Consensus Statement on Dose Modifications of Anti Diabetic Agents used in Patients with Diabetes and Chronic Kidney Disease

Binayak Sinha¹, KK Gangopadhyay², DC Sharma³, Arthur Asirvatham⁴, Parminder Singh⁵

Abstract
Patients with Diabetes and declining renal function pose complex challenges to the clinician, including the management of comorbidities such as hypertension, hyperlipidemias, cardiovascular (CV) disease, anemia, and abnormal bone metabolism. The prevalence of stage 3 or worse chronic kidney disease (CKD) in patients with T2DM is increasing. Diabetes is a leading cause of end-stage renal disease (ESRD) and dialysis.

The aim of the consensus group was to focus on the challenges with glycemic management, with particular emphasis to safe use of anti-diabetic agents across stages of renal dysfunction.

Published Literature, product information and major clinical guidelines from USA and India were reviewed and summarized. These drugs included metformin, the second- or third-generation sulfonylureas (SUs), alpha-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and currently available insulins.

Consensus Recommendations for Glycemic targets and dose modifications of all Anti Diabetic agents are summarized.

Introduction
Type 2 diabetes mellitus (T2DM) is by far the most common form of diabetes, comprising 90% of all diabetes cases and is therefore a major health issue. The prevalence of stage 3 or worse chronic kidney disease (CKD) in patients with T2DM is generally reported to be between 21% and 38%.¹⁴,¹²,¹³

Diabetes is a leading cause of end-stage renal disease (ESRD) and dialysis; 40% of patients in France and 45% in the United States (US) had diabetes at initiation of dialysis. In Canada, 35% of patients who initiated treatment for ESRD in 2010 had diabetes. Diabetes is also associated with one of the lowest 5-year survival rates in patients receiving dialysis.²⁰,¹⁴

Patients with diabetes and declining kidney function present many therapeutic challenges, including the management of comorbidities such as hypertension, hyperlipidemia, cardiovascular (CV) disease, anemia, and abnormal bone and mineral metabolism.⁴ There is a dearth of evidence and recommendations from International and National organizations/bodies regarding glycaemic management in patients with CKD. Regulatory bodies across the globe propose differing statements with respect to dose modifications of anti-diabetic agents. The aim of this consensus was to evaluate existing evidence relevant to glycaemic management of T2DM in the setting of CKD and propose a set of recommendations which may guide clinicians in managing Hyperglycemia in patients CKD with outcomes in mind.

Methods
The Consensus group evaluated existing evidence including current guidelines, published trials and the prescribing information of various Anti Diabetic agents with respect to management of Hyperglycaemia in CKD. Existing Guidelines KDOQI recommendations 2012 was found to be relevant to the discussion compared to KDIGO. The members then discussed and laid down recommendations related to Glycaemic control in patients with CKD and specific recommendations related to dose modification of each class of Anti Diabetic agents.

Glomerular filtration rate is the best measure of overall kidney function in health and disease.¹⁵ The normal level of GFR varies according to age, sex, and body size. Normal GFR in young adults is approximately 120 to 130 ml/min/1.73 m² and declines with age. A GFR level less than 60 ml/min/1.73 m² represents loss of half or more of the adult level of normal kidney function. Below this level, the prevalence of complications of chronic kidney disease increases.¹⁶⁻¹⁸ Decreased kidney function is practically assessed by estimating the GFR (eGFR) using either Cockcroft–Gault or Modification of Diet in Renal Disease (MDRD) study equations.¹⁹,²⁰,²²

The stages of CKD which will
Table 1: Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR 15-29</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>


Consensus Recommendation 1: Glycemic Targets

The ADA, the EASD, and the IDF recommend a glycated hemoglobin (HbA1c) target of <7% for most patients with diabetes. Customization of this general target is based on patient characteristics, with tighter control.

