Effects of DPP-4 Inhibitor Linagliptin Versus Sulfonylurea Glimepiride as Add-on to Metformin on Renal Physiology in Overweight Patients With Type 2 Diabetes (RENALIS): A Randomized, Double-Blind Trial

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OBJECTIVE

To compare effects of the dipeptidyl peptidase 4 (DPP-4) inhibitor linagliptin with those of a sulfonylurea on renal physiology in metformin-treated patients with type 2 diabetes mellitus (T2DM).

RESEARCH DESIGN AND METHODS

In this double-blind randomized trial, 46 overweight T2DM patients without renal impairment received once-daily linagliptin (5 mg) or glimepiride (1 mg) for 8 weeks. Fasting glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by inulin and para-aminohippuric acid clearances. Fractional excretions, urinary damage markers, and circulating DPP-4 substrates (among others, glucagon-like peptide 1 and stromal cell–derived factor-1α [SDF-1α]) were measured.

RESULTS

HbA_{1c} reductions were similar with linagliptin (–0.45 ± 0.09%) and glimepiride (–0.65 ± 0.10%) after 8 weeks ($P = 0.101$). Linagliptin versus glimepiride did not affect GFR, ERPF, estimated intrarenal hemodynamics, or damage markers. Only linagliptin increased fractional excretion (FE) of sodium (FE_{Na}) and potassium, without affecting FE of lithium. Linagliptin-induced change in FE_{Na} correlated with SDF-1α ($R = 0.660$) but not with other DPP-4 substrates.

CONCLUSIONS

Linagliptin does not affect fasting renal hemodynamics compared with glimepiride in T2DM patients. DPP-4 inhibition promotes modest natriuresis, possibly mediated by SDF-1α, likely distal to the macula densa.

Type 2 diabetes mellitus (T2DM) is the leading cause of chronic and end-stage kidney disease worldwide. Novel therapeutic strategies are urgently needed (1). Interestingly, analyses of cardiovascular outcome trials (CVOTs) in T2DM patients with high cardiovascular/renal risk suggest glucose-independent beneficial effects on secondary renal outcomes of new-generation glucose-lowering drug classes (i.e., incretin-based

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therapies and sodium–glucose cotransport 2 inhibitors) (1,2). This has recently changed clinical-recommendations.

In T2DM patients without cardiovascular disease/chronic kidney disease, clinicians have several treatment options, including dipeptidyl peptidase 4 (DPP-4) inhibitors (DPP-4i) and sulfonylureas, to intensify metformin monotherapy (3). However, very few head-to-head studies are available to guide clinicians, and secondary renal outcomes of the CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes (CAROLINA) (clinical trial reg. no. NCT01243424, ClinicalTrials.gov) are yet to be reported.

Preclinical studies, placebo-controlled trials, and CVOTs suggest that DPP-4i may prevent albuminuria onset/progression beyond glucose lowering (2,4). Underlying mechanisms may involve direct actions on the kidney, as membrane-bound DPP-4 and glucagon-like peptide 1 (GLP-1) receptors (GLP-1R) are putatively expressed in various nephron segments (2). We reported that sitagliptin modestly reduced estimated glomerular hydraulic pressure (P_{GLO}) and increased fractional excretion (FE) of sodium (FE_{Na}) in T2DM patients versus placebo (5). Although GLP-1R–mediated effects may underlie actions of DPP-4i on renal vasculature/tubules, GLP-1–independent effects of this drug class may also be implicated (4). Glucose-lowering per se influences renal physiology, underscoring the importance of attainment of glycemic equipoise.

RESEARCH DESIGN AND METHODS

A detailed description of material and methods is provided in the Supplementary Appendix 1. Briefly, this was a phase IV, randomized, double-blind, comparator-controlled, parallel-group, mechanistic intervention trial (clinical trial reg. no. NCT02106104). Eligible T2DM patients were Caucasian, men/postmenopausal women, aged 35–75 years, who received metformin alone and had HbA_{1c} 6.5–9.0%, BMI $\geq$25 kg/m^2, and estimated glomerular filtration rate (GFR) >60 mL/min/1.73 m^2. After a 6-week run-in, patients were randomly assigned to receive once-daily linagliptin 5 mg or glimepiride 1 mg added to ongoing metformin; study drugs were overencapsulated.

