Insulin Glargine U100 Improved Glycemic Control and Reduced Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3 and 4

Carolina C. Betônico, MD[1]; Silvia Maria O. Titan, MD, PhD[2]; Aécio Lira, MD[1]; Tatiana S. Pelaes, MD[1]; Maria Lúcia C. Correa-Giannella, MD, PhD[3]; Márcia Nery, MD, PhD[1]; and Márcia Queiroz, MD, PhD[1]

[1]Endocrinology Division, Internal Medicine Department, Hospital das Clinicas Faculdade de Medicina, Universidade São Paulo, São Paulo, Brazil; [2]Nephrology Division, Internal Medicine Department, Hospital das Clinicas Faculdade de Medicina, Universidade São Paulo, São Paulo, Brazil; and [3]Laboratory of Carbohydrates and Radioimmunoassays (LIM-18), Discipline of Endocrinology and Metabolism, Faculdade de Medicina, Universidade São Paulo, São Paulo, Brazil

ABSTRACT

Purpose: Glycemic control in patients with chronic kidney disease (CKD) is particularly hard to achieve because of a slower insulin degradation by the kidney. It might modify the long-acting insulin analogue pharmacokinetics, increasing its time–action and the risk of hypoglycemia. However, because this insulin has no peak action, it might be a more tolerable approach to patients with CKD. This hypothesis remains to be tested, because no study has thus far examined the efficacy and safety profile of long-acting basal analogues in patients with significant loss of renal function. The purpose of this study was to compare the glycemic response to treatment with glargine U100 or neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes mellitus (T2DM) and CKD stages 3 and 4.

Methods: Thirty-four patients were randomly assigned to glargine U100 or NPH insulin after a 2-way crossover open-label design. The primary end point was the difference in glycosylated hemoglobin (HbA_{1c}) and in the number of hypoglycemic events between weeks 1 and 24, whereas secondary end points included changes in glycemic patterns, weight and body mass index, and total daily dose of insulin. HbA_{1c} was determined by ion-exchange HPLC, and hypoglycemia was defined as glucose concentration of 54 mg/dL (3.0 mmol/L) detected by self-monitoring of plasma glucose or continuous glucose monitoring.

Findings: After 24 weeks, mean HbA_{1c} decreased on glargine U100 treatment (–0.91%; $P < 0.001$), but this benefit was not observed for NPH (0.23%; $P = 0.93$). Moreover, incidence of nocturnal hypoglycemia was 3 times lower with glargine than with NPH insulin ($P = 0.047$).

Implications: Our results found that insulin glargine U100 could be effective, once it improved glycemic control, reducing HbA_{1c} with fewer nocturnal hypoglycemia episodes compared with NPH insulin in this population. These clinical benefits justify the use of basal insulin analogues, despite their high cost to treat patients with T2DM and CKD stages 3 and 4. Clinical Trials identifier: NCT02451917. (*Clin Ther*. 2019;41:2008–2020) © 2019 Published by Elsevier Inc.

Key words: basal insulin analogue, chronic kidney disease, hypoglycemia, insulin therapy, type 2 diabetes mellitus.

Accepted for publication July 12, 2019
https://doi.org/10.1016/j.clinthera.2019.07.011
0149-2918/$ - see front matter

INTRODUCTION

Insulin resistance is the primary pathogenic insult related to type 2 diabetes mellitus (T2DM), although changes in β-cell function are decisive for the onset of frank diabetes and its progression. Over time β cells become refractory to glucose, even though they continue to secrete supraphysiologic amounts of insulin, and a relative insulin deficiency develops, worsening the hyperglycemia. The disease progression is associated with a deterioration of the secretory capacity of the β cell, in terms of maximum response, pulsatility, and plasma insulin level.[1] Afterward, an absolute insulin deficiency develops, and eventually β cells become unresponsive to interventions aimed at improving their function, such as insulin secretagogue therapy. By this point, multiple oral agents used in combination or exogenous insulin are needed to achieve adequate glucose control in these insulinopenic patients with T2DM.[1] The United Kingdom Prospective Diabetes Study identified a linear overall failure rate of ~7% per year in all treatment groups.[2]

Diabetic kidney disease is one of the most frequent microvascular complications related to DM and is the leading cause of end-stage renal disease.[3,4] The kidneys play an important role in the regulation of glucose homeostasis, because they release significant amounts of glucose in the postabsorptive state, and they are responsible for approximately one-third of insulin degradation,[5–7] Moreover, the progressive loss of kidney function, and its consequent reduction in parenchyma and blood flow, has been associated with a lower capacity of renal glucose release, drug metabolism, and excretion and insulin extraction, resulting in a prolonged half-life of some oral antihyperglycemic agents and insulin, besides an impaired response to hypoglycemia.[5,6,8,9] The dose of several antidiabetic drugs should be reduced with glomerular filtration rate (GFR) < 45 mL/min, and some of them are contraindicated when renal function falls <30 mL/min.[10,11] This dose adjustment could not be enough to cover glycemic excursion in individuals with long-term diabetes and diminished β-cell secretory capacity; thus full insulin therapy will be necessary to achieve adequate glucose control. Furthermore, according to progression of chronic kidney disease (CKD) there are changes in insulin signaling, glucose transport, and metabolism related to accumulation of uremic toxins, inflammatory factors, oxidative stress, and vitamin D deficiency, inducing insulin resistance and poor response of target tissues.[12–14]

Since 2004, long-acting modified versions of human insulin (insulin analogues) have been approved to control glycemia in patients with diabetes. In the past years, several studies were conducted to improve understanding of insulin analogues' pharmacokinetics, pharmacodynamics, and safety profile of insulin analogues in specific patient subgroups such as children, the elderly, and pregnant women, but little attention has been directed to the CKD population. The reduction of insulin degradation by the kidney might modify the long-acting insulin analogue pharmacokinetics, increasing its time–action and the risk of hypoglycemia. Nonetheless, because this insulin has no peak action, it might be a more tolerable approach for patients with CKD compared with intermediate-acting insulin, such as neutral protamine Hagedorn (NPH) insulin. This hypothesis remains to be tested, because no study has thus far examined the efficacy and safety profile of long-acting basal analogues in insulinopenic patients with T2DM, exclusively on insulin therapy, and with significant loss of renal function, regarding the risk of hypoglycemia and appropriate adjustment of insulin dose based on creatinine clearance.[8,9,15–17]

Taking into account this gap in diabetes management in individuals with CKD, the purpose of this randomized open-label crossover study was to compare the efficacy and safety profile of a long-acting insulin analogue (glargine U100) and NPH insulin in patients with T2DM and CKD stages 3 and 4. The primary end point was the difference in glycated hemoglobin (HbA_{1c}) levels and the number of hypoglycemic events.

