%)	11 (17)	3 (11)	8 (26)
BMI, kg/m^2	30.0 (4.2)	29.0 (5.0)	30.7 (3.5)
Blood pressure, mmHg			
Systolic	139 (12)	138 (13)	139 (12)
Diastolic	79 (9)	79 (18)	78 (20)
HbA_{1c}, %	7.6 (1.0)	7.6 (0.6)	7.7 (1.1)
HbA_{1c}, mmol/mol	60 (11)	60 (7)	61 (12)
Diabetes duration, years	24.6 (15)	35.9 (13)	16.7 (11)
Serum creatinine, μmol/L	88 (24)	88 (23)	88 (24)
eGFR, mL/min/1.73 m^2	79 (19)	79 (18)	78 (20)
Fasting plasma glucose	9.1 (3.5)	8.6 (3.6)	9.4 (3.5)
UACR, median (25th–75th percentile), mg/g	115 (66–285)	92 (65–282)	149 (73–285)
CV disease history, *n* (%)	21 (33)	9 (35)	12 (32)
Medications, *n* (%)			
Diuretics	32 (51)	15 (58)	17 (46)
Thiazide diuretic	22 (35)	15 (58)	17 (46)
Loop diuretic	11 (17)	10 (38)	5 (14)
MRA	3 (5)	0 (0)	3 (8)
Metformin	28 (44)	2 (8)	26 (70)
Sulfonylurea derivatives	3 (5)	0 (0)	3 (8)
Insulin	43 (68)	26 (100)	17 (46)

Continuous data are reported as mean (standard deviation) except for UACR. Categorical data are reported as numbers (percentage). CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.