The protocol for determination of study end points is described in the Supplementary Appendix 1. The predefined coprimary end point was linagliptin-induced changes in GFR and effective renal plasma flow (ERPF) from baseline to week 8, compared with glimepiride, as derived from inulin and para-aminohippuric acid clearances based on timed urine sampling (Supplementary Appendix 1). Secondary end points included (intra)renal variables (i.e., P_{GLO} and afferent arteriolar resistance [R_A] and efferent arteriolar resistance [R_E] estimated according to the Gomez formulae), tubular functions (i.e., FE_{Na}, FE of endogenous lithium [FE_{Li}] [only assessed in linagliptin-treated patients], of potassium [FE_K], and of urea [FE_U]), urinary damage markers (i.e., urinary albumin-to-creatinine ratio [UACR], neutrophil gelatinase–associated lipocalin, and kidney injury molecule-1), and blood pressure (BP). Changes in body weight, hematocrit, body water percentage, HbA_{1c}, glucose, lipids, renin, insulin, glucagon, DPP-4 activity, DPP-4 substrates (i.e., total and intact GLP-1, substance P, active/pro neuropeptide Y, and stromal cell–derived factor-1α [SDF-1α]), and hypoglycemia were analyzed as safety/exploratory end points.

At the time of study design (2013), no data on effects of DPP-4 inhibition on renal physiology were available, and no formal sample size could be assessed. $N = 21$ per treatment arm should be sufficient to detect a GFR change $\geq$15%, assuming SD 10 mL/min, $\alpha = 0.05$ (two-sided testing), and power ($1 - \beta$) of 80%. To allow for dropouts, we aimed at 24 patients/treatment arm. Multivariable linear regression models were used to examine linagliptin-induced effects compared with glimepiride. Corresponding baseline values were added as an independent variable to correct for potential between-group differences at baseline. Paired *t* tests or Wilcoxon signed rank tests were used appropriately for within-group comparisons. Spearman correlation analyses explored associations between changes in renal physiology and factors deemed relevant.

RESULTS

Demographic and clinical characteristics of the analyzed 46 patients were well balanced between treatment groups (Supplementary Appendixes 2 and 3). Reductions in HbA_{1c} were similar in the linagliptin (mean $\pm$ SEM –0.45 $\pm$ 0.09%) and glimepiride (–0.65 $\pm$ 0.10%) groups after 8 weeks of administration (Table 1 and Supplementary Appendix 4). At week 8, decreases in fasting plasma glucose were –1.17 $\pm$ 0.34 mmol/L with linagliptin and –1.54 $\pm$ 0.40 mmol/L with glimepiride ($P = 0.82$).

Eight-week linagliptin did not change GFR, ERPF, filtration fraction, or renal vascular resistance compared with glimepiride relative to baseline (Fig. 1 and Supplementary Appendix 5). Linagliptin was not associated with differences in P_{GLO}, R_A, or R_E compared with glimepiride (Supplementary Appendix 5). Linagliptin increased FE_{Na} (mean $\pm$ SEM increase of 17 $\pm$ 7%; $P = 0.050$) and FE_K, but this did not reach between-group significance (Table 1 and Fig. 1). Linagliptin did not affect FE_{Li}, FE_U, or urinary pH, whereas glimepiride increased urinary pH. Changes in plasma electrolytes are shown in the Supplementary Appendix 6. Linagliptin tended to reduce UACR by 26% from baseline, whereas glimepiride did not; no between-group differences were observed.

Glimepiride versus linagliptin increased body weight (increase of 0.8 kg) (Table 1). No treatment differences were observed in BP/heart rate (Table 1). Metabolic variables generally did not reveal relevant differences between groups (Table 1 and Supplementary Appendix 6). DPP-4 activity was reduced with linagliptin versus glimepiride. Linagliptin increased intact GLP-1 compared with glimepiride ($P = 0.014$). Linagliptin reduced SDF-1α by ~50% ($P < 0.001$), while SDF-1α remained virtually unchanged with glimepiride (between-group mean difference −838 pg/mL [−970 to −705]; $P < 0.001$) (Table 1 and Supplementary Appendix 5*C*).