PATIENTS AND METHODS

This was a randomized, 2-way, crossover, open-label study conducted at the diabetic nephropathy outpatient clinic, Hospital das Clinicas, Faculdade de Medicina, Universidade São Paulo (HCFMUSP), under Clinical Trials identifier NCT02451917.

Inclusion and Exclusion Criteria

Inclusion criteria were (1) adult individuals with T2DM aged ≥40 years; (2) CKD stages 3 and 4,

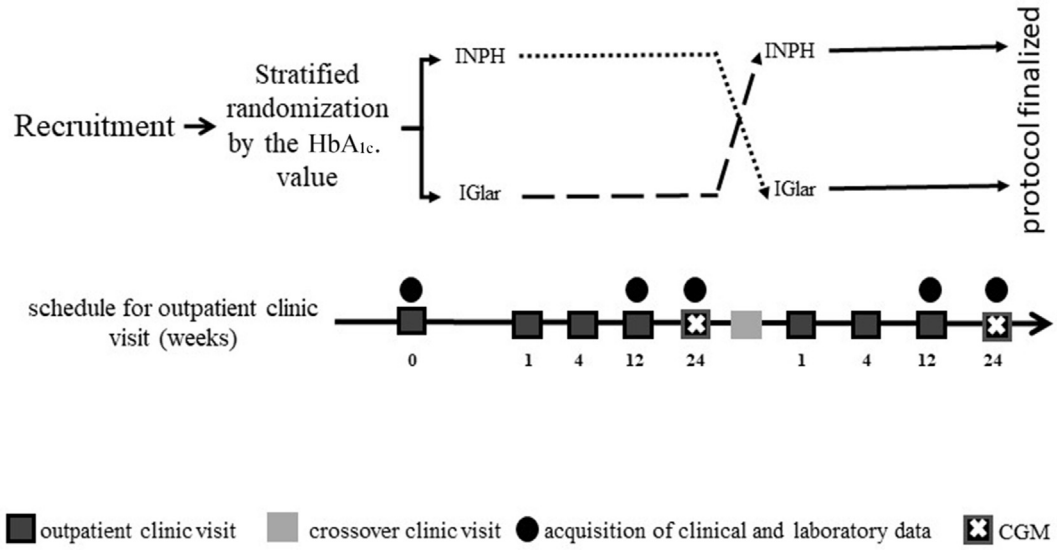

Figure 1. Schematic flowchart of the study. CGM = continuous glucose monitoring system; HbA_{1c} = glycosylated hemoglobin; IGlar = insulin glargine U100; INPH = insulin neutral protamine Hagedorn (NPH).

defined by an estimated GFR ≥15 and < 60 mL/min/1.73 m^2; (3) use of basal bolus insulin at least 3 months before the study, NPH as basal insulin and regular insulin at meals. Exclusion criteria were (1) other causes of kidney failure which were considered in the presence of any of the following circumstances: absence of diabetic retinopathy, low or rapidly decreasing GFR, rapidly increasing proteinuria or nephrotic syndrome, refractory hypertension, presence of active urinary sediment, signs or symptoms of other systemic disease, or >30% reduction in GFR within 2–3 months after initiation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers; (2) use of concomitant oral antidiabetic or antihyperglycemic drugs with insulin therapy; (3) pregnancy or breastfeeding; (4) previous or current diagnosis of neoplasia; (5) HIV infection; and (6) coexistence of psychiatric disorders.

The Institutional Review Board from the Hospital das Clinicas approved this study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided a signed, informed consent.

Randomization and Treatments

A team of physicians (C.C.B., S.M.O.T., A.L., T.S.P., and M.Q.) were responsible for enrolling and assigning participants to interventions. Randomization was stratified by the HbA_{1c} value at baseline: <9.0% or ≥9.0% (75 mmol/mol), in a 1:1 ratio, and the individuals who met all inclusion criteria were allocated alternately to either an IGlar or an INPH treatment. After 24 weeks, basal insulins were switched, patients taking IGlar were transferred to receive INPH (IGlar/INPH sequence), whereas patients using INPH in the first phase switched to IGlar (INPH/IGlar sequence). In this way, all patients were treated with the 2 types of basal insulin evaluated in the study, varying only the prescription sequence of each one. IGlar refers to insulin glargine U100,* whereas INPH refers to NPH insulin.† Figure 1 shows the schematic flowchart of the study.

The initial insulin dose for patients randomly assigned to IGlar was 80% of the total daily NPH

* Trademark: Lantus (Sanofi-Aventis, Sao Paulo, Brazil).

† Trademark: Humulin N (Lilly, Sao Paulo, Brazil).

dose that was being discontinued, as recommended in the package insert by the manufacturer and by several guidelines,[18–20] whereas the same NPH insulin dose and schedule was maintained for patients randomly assigned to INPH. Short-acting insulin analogues were used instead of regular insulin to minimize postprandial glucose excursions, mimicking more closely a normal postprandial physiologic profile; for this reason, pre-prandial regular insulin[‡] was switched to Lispro insulin[§] in both groups at the same dose as in use previously. Patients performed self-monitoring of blood glucose (SMBG), at 8 points per day once a week, which was used to adjust the insulin dose and also to identify hypoglycemic episodes. Basal insulin dose titration (glargine U100 and NPH) were guided by nocturnal and premeal SMBG, targeting values < 120 mg/dL (<6.6 mmol/L). The adjustment of lispro insulin was performed based on SMBG levels 2 h after the meal to reach values < 180 mg/dL (<10.0 mmol/L). This dose titration occurred in each treatment arm, during the outpatient clinic visit at 1, 4, 12, and 24 weeks. When basal insulins were switched, an ongoing prescription of lispro insulin was kept.

