Management of Diabetes in the CKD Patient

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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

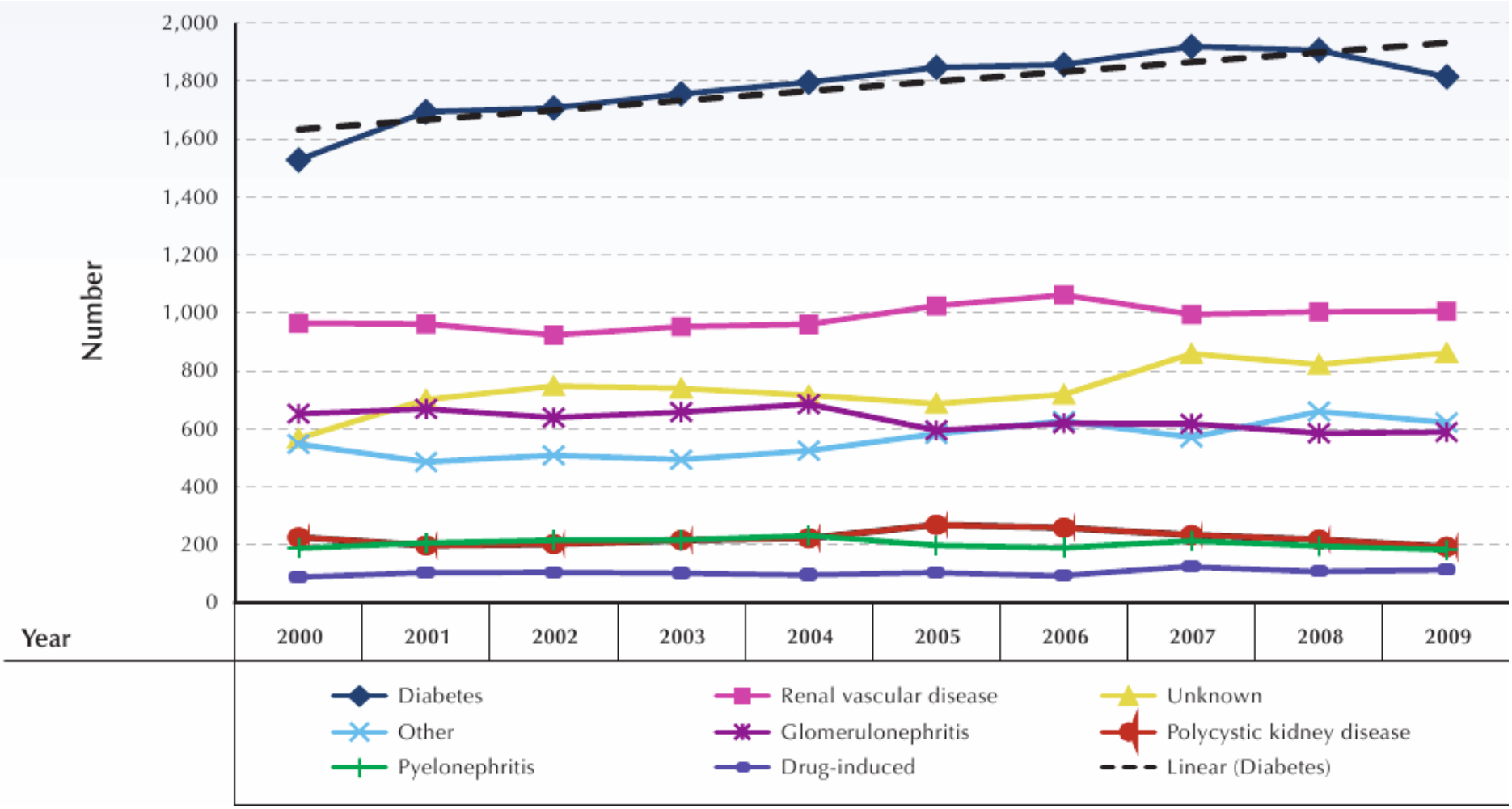
- Diabetes is the leading cause of CKD in the developed world
- Fifty percent of Canadians with diabetes have CKD (including CKD 2º to non-diabetic causes)
- In 2009, diabetes was reported as the primary cause of end-stage renal disease in 34% of cases in Canada