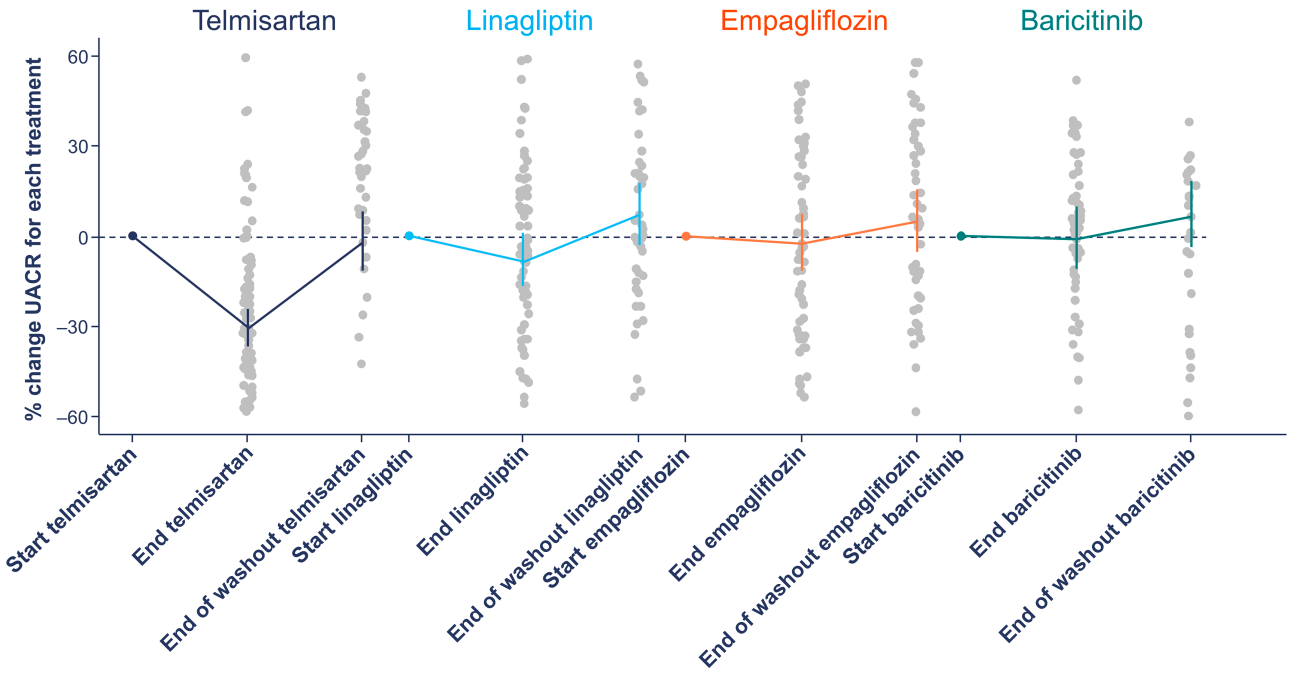

Figure 1—Change from baseline in UACR during each intervention of the rotation scheme. The colored circles represent the mean (95% CI) change from baseline at end of treatment or end of washout. The gray circles represent UACR changes in individual participants.

consistent when each drug class was analyzed separately, with Pearson correlations ranging from 0.36 to 0.47 (Supplementary Fig. 4).

Subgroup analyses demonstrated consistency of the main results across all prespecified subgroups (P for interaction $>$ 0.132 for all) (Fig. 4). No evidence for heterogeneity was observed between the ROTATE-1 and ROTATE-2 groups (P for interaction = 0.263). The correlation in UACR change from baseline between the first and confirmatory treatment periods was also consistent across all prespecified subgroups (P for interaction $>$ 0.132 for all) (Supplementary Fig. 5).

Many participants responding well to one drug responded poorly to another. Overall, among the six possible pairs of treatment responses, there was no significant correlation (Fig. 4). There was, however, one notable exception. In participants with type 1 diabetes, a statistically significant positive correlation in UACR