Study End Points and Assessments

The primary end point was the difference in HbA_{1c} levels and the number of hypoglycemic events between weeks 1 and 24 of each treatment arm. HbA_{1c} (normal range, 4%–6% or 20–42 mmol/mol) was determined in whole blood using ion-exchange HPLC. Hypoglycemia was defined as glucose concentration levels of 54 mg/dL (3.0 mmol/L) detected by self-monitoring of plasma glucose or continuous glucose monitoring (CGM; for at least 20 min), according to the International Hypoglycemia Study Group recommendations. Otherwise, hypoglycemia was classified as severe when it resulted in stupor, seizure, or unconsciousness that precluded self-treatment, thus requiring the assistance of another individual.[21] Nocturnal events were defined as SMBG <70 mg/dL (3.9 mmol/L) occurring after midnight and before wake-up in the morning,[22] whereas values of CGM were not used for this proposal. Prespecified secondary end points included changes in glycemic patterns as defined later in this paragraph, weight and body mass index (BMI), and total daily dose of insulin. Participants wore a blinded CGM (Medtronic/MiniMed, Northridge, Calif) for 3 days before crossover and at the end of the study period to compare variability in interstitial glucose levels for both basal insulin therapies. The accuracy of CGM was confirmed by independently measuring plasma glucose using SMBG. Within-day glycemic variability (GV) was described using SD around the derived mean glucose concentration values obtained from CGM data. The equation suggested by Monnier et al[23] [Log (number of hypoglycemic events): 1.37 – (0.72 × mean 48-h concentration) + (1.33 × SD)] was used for predicting the number of hypoglycemic events per person during the IGlar and INPH treatment. According to these researchers, the risk of asymptomatic hypoglycemia is higher with increasing GV and decreases with increasing mean glucose concentration values over the test period. Changes in glycemic patterns were expressed by the time spent in hypoglycemia (<70 mg/dL or <3.9 mmol/L), hyperglycemia (>180 mg/dL or >10 mmol/L), and euglycemia (70–180 mg/dL or 3.9–10 mmol/L). Weight and BMI were evaluated at baseline and at 24 weeks in each treatment sequence. Likewise, total daily dose of insulin was calculated and presented as units per kilogram per day.

Clinical laboratory and blood biochemical analysis were performed using commercial kits, as part of the routine assessment after overnight fasting, at the Divisão de Laboratório Central, HCFMUSP.

Sample Size Calculation and Statistical Analysis

A sample size of 34 participants provided 90% power to detect a mean difference of 0.7% (7.7 mmol/mol) in the primary end point (HbA_{1c}), considering a 15% dropout rate and assuming a SD of 0.85% and a type I error of 5%. The intention-to-treat (ITT) population consisted of all randomly assigned participants, irrespective of their compliance with the planned course of treatment or deviations from the protocol. Test for data normality (Kolmogorov–Smirnov statistics) was performed at baseline for each sequence of the therapy, indicating adequate randomization. To analyze the proposed variables, we grouped all data obtained according to the type of basal insulin IGlar or INPH, regardless of

‡ Trademark: Humulin R (Lilly, Sao Paulo, Brazil).

§ Trademark: Humalog (Lilly, Sao Paulo, Brazil).

its sequence in the prescription. Primary and continuous secondary efficacy end points were assessed using an ANOVA one-way model and Tukey's test. The *t* test was applied to compare percentages of the time spent in hypoglycemia, hyperglycemia, and euglycemia on CGM readings. Analyses were performed in the ITT population. All statistical analyses were performed with the R Project for Statistical Computing program version 3.2.5 (R Core Team 2016), and P values < 0.05 were considered statistically significant.

Recruitment and Baseline Characteristics

Flowchart of recruitment and drop-offs are shown in Figure 2. From December 2013 to July 2014, 193 individuals were screened at the diabetic nephropathy outpatient clinic. Fifty-one of them had GFR >60 mL/min/1.73 m^2, and the other 102 patients did not fill the inclusion criteria, mostly by not using basal bolus insulin therapy before the randomization period. Forty remaining individuals were first contacted, but only 35 of them agreed to sign the informed consent; afterward 1 patient gave up before being randomly assigned to treatment. Therefore, from August 2014 to August 2016, 16 patients were randomly assigned to the IGlar/INPH sequence and 18 to the INPH/IGlar sequence. Three participants (6.3%) discontinued the study; 1 patient died of acute pulmonary edema, another patient had an acute myocardial infarction, and 1 patient underwent hemodialysis. The other 2 patients were excluded for nonadherence to the protocol; therefore, 29 patients completed both treatment sequences.

RESULTS

The patients randomly assigned to IGlar or INPH had similar age, duration of diabetes, estimated GFR, and insulin dosage (Table I). The sequence allocation and

