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The Association Between Hemoglobin A_{1c} and Complications Among Individuals With Diabetes and Severe Chronic Kidney Disease

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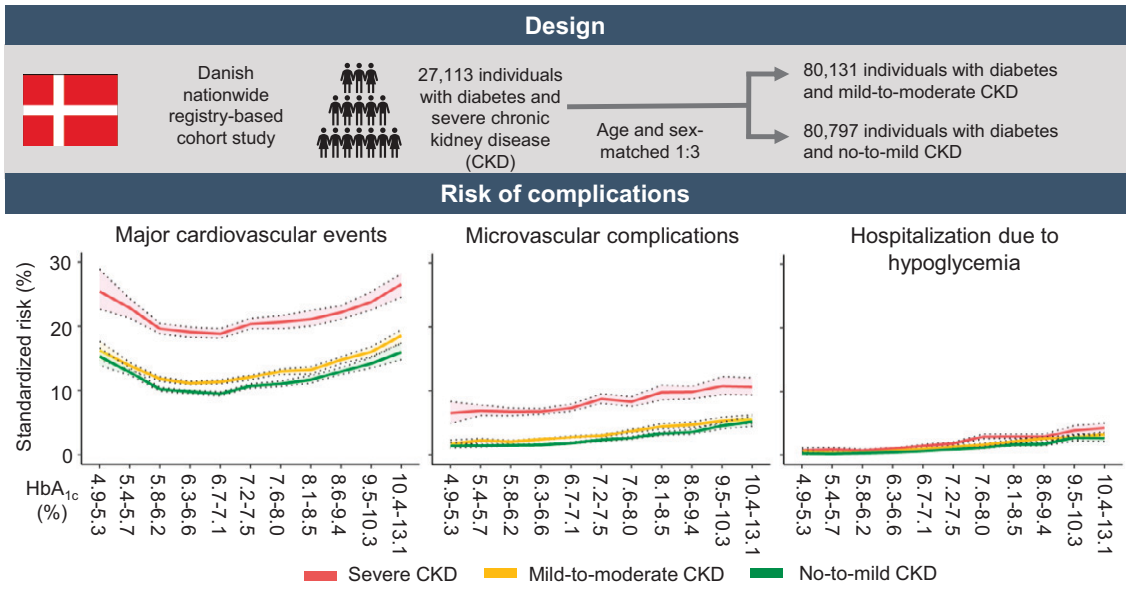

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The optimal glycemic target for individuals with severe chronic kidney disease (CKD) remains uncertain.
- **What is the specific question we wanted to answer?**
  We investigated the association between HbA_{1c} and complications in individuals with diabetes and severe CKD.
- **What did we find?**
  An HbA_{1c} range of 6.7–7.1% (50–54 mmol/mol) was most favorable for reducing long-term complications in this high-risk population.
- **What are the implications of our findings?**
  Our findings align with current guidelines which recommend an HbA_{1c} target of ∼7% (53 mmol/mol) in individuals with diabetes and CKD. However, our data do not support the current recommendations that propose conservative glycemic treatment for individuals with severe CKD.

The Association Between Hemoglobin A_{1c} and Complications Among Individuals With Diabetes and Severe Chronic Kidney Disease

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ORIGINAL ARTICLE

OBJECTIVE

The optimal glycemic target for individuals with severe chronic kidney disease (CKD) remains unclear. We investigated the association between HbA_{1c} and complications in individuals with diabetes and severe CKD.

RESEARCH DESIGN AND METHODS

In a Danish nationwide registry-based cohort study, we included 27,113 individuals ≥18 years old with diabetes and severe CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) between 2010 and 2022. As reference groups, we included an age- and sex-matched cohort of 80,131 individuals with diabetes and mild-to-moderate CKD (eGFR 30–59 mL/min/1.73 m^2) and 80,797 individuals with diabetes and no-to-mild CKD (eGFR ≥60 mL/min/1.73 m^2). Multiple Cox regressions were used to estimate the standardized 1-year risk of major adverse cardiovascular events (MACE), microvascular complications, and hospitalizations due to hypoglycemia across strata of HbA_{1c} levels.

RESULTS

For individuals with severe CKD, the risk of MACE significantly increased at HbA_{1c} levels ≥7.2% (55 mmol/mol) ($P < 0.01$) and <5.8% (40 mmol/mol) ($P < 0.001$), compared with an HbA_{1c} level of 6.3–6.6% (45–49 mmol/mol). The risk of microvascular complications significantly increased at HbA_{1c} levels ≥7.2% (55 mmol/mol) ($P < 0.001$), and the risk of hospitalization due to hypoglycemia significantly increased at HbA_{1c} levels ≥6.7% (50 mmol/mol) ($P < 0.001$). The association patterns between HbA_{1c} and outcomes were similar in the severe CKD cohort compared with the matched cohorts with mild-to-moderate CKD and no-to-mild CKD.

CONCLUSIONS

Our data suggest an HbA_{1c} range of 6.7–7.1% (50–54 mmol/mol) to be most favorable for reducing long-term complications in this high-risk population.

Diabetes is the leading single cause of chronic kidney disease (CKD) globally (1). The combination of diabetes and CKD significantly increases the risk of both short- and long-term complications, as well as death (2). Despite advances in diabetes management, the optimal glycemic target to improve outcomes for individuals with

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diabetes and CKD remains unclear, particularly for those with severe stages of CKD (3,4). Current international guidelines suggest less tight glycemic management as kidney function declines (5,6). However, this recommendation primarily relies on the higher risk of severe hypoglycemia and the reduced life expectancy, which calls into question the benefits of tight glycemic treatment.

Hemoglobin A_{1c} (HbA_{1c}) is the most commonly used biomarker to monitor glycemic levels (7). Previous clinical trials examining the association between HbA_{1c} and diabetes complications primarily included individuals with normal kidney function or early-stage CKD. These trials demonstrated that intensive glycemic treatment reduces microvascular complications (8,9). Moreover, long-term follow-up found a decrease in cardiovascular events and mortality with intensive treatment (10,11). However, more recent trials did not show reduced major cardiovascular events with intensive glycemic treatment (12–14). Notably, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found an increased mortality rate with intensive treatment in individuals with type 2 diabetes who also had high cardiovascular risk (14). Nonetheless, none of these trials included individuals with severe CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2).