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)



Public Health Agency of Canada (2011)

Table 2. Diagnostic criteria for diabetes (adapted from 17)

FPG ≥7.0 mmol/L

Fasting = no caloric intake for at least 8 hours

or

Casual PG ≥11.1 mmol/L + symptoms of diabetes

Casual = any time of the day, without regard to the interval since the last meal

Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss

or

2hPG in a 75-g OGTT ≥11.1 mmol/L

or

A1C ≥6.5%

Using a standardized, validated assay, in the absence of conditions that affect the accuracy of the A1C

Can J Diabetes 2011: 35(3);247-49

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

Am J Kidney Dis 2007; 50(5):865-79

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) ≤ 6%
b) ≤ 6.5%
c) ≤ 7%
d) 7-7.9%

Glycemic Targets for Diabetes

Table 1. Recommended targets for glycemic control

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

Can J Diabetes 2008: 32(Supp 1); S1-S201

Risk Factors for Progression of CKD

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

- <u>Stage 1-2 CKD (eGFR >60 mL/min)</u>:
  - ✓ Reduce development of micro-albuminuria and progression to macroalbuminuria
  - ✓ Prevent/slow progression of other microvascular events
- <u>Stage 3-5 CKD (eGFR <60 mL/min)</u>:
  - ✓ Prevent/slow progression of other microvascular events
  - ✓ Reduce risk of infection and promote wound healing

CMAJ 2008; 179:1154-62

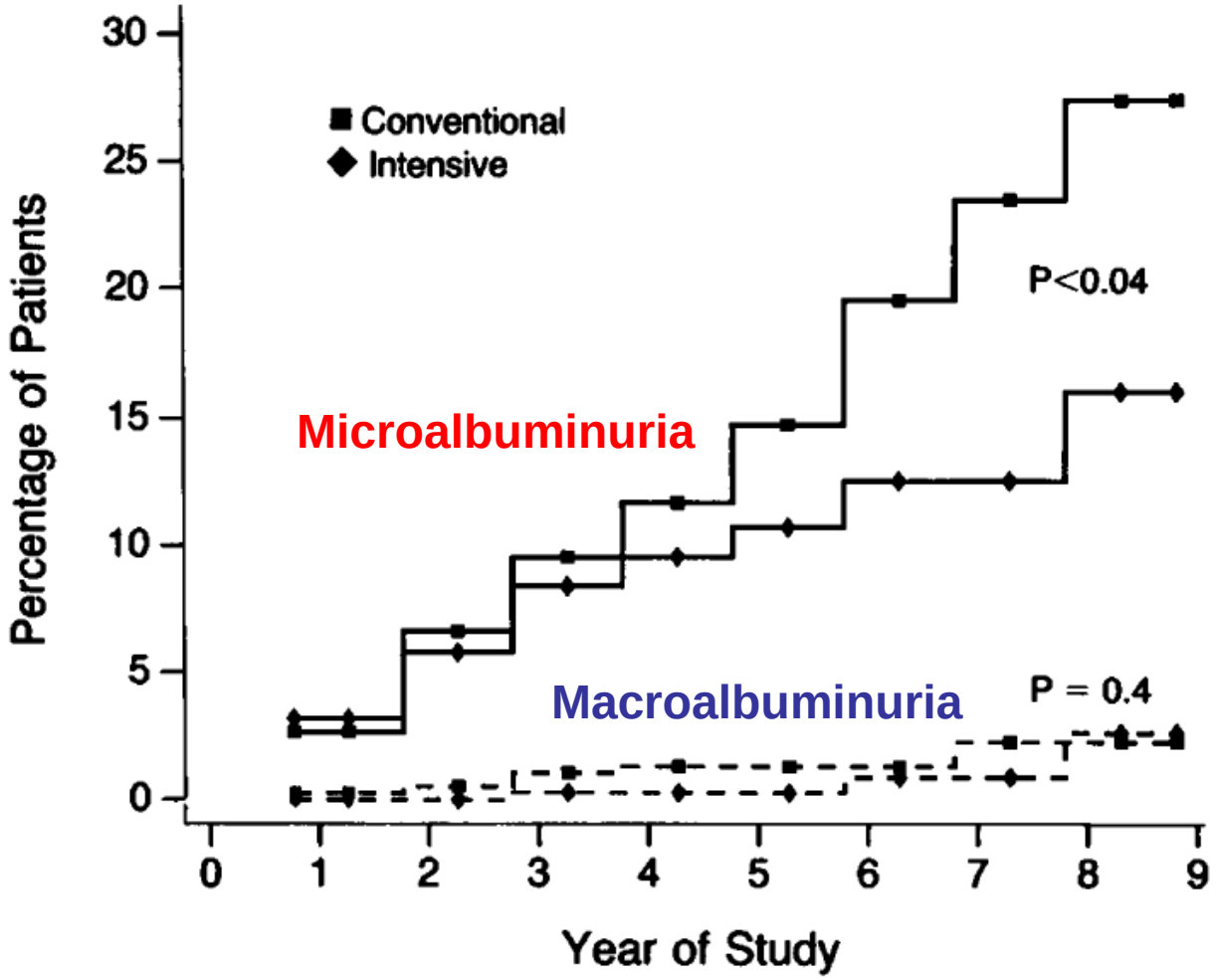
Diabetes Control and Complications Trial (DCCT)