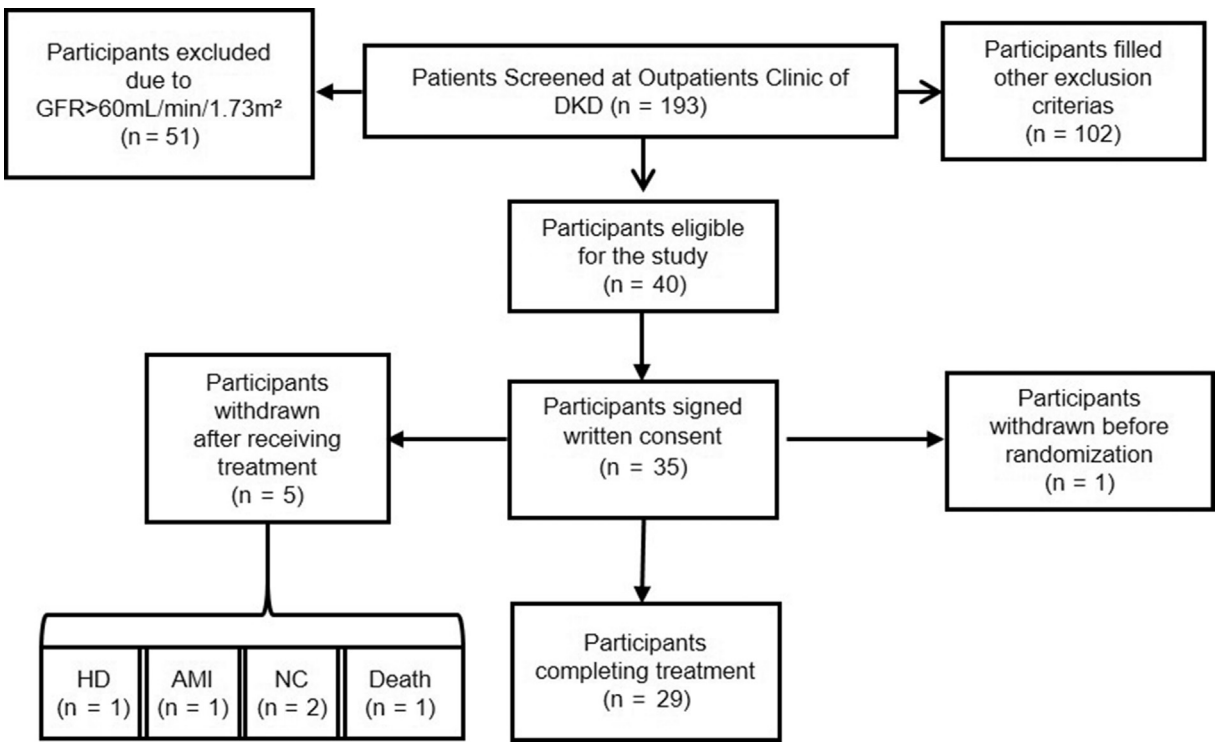

Figure 2. Flow of patients listed for the 2-way crossover study and the randomization to insulin glargine U100 (IGlar)/insulin neutral protamine Hagedorn (NPH; INPH) or INPH/IGlar treatment sequence. AMI = acute myocardial infarction; DKD = diabetic kidney disease; GFR = glomerular filtration rate; HD = hemodialysis; NC = noncompliance.

Table I. Baseline demographic characteristics and characteristics of intention-to-treat population.

Characteristic	IGlar (n = 16)	INPH (n = 18)	P*
Male	12 (75)	11 (61)	0.996
Female	4 (25)	7 (39)	0.996
Age, years	63 [7.0]	60 [8.7]	0.827
Duration of diabetes, years	19 [11.6]	19 [7.0]	0.882
Previous AMI, %	6 [37.5]	5 [27.8]	0.982
SBP, mmHg	147 [22]	136 [18]	0.596
DBP, mmHg	79 [12]	75 [13]	0.698
BMI, kg/m^2	28.6 [4.8]	30.4 [4.3]	0.469
eGFR, mL/min/1.73 m^2	25.1 [8.1]	29.0 [9.8]	0.467
Creatinine, mg/dL	2.6 [0.7]	2.3 [0.6]	0.154
Glycosylated hemoglbin, %	8.9 [1.3]	8.6 [1.1]	0.732
Total cholesterol, mg/dL	175 [56]	170 [62]	0.134
HDL cholesterol, mg/dL	41 [11]	40 [14]	0.905
Triglycerides, mg/dL	173 [80]	167 [90]	0.327
LDL cholesterol, mg/dL	103 [47]	94 [40]	0.827
Insulin dosage, UI/kg/d	0.64 [0.26]	0.64 [0.25]	0.884

Data are presented as n (%) or mean [SD]. All data are for intention-to-treat population, and it comprised 34 participants randomly assigned after filling the written consent.
AMI = acute myocardial infarction; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IGlar = insulin glargine U100; INPH = insulin neutral protamine Hagedorn (NPH); SBP = systolic blood pressure.
* Kolmogorov–Smirnov statistic-test was performed at baseline for each sequence of the therapy.

study periods had no effect on the primary end point in the ANOVA model ($P = 0.878$ and $P = 0.198$, respectively).

After 24 weeks of treatment, the mean HbA_{1c} level declined from 8.86% [1.4%] to 7.95% [1.1%] (72.7 [15.4] mmol/mol to 62.8 [12] mmol/mol) during the IGlar treatment, whereas an increase from 8.21% [1.3%] to 8.44% [1.3%] (66.2 [14.2] mmol/mol to 69.4 [14.2] mmol/mol) occurred during the INPH therapy, and this difference between therapies reached significance with $P = 0.0285$ (Figure 3). The Δ HbA_{1c} between treatment arms for insulin glargine and NPH treatment were –0.91% ($P < 0.001$) and 0.23% ($P = 0.93$), respectively. Data regarding the ITT analyses kept statistical significance ($P = 0.039$).

CGM was recorded during 3 days for all participants at the end of both treatment branches, except for 5 of them, because of unfamiliarity with mechanical procedures or visual impairment. The within-day GV was similar for both therapies; in other words, during the IGlar treatment mean SD was 49 mg/dL or 2.72 mmol/L (range, 31–94 mg/dL or 1.72–5.22 mmol/L), and for INPH the mean SD was 51 mg/dL or 2.83 mmol/L (range, 15–78 mg/dL or 0.83–4.33 mmol/L). The average daily time spent in hyperglycemia was lower with the IGlar treatment than with the INPH therapy (30% and 38%, respectively; $P < 0.05$) (Figure 4). No statistical difference was found on risk of asymptomatic hypoglycemia between IGlar and INPH ($P = 0.54$) using Monnier's suggested equation based on GCM data.

The same trend was observed with the total number of hypoglycemic events per patient, which was lower during IGlar than during INPH (4.9 versus 6.3 events/patient, respectively), although this did not reach statistical significance ($P = 0.35$) (Figure 5A). Likewise, the number of hypoglycemia events <50 mg/dL (2.7 mmol/L) was lower during IGlar (0.7 events/patient) than during INPH (1.03 events/patient; $P = 0.496$) (Figure 5B). No difference was found regarding the

