Management of Diabetes in the CKD Patient

Heather Naylor, BScPharm, ACPR
Clinical Pharmacy Practice Leader, Nephrology
Saint John Regional Hospital
Horizon Health Network, Zone 2

May 26, 2012
Learning Objectives

At the end of this presentation you should be able to:

- Describe the prevalence of chronic kidney disease (CKD) and diabetes
- Understand issues surrounding A1C interpretation in the context of CKD
- Optimize dosing of diabetes medications in CKD
Diabetes and CKD

- What do diabetes and CKD have in common?

  Aging

  Hypertension

  Dyslipidemia

  Vascular inflammation
Diabetes and CKD

- Diabetes is the leading cause of CKD in the developed world

- Fifty percent of Canadians with diabetes have CKD (including CKD 2º to non-diabetic causes)

- In 2009, diabetes was reported as the primary cause of end-stage renal disease in 34% of cases in Canada

AJKD 2007: 50(5);865-879
Public Health Agency of Canada (2011)
Can J Diabetes 2008: 32(Supp 1); S1-S201
Incident Cases of End-Stage Renal Disease, by Primary Diagnosis (Canada)

![Graph showing incident cases of end-stage renal disease by primary diagnosis from 2000 to 2009. The graph includes lines for diabetes, renal vascular disease, glomerulonephritis, pyelonephritis, drug-induced, other, and polycystic kidney disease. The number of cases increases over time, with diabetes showing the highest number.](chart.png)
<table>
<thead>
<tr>
<th>Table 2. Diagnostic criteria for diabetes (adapted from 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG ≥7.0 mmol/L</strong></td>
</tr>
<tr>
<td>Fasting = no caloric intake for at least 8 hours</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td><strong>Casual PG ≥11.1 mmol/L + symptoms of diabetes</strong></td>
</tr>
<tr>
<td>Casual = any time of the day, without regard to the interval</td>
</tr>
<tr>
<td>since the last meal</td>
</tr>
<tr>
<td>Classic symptoms of diabetes = polyuria, polydipsia and</td>
</tr>
<tr>
<td>unexplained weight loss</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td><strong>2hPG in a 75-g OGTT ≥11.1 mmol/L</strong></td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td><strong>A1C ≥6.5%</strong></td>
</tr>
<tr>
<td>Using a standardized, validated assay, in the absence of</td>
</tr>
<tr>
<td>conditions that affect the accuracy of the A1C</td>
</tr>
</tbody>
</table>
Use of A1C to Diagnose Diabetes

- A1C <6.5% does not exclude diabetes that may be diagnosed using standard glucose tests.

- A1C is not recommended for diagnostic purposes in children, adolescents, pregnant women or people with type 1 diabetes.

- A1C may be misleading and therefore should not be used as a diagnostic tool in the setting of various hemoglobinopathies, iron deficiency, hemolytic anemias, or severe hepatic or renal failure.

Can J Diabetes 2011: 35(3);247-49
Glycemia-Related Issues in CKD: Monitoring of Glycemic Control

- **Falsely increased A1c**
  - Elevated BUN causes formation of carbamylated hemoglobin which is indistinguishable from glycosylated hemoglobin
  - Iron deficiency

- **Falsely decreased A1c**
  - Increased erythrocyte turnover (reduced life span)
  - Use of erythropoietin agents and iron

Patient Case: JC

- 66 yo female newly diagnosed with Type 2 DM
- Stage 3 CKD, HTN, gout
- Labs:
  - A1C = 8.5%
  - eGFR = 50 mL/min
  - Albumin:creatinine ratio = 20 mg/mmol (microalbuminuria)
  - BP = 142/88
  - LDL = 2.5 mmol/L
  - TC/HDL = 3.9
- Medications: Ramipril 10 mg/d, Amlodipine 5 mg/d, Allopurinol 200 mg/d, acetaminophen prn
Patient Case: JC

What should JC’s target A1C be?