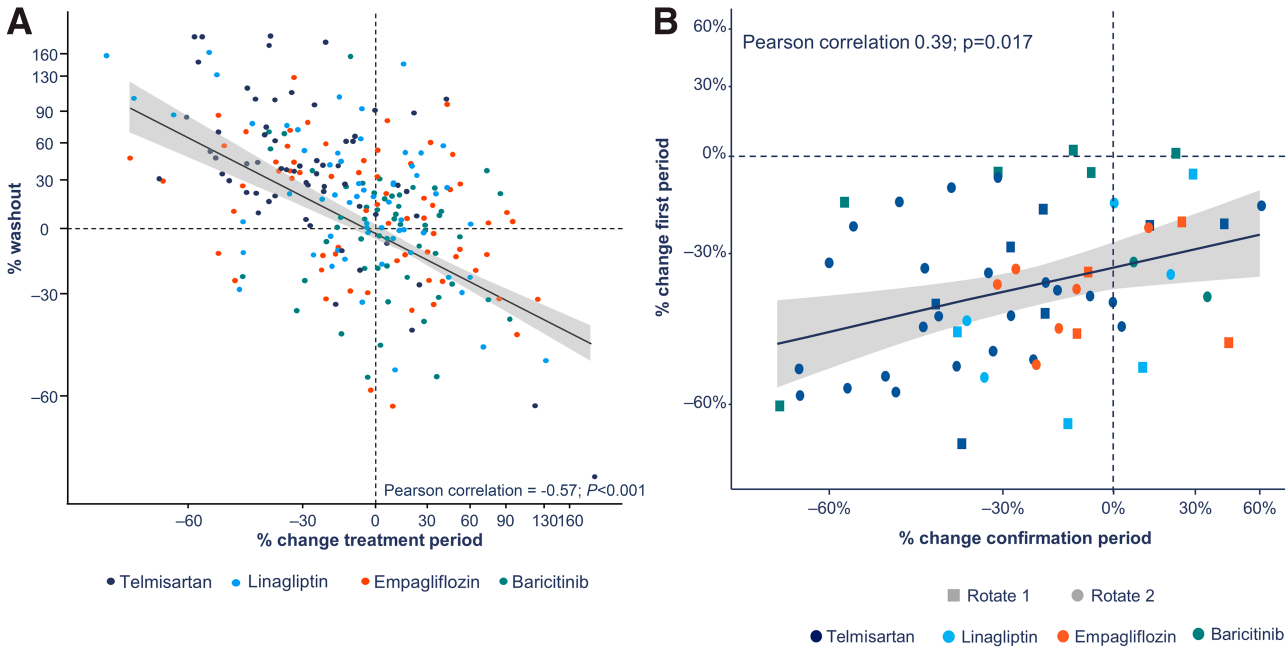

Figure 2—Correlation in UACR changes. *A*: The correlation in UACR changes during each treatment and washout period. A larger reduction in UACR during treatment was associated with a more pronounced increase during washout. *B*: The correlation in UACR changes during the first and confirmation treatment period. UACR changes correlated between first and confirmation treatments.

