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REVIEW ARTICLE

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The role of basal insulins in the treatment of people with type 2 diabetes and chronic kidney disease: A narrative review

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Abstract

The majority of cases of chronic kidney disease (CKD) worldwide are driven by the presence of type 2 diabetes (T2D), resulting in an increase in CKD rates over the past few decades. The existence of CKD alongside diabetes is associated with increased burden of cardiovascular disease and increased risk of death. Optimal glycaemic control is essential to prevent progression of CKD, but achieving glycaemic targets in people with CKD and diabetes can be challenging because of increased risk of hypoglycaemia and limitations on glucose-lowering therapeutic options. This review considers the challenges in management of T2D in people with impaired kidney function and assesses evidence for use of basal insulin analogues in people with CKD.

KEYWORDS
basal insulin, diabetes complications, diabetic nephropathy, hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

Insulin transformed the treatment of diabetes in 1922, when a purified pancreatic extract was successfully used in humans.[1] In the 100 years since, insulins have evolved so that current options more closely mimic physiological insulin secretion than earlier formulations.[1] The development of non-insulin therapies such as sodium-glucose co-transporter 2 inhibitors (SGLT2is) and incretin mimetics [glucagon-like peptide-1 receptor agonists (GLP-1 RAs)] have certainly advanced glucose-lowering and outcome reduction options; however, insulin remains a cornerstone of glycaemic management as beta-cell function deteriorates.[2–4] The use of insulin may be particularly important for the management of glycaemia in people with impaired kidney function. The safety and efficacy of certain glucose-lowering medications in this population may be reduced, highlighting the importance of insulin as a treatment option. This review examines the evidence supporting the role of basal insulin (BI) therapy in patients with type 2 diabetes (T2D) and kidney impairment.

2 | CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES: THE BURDEN REMAINS

Chronic kidney disease (CKD) is defined as abnormalities in kidney structure or function that impact health, with elevated albumin to creatinine ratio [≥30 mg/g (3 mg/mmol)] and/or low estimated glomerular filtration rate (eGFR; <60 ml/min/1.73 m^2) for over 3 months, as per current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[5] CKD is classified based on the cause of disease, eGFR stage (1-5) and albuminuria category (1-3).[5] The risk of developing end stage kidney disease increases as eGFR decreases and/or albuminuria increases, with Stage 5 CKD diagnosed when eGFR decreases below 15 ml/min/1.73 m^2. A person with diabetes with CKD and no clinical evidence of another form of kidney disease is said to have diabetic kidney disease (DKD); confirmation by renal biopsy is generally only required when an alternative cause of CKD is suspected.[6] DKD is the most common type of CKD affecting people with diabetes and is the leading cause of CKD worldwide.[7] The International Diabetes Management Practices Study (IDMPS) in low- to middle-income countries collected data from 66 088 people with T2D between 2005 and 2017.[8] Despite improvements in treatment during that time, including increasing use of renoprotective treatments such as renin-angiotensin system inhibitors, 11.9% of people with T2D had Stage A2 albuminuria and 0.2% were receiving dialysis in 2016-17.[8] The IDMPS captured eGFR data for the first time in 2017; based on data gathered in that year, 20% of people with T2D treated with oral glucose-lowering drugs and 33% with T2D treated with insulin had Stage 3 CKD (moderate impairment) or worse.[8] The Global Burden of Disease study of 195 countries identified CKD because of T2D (i.e. DKD) as the main contributor to increasing rates of CKD over the past few decades.[9] Incident cases of DKD increased from over 1.3 million in 1990 to 2.3 million in 2017, largely because of population expansion and demographic changes.[9] Ageing was the main driver of increasing rates of CKD in the middle to high Sociodemographic Index nations.[9] Population growth was the main driver in the low-middle and low Sociodemographic Index nations with lower life expectancy.[9] In 2017, DKD was responsible for over 8.1 million age-standardized disability-adjusted life years and over 348 000 deaths.[9]

The presence of CKD with diabetes is associated with a greater burden of cardiovascular disease (CVD), more rapid loss of kidney function, and increased risk of death, which influences the management of glycaemia. Therefore, identifying CKD in diabetes is critical to ensure implementation of treatment to reduce CKD progression.[7] This includes optimal blood glucose (BG) and blood pressure control, in addition to use of renin-angiotensin system inhibitors, SGLT2is and mineralocorticoid receptor antagonists such as finerenone.[5,10–12] Glycaemic targets may be difficult to achieve in CKD with diabetes because of limitations of glucose-lowering therapeutic options; these limitations are based on concerns over hypoglycaemia and on contraindications or lack of efficacy in different classes of medication.[13,14]

3 | IMPACT OF CHRONIC KIDNEY DISEASE ON THE RISK OF HYPOGLYCAEMIA

Like other glucose-lowering therapies, the main challenge to achieving glycaemic targets with insulin in people with CKD and diabetes is the increased risk of hypoglycaemia.[14,15] The kidney is the main site of clearance of exogenous insulin from the systemic circulation.[16] Because of reduced degradation of insulin in impaired kidneys, circulating insulin levels can be higher than normal; therefore, CKD is associated with an increased risk of hypoglycaemia.[14,17,18] The kidney plays a more prominent role in insulin clearance in people with diabetes who receive insulin treatment. This is because exogenous insulin administered by subcutaneous injection enters the systemic circulation directly and does not undergo first-pass hepatic metabolism, which is in contrast to endogenous insulin.[15,16,19] While the same process applies to all exogenous insulins, it should be noted that BI analogues have been designed to prolong half-life by delaying resolubilization and absorption, resulting in more stable pharmacokinetic (PK)/pharmacodynamic (PD) profiles that could potentially reduce the risk of hypoglycaemia.[20]