a) $\leq 6\%$

b) $\leq 6.5\%$

c) $\leq 7\%$

d) 7-7.9\%
# Glycemic Targets for Diabetes

## Table 1. Recommended targets for glycemic control

<table>
<thead>
<tr>
<th></th>
<th>A1C* (%</th>
<th>FPG or preprandial PG (mmol/L)</th>
<th>2-hour postprandial PG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 and type 2 diabetes</td>
<td>≤7.0</td>
<td>4.0–7.0</td>
<td>5.0–10.0 (5.0–8.0 if A1C targets not being met)</td>
</tr>
</tbody>
</table>

* A1C: Glycosylated hemoglobin
Risk Factors for Progression of CKD

1. Hypertension
2. Proteinuria
3. Obesity
4. Hyperglycemia
5. Dyslipidemia
6. Smoking

- Stage 1-2 CKD (eGFR >60 mL/min):
  - Reduce development of micro-albuminuria and progression to macroalbuminuria
  - Prevent/slow progression of other microvascular events

- Stage 3-5 CKD (eGFR <60 mL/min):
  - Prevent/slow progression of other microvascular events
  - Reduce risk of infection and promote wound healing

CMAJ 2008; 179:1154-62
Diabetes Control and Complications Trial (DCCT)

- 1441 patients, Type 1 DM
- Follow-up: mean of 6.5 years (range, 3-9)
- Intensive therapy: mean A1C = 7.4%
- Conventional therapy: mean A1C = 9.1%

NEJM 2005: 353;2643-53
NEJM 1993: 329(14);977-86
DCCT: Cumulative Incidence of Nephropathy

Adjusted mean risk of microalbuminuria was reduced by 34% (p<0.04) with intensive therapy.

NEJM 1993: 329(14);977-86
United Kingdom Prospective Diabetes Study (UKPDS)

- 5102 newly diagnosed, Type 2 DM
- Follow-up: 10 years
- Intensive therapy: mean A1C = 7%
- Conventional therapy: mean A1C = 7.9%
- RRR for the development of microalbuminurinuria was 24% (95% CI, 9% to 38%; $P = 0.0006$) after 9 years of intensive therapy.

Lancet 1998; 352:837-53
ACCORD Study

- 10,251 patients, Type 2 DM (average duration of 10+ years) + 2 or more CV risk factors or known heart disease

- Intensive therapy: target A1C < 6%

- Control therapy: target A1C = 7-7.9%

- Clinical question: does intensive diabetes therapy reduce CV events vs. standard therapy?
  - MI, stroke, death from CV complications
ACCORD Study

- Intensive therapy arm (A1C<6%) stopped 18 months early due to an observed increase in mortality rate vs. the control arm.

- 257/5128 died in intensive arm

- 203/5123 died in standard arm

- HR, 1.22 (95% CI, 1.0.-1.46, p=0.04)

NEJM 2008; 358:2545-59
ADVANCE Study

- 11,140 patients, Type 2 DM + micro or macro-vascular disease or at least one risk factor for vascular disease
- Follow-up: 5 years
- Intensive therapy: target A1C <6.5%
- Control therapy: mean A1C = 7.3% (target varied by country)
- Nephropathy reduced with intensive therapy (4.1% vs. 5.2%; HR=0.79; 95% CI, 0.66 to 0.93, p=0.006), but not macrovascular complications

NEJM 2008; 358:2560-2572
Patient Case: JC

What should JC’s target A1C be?

a) \( \leq 6\% \)
b) \( \leq 6.5\% \)
c) \( \leq 7\% \)
d) 7-7.9%
Patient Case: JC

- What if JC had a limited life expectancy?
<table>
<thead>
<tr>
<th>Approach to management of hyperglycemia:</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Comorbid Condition* or Physiologic Age</th>
<th>Microvascular Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent or Mild†</td>
</tr>
<tr>
<td>Absent; &gt;10 y of life expectancy</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Present¶; 5–10 y of life expectancy</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Marked**; &lt;5 y of life expectancy</td>
<td>8–9∥</td>
</tr>
</tbody>
</table>

VA/DoD = Veterans Affairs/Department of Defense.
Glycemia-Related Issues in CKD

**Increased risk of hypoglycemia**

- Impaired renal gluconeogenesis (due to uremia)