- 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 micro-albuminuria 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 microalbuminuria 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

NEJM 2008; 358:2545-59

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

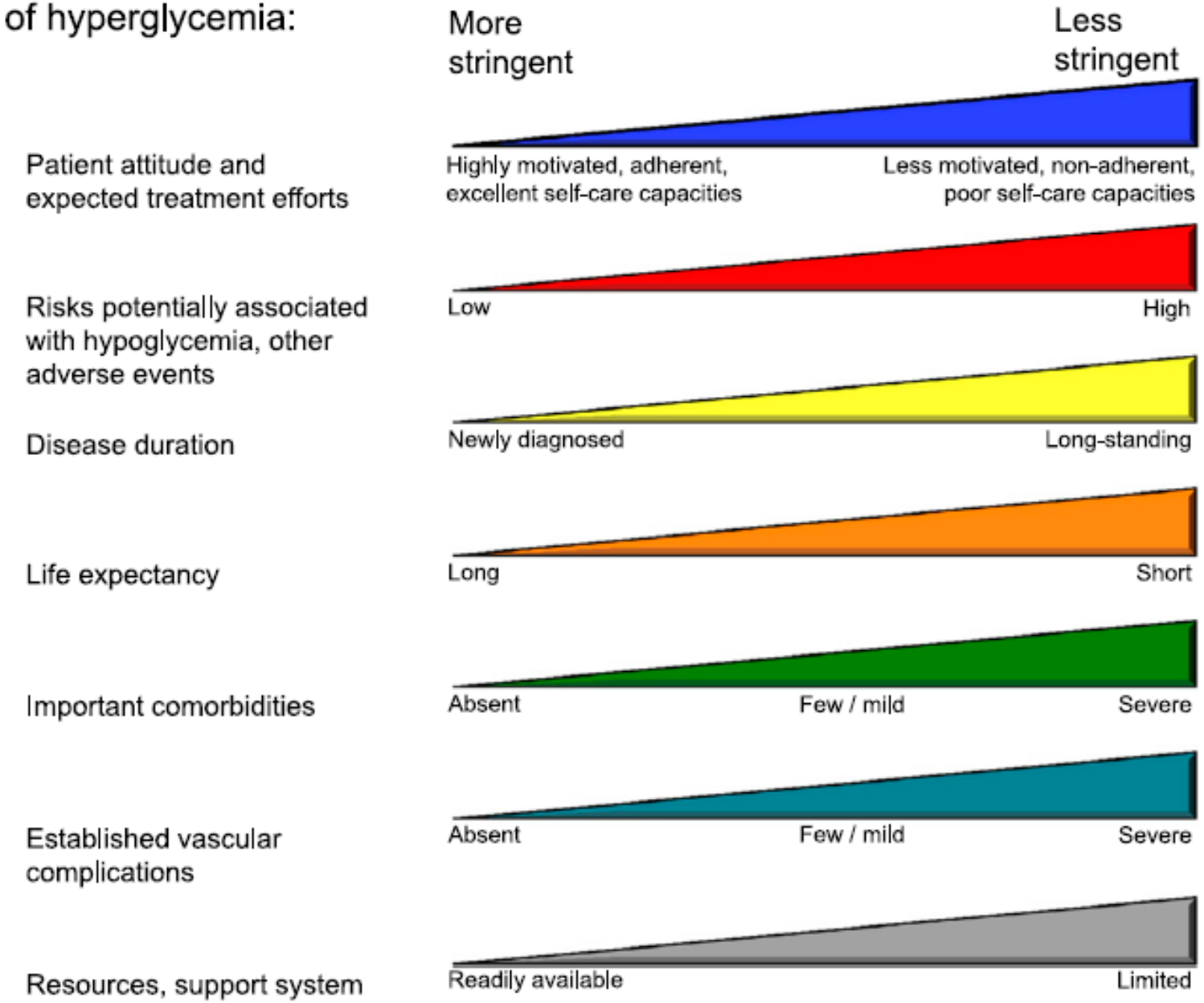
- What should JC's target A1C be?