1.1 We recommend a target glycated hemoglobin A1c (HbA1c) of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD.

1.2 We recommend not treating to an HbA1c target of <7.0% in patients at risk of hypoglycemia.

1.3 We suggest that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia.

1.1 We recommend a target glycated hemoglobin A1c (HbA1c) of ~7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD.

Few long-term observational cohort studies and secondary or post hoc analyses of interventional studies using ACE-I or ARBs found that poorer glycemic control was associated with a greater rate of fall of GFR in patients with type 1 diabetes. The EDIC/DCCT follow up study recently reported that 2.0% (1.6/1000 person-years) of participants in the previously intensive treatment group and 5.5% (3.0/1000 person-years) of those in the previously conventional treatment group developed sustained estimated glomerular filtration rate (eGFR) measurements 60 ml/min/1.73 m² with a relative risk reduction of 50% (p<0.006).

For patients with type 2 diabetes, intensive treatment in the UKPDS was associated with a 67% risk reduction for a doubling of plasma creatinine levels at 9 years (0.71% of the intensive group and 1.76% of the conventional group, p<0.027). None of the three more recent studies mentioned above (ADVANCE, ACCORD, VADT) showed significant benefits of more intensive glycemic control on creatinine-based estimates of GFR.

The three most recent clinical trials (ADVANCE, ACCORD, and VADT) all showed substantial increases (range 1.5-3 fold) in severe and non-severe hypoglycemia among patients with type 2 diabetes who were receiving more intensive therapy. Intensifying glycemic control beyond conventional management did not result in decreased risk of the primary endpoints, defined by composites of major adverse cardiovascular disease (CVD) events, in any of these studies.

Moreover, there was an increase in all-cause mortality among the intensively-treated group compared to the conventionally-treated group in the ACCORD study. The reasons for this finding are uncertain, although further analysis showed that increased mortality was not directly attributable to hypoglycemia. Therefore, lowering HbA1c to levels 7.0% is not recommended in patients with diabetes who are at risk for hypoglycemia, including those treated with insulin or sulfonylureas and/or have advanced CKD.

1.3 We suggest that target HbA1c be extended above 7.0% in individuals with co-morbidities or limited life expectancy and risk of hypoglycemia.

Years of intensive glycemic control (HbA1c <7%) are required before a reduction in the incidence of complications, such as kidney failure or blindness, becomes evident. In individuals 70-79 years of age who are taking insulin, the risk of hypoglycaemia begins to increase with HbA1c 7%.

Moreover, in patients with type 2 diabetes, one study showed that the presence of co-morbidities abrogates benefits of lower HbA1c levels on CVD events. Therefore, a target HbA1c of 7.0% is suggested for patients with diabetes who are at risk of hypoglycemia and have clinically-significant co-morbidities or limited life expectancy.
Table 2: Guidelines and Prescribing information for the use of Sulphonylureas in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>KDOQI 2012</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>No dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Start conservatively at 1 mg daily</td>
<td>Start conservatively at 1 mg daily</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Avoid use</td>
<td>Initial dosing, dose increments, and maintenance dosage should be conservative</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>No dose adjustment</td>
<td>Contraindicated in severe renal failure, dose reduction necessary starting dose should be 30mg in mild to moderate renal failure</td>
</tr>
</tbody>
</table>

Table 3: Guidelines and Prescribing information for the use of Thiazolidinediones in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>KDOQI guidelines 2012 eGFR in ml/min/1.72 m²</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Consensus Recommendation 2: Oral Anti Diabetic agents in CKD

While patients with mild renal insufficiency can receive most antihyperglycemic treatments without concern, patients with stages 3, 4, or 5 CKD often require treatment adjustments according to the degree of renal insufficiency. These adjustments include lowering the dose or discontinuing a drug altogether and, if necessary, initiating treatment with another agent. The following sections of this consensus paper summarize key information from North American and European labels, clinical studies, and guidelines for each of the major antihyperglycemic medications, relevant to the treatment of adults with T2DM and CKD.