Additional factors contributing to the pathophysiology of hypoglycaemia in CKD (Figure 1) include reduced renal gluconeogenesis (particularly, under stress), reduced hepatic insulin metabolism and malnutrition.[14,17,18] In addition to these factors, increased peripheral and autonomic neuropathy, hypoglycaemia unawareness and other chronic complications associated with longstanding diabetes may also increase the risk of hypoglycaemia and sudden death.[14,21,22] Macroalbuminuria has also been reported as a risk factor for hypoglycaemia in patients with a GFR >60 ml/min/1.73 m^2, irrespective of whether the individual is receiving insulin.[22] The risk of hypoglycaemia in T2D with CKD is approximately double that of diabetes alone (10.72 vs. 5.33 events per 100 patient-months).[17] This heightened risk is seen in

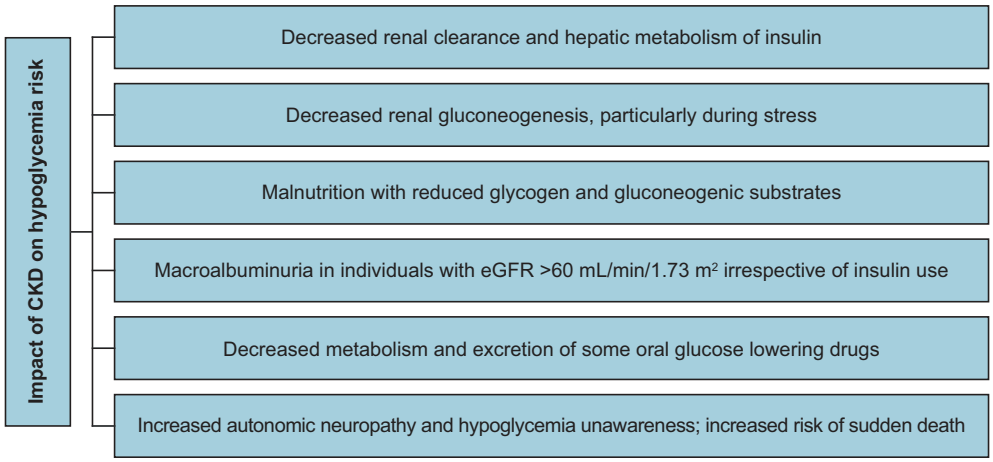

FIGURE 1 Factors contributing to increased hypoglycaemia risk in people with CKD. CKD, chronic kidney disease; eGFR, estimated glomerular filter rate.

continuous glucose monitoring (CGM) data in people with T2D and eGFR <45 ml/min/1.73 m^2 (n = 80).[23] This study found that during the period of CGM measurement (12.7 ± 2.9 days), 76% of patients experienced hypoglycaemia with BG <3.9 mmol/L (70 mg/dl) and 39% experienced prolonged events, that is, ≥120 min with BG <3.0 mmol/L (<54 mg/dl).[23] Experiencing severe hypoglycaemia is associated with increased risk of CVD and mortality,[24] and is of concern in the management of people with CKD and diabetes.

4 | INSULIN USE IN MANAGEMENT OF TYPE 2 DIABETES IN PEOPLE WITH CHRONIC KIDNEY DISEASE

4.1 | Glycaemic assessment in chronic kidney disease

Glycated haemoglobin (HbA1c) measurement is the standard of care for long-term glycaemic monitoring and provides an assessment of glycaemic levels and the risk of developing diabetes complications over time.[5] However, the accuracy and precision of HbA1c measurements declines as CKD progresses, particularly in patients undergoing dialysis and in patients with anaemia taking erythropoiesis-stimulating agents.[5] Conversely, CGM- and self-monitoring of BG (SMBG)-derived BG measurements are not impacted by CKD. As the progression of CKD increases the risk of hypoglycaemia, daily monitoring by CGM or SMBG is particularly important to identify glucose fluctuations and improve the safety of glucose-lowering therapies that raise insulin levels, including insulin. Moreover, CGM technologies (including real-time and intermittently scanned CGM) may further improve safety by allowing the user to set alarms for high and low glucose values.[5] However, despite the benefits and interest in CGM, adoption remains low in people with T2D.[25] Current KDIGO guidance recommends that individuals with T2D and CKD unable to perform daily glycaemic monitoring by CGM or SMBG should preferably receive glucose-lowering agents, which pose a lower hypoglycaemia risk, and should be treated to higher glucose targets.[5]