Correlation analyses between changes in FE_{Na} and selected factors are presented in the Supplementary Appendixes 7 and 8. In all patients, change in FE_{Na} was associated with change in urinary pH ($R = 0.365$; $P = 0.015$) yet was nonsignificant in separate treatment groups. In the linagliptin group, change in FE_{Na} correlated with change in SDF-1α ($R = 0.660$; $P = 0.002$) but not with changes in FE_{Li}, systolic BP, GFR, insulin, glucagon, intact GLP-1, active neuropeptide Y, or substance P.

Fewer patients experienced a probable symptomatic hypoglycemic event with linagliptin versus glimepiride (4% vs. 25%; $P = 0.041$). Reported adverse events were all mild or moderate in intensity (Supplementary Appendix 9).

CONCLUSIONS

As 8-week treatment with linagliptin and glimepiride reduced HbA_{1c} and fasting glucose to a similar extent, nonglycemic advantages and disadvantages of the two drugs could be explored in this trial.

We found that linagliptin affected neither fasting GFR and ERPF nor intrarenal

Table 1—Responses in study end points following linagliptin or glimepiride

Variables	Linagliptin 5 mg QD ($N = 23$)			Glimepiride 1 mg QD ($N = 23$)			Mean (95% CI) difference, linagliptin − glimepiride	*P* value
	Baseline	Week 8	Within-group *P*	Baseline	Week 8	Within-group *P*		
Glycemic variables								
HbA_{1c}, %	7.0 [6.6–7.6]	6.7 [6.4–6.9]	<0.001	7.0 [6.7–7.7]	6.5 [6.2–7.0]	<0.001	0.17 (−0.03 to 0.36)	0.101
Fasting plasma glucose, mmol/L	7.90 [7.30–9.20]	7.00 [6.60–7.50]	0.001	8.50 [7.00–9.80]	6.80 [6.00–8.40]	<0.001	0.09 (−0.72 to 0.91)	0.817
Hormones and DPP-4 substrates								
Plasma renin concentration, ng/L	7.4 [4.0–14.8]	7.3 [4.2–15.8]	0.592	6.9 [4.9–15.4]	6.6 [3.6–17.4]	0.761	0.98 (0.80 to 1.16)$	0.823
Fasting insulin, pmol/L	51.05 [35.05–95.18]	52.05 [34.60–86.45]	0.974	44.30 [31.70–64.15]	42.70 [30.25–68.70]	0.831	4.35 (−6.40 to 15.10)	0.419
Fasting glucagon, pmol/L	50.15 [43.90–55.68]	50.25 [45.53–56.35]	0.170	47.30 [42.00–51.20]	48.35 [43.68–54.78]	0.044	−0.96 (−3.59 to 1.67)	0.464
DPP-4 activity × 10^5, RLA	13.3 ± 1.9	4.7 ± 0.5	0.001	13.4 ± 1.5	15.1 ± 1.5	0.245	−10.4 (−13.4 to −7.5)	<0.001
Total GLP-1, pmol/L	40.5 [35.8–44.0]	43.5 [40.0–46.3]	<0.001	40.0 [36.0–44.0]	41.0 [40.0–47.0]	0.025	0.40 (−2.07 to 2.87)	0.745