- Decreased renal clearance of insulin

- Decreased renal clearance of oral hypoglycemic drugs
  - May require reduced doses of insulin or oral diabetes medications as CKD progresses
Medications

- Metformin
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Acarbose
- Incretins
- Insulin
# Stages of CKD

## Table 10. Stages of Chronic Kidney Disease

<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 ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
Metformin

- Advantages:
  - Inexpensive
  - Weight loss
  - No hypoglycemia
  - May offer protection from CVD and cancer

- Continue in **stable** patients until CrCL < 30 mL/min (stage 4-5 CKD)

- Hold if GI upset/dehydration

- Recommended to discontinue if patient unstable (acute kidney injury; cardiac, respiratory, or hepatic failure; sepsis; bowel obstruction; shock)

CMAJ 2008; 179:1154-62
Metformin: Risk of Lactic Acidosis

- Cochrane review of 206 trials including 47,846 patient-years of exposure to metformin found no cases of fatal or non-fatal lactic acidosis.

- Case reports suggest metformin is rarely a cause of lactic acidosis, but may be a co-precipitant.

- Cases of lactic acidosis seen in acute (or acute on chronic) renal failure precipitated by ACE-I or NSAIDs, or due to another major illness (hepatic failure, sepsis, bowel obstruction, shock).

CMAJ 2008; 179:1154-62
## Metformin

**Table 1—Proposed recommendations for use of metformin based on eGFR**

<table>
<thead>
<tr>
<th>eGFR level (mL/min per 1.73 m²)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>No renal contraindication to metformin</td>
</tr>
<tr>
<td></td>
<td>Monitor renal function annually</td>
</tr>
<tr>
<td>&lt;60 and ≥45</td>
<td>Continue use</td>
</tr>
<tr>
<td></td>
<td>Increase monitoring of renal function (every 3–6 months)</td>
</tr>
<tr>
<td>&lt;45 and ≥30</td>
<td>Prescribe metformin with caution</td>
</tr>
<tr>
<td></td>
<td>Use lower dose (e.g., 50%, or half-maximal dose)</td>
</tr>
<tr>
<td></td>
<td>Closely monitor renal function (every 3 months)</td>
</tr>
<tr>
<td></td>
<td>Do not start new patients on metformin</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Stop metformin</td>
</tr>
</tbody>
</table>

Additional caution is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially interacting medications.
Sulfonylureas

- **Glyburide**
  - Active metabolite that is renally eliminated
  - Accumulation in renal failure $\rightarrow$ prolonged hypoglycemia
  - CKD Stage 3: use with caution
  - CKD Stage 4-5: not recommended

- **Gliclazide**
  - Preferred sulfonylurea; short half-life and no active metabolites
  - No dosage adjustment necessary

KDOQI Guidelines 2007
CMAJ 2008; 179:1154-62
Meglitinides

- **Repaglinide (Gluconorm®)**
  - No dosage adjustment necessary
  - CrCL<40 mL/min: start with 0.5 mg and adjust based on response

- **Nateglinide (Starlix®)**
  - Weakly active metabolites excreted renally
  - CKD Stage 1-4: no dosage adjustment necessary
  - Avoid in CKD Stage 5

KDOQI Guidelines 2007
CMAJ 2008; 179:1154-62
AJKD 2007: 50(5);865-79
Thiazolidinediones (Glitazones)

- **Rosiglitazone (Avandia®)**
  - No dosage adjustment necessary
  
  - **Health Canada Warning, November 2010:**
    - Indicated only in patients with Type 2 DM when all other oral diabetes meds have not lowered blood sugar enough, or are not appropriate.
    - May increase the risk of serious heart problems, including: heart failure, angina, myocardial infarction, fluid retention (with or without rapid weight gain)
    - Signed informed consent required

KDOQI Guidelines 2007
Thiazolidinediones (Glitazones)

- Pioglitazone (Actos®)
  - No dosage adjustment necessary
  - Health Canada Warning, April 2012
    - Potential increased risk of bladder CA with pioglitazone.
    - Pioglitazone should not be used if patients:
      (1) have or have had bladder cancer, or
      (2) have blood in their urine
    - Risk factors for bladder cancer should be assessed before starting pioglitazone (e.g. age, smoking, family history of bladder cancer, exposure to chemicals in the workplace, to certain cancer treatments and radiation therapy).