5 | RATIONALE FOR INSULIN THERAPY IN TYPE 2 DIABETES WITH CHRONIC KIDNEY DISEASE

Many glucose-lowering therapy options are affected by kidney function through either reduced efficacy and/or safety. Metformin can be used in people with T2D and low eGFR but should be stopped when eGFR is <30 ml/min/1.73 m^2, with dose adjustments before that.[5,26] SGLT2is are the recommended first-line therapy for people with T2D and CKD to reduce CKD progression and CV risk, but SGLT2is have limited glucose-lowering effect when eGFR is <45 ml/min/1.73 m^2. If further glucose lowering is required or if an SGLT2i cannot be used, a GLP-1 RA is recommended by KDIGO.[3,5,27] However, GLP-1 RA treatment can cause weight loss, which may be an issue in this population as malnutrition (particularly with regard to protein) is a common issue.[28] Sarcopenic obesity (i.e. high body fat percentage in combination with low skeletal muscle mass) is also common in this population.[29] Dipeptidyl peptidase-4 inhibitors can be safely used in CKD without increasing hypoglycaemia.[30,31] Pioglitazone can be used in people with CKD with no dose adjustments and has been found to decrease rates of all-cause mortality in people with T2D and advanced CKD versus dipeptidyl peptidase-4 inhibitor treatment.[32] However, its use is associated with increased oedema and congestive heart failure. Quick-release bromocriptine (a dopamine receptor agonist that reduces insulin resistance) has been shown to prevent decline in renal function in people with T2D and Stage 4 CKD.[33] Of greatest concern is the use of insulin secretagogues (sulphonylureas) in T2D with CKD. Most sulphonylureas and/or their active metabolites are cleared by the kidneys, and the accumulation of these agents in the context of CKD leads to an increased risk of hypoglycaemia.[14,26] As a result, guidelines recommend that patients with diabetes and CKD using sulphonylureas should closely monitor capillary BG, and treatment

should be avoided altogether in more advanced stages of CKD (eGFR <30 ml/min/1.73 m^2).[26] Therefore, insulin continues to play an important role in helping people living with T2D and CKD to achieve glycaemic targets. In the most recent ADA and KDIGO guidelines, insulin is highlighted as a suitable treatment option in those with kidney impairment if they require potent glucose-lowering or have eGFR <15 ml/min/1.73 m^2.[3,5] The Association of British Clinical Diabetologists guidelines also note that insulin may be required in people with long-standing T2D, because of contraindications and ineffectiveness of oral glucose-lowering therapies.[26] However, it is important to note that concomitant use of therapies that do not cause hypoglycaemia alone (such as incretin mimetics) may increase the risk of hypoglycaemia with insulin, necessitating the consideration of insulin dose adjustment.[5]

6 | IMPACT OF CHRONIC KIDNEY DISEASE ON INSULIN REQUIREMENTS

Patients with CKD have a biphasic pattern of insulin requirements as kidney function declines.[26,34] Initially, increased insulin resistance raises insulin requirements; however, insulin needs decrease with declining kidney function and decreasing insulin clearance and metabolism.[14,26,34] Once eGFR decreases to 10 ml/min, insulin requirements decrease to ~50%.[34] Nonetheless, cross-sectional studies indicate insulin use is higher in more advanced CKD; this is because of decreased insulin production, peripheral insulin resistance and contraindications or lack of efficacy for other glucose-lowering options.[35–37] Therefore, careful monitoring of glycaemic control is required during disease progression for adequate treatment and to reduce the risk of hypoglycaemia.[34,38]

Haemodialysis leads to the clearance of insulin and other glucoregulatory hormones, and the glucose concentration present in the dialysate solution is known to influence glucose levels.[34] Haemodialysis can increase sensitivity to insulin, which may reduce BG, thus possibly making these patients more susceptible to hypoglycaemia after haemodialysis.[34] In a study of people with diabetes undergoing dialysis (n = 20 845), experiencing one severe hypoglycaemic event increased the risk of death by 15% and the risk of subsequent severe events 2.3-fold, while experiencing two or more events increased the risk of death by 19%.[39] Patients receiving haemodialysis may need reduced doses of glucose-lowering medications (including insulin) on the day of dialysis to prevent hypoglycaemia, such as a 25% reduction in the basal bolus insulin dose.[34]

Peritoneal dialysate, unlike the dialysate in haemodialysis, has a higher glucose concentration than blood.[34] Glucose is frequently used as the osmolar agent, and thus can be taken up into the circulation.[34] In patients with higher rates of glucose transport, this can result in hyperglycaemia and may also lead to inadequate dialysis.[14] Careful management of the glucose-lowering medication (usually insulin) regimen and dialysis schedule is required to prevent development of hyperglycaemia.[14] These findings suggest that in high-risk groups (such as those with CKD), insulin treatment should focus on individualized titration to improve glycaemic control while minimizing hypoglycaemia. CGM should be considered in all patients with CKD and diabetes on insulin to reduce their risk for hypoglycaemia and other unfavourable outcomes.

7 | BASAL INSULIN THERAPY IN KIDNEY FUNCTION IMPAIRMENT

The addition of BI to oral glucose-lowering therapies is an effective approach for many individuals with T2D.[40] BIs are designed to protract their activity by delaying absorption into systemic circulation and prolonging their half-life.[20] The key properties of commonly used long-acting insulins are shown in Table 1. Neutral protamine Hagedorn (NPH) was one of the earliest insulins to provide a prolonged duration of activity, but it exhibits substantial PK and PD variability. With a concentration peak at 4.5 h, NPH may be a less preferable basal option than long-acting BI analogues.[41,49] The prolonged and stable activity of BI analogues usually translates to a reduced risk of hypoglycaemia,[20] although hypoglycaemia remains a concern in patients with CKD because of the altered insulin metabolism as outlined earlier. Therefore, it remains important to evaluate BI use in the CKD population. Table 2 summarizes key results of different studies of BI in CKD. Figure 2 shows HbA1c changes according to renal function based on randomized controlled trials (RCT) data.