Intact GLP-1, pmol/L	0.15 [0.0–1.95]	3.1 [1.5–7.0]	0.079	0.0 [0.0–0.0]	0.75 [0.0–2.9]	0.101	2.43 (0.52 to 4.33)	0.014
Substance P, pg/mL	294 [179–365]	302 [165–411]	0.753	302 [213–365]	326 [176–371]	0.690	22 (−66 to 110)	0.618
Active NPY, pg/mL	10.3 [7.9–11.8]	10.1 [8.7–12.0]	0.476	10.1 [7.8–14.4]	8.9 [8.0–11.6]	0.931	1.14 (−0.29 to 2.57)	0.116
Pro-NPY, pg/mL	15.71 [12.53–24.21]	17.49 [14.31–22.01]	0.715	17.73 [13.15–24.00]	16.94 [11.80–21.65]	0.689	−1.15 (−4.47 to 2.16)	0.485
SDF-1α, pg/mL	1,552 ± 52	725 ± 22	<0.001	1,569 ± 60	1,570 ± 69	0.990	−838 (−970 to −705)	<0.001
Body weight and composition								
Body weight, kg	101.5 ± 3.3	102.0 ± 3.4	0.059	95.0 ± 3.1	96.1 ± 3.1	<0.001	−0.8 (−1.5 to −0.1)	0.022
Waist circumference, cm	113.9 ± 2.2	114.6 ± 2.4	0.261	110.2 ± 2.3	111.4 ± 2.3	0.013	−0.5 (−2.0 to 1.0)	0.495
Body water, %	48.3 ± 1.0	48.6 ± 1.1	0.273	48.7 ± 0.8	48.5 ± 0.9	0.548	0.4 (−0.3 to 1.2)	0.216
Systemic hemodynamics								
Systolic BP, mmHg	141 ± 3	140 ± 3	0.560	142 ± 3	145 ± 4	0.174	−4 (−9 to 2)	0.166
Diastolic BP, mmHg	81 ± 2	83 ± 2	0.198	85 ± 2	88 ± 2	0.017	−2 (−5 to 1)	0.122
Mean arterial pressure, mmHg	103 ± 2	103 ± 2	0.503	106 ± 2	108 ± 2	0.028	−2 (−6 to 1)	0.228
Heart rate, bpm	59 ± 2	61 ± 2	0.049	66 ± 2	65 ± 2	0.730	1 (−2 to 4)	0.555
Tubular functions								
FE_{Na}, %	1.19 [0.90–1.54]	1.40 [1.24–1.57]	0.050	1.05 [0.75–1.48]	1.16 [0.69–2.12]	0.148	−0.03 (−0.32 to 0.25)	0.824
FE_{Li}, %	24.7 ± 1.9	26.2 ± 1.8	0.193	NA	NA	NA	NA	NA
FE_{K}, %	21.5 [18.7–25.4]	23.3 [20.1–28.9]	0.046	19.9 [17.9–26.1]	25.2 [20.4–27.5]	0.171	1.8 (−1.8 to 5.3)	0.317
FE_{U}, %	68.2 [59.3–74.4]	69.6 [57.9–74.6]	0.935	63.9 [51.9–69.6]	66.4 [61.9–73.4]	0.301	1.00 (0.95 to 1.05)$	0.969
Urinary pH	5.76 ± 0.11	5.70 ± 0.10	0.471	5.83 ± 0.14	6.02 ± 0.12	0.041	−0.27 (−0.49 to 0.06)	0.014
Urine osmolality, mOsm/kg	150 [126–213]	138 [125–195]	0.831	141 [121–198]	150 [118–177]	0.362	1.02 (0.91 to 1.12)$	0.769
Renal damage markers								
UACR, mg/mmol	0.80 [0.49–3.60]	0.68 [0.29–3.65]	0.055	1.11 [0.47–3.71]	1.03 [0.47–3.16]	0.688	−0.154 (−0.379 to 0.071)$	0.174
NGAL-to-creatinine ratio, ng/mmol	1.16 [0.84–1.43]	1.18 [0.83–1.78]	0.940	1.60 [0.91–2.49]	1.64 [0.67–2.44]	0.723	−0.013 (−0.178 to 0.152)$	0.872
KIM-1–to–creatinine ratio, ng/mmol	0.10 [0.07–0.13]	0.11 [0.06–0.12]	0.405	0.11 [0.08–0.21]	0.11 [0.08–0.17]	0.385	0.036 (−0.076 to 0.147)$	0.522