2. Oral Anti Diabetic Agents in CKD:

2.1 Metformin:

2.1.1 Metformin must be avoided when the eGFR <30 ml/min/1.73 m².

2.1.2 Dose Modification is necessary when eGFR <45 and >30 ml/min/1.73 m².

2.1.3 Monitor eGFR every 3 months

The British National formulary and The Japanese society of Nephrology state that an eGFR of ≤30 ml/min/1.73 m² mandates discontinuation of Metformin. The USFDA states that Metformin is contraindicated when Serum Creatinine is ≥1.5 mg/dl in men and ≥1.4 mg/dl in women. The current prescribing labels for metformin use reflect a more conservative approach than is seen in clinical practice, or in most recent diabetes guidelines.

Based on available data, we recommend that metformin may be suitable for patients with eGFR >30 and <60 ml/min/1.73 m², with appropriate caution and monitoring. Care must always be taken in patients with other risk factors for lactic acidosis.

2.2 Sulfonylureas

2.2.1 To be avoided in patients prone to Hypoglycemia

2.2.2 Gliclazide and Glipizide can be recommended as safer agents among sulphonylureas. The summary of Guidelines and prescribing information for the use of Sulphonylureas in CKD is provided in Table 2. The NFK-KDOQI recommends no dose adjustment with Glipizide and Gliclazide in CKD stages 3-5. Glimepiride may need to be started conservatively at a dose of 1 mg daily and then titrated to reach targets. Glyburide, a second generation agent, is better avoided and other agents are to be preferred. The glyburide prescribing information though proposes a conservative approach to initiation and titration of the dose in patients with CKD.

Given the propensity of sulphonylureas to cause hypoglycemia in patients with CKD who are already at a high risk to develop hypoglycemia, we recommend a watchful approach in using these agents. They are to be avoided in patients with a history of hypoglycemic episodes. Gliclazide and Glipizide can be the better options within the class of sulphonylureas.

2.3: Thiazolidinediones

2.3.1 Thiazolidinediones can be used with caution.

2.3.2 These agents are to be avoided in patients with fluid retention.

The summary of Guidelines and prescribing information for the use of Thiazolidinediones in CKD is provided in Table 3. Available PK data suggest that there is no difference in pioglitazone serum half-life in patients with severe CKD and those with normal renal function.

Given the elimination characteristics of pioglitazone, we recommend that Pioglitazone can be used with in patients with CKD but with caution. The existing data on fluid retention and Congestive Heart Failure as mentioned in the product leaflets mandate us to restrict the use of Pioglitazone in patients with a history of fluid retention.

2.4 Alpha Glucosidase inhibitors

2.4.1 To be avoided in patients with eGFR< 30 ml/min/1.73 m²

With acarbose, increased levels of the parent drug and metabolites are observed with CKD, although an increased risk of hypoglycemia has not been documented. Miglitol has greater systemic absorption that acarbose, with 50–100% of a dose being absorbed. This drug has
minimal protein binding
and is not metabolized, but
undergoes renal excretion,
with as much as 95% of a dose
recovered in the urine.47
Prescribing information for
these 2 agents are consistent
with the recommendations
from the KDOQI (Table 4).48,49
Given the lack of clinical data
for use in this population, we
do not recommend the use of
alpha glucosidase inhibitors
below the eGFR of 30 ml/
min/1.73 m².

2.5 DPP4 Inhibitors.

2.5.1 DPP4 inhibitors can be
used safely though dose
modifications have to be done
based on eGFR.

The summary of Guidelines
and prescribing information
for the use of DPP4 Inhibitors
in CKD is provided in Table
5. Most DPP-4 inhibitors
(sitagliptin, vildagliptin,
saxagliptin, alogliptin) are
predominantly excreted by the kidneys.
Thereby, pharmacokinetic
studies showed that total
exposure to the drug is
increased in proportion to
the decline of GFR, leading
to recommendations for
appropriate dose reductions
according to the severity of
CKD. In contrast, linagliptin
is eliminated by a predominantly
hepatobiliary route.

Patients with CKD represent
a specific subpopulation that
may take advantage of using
a DPP-4 inhibitor instead of
a sulphonylurea in order to
reduce the potential risk of
hypoglycaemia.50

The KDOQI guidelines 2012 and the prescribing
information for these agents are consistent with
dose changes.19 Based on
this data, we recommend
that DPP4 inhibitors can be
used safely in CKD though
dose modifications may be
necessary.