7.1 | Pharmacokinetic and pharmacodynamic studies

There are limited data on the PK/PD of BI in people with CKD. However, one small, single-centre PK study (n = 30; n = 11 participants with T2D) did report that the absorption and clearance of second-generation BI analogue insulin degludec (iDeg) was preserved in people with all stages of kidney impairment compared with those with normal kidney function.[50]

7.2 | Randomized controlled trials data and subanalyses

An RCT (n = 34) comparing insulin glargine 100 U/ml (Gla-100) versus NPH insulin in people with T2D and CKD Stage 3 and 4 showed improvements in HbA1c and hypoglycaemia, favouring Gla-100.[51] A meta-analysis of the EDITION 1, 2 and 3 RCTs stratified participants (N = 2496) by eGFR <60 and ≥60 ml/min/1.73 m^2 and concluded that versus first-generation BI analogue Gla-100, second-generation insulin glargine 300 U/ml (Gla-300) was associated with similar HbA1c reduction and less hypoglycaemia, regardless of level of kidney function.[52] In the DEVOTE trial, iDeg 100 U/ml was associated with a reduced risk of severe hypoglycaemia and similar HbA1c improvement compared with Gla-100, in a population of whom 85.2% had CVD, CKD, or both.[57]

TABLE 1 Key properties of commonly used long-acting insulins.

	Onset of action	Peak	Half-life	Duration	Mechanism of action
Neutral Protamine Hagedorn insulin[20,41,42] (intermediate-acting)	1 h	4.5 h	4.4 h	13.2 h	Suspension of crystals produced by combining insulin, protamine and zinc, which delays the dissociation of insulin hexamers into the circulation
Insulin glargine 100 U/ml[42–45]	1.5 h	None	13.5 hours	Up to 24 h	Recombinant human insulin analogue Modification of key amino acids allows insulin glargine to remain soluble at pH 4.0 but insoluble at physiological pH. Once injected, glargine is slowly released from the insoluble microprecipitates
Insulin glargine 300 U/ml[45]	6 h	None	19 h	Up to 36 h	More concentrated formulation of insulin glargine
Insulin detemir[43,46]	3-4 h	6-8 h (although relatively flat)	5-7 h	Up to 24 h	Recombinant human insulin analogue Deletion of one amino acid and modification of another with the addition of a fatty acid chain. Slowed systemic absorption because of molecule self-association; slowed distribution to peripheral tissues because of albumin binding
Insulin degludec[43,47,48]	1 h	None	25 h	42 h	Recombinant human insulin analogue Modification of one amino acid and addition of a glutamic acid spacer and linked fatty acid chain render insulin degludec capable of forming multihexamers. This leads to delayed absorption into systemic circulation, and to a lesser extent binding to circulating albumin

7.3 | Head-to-head trials of glargine 300 U/ml and insulin degludec

An analysis of the CONCLUDE RCT (n = 1609), stratified by baseline eGFR, found no impact of eGFR groups on the relative efficacy and safety of the second-generation BI analogue, Gla-300 and iDeg 200 U/ml.[53] In a prespecified analysis of data from the BRIGHT multicentre RCT of Gla-300 (n = 466) compared with iDeg 100 U/ml (n = 463), stratified by eGFR, Gla-300 showed benefit in terms of HbA1c reduction in the group with eGFR <60 ml/min/1.73 m^2, with no difference in hypoglycaemia.[55]

7.4 | Real-world evidence

A post-hoc analysis of the ACHIEVE RCT (a 12-month, pragmatic, open-label trial carried out in real-world clinical settings in the United States and Canada) showed benefits for Gla-300 versus standard of care BI in those with CKD, in terms of HbA1c target attainment without hypoglycaemia.[58] In the DELIVER-High Risk US retrospective study, switching from a first-generation BI analogue (Gla-100 or insulin detemir) to the second-generation analogue Gla-300 in people with T2D and moderate-to-severe renal impairment (n = 861) was associated with reduced incidence and rate of hypoglycaemia, versus switching to a different first-generation analogue (Gla-100 or insulin detemir).[59] Similarly, a retrospective analysis in people with T2D and Stage 2-3B CKD who switched to iDeg from any other long-acting BI concluded that iDeg was associated with a reduced risk of hypoglycaemia and improved glycaemic control.[65] The REALI pooled database documented improvements in glycaemic control, without undue safety concerns, with the initiation of Gla-300 in people with T2D and reduced kidney function.[60] A subanalysis of the ATOS observational study showed that initiation of Gla-300 is similarly effective in those with renal impairment as in those without, in terms of HbA1c reduction target achievement.[61] In a single-centre, retrospective study of people with T2D suboptimally controlled with oral glucose-lowering drugs with or without prandial insulin and Stage 3 (n = 60) or Stage 4 (n = 35) CKD, Gla-100 was associated with improvements in glycaemic control compared with previous treatment, without significant weight gain or unexpectedly high rates of hypoglycaemia.[62] Beneficial glycaemia, body weight and hypoglycaemia outcomes were also observed with Gla-100 compared with previous treatment in another study including people with T2D suboptimally controlled with oral glucose-lowering drugs or NPH insulin

TABLE 2 Details and main results of studies investigating use of basal insulin analogues in people with renal impairment.