a) ≤ 6%
b) ≤ 6.5%
c) ≤ 7%
d) 7-7.9%

Patient Case: JC

- What if JC had a limited life expectancy?

Approach to management of hyperglycemia:



Inzucchi et al. Diabetes Care 2012.

Table. **Target Ranges of Hemoglobin A_{1c} Recommended by the VA/DoD Diabetes Practice Guidelines Working Group**

Major Comorbid Condition* or Physiologic Age	Microvascular Complications, %		
	Absent or Mild†	Moderate‡	Advanced§
Absent; >10 y of life expectancy	<7	<8	8–9‖
Present¶; 5–10 y of life expectancy	<8	<8	8–9‖
Marked**; <5 y of life expectancy	8–9‖	8–9‖	8–9‖

VA/DoD = Veterans Affairs/Department of Defense.

Ann Intern Med 2011; 155(5):340

Glycemia-Related Issues in CKD

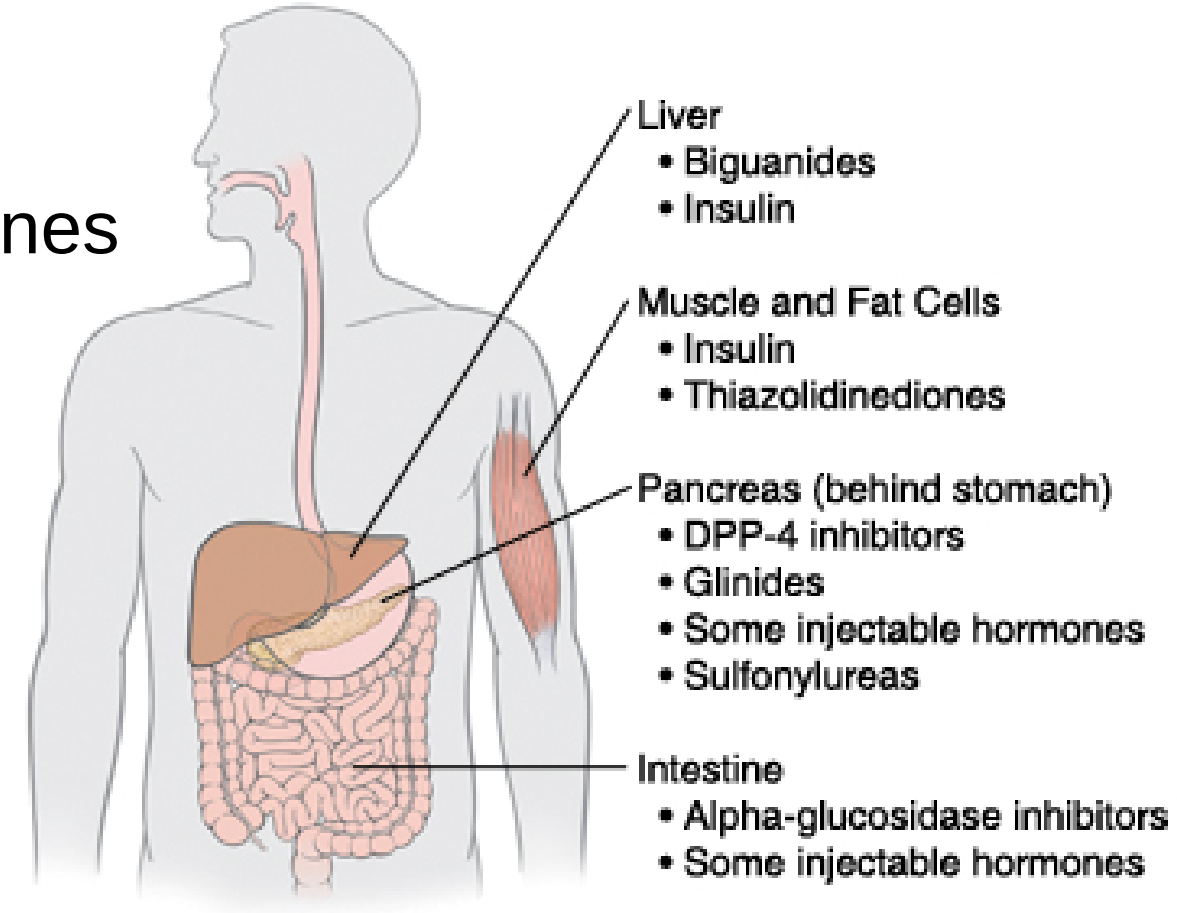
Increased risk of hypoglycemia

- 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

Am J Kidney Dis 2007; 50(5):865-79

Medications

- Metformin
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Acarbose
- Incretins
- Insulin



Stages of CKD

Table 10. Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

KDOQI Guidelines

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

Cochrane Database Syst Rev 2006(1):CD002967

Metformin

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

eGFR level (mL/min per 1.73 m^2)	Action
≥60	No renal contraindication to metformin
	Monitor renal function annually
<60 and ≥45	Continue use
	Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution
	Use lower dose (e.g., 50%, or half-maximal dose)
	Closely monitor renal function (every 3 months)
	Do not start new patients on metformin
<30	Stop metformin

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.

Diabetes Care 2011: 24(6);1431-1437

Sulfonylureas

- **Glyburide**
  - Active metabolite that is renally eliminated
  - Accumulation in renal failure → 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

Thiazolidinediones (Glitazones)