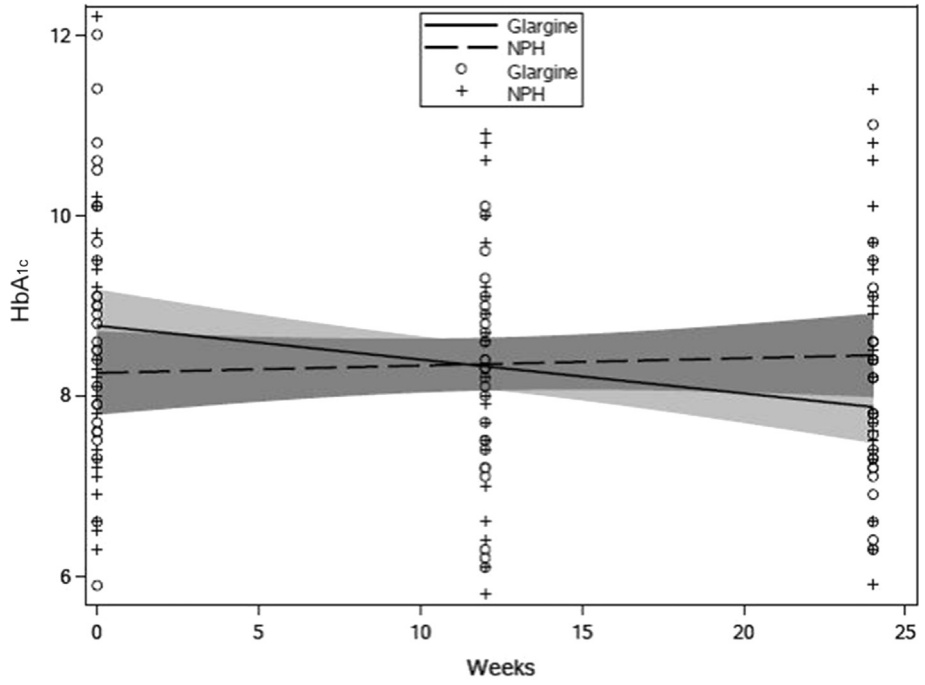

Figure 3. Result of glycosylated hemoglobin (HbA_{1c}) during treatment with glargine U100 and neutral protamine Hagedorn (NPH) insulin at baseline and after 12 and 24 weeks of treatment. Data are presented as mean [SD]. O = HbA_{1c} of each patient on glargine U100 insulin; + = HbA_{1c} of each patient on NPH insulin; — = mean of HbA_{1c} during glargine U100 treatment, ——— = mean of HbA_{1c} during NHP insulin treatment; shaded gray area = SD of HbA_{1c} during glargine U100 treatment; shaded light gray area = SD of HbA_{1c} during NHP insulin treatment.

number of hypoglycemic episodes evaluated right after the protocol started (1 week) and the same period after crossover with insulin switch ($P = 0.32$). Moreover, 2 participants (6.25%) experienced severe hypoglycemia during the use of NPH insulin, whereas these events were not observed during the use of IGlar therapy (Figure 5C). The incidence of nocturnal hypoglycemia was 3 times lower with IGlar (0.5 events/patient) than with INPH (1.5 events/patient; $P = 0.047$) (Figure 5D).

There was a weight gain in both therapies, with an increment in BMI from 29.7 to 30.0 kg/m^2 during insulin glargine treatment and from 30.0 to 30.4 kg/m^2 for NPH insulin ($P = 0.99$). Insulin doses were similar at the 24th week, both for basal insulin (0.31 [0.13] U of IGlar and 0.34 [0.15] U of INPH; $P = 0.45$) and total daily dose (0.64 U/kg; $P = 0.66$). Likewise, general laboratory tests and other biochemical analyzes, such as GFR, serum creatinine, blood urea nitrogen, calcium, parathormone, plasma lipids, and blood cell count, did not reach statistical difference between the therapies (Table II).

DISCUSSION

This open-label, randomized, 2-way crossover study clearly indicates a benefit of glargine U100 insulin over the NPH insulin in participants with T2DM and kidney disease stages 3 and 4. This proposition is based on a significant decrease in HbA_{1c} and a concurrent reduction in the nocturnal hypoglycemic events with the use of glargine U100 insulin as basal insulin for 24 weeks. Even considering the complex relationship between HbA_{1c} and glycemia in patients with CKD, because of a larger variability in hemoglobin, inflammation, and nutritional status with advancing uremia,[24] HbA_{1c} continues being the preferential laboratory variable to evaluate glycemic control in this population. Our results found a statistical significance in Δ HbA_{1c} between insulin

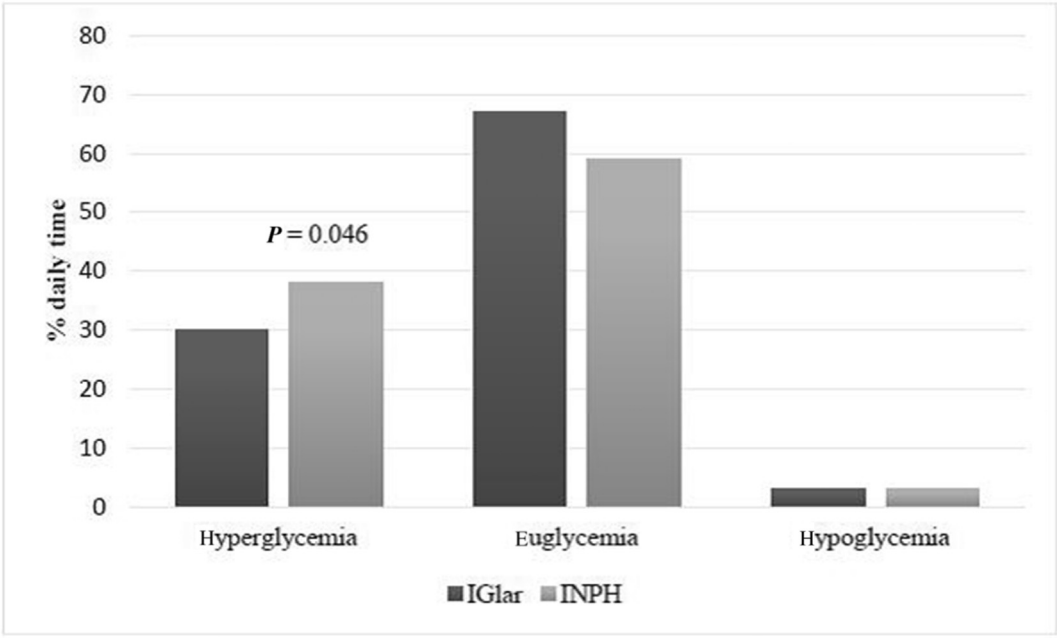

Figure 4. The average daily time spent in hyperglycemia, euglycemia, and hypoglycemia, according to continuous glucose monitoring records. Data are presented as mean; n = 24 patients; $P < 0.05$ determined by the Student *t* test. IGlar = insulin glargine U100; INPH = insulin neutral protamine Hagedorn (NPH).