Data are mean ± SEM, median [IQR], or baseline-corrected mean difference (95% CI) with use of multiple linear regression to examine baseline-corrected linagliptin-induced effects compared with glimepiride. Paired *t* tests or Wilcoxon signed rank tests were used for within-group comparisons. KIM-1, kidney injury molecule-1; NA, not available; NGAL, neutrophil gelatinase–associated lipocalin; NPY, neuropeptide Y; RLA, relative luciferase activity. $Indicates baseline-corrected ratio with use of multiple linear regression.

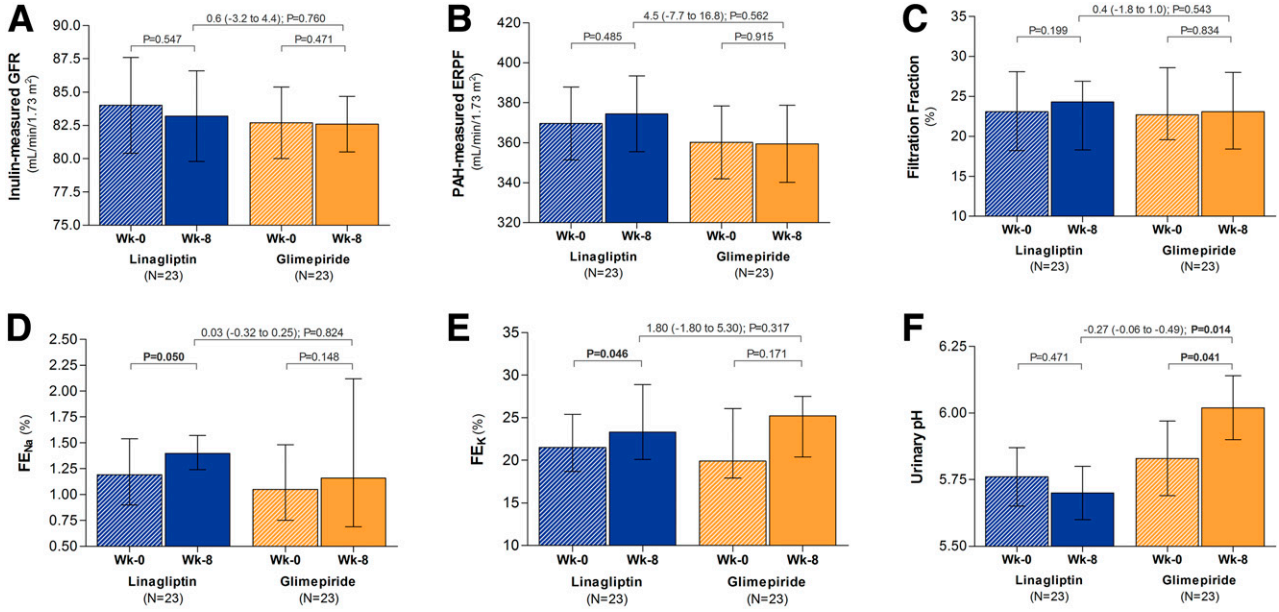

Figure 1—Renal hemodynamic and tubular effects of linagliptin and glimepiride after 8 weeks of treatment. Mean ± SEM (*A–C* and *F*), median [IQR] (*D* and *E*), and baseline-corrected mean difference (95% CI). Multivariable linear regression models were used to examine baseline-corrected linagliptin-induced effects compared with glimepiride. Paired *t* tests (*A–C* and *F*) or Wilcoxon signed rank tests (*D* and *E*) were used for within-group comparisons. Significant differences are indicated in boldface type. PAH, para-aminohippuric acid; Wk, week.

hemodynamic functions compared with glimepiride. This neutral effect of DPP-4i on fasting inulin–measured GFR and para-aminohippuric acid–measured ERPF is in accordance with two placebo-controlled trials studying the renal effect of 4-week linagliptin (6) and 12-week sitagliptin (5) in T2DM patients without renal impairment. In the latter trial, sitagliptin was associated with a placebo-corrected P_{GLO} reduction of 2.8 mmHg ($P = 0.043$), possibly caused by glucose-lowering per se. Indeed, in the current study—which attained euglycemic between-group conditions—we did not observe such P_{GLO} decrease following DPP-4 inhibition, albeit identical methodologies in a comparable T2DM population. We assume that any renoprotective potential of DPP-4i does not involve changes in fasting renal hemodynamics.