Author, year, study details	Participant population	Interventions	HbA1c effect	Hypoglycaemia	Insulin dose	Other key findings
Pharmacokinetic/pharmacodynamic studies						
Kiss 2014[50] Single-centre, single-dose, open-label PK study (N = 30, including n = 11 with T2D)	Grouped by renal function: normal, mild, moderate, or severe RI, or ESKD with haemodialysis requirement. Participants had impaired glucose tolerance or diabetes with RI	Single-dose iDeg 0.4 U/kg sc				PK properties ($AUC_{0\text{-}120h}$) are not significantly affected by degree of RI ($p = .26$)
Randomized controlled trials (RCT) data and subanalyses						
Betônico 2019[51] Two-way crossover open-label, 24-week, Phase 4 study (N = 34)	T2D and CKD Stage 3-4 defined by ≥15 and <60 ml/min/1.73 m^2	Gla-100 NPH insulin	Mean HbA1c decreased with Gla-100 (−0.91%; $p < .001$), but this benefit was not observed with NPH (0.23%; $p = .93$)	Incidence of nocturnal hypoglycaemia 3 times lower with Gla-100 than NPH insulin ($p = .047$)	At week 24, BI doses were similar between iGlar (0.31 U) and NPH (0.34 U)	
Escalada 2018[52] (EDITION 1-3) Meta analysis of 6-month pooled data. (N = 2496)	T2D and mild to moderate RI. Pooled results assessed by subgroups: eGFR <60 and eGFR ≥60 ml/min/1.73 m^2	Gla-300 qd Gla-100 qd	HbA1c reductions from BL similar in Gla-300 and Gla-100 groups, regardless of renal function [LS mean difference 0.14 (95% CI: −0.04, 0.32) and −0.03 (95% CI: −0.11, 0.05)] in the eGFR <60 and ≥60 ml/min/1.73 m^2 subgroups, respectively	Reduced risk of confirmed [≤3.9 mmol/L (≤70 mg/dl)] or severe hypoglycaemia with Gla-300 vs. Gla-100 Nocturnal: RR: 0.76 (95% CI: 0.62, 0.94); RR: 0.75 (95% CI: 0.67, 0.85) in the lower and higher eGFR subgroups, respectively Any time of day: RR: 0.94 (95% CI:0.86,1.03) and RR: 0.90 (95% CI 0.85, 0.95) in the lower and higher eGFR subgroups, respectively	Difference over 6 months in insulin dose increase between lower vs. higher eGFR subgroups was −23.7% for Gla-300 and −18.8% for Gla-100	
Pieber 2020 and 2022[53,54] (CONCLUDE) Head-to-head RCT; post hoc analysis (N = 1609)	T2D with ≥1 risk factor for hypoglycaemia at BL, including moderate RI Results stratified by BL eGFR: 30-60, 60 to <90 and ≥90 ml/min/1.73 m^2	iDeg 200 U/ml Gla-300	HbA1c change from BL to EOT was similar in the eGFR subgroups with a non-clinically significant decrease in HbA1c with iDeg 200 vs. Gla-300. Estimated treatment	RRs for all events were comparable across eGFR subgroups (<60, 60 to <90 and ≥90 ml/min/1.73 m^2): Overall symptomatic: RR 0.89 (95% CI 0.57, 1.39), 0.80 (95% CI 0.59,	Across eGFR subgroups, end-of-treatment mean insulin dose was lower for iDeg-200 (60.9-73.6 U) than Gla-300 (65.3-78.8 U)	

TABLE 2 (Continued)

Author, year, study details	Participant population	Interventions	HbA1c effect	Hypoglycaemia	Insulin dose	Other key findings
			difference: −0.10% (95% CI −0.18, −0.02)	1.09) and 0.80 (95% CI 0.58, 1.09), respectively Nocturnal symptomatic: RR 0.44 (95% CI 0.23, 0.87), 0.57 (95% CI 0.37, 0.89) and 0.81 (95% CI 0.52, 1.28), respectively Severe: RR 0.22 (95% CI 0.03, 1.23), 0.17 (95% CI 0.02, 0.72) and 0.25 (95% CI 0.01, 1.91), respectively		
Haluzík 2019,[56] 2020[55] (BRIGHT) Head-to-head RCT; post hoc analysis (N = 929)	T2D, uncontrolled and insulin-naïve Results stratified by BL eGFR: <60, 60 to <90 and ≥90 ml/min/1.73 m^2	Gla-300 qd iDeg qd	Significantly greater reduction in mean HbA1c from BL to week 24 with Gla-300 (8.58%-6.94%) vs. iDeg-100 (8.30%-7.28%) in the eGFR <60 ml/min/1.73 m^2 group HbA1c reductions from BL to week 24 were similar between treatment groups for the eGFR subgroups	Incidence and rates of hypoglycaemia increased with decreasing renal function. Incidence and rates were similar between treatments in the eGFR <60 ml/min/1.73 m^2 group. Annualized rates of confirmed ≤70 mg/dl hypoglycaemia showed less hypoglycaemia with Gla-300 vs. iDeg in the ≥90 ml/min/1.73 m^2 group	In each group, insulin dose was higher with Gla-300 vs. iDeg-100 at BL and throughout the study. Insulin doses were highest in those with normal renal function	
Marso 2017[57] (DEVOTE) Head-to-head RCT (N = 7637)	T2D and at least one coexisting CV or renal condition (those >50 years) or at least one CV risk factor (those >60 years) Analysis according to renal function subgroups: normal, mild, moderate or severe RI	iDeg qd Gla-100 qd	No statistically significant difference between treatment groups for change in HbA1c over time (HbA1c was 7.5% in both treatment groups with estimated difference of	Severe hypoglycaemia: no statistically significant change in the between-treatment difference in incidence across renal function subgroups ($p = .992$): Normal: RR 0.63 (95% CI 0.37, 1.08)	There were no significant between-group differences in insulin dose over the treatment period	Major adverse CV events: no statistically significant difference in the incidence between patients across renal function subgroups ($p = .5785$): Normal: RR 0.73 (95% CI 0.50, 1.08)

(Continues)

TABLE 2 (Continued)