glargine U100 and NPH treatment ($P < 0.001$), which was kept with ITT analyses ($P = 0.039$). This HbA_{1c} reduction during insulin glargine U100 treatment was also accompanied by an improvement in the secondary end points such as a decrease in time spent in hyperglycemia and lower GV. Moreover, the results of this clinical trial found 3 times fewer nocturnal hypoglycemic events and no severe episodes that required medical or another individual's assistance during insulin glargine U100 therapy ($P = 0.047$). Recently, Lipska et al[25] reported data from a retrospective cohort study that indicated visits to emergency medical or hospitalization for hypoglycemia did not differ significantly between patients who started basal insulin analogues and NPH insulin. These results have brought to the discussion the need for studies to investigate the relative clinical benefits of basal insulin analogues, clearly and convincingly to justify their high cost. The confluence of several factors alter the regulation of glycemic homeostasis associated with slower insulin degradation and may contribute to an increased risk of hypoglycemia, making this complication a significant threat to CKD patient safety.[7,26,27] Thus, an insulin excess related to peak time of NPH insulin of 6–10 h after subcutaneous injection in the presence of decline of renal function could justify the severe hypoglycemia experienced by 2 participants during INPH therapy. Nocturnal hypoglycemia is particularly dangerous because several clinical trials reported its tight relationship with cardiovascular events and also with sudden nocturnal death in diabetic individuals.[7,28–30] A large retrospective cohort analysis of 243,222 patients at the Veterans Health Administration concluded that CKD itself represents a risk for hypoglycemia and that it is more frequently reported in patients with T2DM and kidney impairment.[31] The results of the DEVOTE study (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events) found an association between

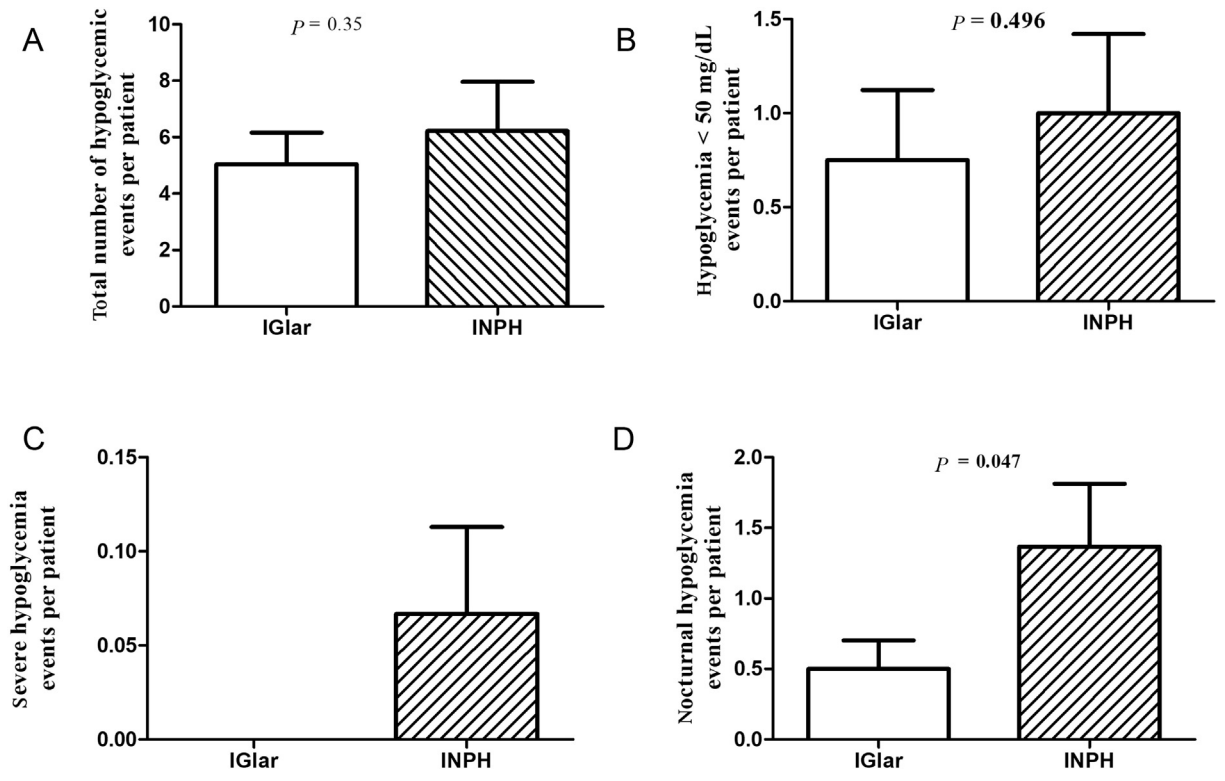

Figure 5. (A) Total number of hypoglycemic events per patient during glargine and neutral protamine Hagedorn (NPH) insulin treatments. (B) Hypoglycemia <50 mg/dL events per patient during glargine and NPH insulin treatments. (C) Severe hypoglycemia events per patient during glargine and NPH insulin treatments. (D) Nocturnal hypoglycemia events per patient during glargine and NPH insulin treatments. *P* values were determined by the ANOVA test. IGlar = insulin glargine U100; INPH = insulin NPH.

severe hypoglycemia and all-cause mortality.[32] Besides, patients who experienced severe hypoglycemia were particularly at greater risk of death in the short term after the hypoglycemic episode.

It is known that diabetes may be present for many years before its diagnosis, justifying a higher proportion of individuals with T2DM with evident nephropathy soon after their diagnosis of diabetes. Moreover, ~20% of patients with T2DM will progress to end-stage renal disease within 20 years after the initial diagnosis of nephropathy.[33] Over the years, there is a deterioration the secretory capacity of β cells, and frequently the combination of different classes of oral antidiabetic agents and exogenous insulin is necessary to achieve adequate glucose control.[1] However, almost all medications available to treat hyperglycemia need to have their dosages adjusted when GFR becomes <45 mL/min/1.73 m^2.[11] Taking this into consideration, it is possible to assume that the patients enrolled in this protocol are insulinopenic, because they have long-term diabetes (19 [9.7] years). In this case, the adjustment of antidiabetic medications proposed, in the face of renal impairment, is not enough to keep diabetes under control, and insulin is the most effective therapy for achieving glycemic goals. Therefore, this protocol included only patients with on-going treatment with basal bolus insulin therapy, without association with antidiabetic drugs, to avoid possible interferences in the analyzed outcomes. The results hereby presented contribute to the better understanding of the insulin requirement of patients with CKD. Because we observed no significant difference between glargine U100 and NPH insulin

Table II. General laboratory tests and other biochemical analyses of intention-to-treat population.