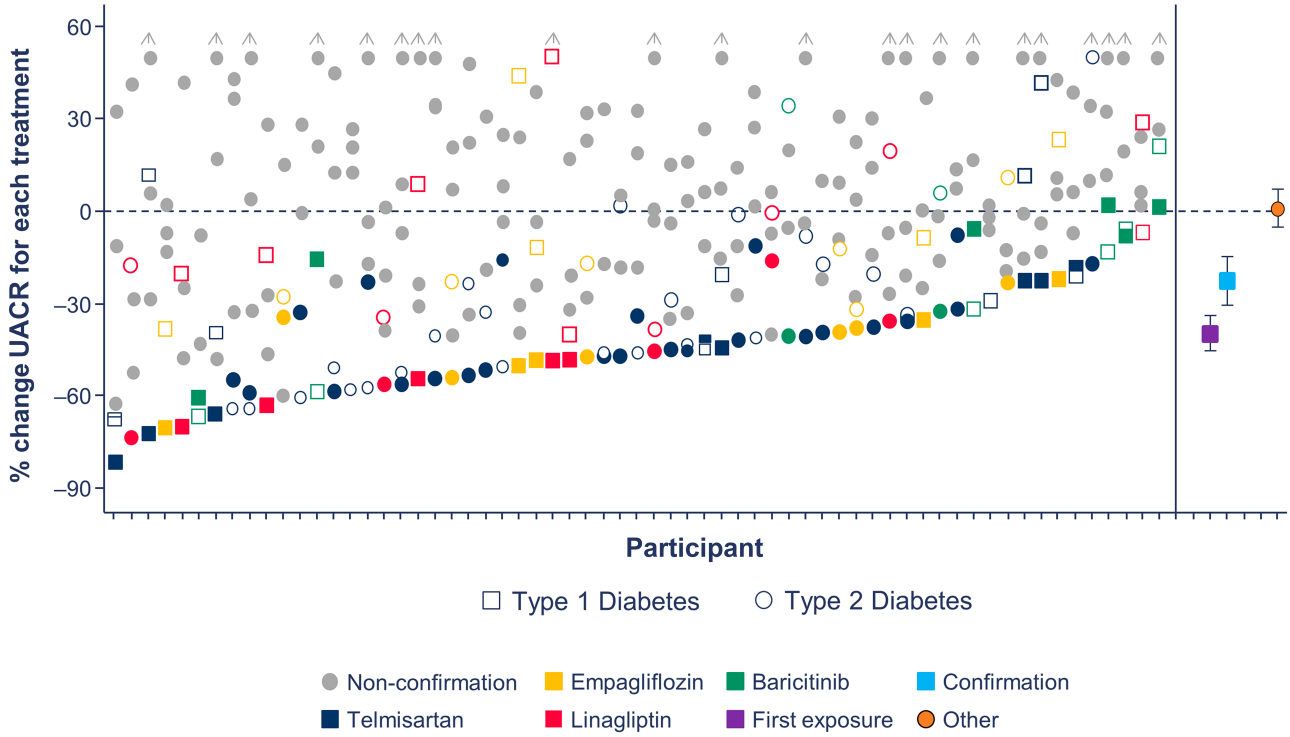

Figure 3—UACR changes of each individual during each treatment of the rotation scheme. The closed colored squares (type 1 diabetes) or circles (type 2 diabetes) represent the UACR change of best drug during the first exposure. The open colored squares or circles represent the UACR change during the confirmation treatment period. The gray circles represent the UACR changes of the other three drugs. The squares to the right of the vertical line represent the mean UACR (95% CI) change of the individual's best-performing drug during the first and confirmation treatment periods. The orange circle to the right of the vertical line shows the mean UACR change of the other three drugs of the rotation scheme. The primary outcome was the difference in UACR between the confirmatory exposure of the participants' best-performing drug compared with the mean UACR response of the other three drugs (represented by the light blue square and orange circle). ACR, albumin to creatinine ratio.

response was observed between telmisartan and linagliptin (r = 0.58; P = 0.021). In contrast, in participants with type 2 diabetes, a statistically significant negative correlation was observed (r = −0.19; P = 0.036).

Predictors of Response

To assess if the individual participant's UACR response could be predicted, we compared baseline characteristics of the individual's best-performing drug. Generally, clinical characteristics did not differ among participants when stratified by their best-performing drug or when responders were compared with all nonresponder participants with each drug class separately (Supplementary Table 2 and Supplementary Table 3). The only exception was that participants who responded best to telmisartan were more likely to have type 2 diabetes, whereas participants who responded best to baricitinib were more likely to have type 1 diabetes (Supplementary Table 3).

Safety

Among 76 randomized participants, 62 (82%) reported at least one adverse event (AE) (Supplementary Table 4). Among 63 participants included in the efficacy analysis, 49 (78%) reported at least one AE. Of these, 6 (12.2%) reported only an AE during their first or confirmatory treatment with the best individual drug, 22 (44.9%) reported only an AE during at least one treatment period with the other three study drugs, and 15 participants (30.6%) reported AEs during treatment with their best individual drug and at least one of the other three drugs. Six participants (12.2%) only reported an AE during the washout periods. In participants with type 1 diabetes compared with type 2 diabetes, hypoglycemia-related AEs were more common (Supplementary Table 5). Participants with type 2 diabetes more frequently reported AEs related to uro-renal, general, and gastrointestinal disorders (Supplementary Table 6). There were no cases of diabetic ketoacidosis during empagliflozin treatment in the ROTATE-1 or ROTATE-2 trials, although AEs were more commonly seen for empagliflozin compared with the other study drugs.

CONCLUSIONS

We observed significant variability in the albuminuria response to four drugs with different mechanisms of action among individuals with type 1 and type 2 diabetes and elevated albuminuria. We found variability to the four drugs within an individual such that many participants had only one treatment that reached the criteria for good response of 30% reduction in albuminuria. We also observed marked variability in response between participants such that for a given drug, some individuals had a large reduction in albuminuria, whereas others did not. We confirmed that this response variability is, in part, reproducible upon re-exposure. The clinical consequences of these findings are that for approximately one-third of participants, the first drug of the rotation scheme was the best-performing treatment, whereas for nearly 75% of participants, a >30% reduction in albuminuria was achieved with their best-performing drug supporting the need for systemic rotation. There were no baseline clinical characteristics that predicted the response to these drugs except that participants