Author, year, study details	Participant population	Interventions	HbA1c effect	Hypoglycaemia	Insulin dose	Other key findings
			0.01 percentage points; $p = .78$)	Mild: RR 0.62 (95% CI 0.43, 0.91) Moderate: RR 0.63 (95% CI 0.43, 0.92) Severe: RR 0.77 (95% CI 0.21, 2.85)		Mild: RR 0.97 (95% CI 0.76, 1.24) Moderate: RR 0.96 (95% CI 0.75, 1.21) Severe: RR 0.76 (95% CI 0.39, 1.50)
Real-world evidence						
Anderson 2021[58] (ACHIEVE) Head-to-head pragmatic RCT (post hoc analysis) (N = 3304, including 268 with CKD and 566 with eGFR <60 ml/min/1.73 m^2)	T2D, insulin-naïve, HbA1c ≥8%, and at least 1 risk factor for hypoglycaemia (CKD, CVD, dementia or blindness, age ≥65 years, history of hypoglycaemia)	Gla-300 SoC BI	There was no between-treatment difference in likelihood of attaining HbA1c target at 12 months (OR 1.15, 95% CI 0.70, 1.89) among the CKD subgroup	Likelihood of achieving HbA1c target without hypoglycaemia favoured Gla-300 vs. SoC insulin at both 6 and 12 months: BG target ≤3.9 mmol/L at 12 months: OR 1.91; 95% CI 1.13, 3.25 BG target <3.0 mmol/L at 12 months: OR 2.06; 95% CI 1.09, 3.89	At 6 and 12 months, insulin dose was slightly higher with SoC insulin (0.20 and 0.23 U/kg) than Gla-300 (0.17 and 0.22 U/kg)	
Sullivan 2022[59] (DELIVER-High Risk) Retrospective database analysis (N = 5100, including 861 with moderate to severe renal impairment)	T2D at high risk for hypoglycaemia (GFR 30-69 ml/min/1.73 m^2; insulin for >4 years; recent episode of hypoglycaemia) switching to Gla-300 or another BI analogue	Gla-300 Gla-100/iDet	HbA1c reduction was comparable between patients switching to Gla-300 (−0.51 ± 1.82%) or to Gla-100/iDet (−0.53 ± 1.89%) with LS mean difference of −0.02 (95% CI: −0.13, −0.08)	Among patients with moderate to severe renal impairment at risk for hypoglycaemia, switching to Gla-300 was associated with a significantly lower incidence of hypoglycaemia compared with switching to other BIs after 12 months (33.33% vs. 39.69%; $p = .006$) Hypoglycaemia event rate was also lower following a switch to Gla-300 vs. other BIs (0.98 vs. 1.29 events PPPY; $p = .006$)		
Mauricio 2019[60] (REALI)	T2D; results stratified by BL eGFR: <60 or	Gla-300	LS mean change from BL to week 24 in HbA1c was	No difference between the two subgroups with	Daily Gla-300 dose was comparable between	

TABLE 2 (Continued)

Author, year, study details	Participant population	Interventions	HbA1c effect	Hypoglycaemia	Insulin dose	Other key findings
Pooled analysis of data from various study types (N = 1069)	≥60 ml/min/1.73 m^2		−0.79 (95% CI: −0.96, −0.63) and −1.01 (95% CI: −1.08, −0.95) in the lower and higher eGFR subgroups, respectively Proportion of patients reaching the HbA1c target of <7% at week 24 was 23.4% and 30.2%, respectively	regard to rates of symptomatic, severe, or nocturnal hypoglycaemia	subgroups at weeks 12 (33.2-37.3 U; 0.37-0.41 U/kg) and 24 (35.6-39.4 U; 0.40-0.43 U/kg), although slightly higher in those with normal renal function	
Tirosh 2021[61] Prospective, observational (RI, n = 581; no RI, n = 3841)	T2D, initiating Gla-300	Gla-300	Change from BL to month 6: HbA1c decreased by 1.5% in both the RI and no-RI groups, to 7.82% and 7.76%, respectively	Event rate of documented symptomatic (≤3.9 mmol/L) hypoglycaemia over 6 months was low in both groups, but slightly higher in the RI group (1.72) than in the no-RI group (0.73)	Change from BL to month 6: BI dose increased by 0.10 and 0.08 U/kg in both the RI and no-RI groups, to 0.28 and 0.27 U/kg, respectively	
Majumder 2019[62] Retrospective, observational (N = 95)	T2D with Stage 3 or 4 CKD	Gla-100	Overall reduction in HbA1c of 1.2% in patients with Stage 3 or 4 after 24 weeks (mean HbA1c 7.5% ± 0.13) Stage 3 CKD: HbA1c at week 24 of 7.6 ± 0.15 (p < .001 vs. BL) Stage 4 CKD: HbA1c at week 24 of 7.4 ± 0.22 (p < .001 vs. BL)	Overall, 32 cases of documented hypoglycaemia (33.68%) and 8 cases of nocturnal hypoglycaemia (25%)		
Niafar 2012[63] Multicentre, single-arm (N = 89)	T2D with diabetic nephropathy (CRCL <50 ml/min; mean eGFR 34.1 ± 11.5 ml/min)	Gla-100	Significant reduction in HbA1c after 4 months from 8.4% ± 1.6 to 7.7% ± 1.2 (p < .001)	Mild symptomatic hypoglycaemia reported in 12.5% of patients		
Pettus 2019[64] (LIGHTNING) Retrospective database analysis (N = 831 456)	T2D receiving a BI during the data collection period (1 January 2007 to March 2017). Results stratified by insulin-naïve and patients	Gla-300 Gla-100 iDet iDeg	In the propensity score matching analysis, HbA1c reductions were comparable between BIs within both	Among the group with moderate to severe RI, statistically significantly lower rates of severe hypoglycaemia		