2.6 SGLT2 inhibitors

2.6.1 Avoid when eGFR <45 ml/
min/1.73 m² BSA.

These agents have reduced efficacy in
patients with renal impairment.

None of the SGLT2 inhibitors in
use currently need dose adjustment
in patients with mild renal
impairment, and these drugs are
generally not recommended or are
contraindicated in patients with
severe CKD or ESRD. Usage and
dose recommendations in moderate
CKD vary between the labels for
the different agents (canagliflozin,
dapagliflozin, and empagliflozin),
with some agents not recommended
below CrCl of 60 mL/min and others
below 45 mL/min.55

SGLT2 inhibitors have only
recently been approved and have
not been included in many of
the available guidelines. The 2013
AACE guidelines mention that
canagliflozin should not be used if
eGFR is 1.45 mL/ min/ 1.73 m², and
the 2015 AACE/ACE update reminds
us that these agents have limited
efficacy in patients with CKD since
they exert their glycemic effects in
the kidney. The 2015 update of the
ADA/EASD position statement state
that the labels have varying renal
restrictions.

Elevations in serum creatinine,
and decreases in eGFR, occurring
during the initial period of clinical
use, have been demonstrated with
all three of the SGLT2 inhibitors, and
seem to be most notable in patients
with moderate CKD. 56-61

Based on the available evidence
with this class of agents, we
recommend that SGLT2 inhibitors
be avoided when the eGFR <45 ml/
min/1.73 m². Clinicians also need
to be aware that there is loss of
glycaemic efficacy with deteriorating
renal function while using SGLT2
inhibitors.

Consensus

Recommendation 3: Non-
Insulin Anti Injectables in
CKD:

3.1 GLP1 Analogues

3.1.1 GLP1 Analogues can be
considered when eGFR >30
ml/min/1.73 m² BSA.

3.1.2 Liraglutide has demonstrated
efficacy and safety in
patients with moderate renal
dysfunction.

Pharmacokinetic studies have
been performed with all of the GLP-1
receptor agonists in patients with
minimal protein binding
and is not metabolized, but
undergoes renal excretion,
with as much as 95% of a dose
recovered in the urine.47
Prescribing information for
these 2 agents are consistent
with the recommendations
from the KDOQI (Table 4).48,49
Given the lack of clinical data
for use in this population, we
do not recommend the use of
alpha glucosidase inhibitors
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Patients with CKD represent
a specific subpopulation that
may take advantage of using
a DPP-4 inhibitor instead of
a sulphonylurea in order to
reduce the potential risk of
hypoglycaemia.50

The KDOQI guidelines 2012 and the prescribing
information for these agents are consistent with
dose changes.19 Based on
this data, we recommend
that DPP4 inhibitors can be
used safely in CKD though
dose modifications may be
necessary.

2.6 SGLT2 inhibitors

2.6.1 Avoid when eGFR <45 ml/
min/1.73 m² BSA.

These agents have reduced efficacy in
patients with renal impairment.

None of the SGLT2 inhibitors in
use currently need dose adjustment
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be avoided when the eGFR <45 ml/
min/1.73 m². Clinicians also need
to be aware that there is loss of
glycaemic efficacy with deteriorating
renal function while using SGLT2
inhibitors.

Consensus

Recommendation 3: Non-
Insulin Anti Injectables in
CKD:

3.1 GLP1 Analogues

3.1.1 GLP1 Analogues can be
considered when eGFR >30
ml/min/1.73 m² BSA.

3.1.2 Liraglutide has demonstrated
efficacy and safety in
patients with moderate renal
dysfunction.

Pharmacokinetic studies have
been performed with all of the GLP-1
receptor agonists in patients with

Table 4: Guidelines and Prescribing information for the use of Alpha Glucosidase Inhibitors in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>KDOQI guidelines 2012</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR in ml/min/1.72 m</td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>&lt;90 - &gt;60</td>
<td>&lt;30</td>
</tr>
<tr>
<td></td>
<td>60 - &gt;30</td>
<td></td>
</tr>
<tr>
<td>Miglitol</td>
<td>&lt;60 - &gt;30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
</tbody>
</table>