Data on the association between HbA_{1c} and complications in individuals with severe CKD remain sparse (3,4,15). This population is largely excluded from clinical trials, and there have been only a few observational studies with a limited number of individuals with eGFR <30 mL/min/1.73 m^2 (16–19). Furthermore, concerns arise regarding the reliability of HbA_{1c} in individuals with severe CKD (5,20). As kidney function declines, HbA_{1c} metabolism changes. Inflammation and metabolic acidosis promote hemoglobin glycation, increasing HbA_{1c}. Conversely, HbA_{1c} is decreased due to a reduction in erythrocyte life span and use of erythropoietin-stimulating agents and iron-replacement therapies (5).

Therefore, data on the correlation between HbA_{1c} and complications, particularly focusing on individuals with severe CKD, are required to improve outcomes in this high-risk population. In this study, we investigated the association between HbA_{1c} levels and major adverse cardiovascular events (MACE), microvascular complications, and hospitalizations due to hypoglycemia in individuals with diabetes and severe CKD.

RESEARCH DESIGN AND METHODS

Data Sources

In Denmark, all residents have free access to tax-funded public health care. Health care data are collected and stored in national health registries. Each resident is provided a unique personal identification number, which allows for data linking at an individual level between registries (21). The Danish National Patient Registry records hospital discharge diagnoses, one primary and an optional secondary, after each outpatient or inpatient hospital encounter. The discharge diagnoses codes were used to identify conditions leading to a hospital contact, based on the ICD-10 and the Nordic Medico-Statistical Committee Classification of Surgical Procedures (21).

The Danish National Database of Reimbursed Prescriptions was used to obtain information about redeemed prescription medications recorded via the Anatomical Therapeutic Chemical Classification System codes (22). This registry was used to identify individuals with diabetes and hypertension, which are often managed by primary care physicians and are thus not completely registered in the Danish National Patient Registry (21). Laboratory data were gathered using the Nomenclature, Properties, and Units coding system through the National Register of Laboratory Results, which contains data from primary care, outpatient services, and hospital records in four of five administrative regions in Denmark (23). Mortality data were extracted from the Danish Registry of Causes of Death (21). All administrative codes used in this study are provided in Supplementary Table 1.

Study Design and Population

This was a Danish registry-based cohort study including individuals with diabetes and severe CKD from 1 January 2010 to 31 December 2022. The Chronic Kidney Disease Epidemiology Collaboration's 2021 equation was used to estimate the eGFR based on the recorded plasma creatinine level (24). Severe CKD was defined by two registered eGFR measurements <30 mL/min/1.73 m^2 $\geq$90 days apart. Individuals were included in the study on the basis of the date of the second eGFR measurement (the index day). Individuals with diabetes were identified by redemption of one or more prescriptions for glucose-lowering medication within 5 years before the index day.

We excluded individuals without a registered HbA_{1c} measurement between 4.9% and 13.1% (30 and 120 mmol/mol) taken within 1 year before the index. Additionally, those younger than 18 years and those with a history of maintenance dialysis or kidney transplantation were excluded. As reference groups, each individual with severe CKD was matched (using exposure density matching) on birth year and sex with three individuals with diabetes and mild-to-moderate CKD and three individuals with diabetes and no-to-mild CKD. The same exclusion criteria applied for the matched cohorts as for the cohort with severe CKD. Mild-to-moderate CKD was defined by two registered eGFR measurements of 30–59 mL/min/1.73 m^2 $\geq$90 days apart, and no-to-mild CKD was defined by two registered eGFR measurements $\geq$60 mL/min/1.73 m^2 $\geq$90 days apart, with or without albuminuria. There was 99.86% matching for the mild-to-moderate CKD cohort and 99.98% for the no-to-mild CKD cohort. Individuals without a match were excluded.

Covariates

The classification of type 1 diabetes was based on diagnosis codes. Individuals with type 1 diabetes are primarily treated in outpatient clinics. and identifying type 1 diabetes in this setting has been validated with a 94.3% positive predictive value (25). Individuals without a type 1 diabetes diagnosis were classified as having type 2 diabetes. The duration of diabetes was determined by the time from the first prescription of glucose-lowering medication to the index.

Comorbid conditions were identified using the diagnosis and procedure codes recorded within 5 years before the index, except for hypertension, which was defined as having been prescribed at least two different classes of antihypertensive drugs within 5 years before the index. This definition of hypertension has been validated in a Danish cohort (26). Concomitant medications were based on redeemed prescriptions within 6 months before the index. Plasma hemoglobin and LDL cholesterol levels were based on the most recent measurement before

the index. Albuminuria was assessed using the most recently measured urinary albumin-to-creatinine ratio (UACR) or 24-h urine collection. Albuminuria status was classified as normoalbuminuria (<30 mg/24 h or UACR <30 mg/g), microalbuminuria (30–299 mg/24 h or UACR 30–299 mg/g), or macroalbuminuria (≥300 mg/24 h or UACR ≥300 mg/g).

Study Outcomes and Follow-up

The outcomes were as follows: *1*) MACE, defined as a composite outcome of acute myocardial infarction, stroke, and all-cause mortality; *2*) microvascular complications, defined as a composite outcome of diabetic retinopathy, major lower-extremity amputation (any amputation performed proximal to the ankle), and end-stage kidney disease (start of maintenance dialysis, kidney transplantation, or a sustained eGFR <15 mL/min/1.73 m^2 [two registered eGFR measurements <15 mL/min/1.73 m^2 ≥90 days apart]; and *3*) hospitalizations due to hypoglycemia. Eligible individuals were followed from the index day until the occurrence of an outcome, death, emigration, or administrative censoring (31 December 2022), whichever occurred first.