In the current study, linagliptin modestly increased fasting FE_{Na} from baseline to week 8 in diuretic-naive patients, albeit not significantly compared with glimepiride. The observed linagliptin-induced natriuresis is consistent with two previous placebo-controlled studies in T2DM, in which sitagliptin enhanced fasting inulin–based FE_{Na} after 2 weeks (5) and creatinine-based FE_{Na} after 1 month (7) by up to 40%. DPP-4i–mediated natriuresis may involve inhibition of the Na-H exchanger (NHE)3—located at the brush border of the proximal tubule, bound to a complex that also contains DPP-4—either through direct membrane-bound pathways or mediated by active GLP-1 levels (2). Indeed, acute GLP-1 receptor agonist (GLP-1RA) administration confers natriuresis (8–10), perhaps by NHE3 inhibition (2). Moreover, GLP-1RA administration increases FE_{Li} (a marker of proximal tubular Na reabsorption) and urinary pH (8,10). In the current study, linagliptin augmented intact GLP-1 concentrations, but urinary pH and FE_{Li} remained unaffected, which is in disagreement with an inhibitory effect of linagliptin on NHE3. Also, we did not observe an association between linagliptin-induced changes in FE_{Na} and intact GLP-1. Rather, DPP-4i may (at least partly) promote natriuresis through pathways independent of GLP-1R signaling and NHE3 (7,11). Indeed, in mice lacking a functional GLP-1R, DPP-4 inhibition but not GLP-1RA demonstrated natriuresis (12). DPP-4 has numerous physiological substrates other than GLP-1 that are associated with natriuresis (e.g., neuropeptide Y, substance P, and SDF-1α) (4). While linagliptin did not affect circulating active neuropeptide Y or substance P in our trial, the drug did reduce a subfraction of SDF-1α, as was seen in other DPP-4i studies that used the identical assay for this DPP-4 substrate (13). SDF-1α is widely expressed in the kidney and localizes to glomerular podocytes and distal tubular cells (14). Also, SDF-1α/CXCR4 receptor signaling suppresses renal oxidative stress/fibrosis. Parallel with sitagliptin-induced natriuresis, DPP-4 inhibition robustly increased intact SDF-$1\alpha^{1\text{-}67}$ ("active" form) and markedly decreases truncated SDF-$1\alpha^{3\text{-}67}$ ("inactive" form) (7). Conversely, the SDF-1α/CXCR4 antagonist AMD3100 reversed the natriuretic effects of linagliptin (11). Our exploratory correlation analyses also link DPP-4 inhibition to enhanced FE_{Na} via SDF-1α.

As proximal NHE3 does not seem to be primarily involved, and FE_{Li} was unchanged in the current and a previous study (7), DPP-4i may induce natriuresis by blocking distal rather than proximal tubular Na reabsorption. Moreover, whereas agents that induce proximal tubular natriuresis—e.g., sodium–glucose cotransporter 2 inhibitors and carbonic anhydrase inhibitors—activate tubuloglomerular feedback and thereby affect renal hemodynamics, DPP-4i do not seem to exhibit a renal hemodynamic effect, suggesting that the drug class acts on a segment distal to the macula densa and its effect is consequently not coupled to this intrarenal autoregulatory mechanism. Potential distal tubular ion-transport channels that may link DPP-4i to distal natriuresis include the Na^+/Cl^- thiazide-sensitive channel and the epithelial Na channel (7).

Our study has limitations. First, the sample size was relatively small, potentially leading to heterogeneity. Second, estimation of glomerular characteristics with Gomez formulae requires assumptions. Third, we did not measure 24-h Na excretion or standardize/monitor Na intake; variability in FE_{Na} results may have occurred. Fourth, as most DPP-4 substrates are secreted postprandially, we cannot assess the net renal effect of DPP-4i over 24 h. Finally, our findings in T2DM patients with late-phase glomerular hyperfiltration and normal GFR (i.e., baseline filtration fraction ~23% [15]) cannot be generalized to T2DM patients with either early-phase hyperfiltration or late-phase renal impairment.

We did not find any glucose-independent differences in fasting (intra)renal hemodynamics with linagliptin versus glimepiride in T2DM patients without overt nephropathy. The suggested renoprotective properties of DPP-4i may be produced by modest benefits in other renal risk factors (body weight, BP, or dyslipidemia) or preservation of DPP-4 substrates (notably, SDF-1α) that may have anti-inflammatory/antifibrotic properties. Linagliptin promotes modest natriuresis, possibly caused by SDF-1α at a tubular segment distal to the macula densa.

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Author Contributions. M.H.A.M. participated in the design and planning of the study, coordinated the test visits and performed measurements, performed statistical analyses, produced the graphical representation of the data, interpreted the data, and wrote the manuscript. L.T. helped with data collection, performed statistical analyses, interpreted the data, and critically reviewed the manuscript. M.M.S., M.H.H.K., J.A.J., and D.H.v.R. contributed to the interpretation of the data, discussion of the intellectual content, and critical review of the manuscript. D.M.O., B.H., J.J.H., D.J.T., and A.H.J.D. generated data and/or contributed to the discussion of the intellectual content and critical review of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. M.H.A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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