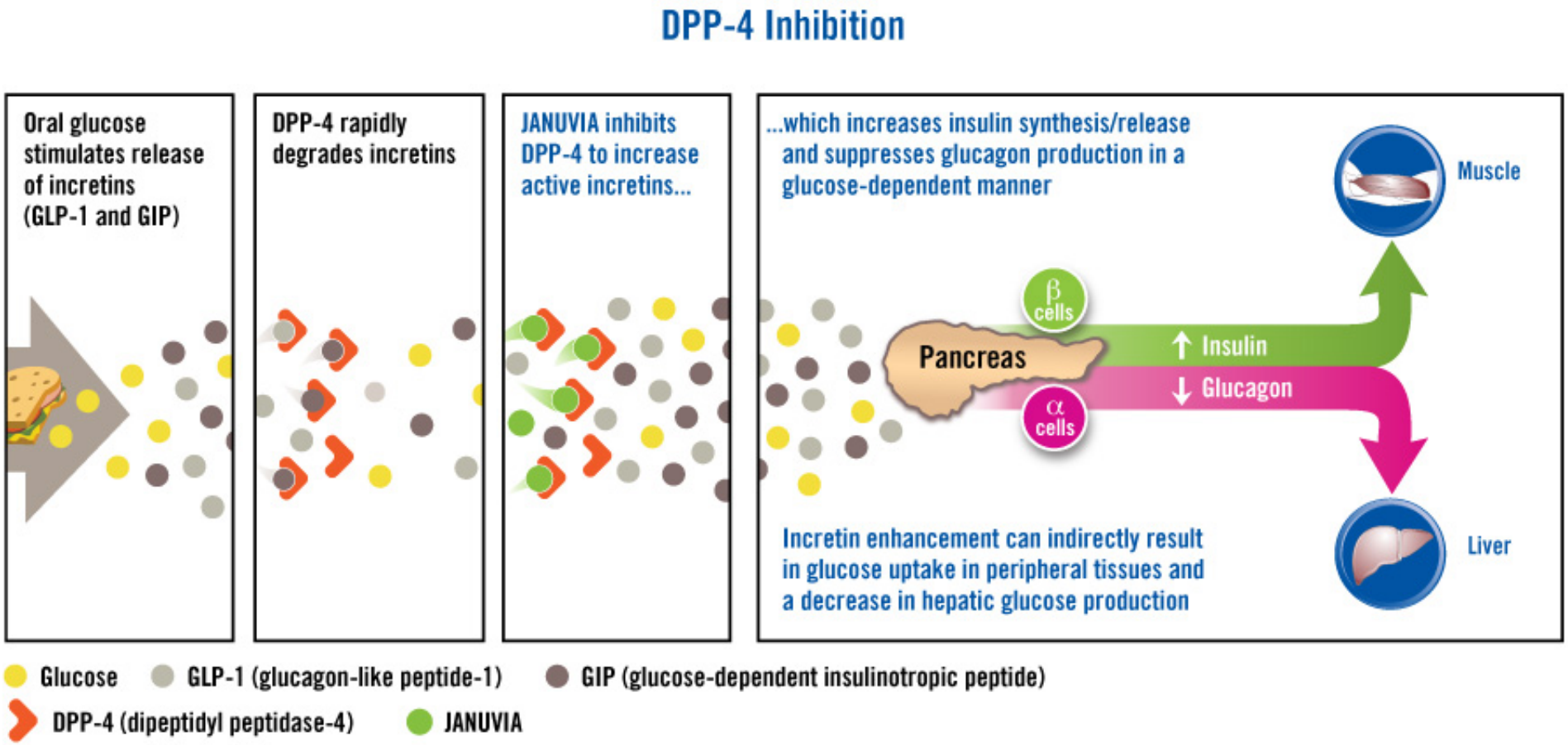
- **Pioglitazone (Actos®)**
  - No dosage adjustment necessary
  - Health Canada Warning, April 2012
    - Potential increased risk of bladder CA with pioglitazone.
    - Pioglitazone should not be used if patients:
      (1) have or have had bladder cancer, or
      (2) have blood in their urine
    - 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).

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)