Statistical Analyses

Baseline characteristics were reported as a count (percentage) for categorical data and as a mean (SD) or median (interquartile range [IQR]) for normally or nonnormally distributed data, respectively. The median follow-up was calculated based on the reverse Kaplan-Meier estimates for censored times. The association between HbA_{1c} and study outcomes was assessed across strata of HbA_{1c} levels (% [mmol/mol]: 4.9–5.3 [30–34], 5.4–5.7 [35–39], 5.8–6.2 [40–44], 6.3–6.6 [45–49], 6.7–7.1 [50–54], 7.2–7.5 [55–59], 7.6–8.0 [60–64], 8.1–8.5 [65–69], 8.6–9.4 [70–79], 9.5–10.3 [80–89], 10.4–13.1 [90–120]). The most recent HbA_{1c} value within the previous year was used for the main analyses.

We conducted multiple Cox regressions, stratified by matching variables (birth year and sex), and adjusted for hemoglobin level and cardiovascular disease (ischemic heart disease, heart failure, and stroke) to calculate the hazard ratios for the outcomes across the strata of HbA_{1c} levels and CKD groups (severe, mild-to-moderate, no-to-mild CKD). To include all eligible individuals, we performed imputation of hemoglobin values in individuals without a preexisting measurement of plasma hemoglobin, assuming random missingness using a multiple linear regression model adjusted for age, sex, eGFR, HbA_{1c}, cardiovascular disease, and hypertension. For the analyses of microvascular complications, we excluded individuals with a history of diabetic retinopathy or major lower-extremity amputations, because these conditions are considered persistent from the moment of initial diagnosis, and we were unable to assess their progression. Therefore, we specifically examined the new onset of diabetic retinopathy or major lower-extremity amputations.

The 1-year risk of the outcomes was estimated based on the Cox regressions, standardized to the distribution of risk factors of all individuals in the study (27). In the risk estimation of microvascular complications and hospitalization due to hypoglycemia, death was considered a competing risk, using the cause-specific approach (28). Specifically, the 1-year risk was estimated based on hazard ratios of the event of interest and the competing risk of death (i.e., the risk estimate model incorporated two Cox models, one with the outcome of interest and one for the competing risk of death) (27,28). The risk estimates are reported with a 95% bootstrap CI. Subgroup analyses were performed stratified by sex, age, and diabetes type. Furthermore, in individuals with type 2 diabetes, we stratified the analyses according to whether they received insulin treatment at baseline.

The software programs SAS (version 9.4; SAS Institute, Cary, NC) and *R* (version 4.0.1; R Core Team, 2019) were used for data management and statistics. *P* values <0.05 were considered statistically significant, and all statistical tests were two-tailed.

Sensitivity Analyses

To address potential bias related to the imputation of hemoglobin values, we conducted a complete-case reanalysis of main results, including only those individuals with a preexisting hemoglobin measurement. For individuals with more than one HbA_{1c} measurement within the year before the index, we investigated the association between the mean HbA_{1c} and study outcomes. To evaluate potential period effects, main results were reanalyzed across strata of the index year (2010–2014, 2015–2018, 2019–2022). Because of the potential risk of misclassification of acute kidney injury as CKD, additional analyses were conducted in a cohort using only outpatient creatinine measurements. To further assess whether baseline kidney function modified the association between HbA_{1c} and outcomes, we stratified the whole population according to baseline eGFR level. Moreover, the relationship between HbA_{1c} and eGFR were modeled using Cox regression with restricted cubic splines, allowing for nonlinear interactions across the full range of both variables. An interaction term between HbA_{1c} and eGFR was included, and effect modification was illustrated by plotting hazard ratios for the study outcomes across HbA_{1c} values at a range of eGFR levels.

To address potential confounding, we reanalyzed the main results with additional adjustments alongside the original covariates in the following models: *1*) additionally adjusted for noninsulin glucose-lowering medication (dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 analogs, sodium–glucose cotransport 2 inhibitors, biguanides, and sulfonylureas); *2*) additionally adjusted for hypertension, obesity, and baseline eGFR; *3*) further adjusted for albuminuria and LDL cholesterol levels in individuals with a valid measurement of these factors. Moreover, in individuals with type 2 diabetes, we reanalyzed the risk of hospitalizations due to hypoglycemia with additional adjustment for insulin and noninsulin glucose-lowering medication. Furthermore, we limited the analysis of hospitalizations due to hypoglycemia by including only events in which hypoglycemia was the primary discharge diagnosis.

Last, we conducted restricted cubic splines using continuous HbA_{1c} modeling, with spline knots set at HbA_{1c} levels (mmol/mol) of 4.9% (30), 5.4% (35), 5.8% (40), 6.3% (45), 6.7% (50), 7.2% (55), 7.6% (60), 8.1% (65), 8.6% (70), 9.5% (80), and 10.4% (90). To account for differences in CKD group, sex, age, cardiovascular disease, and hemoglobin levels, we estimated the 1-year risk of outcomes within specific subgroups of these covariates. The other covariates were fixed at the severe CKD group, male sex, age-group 70–79 years, no prior cardiovascular disease, and a hemoglobin level of 7–7.9 mmol/L.

Ethics

The Danish Data Protection Agency approved the use of study data (reference P–2019-191). In Denmark, registry-based studies do not require approval from the Scientific Ethics Committee. Data are maintained within a secure research platform managed through Statistics Denmark.

Data and Resource Availability

The data set generated and analyzed during this study is not publicly accessible due to the potential risk of identifying individuals, but it is available from the corresponding author upon reasonable request.

RESULTS

Between 1 January 2010, and 31 December 2022, a total of 27,113 individuals with diabetes and severe CKD (eGFR <30 mL/min/1.73 m^2) were included (Supplementary Fig. 1). There were 80,131 individuals in the matched cohort with mild-to-moderate CKD (eGFR 30–59 mL/min/1.73 m^2), and 80,797 individuals in the matched cohort with no-to-mild CKD (eGFR $\geq$60 mL/min/1.73 m^2). The median follow-up period was 5.4 (IQR = 2.5–8.1) years for the severe CKD cohort, 5.2 (IQR = 2.4–7.7) years for the mild-to-moderate CKD cohort, and 5.2 (IQR = 2.4–7.9) years for the no-to-mild CKD cohort.