KDOQI Guidelines 2007
Alpha-Glucosidase Inhibitors

- **Acarbose (Glucobay®)**
  - Metabolized in the GI tract. <2% excreted renally as drug or active metabolite
  - CKD Stage 1-3: No dosage adjustment necessary
  - CKD Stage 4-5: Limited data; **not** recommended
  - Note: when treating hypoglycemia in patients on acarbose, do not use table sugar (i.e. sucrose → a disaccharide). Other options: 15 g glucose tablets, 1 cup of milk or 1 tablespoon of honey.

Practical Tips for People with Diabetes and CKD. CDA 2008.
DPP-4 Inhibitors (Gliptins)

**DPP-4 Inhibition**

- Oral glucose stimulates release of incretins (GLP-1 and GIP)
- DPP-4 rapidly degrades incretins
- JANUVIA inhibits DPP-4 to increase active incretins...
- ...which increases insulin synthesis/release and suppresses glucagon production in a glucose-dependent manner

Incretin enhancement can indirectly result in glucose uptake in peripheral tissues and a decrease in hepatic glucose production.

- Glucose
- GLP-1 (glucagon-like peptide-1)
- GIP (glucose-dependent insulino tropic peptide)
- DPP-4 (dipeptidyl peptidase-4)
- JANUVIA

www.januvia.com
DPP-4 Inhibitors (Gliptins)

- **Sitagliptin (Januvia®)**
  - CKD Stage 1-2: 100 mg po once daily
  - CKD Stage 3 (CrCL 30-50 mL/min): 50 mg po once daily
  - CKD Stage 4-5 (CrCL 30 mL/min): 25 mg po once daily
  - *Note: Sitagliptin only available as 100 mg tabs in Canada, therefore difficult to split*

- **Saxagliptin (Onglyza®)**
  - CKD Stage 1-2: 5 mg po once daily
  - CKD Stage 3-5 (CrCL<50 mL/min): 2.5 mg po once daily

- **Linagliptin (Trajenta®)**
  - No dosage adjustment necessary
DPP-4 Inhibitors (Gliptins)

- Common side effects:
  - Upper respiratory tract infection
  - Nasopharyngitis
  - Headache
  - Hypoglycemia associated with co-existing sulfonylurea therapy

- Only sitagliptin is currently covered by NBPDP
  - Special authorization
  - Restricted to Type 2 DM with inadequate BG control on optimal doses of metformin + sulfonylurea, and NPH insulin is not a feasible option
GLP-1 Receptor Agonists
GLP-1 Receptor Agonists

- **Liraglutide (Victoza®)**
  - Start with 0.6 mg SC once daily x 1 week to reduce GI side effects, then increase to 1.2 mg SC once daily.
  - Max daily dose = 1.8 mg
  - CKD Stage 1-2: No dosage adjustment necessary
  - CKD Stage 3-5: Very limited experience. Appears no dosage adjustment necessary. Product monograph advises against use.
  - Adverse effects: nausea (28%), diarrhea (17%), vomiting (11%), headache, dizziness
GLP-1 Receptor Agonists

- Exenatide (Byetta®)
  - Starting dose: 5 mcg SC bid within 60 min before meal. May increase to 10 mcg SC bid after 1 month
  - May need to reduce sulfonylurea dose by 50%
  - CKD Stage 1-3: No dosage adjustment necessary
  - CKD Stage 4-5 (CrCL<30 mL/min): Do not use
  - Adverse effects: nausea (up to 44%), vomiting, diarrhea, dyspepsia, pancreatitis (post-marketing case reports)
GLP-1 Receptor Agonists

FDA Warning November 2009

- From April 2005 through October 2008, FDA received 78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency), in patients using exenatide. Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems.

- Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.