Variable	IGlar (n = 29)	INPH (n = 29)	P*
Creatinine, mg/dL			
Basal	2.4 [0.7]	2.5 [0.7]	0.998
12 weeks	2.6 [0.9]	2.4 [1.0]	0.994
24 weeks	2.6 [0.8]	2.6 [1.0]	0.999
Slope of Cr (24 weeks − basal)	0.2	0.1	
Estimated glomerular filtration rate,† mL/min/1.7 m^2			
Basal	28.0 [9.6]	27.4 [9.1]	0.997
12 weeks	27.0 [9.8]	28.2 [9.2]	0.992
24 weeks	26.9 [10.0]	25.6 [9.7]	0.994
Delta eGFR (24 weeks − basal)	1.1	1.8	
Blood urea nitrogen, mg/dL			
Basal	84 [30]	87.8 [33.8]	0.996
12 weeks	92 [36]	80.9 [24.7]	0.697
24 weeks	87 [26]	85.2 [27.0]	0.999
Serum total calcium, mg/dL			
Basal	9.4 [0.5]	9.3 [0.6]	0.992
2 weeks	9.3 [0.6]	9.3 [0.5]	0.995
24 weeks	9.2 [0.5]	9.2 [0.5]	0.999
Parathormone, mg/dL			
Basal	102.8 [54.2]	114.9 [81.1]	0.984
12 weeks	117.1 [85.3]	112.1 [81.9]	0.999
24 weeks	120.7 [80.3]	136.4 [118.4]	0.971
Red blood cell count, mg/dL			
Basal	12.8 [1.8]	12.8 [1.8]	0.988
12 weeks	13.0 [1.8]	12.8 [1.9]	0.991
24 weeks	13.1 [1.7]	12.9 [1.9]	0.791

Data are presented as mean [SD] unless otherwise indicated. All data are for intention-to-treat population, and it comprised 34 participants randomly assigned after filling the written consent.
IGlar = insulin glargine U100; INPH = insulin neutral protamine Hagedorn (NPH).
* Determined by ANOVA test.
† Determined by the Chronic Kidney Disease Epidemiology Collaboration.

doses at the 24th week of therapy, both groups received the same proportion of basal bolus insulin and similar amount of insulin per kilogram per day (0.31 U of IGlar and 0.34 U of INPH). The use of insulin glargine U100 was associated with a reduced risk of nocturnal hypoglycemic events, and no severe episodes required medical or another individual's assistance. Probably our results are related to the type of basal insulin prescribed, once this was not associated with the reduction of insulin doses. Previous studies evaluating the use of insulin glargine U100 in patients with T2DM and preserved renal function have found divergent results, ranging from better glycemic control to non-inferiority to NPH insulin, similar values of HbA_{1c},[34–37] and a clear advantage of insulin glargine U100 over NPH insulin in reducing nocturnal and overall hypoglycemia.[9,20] Nevertheless, it is difficult to extrapolate these results to a specific population such as patients with CKD stages 3 and 4, because insulin metabolism and degradation are modified by worsening renal function, frequently requiring a lower insulin dose.

Some factors unrelated to glycemic control, and common to CKD, might also influence HbA_{1c}, such

as decreased erythropoiesis, caused by iron or vitamin B_{12} deficiency. However, progression to uremia is associated with decreased insulin sensitivity of peripheral tissues, worsening the hyperglycemia and subsequently affecting HbA_{1c}.[38] Therefore, laboratorial variables related to renal function, bone metabolism, and anemia were analyzed, and they remained stable; thus, other factors besides glycemic control are unlikely to have influenced the HbA_{1c} evolution between the groups.

There was discrete weight gain, but BMI was the same at the end of each study arm, which is in accordance with other studies involving patients with T2DM without renal disease treated with insulin therapy.[28]

It is relevant to point out that this study was limited to a specific population of insulinopenic patients with T2DM on basal bolus insulin therapy and CKD stages 3 and 4; hence, results should not be extrapolated to other populations such as patients on dialysis or with initial stages of CKD. Because our patients required continuous treatment, we could not contemplate a washout period or adopt a double-blind design, which would be ideal to avoid a carry-on effect and biases. Nevertheless, this study has favorable points because it is the first randomized trial aimed to assess glycemic control and hypoglycemia risk in a population with diabetes and advanced kidney disease treated with long-acting insulin analogues under basal bolus therapy. The usual bias resulting from differences in education and patient–health care provider interaction was prevented by conducting this study in a single center, which may also have contributed to reducing the number of participants who missed follow-up appointments.

In the face of several new products and new formulations of existing products recently approved for the treatment of DM2,[39,40] future studies should be directed to better understand the pharmacokinetics of these medications to promote better glycemic control and reduction of adverse effects with adequate dose adjustments according to renal function impairment, principally of those drugs with longer duration such as insulin regular U500 and insulin analogues lispro U200, glargine U300, and degludec.

CONCLUSIONS

The treatment of patients with T2DM and CKD stages 3 and 4 with insulin glargine U100 could be effective once it provided better glycemic control, reducing HbA_{1c} with fewer nocturnal hypoglycemia episodes compared with NPH insulin. These clinical benefits justify the use of basal insulin analogues, despite their high cost to treat this specific population.

ACKNOWLEDGMENTS

The authors thank Medtronic Brazil for donation of CGM sensors. This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector. Preliminary results were presented and published as an abstract at the Annals of Congress of American Diabetes Association, 2016.

C.C. Betônico contributed to the study design, implemented the study protocol, collected and interpreted the data, wrote the first draft of the manuscript, contributed to subsequent revisions, and contributed to its intellectual content; S.M.O. Titan oversaw the implementation of the study protocol and contributed to its intellectual content; A. Lira contributed to the implementation of the study protocol and collected the data; T.S. Pelaes contributed to the implementation of the study protocol and collected the data; M.L.C. Correa-Giannella interpreted the data and contributed to its intellectual content; M. Nery oversaw the implementation of the study protocol, interpreted the data, and contributed to its intellectual content; and M. Queiroz conceived and designed the study, oversaw the study implementation and collection of data, interpreted the data, contributed to the writing of the first draft of the manuscript and its subsequent revisions, and contributed to its intellectual content. C.C. Betônico and M. Queiroz are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of data and the accuracy of the data analyses.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes. Implications for clinical practice. *Prim Care*. 1999;26:771–789.
2. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med*. 1998;15:297–303.