www.januvia.com

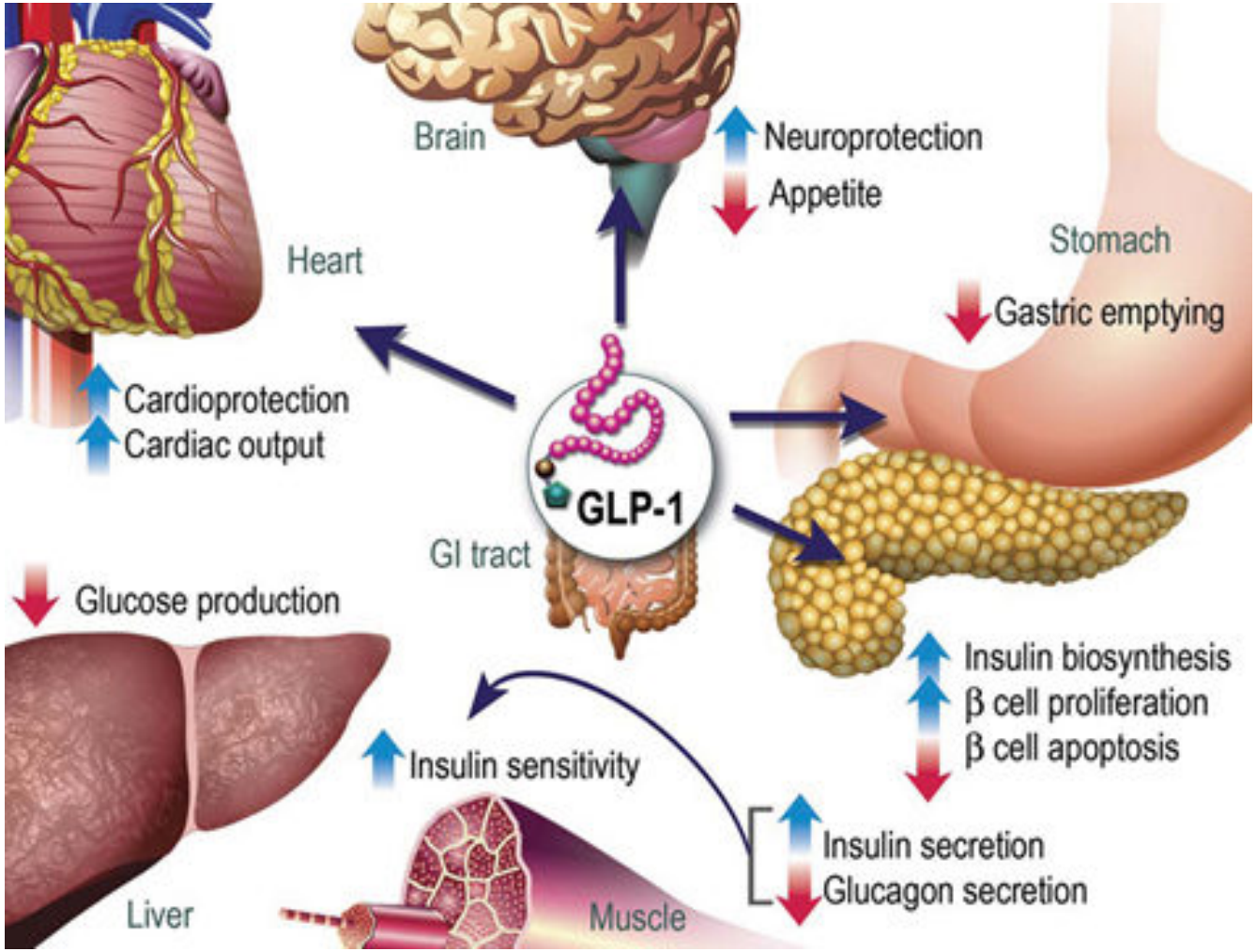
DPP-4 Inhibitors (Gliptins)

- **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 mLmin): 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 1. Pharmacology and clinical considerations for the incretin agents

	GLP1 RECEPTOR AGONISTS		DPP4 INHIBITORS	
CONSIDERATIONS	EXENATIDE[20,22,24-31]	LIRAGLUTIDE[18,23,32-34]	VILDAGLIPTIN[35,36]	SITAGLIPTIN[35,37]
Administration	SC injection		Oral tablet	
Half-life, h	2.4	11-15	2.5	12-14
Dose	5 or 10 µg, twice daily	0.6, 1.2, or 1.8 mg, once daily	50 mg, twice daily	100 mg, once daily
Origin of active incretins following treatment	Exogenous and endogenous		Endogenous	
Effect on insulin level	Large increase		Moderate increase	
Effect on glucagon level	Moderate decrease			
Mean decrease in HbA_{1c} vs placebo, %	Approximately 0.8	0.8-1.6	Approximately 0.7	0.6-1.0
Postprandial hyperglycemia	Moderate decrease		Small decrease	
Gastric emptying	Inhibited		No clinically significant effect	
Body weight	Moderate decrease		Neutral	
Tolerability issues*	Nausea		Upper respiratory tract infection	
Incidence of hypoglycemia	Low rate of hypoglycemia when administered as monotherapy in patients with T2DM; risk might increase when used in combination with sulfonylureas			

DPP4—dipeptidyl peptidase 4, GLP1—glucagonlike peptide 1, HbA_{1c}—glycated hemoglobin A_{1c}, SC—subcutaneous, T2DM—type 2 diabetes.
*For more complete listings of adverse events, consult the respective product monographs.