Safe  Cautious Use  Contraindicated

Table 5: Guidelines and Prescribing information for the use of DPP4 Inhibitors in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>KDOQI 2012</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR (ml/min/1.73 m²)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>50-30</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100mg OD</td>
<td>50 mg OD</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5 mg OD</td>
<td>2.5 mg OD</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg OD</td>
<td>50 mg OD</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Safe  Cautious Use  Contraindicated
Liraglutide and dulaglutide are large proteins, which are broken down by general protein catabolism. Liraglutide showed no increase in systemic exposure in patients with worsening CKD. Dulaglutide also showed small increases in systemic exposure that were not clinically relevant.

Liraglutide has been evaluated for efficacy and safety as an add-on to existing glucose-lowering edications in patients with inadequately controlled type 2 diabetes and moderate renal impairment. No changes in renal function were observed. No difference in hypoglycemic episodes was observed between treatment groups.

All the reviewed guidelines state that exenatide is either contraindicated or not recommended for patients with eGFR \( \leq 30 \text{ mL/min/1.73 m}^2 \). The 2015 AACE/ACE guidelines state that there are no noted precautions for liraglutide in patients with CKD. Lixisenatide, Albiglutide and Dulaglutide are not yet mentioned in the guideline statements.

All GLP-1 receptor agonists may be used without dose adjustment in mild CKD. Exenatide should be used with caution in patients with eGFR 30–50 mL/min/1.73 m\(^2\), and not at all in patients with severe CKD.

We can summarize that there is general agreement between product labels and guidelines that the GLP-1 receptor agonists may be used in mild CKD with no dose adjustment. For moderate CKD, Exenatide should be used with caution, and in severe CKD, not used at all. For the GLP-1 receptor agonists, which are cleared by general protein catabolism, there are varying recommendations, with the EU/Canada generally not recommending use in severe CKD (for which there was limited clinical experience), and with no restrictions and no dose adjustments in the US labels.

Based on the available evidence with this class of agents, we recommend that GLP1 Analogues can be considered when the eGFR >30 mL/min/1.73 m\(^2\). Liraglutide has efficacy and safety data from a trial conducted in patients with moderate renal failure and thus can be considered as a therapeutic option in this population.

### Consensus Recommendation 4: Insulins in CKD:

1. **Newer Insulin Analogs** to be preferred as they have pharmacokinetics unaltered in CKD including ESRD.
2. **Insulin to be initiated at small doses with strict monitoring**
3. **Insulin dose needs to be titrated to requirements to reduce the risk of Hypoglycemia**
4. **Insulin pumps are an option for suitable patients.**

Exogenous insulin is primarily cleared via renal metabolism, impaired renal function in patients with diabetes can result in decreased clearance of insulin and, consequently, prolonged exposure. Diabetes patients with impaired renal function may therefore be at increased risk of hypoglycemia. In addition, deterioration of renal function can lead to increased exposure to insulin therapy, potentially increasing the risk of hypoglycaemia.

Some authors recommend avoiding intermediate- and long-acting insulins while others are active proponents. The absence of comparative studies does little to recommend usage, as does the little information available on clinical consequences for the different types of insulin in such patients.

Impaired renal function in patients with Diabetes can affect the pharmacokinetics of some insulin formulations including regular Human Insulin and insulin Lispro. Insulin Aspart and Insulin Detemir though have demonstrated unaffected pharmacokinetics. Published evidence indicates that Insulin analogs may maintain their pharmacokinetic profiles in this patient population.

Pharmacokinetic properties of insulin degludec in subjects with varying degrees of renal function; normal, mild, moderate or severe renal impairment; or end-stage renal disease (ESRD) undergoing hemodialysis was evaluated in 30 patients. The ultra-long pharmacokinetic properties of insulin degludec were preserved with no statistically significant differences in absorption or clearance, compared with subjects with normal renal function.

The NKF-KDOQI 2012 guidelines do not recommend dose adjustment with long acting insulins such as Insulin Glargine, Insulin Detemir, Neutral Protamine Hagedorn or rapid acting insulins such as Regular Human Insulin, Insulin Aspart, Insulin Lispro or Insulin Glulisine.