Baseline Characteristics

Table 1 presents the baseline characteristics of individuals with severe CKD and

Table 1—Baseline characteristics of individuals with diabetes and severe CKD (eGFR <30 mL/min/1.73 m^2), mild-to-moderate CKD (eGFR 30–59 mL/min/1.73 m^2), and no-to-mild CKD (eGFR ≥60 mL/min/1.73 m^2)

Characteristic	Severe CKD (*n* = 27,113)	Mild-to-moderate CKD (*n* = 80,131)	No-to-mild CKD (*n* = 80,797)
Sex, *n* (%)			
Female	12,575 (46.4)	37,129 (46.3)	37,435 (46.3)
Male	14,538 (53.6)	43,002 (53.7)	43,362 (53.7)
Age, median (IQR), years	77.4 (70.4–83.7)	77.4 (70.4–83.6)	77.2 (70.2–83.4)
eGFR, median (IQR), mL/min/1.73 m^2	26 (22–28)	54 (45–62)	82 (68–92)
HbA_{1c}, median (IQR), %	7.0 (6.3–8.0)	6.9 (6.3–7.7)	6.8 (6.3–7.6)
HbA_{1c}, median (IQR), mmol/mol	53 (45–64)	52 (45–61)	51 (45–60)
Type 1 diabetes, *n* (%)	8,283 (30.5)	19,780 (24.7)	15,152 (18.8)
Diabetes duration, *n* (%), years			
0–6	7,686 (28.3)	20,602 (25.7)	21,520 (26.6)
7–13	8,526 (31.4)	30,074 (37.5)	32,560 (40.3)
≥14	10,901 (40.2)	29,455 (36.8)	26,717 (33.1)
Glucose-lowering medication, *n* (%)			
Insulin treatment	12,449 (45.9)	28,953 (36.1)	22,039 (27.3)
Noninsulin treatment	16,805 (62.0)	58,288 (72.7)	63,243 (78.3)
Dipeptidyl peptidase 4 inhibitors	4,694 (17.3)	8,921 (11.1)	6,118 (7.6)
Glucagon-like peptide 1 analogs	2,628 (9.7)	9,703 (12.1)	8,424 (10.4)
Sodium–glucose cotransport 2 inhibitors	1,792 (6.6)	5,615 (7.0)	6,307 (7.8)
Biguanide	9,864 (36.4)	44,298 (55.3)	51,602 (63.9)
Sulfonylurea	3,016 (11.1)	10,496 (13.1)	11,421 (14.1)
Comorbid conditions, *n* (%)			
Ischemic heart disease	7,564 (27.9)	16,922 (21.1)	10,685 (13.2)
Stroke	2,384 (8.8)	5,361 (6.7)	4,017 (5.0)
Heart failure	7,008 (25.8)	10,331 (12.9)	4,405 (5.5)
Peripheral artery disease	2,207 (8.1)	4,552 (5.7)	2,894 (3.6)
Hypertension	23,830 (87.9)	66,599 (83.1)	54,947 (68.0)
Obesity	2,983 (11.0)	6,794 (8.5)	4,240 (5.2)
Diabetic retinopathy	5,519 (20.4)	13,182 (16.5)	10,593 (13.1)
Major lower-extremity amputation	548 (2.0)	791 (1.0)	482 (0.6)
Concomitant medication, *n* (%)			
Renin-angiotensin inhibitors	18,875 (69.6)	57,792 (72.1)	52,738 (65.3)
Diuretics	10,224 (37.7)	35,002 (43.7)	30,545 (37.8)
Acetylsalicylic acid	9,716 (35.8)	29,355 (36.6)	26,745 (33.1)
Lipid modifiers	18,614 (68.7)	57,673 (72.0)	55,125 (68.2)
Hemoglobin value, mean (SD), mmol/L	7.3 (1.2)	8.0 (1.0)	8.4 (1.0)
Albuminuria status, *n* (%)*			
Normoalbuminuria	6,894 (31.6)	35,541 (53.4)	44,286 (68.3)
Microalbuminuria	8,505 (38.9)	23,146 (34.8)	17,543 (27.1)
Macroalbuminuria	6,452 (29.5)	7.838 (11.8)	3,014 (4.6)
LDL cholesterol, mean (SD), mmol/L†	2.0 (1.1)	2.0 (0.9)	2.0 (1.1)

*Data missing for 34,822 participants. †Data missing for 16,882 participants.