(Continues)

TABLE 2 (Continued)

Author, year, study details	Participant population	Interventions	HbA1c effect	Hypoglycaemia	Insulin dose	Other key findings
	switching from other BI agents Subgroup analysis conducted for patients with moderate RI		subgroups (both $p > .05$)	were predicted for Gla-300 vs. iDet for the insulin-naïve cohort and for Gla-300 vs. iDet and Gla-100 for the BI-switcher cohort: Insulin-naïve: median predicted event rate (PPPY): Gla-300: 0.10 iDeg: 0.13 Gla-100: 0.19 ($p < .05$ vs. Gla-300) iDet: 0.19 ($p < .05$ vs. Gla-300) BI switchers: median predicted event rate (PPPY): Gla-300: 0.31 iDeg: 0.32 Gla-100: 0.38 iDet: 0.42 ($p < .05$ vs. Gla-300)		
Garcia de Lucas 2020[65] Retrospective observational (N = 103)	T2D with Stage 2-3B CKD	iDeg (switch from other long-acting BI)	Switching to iDeg significantly improved glycaemic control (−1.68 ± 1.73% in CKD2 and −1.38 ± 1.13% in CKD3B, $p < .0001$)	Switching to iDeg significantly reduced the risk of hypoglycaemia Severe symptomatic: (14.95% post-switch vs. 75.38% pre-switch, $p < .001$)	Over 36 months, daily iDeg dose decreased significantly in those with Stage 2 (−6.91 ± 13.99 U $p < .001$) and Stage 3B CKD (−9.14 ± 20.28 U, $p < .035$)	
Kosjerina 2023[66] Registry cohort (N = 6519)	T2D with moderate to end-stage CKD	Gla-300 iDeg	No significant difference between iDeg vs. Gla-300 in HbA1c reduction	Similar rate of hospitalization for hypoglycaemia with iDeg vs. Gla-300 (RR: 1.02; 95% CI: 0.70, 1.49)		Similar rate of all-cause mortality with iDeg vs. Gla-300 (RR: 0.98; 95% CI: 0.84, 1.15)

Abbreviations: AUC, area under the curve; BG, blood glucose; BI, basal insulin; BL, baseline; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; ESKD, end-stage kidney disease; Gla-100, insulin glargine 100 U/ml; Gla-300, insulin glargine 300 U/ml; HbA1c, glycated haemoglobin; iDeg, insulin degludec; iDet, insulin detemir; LS, least squares; NPH, neutral protamine Hagedorn; OR, odds ratio; PK, pharmacokinetic; PPPY, per patient per year; qd, once daily; RCT, randomized controlled trials; RI, renal impairment; RR, rate ratio; sc, subcutaneous; SoC, standard-of-care; T2D, type 2 diabetes.

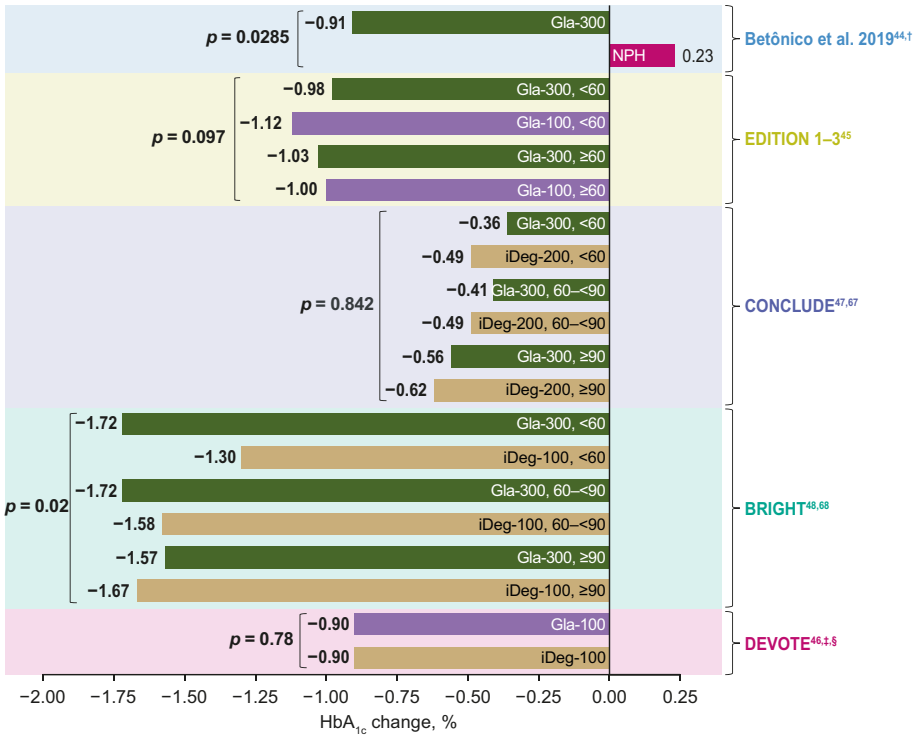

FIGURE 2 Changes in HbA1c in randomized-controlled trials investigating the use of basal insulin analogues in people with chronic kidney disease. Data reported by investigational medicinal product and by estimated glomerular filtration rate subgroup, <60, 60 to <90 and ≥90 ml/min/1.73 m^2, where listed for the studies shown. †Betônico et al.[51] study population: type 2 diabetes and chronic kidney disease Stages 3-4 defined by ≥15 and <60 ml/min/1.73 m^2. ‡DEVOTE study population: type 2 diabetes and at least one coexisting cardiovascular or renal condition (those ≥50 years) or at least one cardiovascular risk factor (those ≥60 years). §DEVOTE HbA1c change calculated based on published baseline and month 24 values. Gla-100, insulin glargine 100 U/ml; Gla-300, insulin glargine 300 U/ml; iDeg-100, insulin degludec 100 U/ml; iDeg-200, insulin degludec 200 U/ml; NPH, neutral protamine Hagedorn.