Can Fam Physician 2010; 56:639-48

Insulin

Table 1. Currently available insulins in Canada		
Insulin category	**Human insulin**	**Analogue insulin**
Bolus	Humulin Regular Novolin Toronto	Aspart (NovoRapid) Glulisine (Apidra) Lispro (Humalog)
Basal	Humulin N Novolin NPH	Detemir (Levemir) Glargine (Lantus)
Premixed	Humulin 30/70 Novolin 30/70 Novolin 40/60 Novolin 50/50	Humalog Mix25 Humalog Mix50 NovoMix 30

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

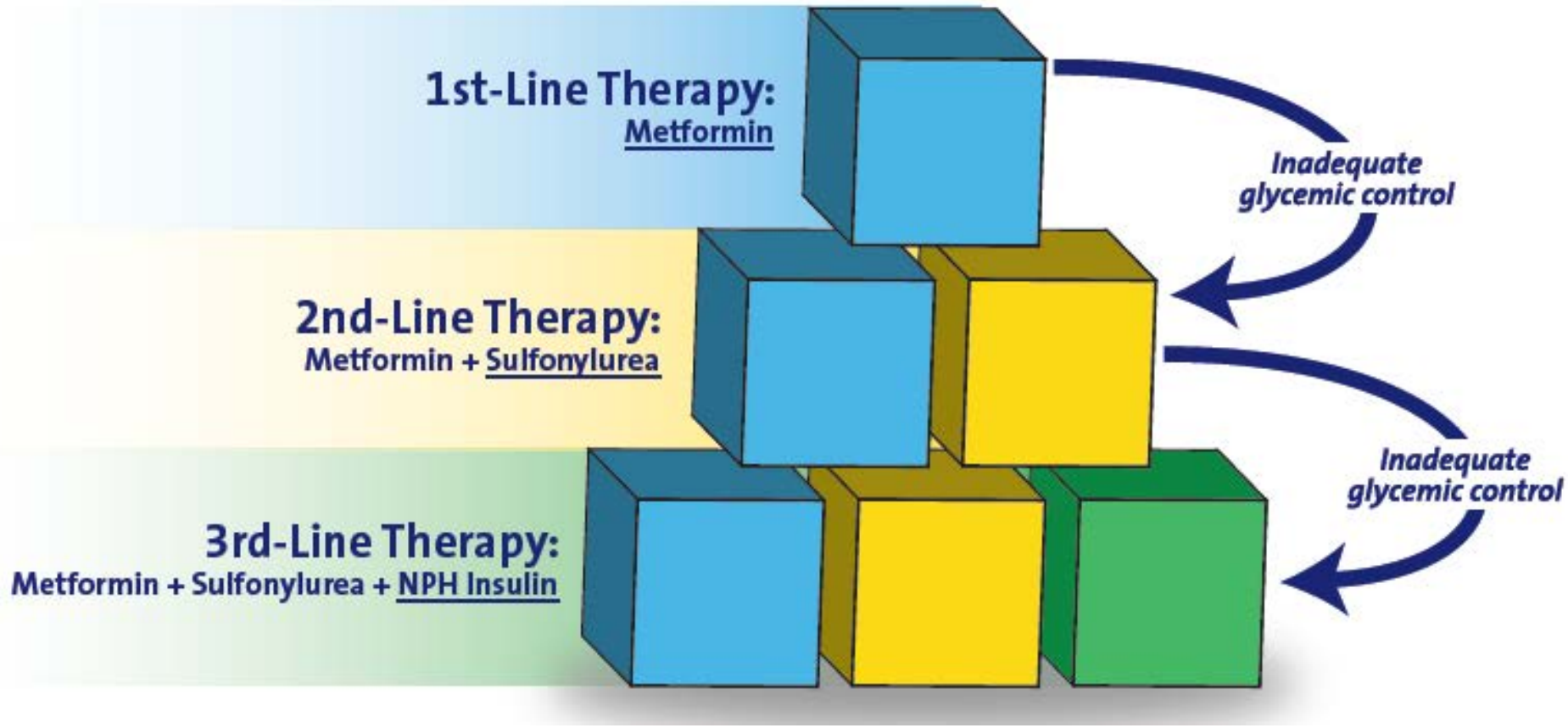
Patient Case: JC

- 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?