Table 2—Hazard ratios (95% CI) of complications

	Severe CKD		Mild-to-moderate CKD		No-to-mild CKD	
HbA_{1c} level, % (mmol/mol)	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MACE						
4.9–5.3 (30–34)	1.41 (1.26–1.57)	<0.001	1.51 (1.39–1.65)	<0.001	1.63 (1.50–1.78)	<0.001
5.4–5.7 (35–39)	1.24 (1.16–1.32)	<0.001	1.27 (1.21–1.34)	<0.001	1.34 (1.28–1.41)	<0.001
5.8–6.2 (40–44)	1.03 (0.98–1.09)	0.24	1.06 (1.03–1.10)	<0.001	1.04 (1.01–1.08)	0.02
6.3–6.6 (45–49)	Ref.		Ref.		Ref.	
6.7–7.1 (50–54)	0.98 (0.93–1.04)	0.51	1.02 (0.98–1.06)	0.27	0.96 (0.93–1.00)	0.04
7.2–7.5 (55–59)	1.08 (1.02–1.14)	0.009	1.09 (1.05–1.13)	<0.001	1.10 (1.06–1.15)	<0.001
7.6–8.0 (60–64)	1.10 (1.03–1.16)	0.003	1.18 (1.13–1.23)	<0.001	1.14 (1.09–1.19)	<0.001
8.1–8.5 (65–69)	1.12 (1.05–1.20)	<0.001	1.21 (1.15–1.27)	<0.001	1.21 (1.15–1.28)	<0.001
8.6–9.4 (70–79)	1.19 (1.12–1.27)	<0.001	1.37 (1.31–1.43)	<0.001	1.36 (1.29–1.43)	<0.001
9.5–10.3 (80–89)	1.30 (1.20–1.40)	<0.001	1.50 (1.41–1.59)	<0.001	1.50 (1.40–1.61)	<0.001
10.4–13.1 (90–120)	1.48 (1.37–1.61)	<0.001	1.77 (1.66–1.89)	<0.001	1.71 (1.57–1.86)	<0.001
Microvascular complications						
4.9–5.3 (30–34)	1.00 (0.80–1.25)	0.98	0.74 (0.58–0.94)	0.02	0.94 (0.72–1.23)	0.66
5.4–5.7 (35–39)	1.05 (0.92–1.21)	0.45	0.95 (0.84–1.07)	0.42	0.94 (0.81–1.08)	0.38
5.8–6.2 (40–44)	1.00 (0.90–1.11)	0.97	0.86 (0.79–0.94)	<0.001	0.98 (0.89–1.08)	0.69
6.3–6.6 (45–49)	Ref.		Ref.		Ref.	
6.7–7.1 (50–54)	1.09 (0.98–1.20)	0.10	1.15 (1.06–1.24)	<0.001	1.17 (1.07–1.28)	<0.001
7.2–7.5 (55–59)	1.32 (1.19–1.47)	<0.001	1.26 (1.16–1.37)	<0.001	1.48 (1.35–1.63)	<0.001
7.6–8.0 (60–64)	1.26 (1.12–1.41)	<0.001	1.57 (1.44–1.72)	<0.001	1.69 (1.53–1.87)	<0.001
8.1–8.5 (65–69)	1.48 (1.31–1.67)	<0.001	1.89 (1.72–2.08)	<0.001	2.15 (1.93–2.40)	<0.001
8.6–9.4 (70–79)	1.49 (1.33–1.67)	<0.001	2.03 (1.85–2.22)	<0.001	2.32 (2.09–2.58)	<0.001
9.5–10.3 (80–89)	1.64 (1.43–1.89)	<0.001	2.29 (2.05–2.57)	<0.001	3.01 (2.64–3.44)	<0.001
10.4–13.1 (90–120)	1.68 (1.43–1.96)	<0.001	2.41 (2.13–2.73)	<0.001	3.44 (2.98–3.98)	<0.001
Hospitalizations due to hypoglycemia						
4.9–5.3 (30–34)	0.75 (0.42–1.35)	0.34	0.93 (0.61–1.40)	0.71	0.61 (0.33–1.15)	0.13
5.4–5.7 (35–39)	0.88 (0.64–1.23)	0.46	0.53 (0.40–0.70)	<0.001	0.52 (0.36–0.74)	<0.001
5.8–6.2 (40–44)	0.72 (0.56–0.93)	0.01	0.55 (0.46–0.66)	<0.001	0.72 (0.59–0.88)	0.001
6.3–6.6 (45–49)	Ref.		Ref.		Ref.	
6.7–7.1 (50–54)	1.44 (1.17–1.77)	<0.001	1.39 (1.22–1.59)	<0.001	1.49 (1.27–1.74)	<0.001
7.2–7.5 (55–59)	1.83 (1.48–2.25)	<0.001	1.99 (1.75–2.27)	<0.001	2.14 (1.81–2.51)	<0.001
7.6–8.0 (60–64)	2.87 (2.35–3.51)	<0.001	2.41 (2.10–2.76)	<0.001	2.89 (2.44–3.42)	<0.001
8.1–8.5 (65–69)	2.92 (2.36–3.62)	<0.001	3.17 (2.76–3.65)	<0.001	4.02 (3.39–4.76)	<0.001
8.6–9.4 (70–79)	2.92 (2.38–3.57)	<0.001	3.90 (3.42–4.43)	<0.001	4.25 (3.59–5.03)	<0.001
9.5–10.3 (80–89)	3.97 (3.19–4.95)	<0.001	4.24 (3.64–4.95)	<0.001	6.69 (5.54–8.07)	<0.001
10.4–13.1 (90–120)	4.48 (3.56–5.63)	<0.001	4.96 (4.23–5.83)	<0.001	6.53 (5.27–8.10)	<0.001

Ref., reference.

the matched cohorts. Among those with severe CKD, the median age was 77 (IQR = 70–84) years, 54% were men, and 31% had type 1 diabetes. Individuals with severe CKD had a higher prevalence of all reported comorbid conditions compared with the matched cohorts. The distribution across HbA_{1c} strata was similar among the three cohorts (Supplementary Table 2).

Risk of Complications

The hazard ratios and standardized 1-year risks of outcomes across the strata of HbA_{1c} levels for the three cohorts are displayed in Table 2 and Fig. 1, respectively. For individuals with severe CKD, the risk of MACE increased significantly at HbA_{1c} levels <5.8% (40 mmol/mol) and ≥7.2% (55 mmol/mol), compared with an HbA_{1c} level of 6.3–6.6% (45–49 mmol/mol). The risk of microvascular complications increased significantly at HbA_{1c} levels ≥7.2% (55 mmol/mol), whereas there was no statistically significant difference at HbA_{1c} levels ranging from 4.9% to 7.1% (30–54 mmol/mol). Finally, the risk of hospitalization due to hypoglycemia was lowest for individuals with an HbA_{1c} level of 5.8–6.2% (40–44 mmol/mol), and the risk significantly increased with increasing HbA_{1c} levels ≥6.3% (45 mmol/mol). The association between HbA_{1c} levels and outcomes in the severe CKD cohort followed a pattern similar to that observed in the mild-to-moderate and no-to-mild CKD cohorts.

Complication Risk Across Subgroups

Figure 2 depicts the subgroup analyses of the association between HbA_{1c} levels and outcomes in the individuals with severe CKD. Generally, the association patterns between HbA_{1c} level and outcomes remained consistent across the strata of sex, age, and diabetes type. Furthermore, among individuals with type 2 diabetes, the overall patterns between HbA_{1c} level and outcomes remained consistent in individuals with and without insulin treatment (Supplementary Fig. 2).