who had a mean GFR of 34.1 ml/min/1.73 m^2 (n = 89).[63] The LIGHTNING study analysed electronic health record data using propensity score matching and predictive modelling in people with moderate or severe kidney function impairment.[64] Results indicated that rates of severe hypoglycaemia were similar with Gla-300 and iDeg and generally lower with Gla-300 than first-generation BI analogues Gla-100 and insulin detemir.[64] Another real-world comparison of Gla-300 and iDeg in a Danish cohort of people with T2D and moderate to end-stage CKD found no difference between the two BIs in terms HbA1c reduction, hospitalization for hypoglycaemia, or all-cause mortality.[66] The double-blind trial DEVOTE (N = 7637), investigated iDeg and Gla-100 in patients with T2D and a high CV risk. A secondary analysis of DEVOTE (DEVOTE 11) indicated that the lower rate of hypoglycaemia incidence in iDeg users was independent to baseline GFR, and lower baseline GFR was associated with high risk of major adverse CV events, all-cause mortality and CV death.[67]

8 | PRACTICAL CONSIDERATIONS FOR INSULIN IN CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETES

Insulin is an appropriate therapeutic option at all stages of CKD.[26] However, as described earlier, patients are at a higher risk of hypoglycaemia as eGFR declines and insulin requirements decrease. While insulin doses may need to be reduced in people with T2D and CKD, there are limited studies on the use of insulins in this population, particularly those with more advanced stages of CKD (eGFR <30 ml/min/1.73 m^2). Therefore, there are no clear guidelines on dose adjustments other than according to individual patient responses.[26,49]

There are limited therapeutic options for people with late stage CKD requiring haemodialysis so insulin management alone is frequently used.[34,68] On dialysis days, glucose levels and glycaemic variability may be unpredictable, so adjustment of insulin may be needed depending on the type of dialysis.[68] A 25% reduction in the basal and bolus insulin doses may be required on days when an individual is receiving haemodialysis to avoid the risk of hypoglycaemia.[34] In contrast, the glucose in the dialysate used for peritoneal dialysis may induce hyperglycaemia, therefore insulin requirements will change, and targeted regimens may be necessary. These may include adjusting the timing of BI administration to match the timing of the dialysate, selecting intermediate-acting BI to match the duration of the dwell time of the dialysate, adding insulin to the peritoneal dialysis solution, or using insulin pump therapy with closed loop CGM.[34]

9 | CONCLUSION

CKD is prevalent in people with diabetes and is associated with the increased risk of hypoglycaemia, CV events, and death. The presence of reduced kidney function can impact the efficacy and safety of glucose-lowering therapies and must be considered when selecting treatments. Choice of therapy in this high-risk population must minimize hypoglycaemia. Sulphonylureas in particular should be used with caution, because of the high risk of hypoglycaemia in people with T2D and CKD. While glucose-lowering therapies (e.g. SGLT2is

and incretin mimetics) play important roles for CV and kidney protection for this population, the glycaemic efficacy of SGLT2is can be limited as eGFR decreases; in the case of GLP-1 RA, there may be excessive weight loss, which may be undesirable in this population. BI therapy, therefore, remains an important treatment option. The second-generation BI analogues Gla-300 and iDeg are associated with a lower risk of hypoglycaemia versus first-generation BI analogues, so they are particularly relevant in the choice of treatment for people with T2D and kidney disease.

AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of the literature, writing and editing of this review, and had responsibility for approving the final version.

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CONFLICT OF INTEREST STATEMENT

LS has served as an investigator for AbbVie, Amgen, Boehringer Ingelheim, GSK, Janssen, Lilly, Merck, Novo Nordisk, Novartis and Sanofi. He serves on advisory boards for and has received honoraria from all of the above in addition to Abbott, AstraZeneca and Bayer. AYYC declares advisory board and/or speaking honoraria from Abbott, Amgen, AstraZeneca, Bausch, Bayer, Boehringer Ingelheim, Dexcom, Eisai, Eli Lilly and Company, GSK, HLS Therapeutics, Insulet, Janssen, Medtronic, Merck, Novo Nordisk, Pfizer, Sanofi and Takeda. JE has received fees as a speaker or consultant from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Esteve, MSD and Novo Nordisk; he has been an investigator in clinical trials for Eli Lilly and Novo Nordisk. MH has served on advisory panels for Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca and Mundipharma; served as a consultant for Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca and Mundipharma; received research support from AstraZeneca, Eli Lilly, Bristol Meyers Squibb and Sanofi; and received honoraria or consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Johnson & Johnson. DM has received advisory and/or speaking fees from AB-Biotics, Almirall, Esteve, Ferrer, Janssen, Lilly, Menarini, MSD, Novo Nordisk and Sanofi; he has received research grants to the institution from MSD, Novo Nordisk and Sanofi.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this work.

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