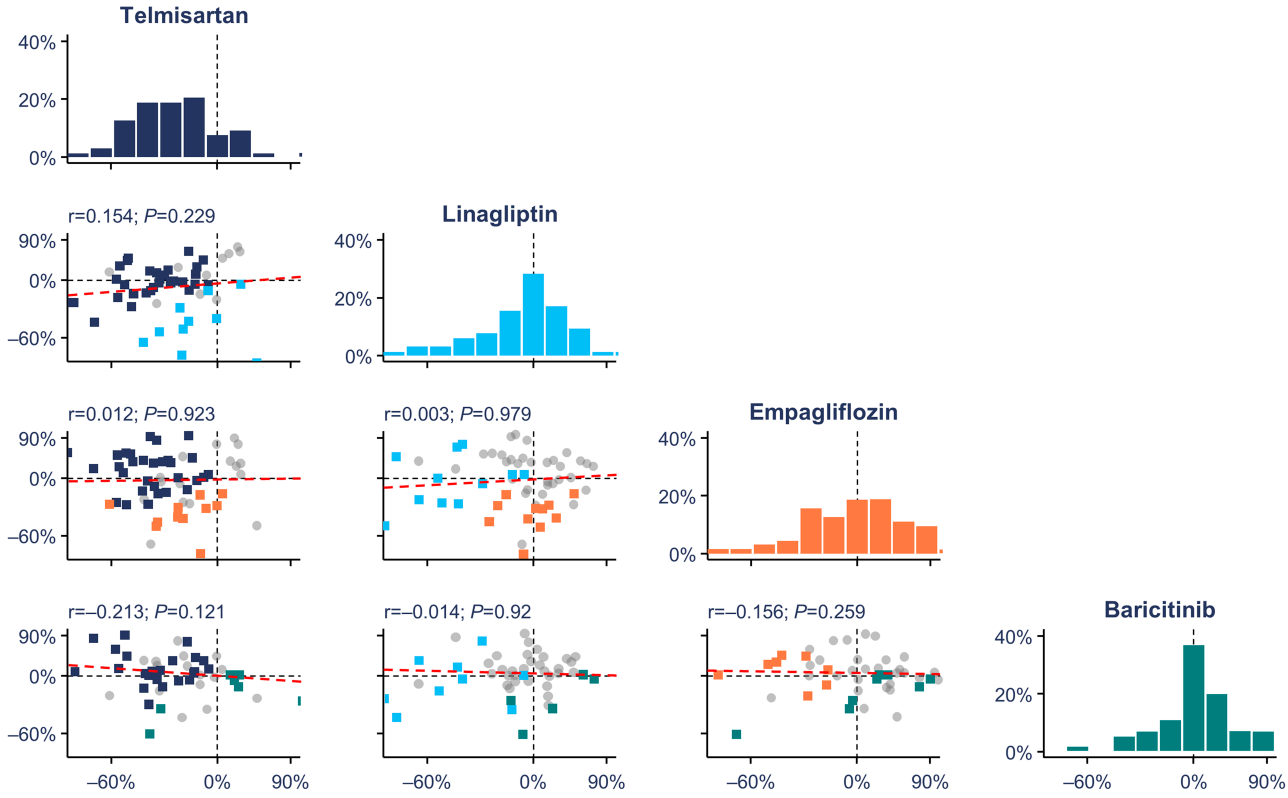

Figure 4—Correlation between UACR changes resulting from four drugs used by participants with type 1 or type 2 diabetes. The figure shows (down the diagonal) the frequency plot for the UACR change for each treatment and (in the other six panels) the correlations between the UACR change on each drug pairing. The UACR changes for participants showing one of the four best responses to any of the four treatments are indicated by colored symbols.

receiving diuretic treatment were more likely to respond to telmisartan.

Results from parallel-group clinical trials, which determine the mean effect of an intervention at a group level, are often used to inform clinical practice guidelines. Clinical practice guidelines often recommend a stepped-care approach to reach treatment targets, leading to many patients being treated with multiple drugs to achieve guideline targets. Moreover, despite the use of multiple drugs, many patients with diabetes do not reach guideline targets. For example, in the STENO-2 trial in patients with type 2 diabetes and microalbuminuria, only 45% of participants reached blood pressure targets (34) and, in only 36%, albuminuria regressed to normal levels (35). In contrast to parallel group trials, which cannot determine the response of an individual patient, our trial was specifically designed to determine the individual patient response using a rotation scheme. We demonstrate that the American Diabetes Association guideline recommended target of 30% reduction in albuminuria to slow progression of kidney function decline was only achieved in half of all participants with telmisartan, the first recommended drug class to reduce albuminuria. In contrast, a >30% albuminuria reduction was achieved by 74% of participants with the individuals' best-performing drug, suggesting that the guideline targets can be met with a single drug in many patients as long as individual variation in drug response is duly considered.