Sensitivity Analyses

The main results remained consistent for all outcomes in the complete-case analyses (*n* = 174,769) and in the analyses using mean HbA_{1c} (*n* = 150,990) (Supplementary Figs. 3 and 4). Furthermore, the main results remained consistent in the analyses stratified by the index year and in the cohort defined only by outpatient

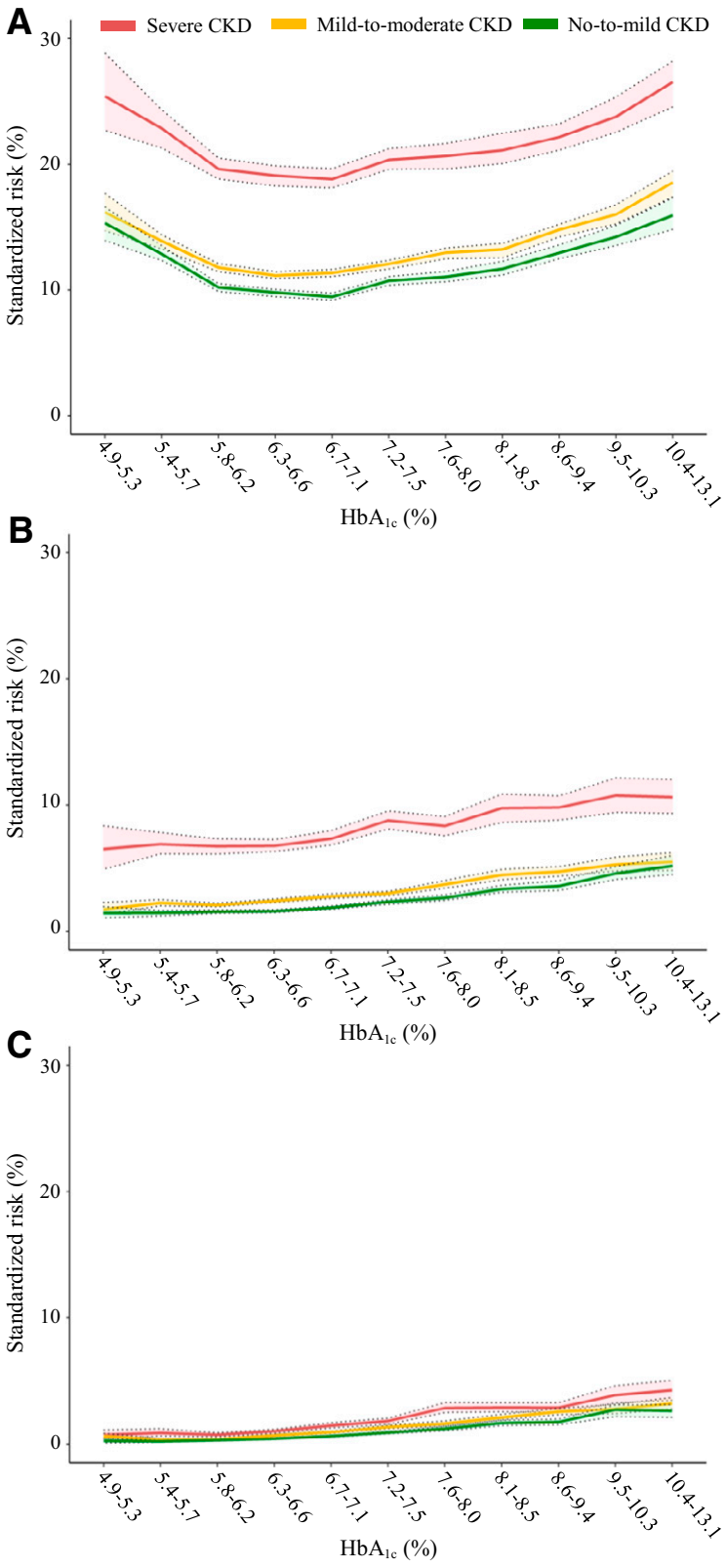

Figure 1—Standardized 1-year risk with 95% CI for MACE (*A*), microvascular complications (*B*), and hospitalizations due to hypoglycemia (*C*) across strata of HbA_{1c} in severe CKD and the matched cohorts.

creatinine measurements (n = 141,862) (Supplementary Figs. 5 and 6). Baseline eGFR modified the association between HbA_{1c} and study outcomes, with the highest hazard ratio and risk among those with the lowest kidney function (Supplementary Figs. 7 and 8). A significant interaction between HbA_{1c} and eGFR was observed, with P values <0.001 for all three outcomes. However, the overall association patterns were similar for all eGFR strata.

In the sensitivity analyses with further adjustment for clinical and paraclinical variables as well as glucose-lowering medication, the main results remained unchanged (Supplementary Fig. 9). Moreover, the positive association between HbA_{1c} and hospitalizations due to hypoglycemia persisted after adjusting for insulin and noninsulin glucose-lowering medication, as well as in the analysis restricted to primary codes of hospitalizations due to hypoglycemia (Supplementary Figs. 10 and 11). The 1-year risk of outcomes using restricted cubic splines confirmed the main findings (Supplementary Fig. 12).

CONCLUSIONS

In this nationwide cohort study, we found a strong association between HbA_{1c} levels and complications in individuals with diabetes and severe CKD. The association between HbA_{1c} level and MACE had a U-shape, with the lowest risk at HbA_{1c} levels around 6.3–7.1% (45–54 mmol/mol). Moreover, HbA_{1c} levels ≥7.2% (55 mmol/mol) were associated with an increased risk of microvascular complications, and HbA_{1c} levels ≥6.3% (45 mmol/mol) were associated with an increased risk of hospitalization due to hypoglycemia. Of note, the patterns of association between HbA_{1c} and outcomes were similar in the severe CKD cohort compared with those in the matched cohorts with no-to-mild or mild-to-moderate CKD.

In the general diabetes population, the beneficial effects of normal or near-normal HbA_{1c} levels on the risk of microvascular complications are well established, whereas the link between HbA_{1c} levels and the risk of cardiovascular disease and death is less clear (8–14,29,30). Data concerning the relationship between HbA_{1c} level and the risk of complications, particularly in individuals with an eGFR <30 mL/min/1.73 m^2, are limited and have conflicting findings (16–19). Drawing upon data from 27,113 individuals with diabetes and an eGFR <30 mL/min/1.73 m^2, the present study provides 1-year risk estimates of complications across a range of HbA_{1c} levels and in various subgroups.