- Caution should be applied when initiating or increasing doses of exenatide from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min).
<table>
<thead>
<tr>
<th>CONSIDERATIONS</th>
<th>GLP1 RECEPTOR AGONISTS</th>
<th>DPP4 INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXENATIDE&lt;sup&gt;10,22,24-31&lt;/sup&gt;</td>
<td>LIRAGLUTIDE&lt;sup&gt;18,23,32-34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Administration</td>
<td>SC injection</td>
<td></td>
</tr>
<tr>
<td>Half-life, h</td>
<td>2.4</td>
<td>11-15</td>
</tr>
<tr>
<td>Dose</td>
<td>5 or 10 µg, twice daily</td>
<td>0.6, 1.2, or 1.8 mg, once daily</td>
</tr>
<tr>
<td>Origin of active incretins following treatment</td>
<td>Exogenous and endogenous</td>
<td></td>
</tr>
<tr>
<td>Effect on insulin level</td>
<td>Large increase</td>
<td></td>
</tr>
<tr>
<td>Effect on glucagon level</td>
<td>Moderate decrease</td>
<td></td>
</tr>
<tr>
<td>Mean decrease in HbA&lt;sub&gt;1c&lt;/sub&gt; vs placebo, %</td>
<td>Approximately 0.8</td>
<td>0.8-1.6</td>
</tr>
<tr>
<td>Postprandial hyperglycemia</td>
<td>Moderate decrease</td>
<td></td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Inhibited</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>Moderate decrease</td>
<td></td>
</tr>
<tr>
<td>Tolerability issues*</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Incidence of hypoglycemia</td>
<td>Low rate of hypoglycemia when administered as monotherapy in patients with T2DM; risk might increase when used in combination with sulfonylureas</td>
<td></td>
</tr>
</tbody>
</table>

DPP4—dipeptidyl peptidase 4, GLP1—glucagonlike peptide 1, HbA<sub>1c</sub>—glycated hemoglobin A<sub>1c</sub>, SC—subcutaneous, T2DM—type 2 diabetes.

*For more complete listings of adverse events, consult the respective product monographs.
Insulin

- Insulin dose may need to be decreased as CKD progresses and eGFR declines.
- Humalog (or other short acting) may decrease risk of hypoglycemic episodes.

---

**Table 1. Currently available insulins in Canada**

<table>
<thead>
<tr>
<th>Insulin category</th>
<th>Human insulin</th>
<th>Analogue insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus</td>
<td>Humulin Regular</td>
<td>Aspart (NovoRapid)</td>
</tr>
<tr>
<td></td>
<td>Novolin Toronto</td>
<td>Glulisine (Apidra)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lispro (Humalog)</td>
</tr>
<tr>
<td>Basal</td>
<td>Humulin N</td>
<td>Detemir (Levemir)</td>
</tr>
<tr>
<td></td>
<td>Novolin NPH</td>
<td>Glargine (Lantus)</td>
</tr>
<tr>
<td>Premixed</td>
<td>Humulin 30/70</td>
<td>Humalog Mix25</td>
</tr>
<tr>
<td></td>
<td>Novolin 30/70</td>
<td>Humalog Mix50</td>
</tr>
<tr>
<td></td>
<td>Novolin 40/60</td>
<td>NovoMix 30</td>
</tr>
<tr>
<td></td>
<td>Novolin 50/50</td>
<td></td>
</tr>
</tbody>
</table>
Patient Case: JC

- 66 yo female newly diagnosed with Type 2 DM
- Stage 3 CKD, HTN, gout
- Labs:
  - A1C = 8.5%
  - eGFR = 50 mL/min
  - Albumin:creatinine ratio = 20 mg/mmol (microalbuminuria)
  - BP = 142/88
  - LDL = 2.5 mmol/L
  - TC/HDL = 3.9
- Medications: Ramipril 10 mg/d, Amlodipine 5 mg/d, Allopurinol 200 mg/d, acetaminophen prn
Patient Case: JC

- What medication should JC be started on for her newly diagnosed Type 2 DM?
  
  a) Glyburide
  b) Gliclazide
  c) Metformin
  d) Sitagliptin
- If insulin is not an option then sitagliptin is available through NBPDP via special auth

- Saxagliptin, linagliptin liraglutide, and exenatide are not benefits of NBPDP at this time
Questions?