A key aspect of the trial design was the re-exposure of participants to their best-performing drug to confirm the individual treatment response. We observed a statistically significant correlation between the first and confirmatory exposures, indicating that the individual response is reproducible and unlikely to be a chance finding. This notion is supported by the finding that the albuminuria change during treatment inversely correlated with the change in albuminuria during the washout period. Nevertheless, because of the large, biological, day to day variation in albuminuria (36,37), we had not expected that the individual response to the first exposure would be completely reproducible at re-exposure. Indeed, there was considerable residual variation. Many other factors could have influenced the reproducibility in response, including variation in dietary patterns and differences in disease activity. Moreover, the interval between the first and confirmatory exposures could be up to 28 weeks, during which participants were treated with different interventions that may have introduced random variations. In addition, the albuminuria reduction during the confirmation period was less compared with the at first exposure. This may be explained, in part, by regression to the mean. These aspects should be considered in the design of clinical trials focused on individual drug response.

The best-performing drug in most participants with type 2 diabetes was telmisartan, whereas very few responded to baricitinib. In contrast, in participants with type 1 diabetes, baricitinib was best performing in a substantially greater proportion of participants. These different response patterns may reflect differences in underlying pathophysiology between type 1 and type 2 diabetes.

Baricitinib suppresses the immune system and inflammatory pathways (38), both key pathogenic mechanisms involved in progressive kidney function loss in type 1 diabetes.

Comparing efficacy of multiple drugs usually requires dose up-titration to ensure that comparisons are made at the maximum of the dose-response curve for each drug. Dose titration in a crossover trial like ours is practically not feasible. Moreover, our aim was not to compare the mean efficacy of the different drug classes but to assess whether the response to these drugs varied among individuals. We used the same doses used in previous trials that determined the albuminuria-lowering efficacy of these drugs. When we designed our study, clinical trials had demonstrated that the four drug classes significantly reduced albuminuria. However, in our study, the mean response to empagliflozin and baricitinib was unexpectedly lower than anticipated based on previous studies, which may be attributed to differences in study population or design (16,17,39). Notably, in prior studies, both SGLT2i and baricitinib were often used as adjuncts to angiotensin-converting enzyme (ACE) inhibitors or ARBs, in contrast to our study (13,16,25). Linagliptin was, on average, the least efficacious drug, although a large individual variation in response was observed in accord with findings of a previous trial (18). Telmisartan was the best-performing drug for most participants. In this respect, it is noteworthy that before the study, all participants were already treated with ACE inhibitors or ARBs. These agents were discontinued during the run-in period. Whether prior exposure to ACE inhibitors or ARBs explains the large albuminuria response to telmisartan requires further study.

This study has limitations. Because of the demanding protocol, six participants did not complete the study, and another six were omitted from analysis because of factors influencing the individual UACR response. Second, owing to the relatively long study period, we cannot exclude that some of the within- and between-individual variation in albuminuria over time is explained by disease progression and/or changes in other factors causing albuminuria fluctuations. Third, we did not study the participants' individual response to combination therapies, which will be a topic for future studies. Fourth, the open-label design may have influenced safety assessment, and adverse events may have affected study outcomes, particularly in relatively small studies of short duration. Finally, the treatment periods lasted only 4 weeks, and the individual response to long-term effects of each drug class was not determined. We cannot rule out the possibility that the long-term benefit of the included interventions go through mechanisms independent of albuminuria reduction. Therefore, the results of this study cannot be used to directly derive clinical practice recommendations.

The present trial has demonstrated that patients with type 1 or type 2 diabetes exhibit a substantial reproducible within- and between-patient variation in individual response to different albuminuria-lowering drug classes. Our results support the need for personalized therapy approaches in diabetes to overcome therapy resistance to guideline-recommended treatment and to optimize long-term prognosis for each individual.

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