Consistent with our findings regarding the risk of MACE, a prior study in

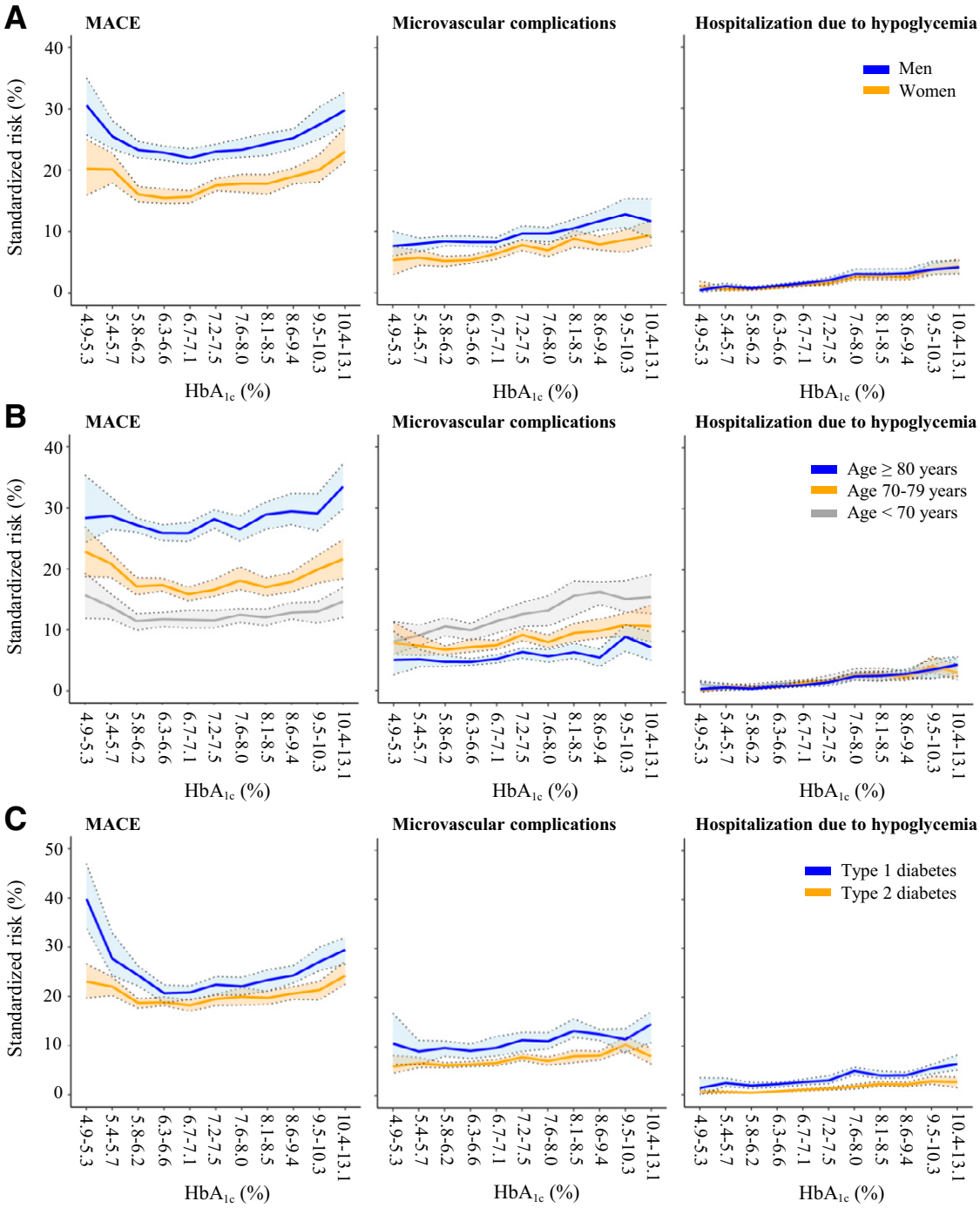

Figure 2—Standardized 1-year risk with 95% CI for MACE, microvascular complications, and hospitalizations due to hypoglycemia in individuals with severe CKD stratified by sex (*A*), age (*B*), or diabetes type (*C*) across HbA_{1c} categories.

individuals with an eGFR <60 mL/min/1.73 m^2 found a U-shaped association between HbA_{1c} and death, with the lowest risk ~7% (53 mmol/mol) (16). The same was illustrated in a meta-analysis of individuals receiving hemodialysis (31) and a cohort study of a general type 2 diabetes population (32). The increasing risk of MACE at HbA_{1c} levels <5.8% (40 mmol/mol) may reflect confounding by comorbid conditions or malnutrition, which can lead to low HbA_{1c} levels and higher mortality risk (33). The increasing risk of MACE may also result from adverse effects of tight glycemic management. It has been speculated that the increased mortality risk associated with tight glycemic management is at least partially mediated by a higher risk of severe hypoglycemia. In the ACCORD trial (14), tight glycemic management was associated with a threefold increase in severe hypoglycemic events; however, the impact of hypoglycemia on mortality risk remains uncertain (34,35).

In this study, we found that the risk of hospitalization due to hypoglycemia increased with increasing levels of HbA_{1c} across all three cohorts. Of note, this association persisted after adjustment for glucose-lowering medication. This finding

may seem to contradict the findings from clinical trials that randomized individuals to tight versus standard glycemic treatment, where the former was associated with a higher risk of hypoglycemia (8,9,12,14). However, the relationship between treatment intensity and hypoglycemia risk in clinical trials is unlike the link between the achieved HbA_{1c} level and hypoglycemia risk in observational data. In a real-life setting, treatment intensity is modified according to several considerations. Consequently, the association between achieved HbA_{1c} level and hypoglycemia in observational studies is affected by several factors, which may explain the finding. First, data suggest higher HbA_{1c} correlates with larger doses of glucose-lowering medication, including insulin, which is associated with a higher risk of hypoglycemia (36). Second, individuals who are prone to hypoglycemia and experience large glycemic excursions often have less tightly regulated glycemic management (37). Previous observational studies also found high HbA_{1c} levels associated with a higher risk of hypoglycemia in individuals with type 1 diabetes and those with type 2 diabetes (38,39).