The prescribing information for these insulin formulations including

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**Table 6: Recommendations for the use of oral anti diabetic agents in CKD**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Avoid if eGFR ( \leq 30 \text{ mL/min/1.73 m}^2 ) BSA, Dose modification when eGFR between 30-45 mL/min/1.73 m Monitor eGFR every 3 months</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>1 choice Gliclazide, 2 choice: Glipizide</td>
</tr>
<tr>
<td></td>
<td>Avoid in patients prone to Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Treatment should be individualised.</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Can be used with caution</td>
</tr>
<tr>
<td></td>
<td>To be avoided in patients with fluid retention</td>
</tr>
<tr>
<td>Alpha Glucosidase</td>
<td>Avoid in patients with eGFR &lt;30 mL/min/1.73 m^2 BSA</td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Dose to be titrated based on eGFR, safe</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Avoid when eGFR &lt;45 mL/min/1.73 m BSA</td>
</tr>
<tr>
<td></td>
<td>Loss of efficacy in reduced renal function</td>
</tr>
</tbody>
</table>

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Pharmacokinetic properties of insulin degludec in subjects with varying degrees of renal function; normal, mild, moderate or severe renal impairment; or end-stage renal disease (ESRD) undergoing hemodialysis was evaluated in 30 patients. The ultra-long pharmacokinetic properties of insulin degludec were preserved with no statistically significant differences in absorption or clearance, compared with subjects with normal renal function.

The NKF-KDOQI 2012 guidelines do not recommend dose adjustment with long acting insulins such as Insulin Glargine, Insulin Detemir, Neutral Protamine Hagedorn or rapid acting insulins such as Regular Human Insulin, Insulin Aspart, Insulin Lispro or Insulin Glulisine.

The prescribing information for these insulin formulations including
newer analogues such as Insulin Degludec with Insulin Aspart recommend that dose adjustment may be necessary. 

Based on the available evidence, we recommend Newer Insulin Analogs to be preferred over regular human insulin as they have pharmacokinetics unaltered in CKD including ESRD. We recommend that Insulin be initiated at small doses with strict monitoring. The dose needs to be titrated to requirements to reduce the risk of Hypoglycemia. Hypoglycaemic pumps can be an option in suitable settings.

**Conclusion**

Use of Anti-Diabetic agents in patients with renal insufficiency pose significant challenges due to lack of a clear consensus. A review of existing evidence including guidelines, published literature and package inserts helped draft this consensus recommendations (Tables 6-8). These recommendations can assist clinicians make informed choices while managing patients with chronic kidney disease.

**Acknowledgements**

We thank the consensus group members; B Seetharam, Y Sadasiva Rao, G Sureendra, Sanjay Jain, Latif Khan, Mary John, Bikash Bhattacharya, Debojit Maji, Neeraj Latif Khan, Mary John, Bikash Rao, G Surenda, Regular Human Insulin as they have pharmacokinetics unaltered in CKD including ESRD.

Table 7: Recommendations for the use of Non Insulin Injectable Anti Diabetic Agents in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1 analogs</td>
<td>Not recommended when eGFR &lt;30 ml/min/1.73 m² BSA.</td>
</tr>
<tr>
<td>Efficacy in CKD better than other oral agents</td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Recommendations for the use of Insulins in CKD

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Recommendation Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>• Newer Insulin Analogs may be preferred as they have pharmacokinetics unaltered in CKD including ESRD.</td>
</tr>
<tr>
<td>Detemir</td>
<td>• Initiate at small doses with strict monitoring</td>
</tr>
<tr>
<td>Neutral Protamine Hagedorn (NPH)</td>
<td>• Dose needs to be titrated to requirements to reduce risk of Hypoglycemia</td>
</tr>
<tr>
<td>Regular Aspart</td>
<td>Biphasic Insulin Aspart</td>
</tr>
<tr>
<td>Lispro</td>
<td>Insulin pumps are an option for suitable patients.</td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
</tr>
</tbody>
</table>


**References**