3. Sampanis C. Management of hyperglycemia in patients with diabetes mellitus and chronic renal failure. *Hippokratia*. 2008;12:22—27.
4. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. *Diabetologia*. 1984;27:351—357.
5. Mak RH, De Fronzo RA. Glucose and insulin metabolism in uremia. *Nephron*. 1992;61:377—382.
6. Cersosimo E, Garlick P, Ferretti J. Renal glucose production during insulin-induced hypoglycemia in humans. *Diabetes*. 1999;48:261—266.
7. Papademetriou V, Lovato L, Doumas M, et al. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. *Kidney Int*. 2015;87:649—659.
8. Heise T, Kaplan K, Haahr HL. Day-to-day and within-day variability in glucose-lowering effect between insulin degludec and insulin glargine (100 U/mL and 300 U/mL): a comparison across studies. *J Diabetes Sci Technol*. 2018;12:356—363.
9. Rys P, Wojciechowski P, Rogoz-Sitek A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. *Acta Diabetol*. 2015;52:649—662.
10. Davies M, Chatterjee S, Khunti K. The treatment of type 2 diabetes in the presence of renal impairment: what we should know about newer therapies. *Clin Pharmacol*. 2016;8:61—81.
11. Pecoits-Filho R, Abensur H, Betônico CCR, et al. Interactions between kidney disease and diabetes: dangerous liaisons. *Diabetol Metab Syndr*. 2016;8:50.
12. Hager SR. Insulin resistance of uremia. *Am J Kidney Dis*. 1989;14:272—276.
13. Fliser D, Pacini G, Engelleiter R, et al. Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int*. 1998;53:1343—1347.
14. Horita S, Nakamura M, Suzuki M, Satoh N, Suzuki A, Seki G. Selective insulin resistance in the kidney. *Biomed Res Int*. 2016;2016:5825170.
15. Niafar M, Nakhjavani M. Efficacy and safety of insulin glargine in type 2 diabetic patients with renal failure. *J Diabetes Metab*. 2012;3(4).
16. Garcia de Lucas MD, Olalla Sierra J, Aviles Bueno B. Degludec is effective and safe in real-life treatment for patients with type 2 diabetes mellitus and chronic kidney disease stage 3B. *Int J Clin Pract*. 2018;72, e13098.
17. Yale J-F, Berard L, Groleau M, Javadi P, Stewart J, Harris SB. TITRATION: a randomized study to assess 2 treatment algorithms with new insulin glargine 300 units/mL. *Can J Diabetes*. 2017;41:478—484.
18. Cupp M. How to switch between insulin products. *Pharm Lett*. 2009;25(10):201005.
19. Mauricio D, Hramiak I. Second-generation insulin analogues — a review of recent real-world data and forthcoming head-to-head comparisons. *Eur Endocrinol*. 2018;14(Supp 1):2—9.
20. Hedrington MS, Pulliam L, Davis SN. Basal insulin treatment in type 2 diabetes. *Diabetes Technol Ther*. 2011;13(S1):S33—S42.
21. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes: table 1. *Diabetes Care*. 2017;40:155—157.
22. Gabriely I, Shamoon H. Hypoglycemia in diabetes: common, often unrecognized. *Cleve Clin J Med*. 2004;71:335—342.
23. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther*. 2011;13:813—818.
24. Speeckaert M, Van Biesen W, Delanghe J, et al. Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? *Nephrol Dial Transpl*. 2014;29:2167—2177.
25. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. *JAMA*. 2018;320:53—62.
26. Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials. *N Engl J Med*. 2008;358:2630—2633.
27. Alsahli M, Gerich J. Hypoglycemia in patients with diabetes and renal disease. *J Clin Med*. 2015;4:948—964.
28. Riebenfeld D, Spirk D, Mathis A, et al. Treatment intensification with insulin glargine in patients with inadequately controlled type 2 diabetes improves glycaemic control with a high treatment satisfaction and no weight gain. *Swiss Med Wkly*. 2015;145:w14114.
29. Cha S-A, Yun J-S, Lim T-S, et al. Severe hypoglycemia and cardiovascular or all-cause mortality in patients with type 2 diabetes. *Diabetes Metab J*. 2016;40:202—210.
30. Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and cardiovascular risk: is there a major link? *Diabetes Care*. 2016;39(Supplement 2):S205—S209.
31. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:1121—1127.
32. Pieber TR, Marso SP, McGuire DK, et al. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular

outcomes and mortality. *Diabetologia*. 2018;61:58—65.
33. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. *Diabetes Care*. 2004;27(Suppl 1):S79—S83.
34. Pandya N, DiGenio A, Gao L, Patel M. Efficacy and safety of insulin glargine compared to other interventions in younger and older adults: a pooled analysis of nine open-label, randomized controlled trials in patients with type 2 diabetes. *Drugs Aging*. 2013;30:429—438.
35. HOE 901/2004 Study Investigators Group. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in Type 2 diabetic patients. *Diabet Med*. 2003;20:545—551.
36. Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V. Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabet Med*. 2008;25:924—932.
37. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. *Clin Ther*. 2003;25:1541—1577. discussion 1539-1540.
38. Adrogué HJ. Glucose homeostasis and the kidney. *Kidney Int*. 1992;42: 1266—1282.
39. Brady VJ. Insulin therapy: the old, the new and the novel-an overview. *Nurs Clin North Am*. 2017;52:539—552.
40. George CM, Byun A, Howard-Thompson A. New injectable agents for the treatment of type 2 diabetes part 1 - injectable insulins. *Am J Med*. 2018;131:752—754.

Address correspondence to: Márcia Queiroz, MD, PhD, Endocrinology Division, Internal Medicine Department, Hospital das Clinicas, Faculdade de Medicina, Universidade São Paulo, Av. Dr. Enéas Carvalho de Aguiar, 155 - 8o. andar - Bloco 8A, Setor Azul, 05403-000, Brazil. E-mail: marciasqz@gmail.com

APPENDIX. CONSORT 2010 CHECKLIST OF INFORMATION TO INCLUDE WHEN REPORTING A RANDOMISED TRIAL*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions(for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NO
Sample size	7a	How sample size was determined	6-7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequencegeneration	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocationconceal -mentmechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5

(*continued on next page*)

(*Continued*)

Section/Topic	Item No	Checklist item	Reported on page No
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NO
	11b	If relevant, description of the similarity of interventions	NO
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation,together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	7 (16)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	no
Harms	19	All important harms or unintended effects in each group(for specific guidance see CONSORT for harms)	7

(*Continued*)

Section/Topic	Item No	Checklist item	Reported on page No
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	9-10-11
Other information			NCT02451917**Glargine Versus NPH in Patients With Chronic Kidney Disease**
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	NCT clinical trials
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	University of São Paulo

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.