Although the risk of microvascular complications increased at HbA_{1c} levels $\geq$7.2% (55 mmol/mol), our data suggest there is no further benefit to lowering HbA_{1c} below 6.7% (50 mmol/mol) in individuals with severe CKD. A previous study in a general type 1 diabetes population proposed a glycemic threshold of an HbA_{1c} level of 7.6% (60 mmol/mol), below which there was no additional risk reduction in clinically significant microvascular complications (29). In contrast, the Diabetes Control and Complications Trial demonstrated a beneficial effect of lowering HbA_{1c} toward the normal range in individuals with type 1 diabetes (40). Similarly, for individuals with type 2 diabetes, the UK Prospective Diabetes Study reported that any reduction in HbA_{1c} toward the normal range reduced the risk of microvascular complications (30). Additionally, we found that risk was higher in individuals aged $<$70 years compared with older age-groups. This likely reflects a selection bias, because our analysis included only individuals without prior retinopathy or amputations. Consequently, older individuals with a longer duration of diabetes but without these conditions may be less prone to developing them.

Overall, an HbA_{1c} range of 6.7–7.1% (50–54 mmol/mol) seems to be the most favorable in regard to long-term complications and death in individuals with severe CKD. This is aligned with current guidelines, which recommend an HbA_{1c} target of approximately 7% (53 mmol/mol) in individuals with diabetes and CKD (5,15). Our data do not support the current recommendations that propose conservative glycemic treatment of those with severe CKD. Contrarily, the data suggest the association between HbA_{1c} and long-term complications is similar for individuals with severe CKD as it is for those with no-to-mild and mild-to-moderate CKD.

It is important to recognize that our data exclude hypoglycemic episodes not requiring hospitalization. Individuals with severe CKD have an increased risk of hypoglycemia due to reduced gluconeogenesis, decreased insulin clearance, and impaired counter-regulatory responses to hypoglycemia (3,7). Intensifying glycemic treatment to lower HbA_{1c} may augment this risk. Therefore, balancing the risk of long-term complications with hypoglycemia is fundamental to improve both the prognosis and quality of life in this high-risk population. Clinical studies specifically in individuals with severe CKD are needed to determine whether optimizing glycemic management improves outcomes safely. Continuous glucose monitoring may improve glycemic management but still requires validation in individuals with severe CKD (6).

The strengths of this study include the large sample size identified from the well-validated Danish data registries. We identified individuals with diabetes based on redeemed prescriptions for glucose-lowering medication, a validated method for identifying those with diabetes in Denmark (21). This includes those who were treated only with metformin, which may have led to the inclusion of a small number of individuals without diabetes. However, excluding metformin-only users would result in a significant exclusion of individuals with type 2 diabetes. We were not able to identify individuals treated with lifestyle modification only, which may result in a study population with a higher risk of complications. As such, the generalizability of our findings is limited to individuals with diabetes who are treated with glucose-lowering medication and have an HbA_{1c} level between 4.9% and 13.1% (30–120 mmol/mol). Moreover, our microvascular complications findings were restricted to individuals without a history of diabetic retinopathy and major lower-extremity amputations, which narrows the generalizability of our findings related to microvascular complications. The MACE outcome, in addition to all-cause mortality, was restricted to acute myocardial infarction and stroke because these events can be identified as acute and recurrent.

Further limitations include the observational design, which prevents us from making any causal inferences. We cannot rule out unmeasured confounding, and we did not have data on ethnicity, lifestyle, BMI, or blood pressure. The analyses were based on baseline HbA_{1c} values, and changes during follow-up were not accounted for, because HbA_{1c} measurements beyond baseline were not collected systematically. Therefore, the very presence of updated values would represent more information than the actual HbA_{1c} level. This and the short follow-up period prompted us not to include time-updated values. The imputation of missing plasma hemoglobin values could potentially introduce bias due to differences between those individuals with a measurement and those without. However, principal results remained consistent in sensitivity analyses that included only those with a preexisting measurement. Additionally, we did not have access to data on hypoglycemic events that did not require hospitalization, nor on dosage of insulin or other glucose-lowering medication.

In conclusion, in this study, HbA_{1c} remained an important predictor for complications in severe CKD. Our data suggest an HbA_{1c} range of 6.7–7.1% (50–54 mmol/mol) to be most favorable for reducing long-term complications and mortality risk. Thus, achieving an HbA_{1c} target of 6.7–7.1% (50–54 mmol/mol) may improve outcomes in this high-risk population.

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Duality of Interest. D.H.K. has received speaker honoraria from Bayer outside the submitted work. T.P.A. owns stocks in Novo Nordisk. T.B. has served as an advisory board member for Medtronic and AstraZeneca; has been a speaker and lecturer for AstraZeneca and Boehringer Ingelheim; and has received research grant support from Novo Nordisk. K.N. serves as an advisor to Medtronic, Abbott, Convatec, and Novo Nordisk; owns shares in Novo Nordisk; has received research grants from Novo Nordisk, Zealand Pharma, Dexcom, and Medtronic to her institution; and received speaking fees from Medtronic and Novo Nordisk. J.H.S. serves on the advisory boards for Vital Beats and Medtronic and has received research grants from Medtronic outside this work. M.H. has served on scientific advisory boards for the following companies outside the scope of this study: Astra Zeneca, Novo Nordisk, Boehringer Ingelheim, GSK, and CSL Vifor Pharma; has served as a moderator of a symposium and an educational meeting for Astra Zeneca and Novo Nordisk; has received research grants from the A.P. Møller Foundation, Augustinus Foundation, Helen Bjørnow Foundation, and Lundbeck Foundation; and has received a Twinning Horizon 2020 Europe Grant. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.H.K., N.C., T.P.A., T.B., B.F.-R., and M.H. were involved in the conception and design of the study. D.H.K. and N.C. performed the statistical analyses. D.H.K., N.C., T.P.A., T.B., C.T.-P., K.N., J.H.S., B.F.-R., and M.H. were involved in the interpretation of the data. D.H.K. wrote the first draft of the manuscript. All authors edited, reviewed, and approved the final version of the manuscript. D.H.K. 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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