Diabetes Management in CKD

March 23rd, 2012
Renal Pharmacists Network
Nephrology Education Day
Toronto, Ontario
Anar Dossa BScPharm Pharm D CDE
Vancouver General Hospital

Outline

- Blood glucose monitoring
  - How often should blood glucose be measured?
  - Canadian Diabetes Association Statement
- A1c interpretation in the context of CKD
  - Role of A1c in diagnosing diabetes
- Diabetes Medications
  - How to optimize dosing in CKD patients

How often should blood sugars be measured at home?-OLD

- Canadian Diabetes Association Guidelines 2003
  - Type 1 – at least **3 times** a day
  - Type 2 – at least **once** a day
  - More **frequent testing** is required to make adjustments to **daily activity, food intake** and **medication**.
- Testing is particularly important **before, during** and for many hours **after** exercise.

Can J Diabetes.2003;27(suppl 2)

How often should blood sugars be measured at home?-NEW

- Canadian Diabetes Association Guidelines 2008
  - Type 1&2 on insulin
    - at least **3 times** a day
  - Type 2 (once a day insulin+ oral agents)
    - at least **once** a day
  - Type 2 (oral agents or lifestyle)
    - individualize

Can J Diabetes. 2008;32(suppl 1)

How often should blood sugars be measured at home?

OLD vs. **NEW**

- **Canadian Diabetes Association Guidelines 2003**
  - Type 2 – at least **once** a day
- **Canadian Diabetes Association Guidelines 2008**
  - Type 2 (oral agents or lifestyle)
    - individualize

ESMON Study

- What is the effect of blood glucose monitoring on
  - A1C
  - Psychological indices
  - Use of oral hypoglycemic agents
  - BMI
  - Hypoglycemia
- Randomized controlled trial
- Ireland

BMJ 2008;336:1174-77

Monitoring Group

- Provided single glucose monitor
- 4 fasting and 4 post-meal readings weekly
- Advised on how to respond to low or high readings
  - Adjust/review diet and/or exercise

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Study Participants

Table 1 | Baseline characteristics of patients with newly diagnosed diabetes according to self monitoring or no monitoring (control) of blood glucose. Figures are means (SD) unless stated otherwise

	Monitoring group	Control
No of patients (men/women)	96 (55/41)	88 (56/32)
Age (years)	57.7 (11.04)	60.9 (11.5)
Body mass index	34 (6.98)	32 (6.23)
% HbA_{1c}	8.8 (2.1)	8.6 (2.3)

BMJ 2008;336:1174-77

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Both Groups

- Identical structured education program
- Identical treatment algorithm

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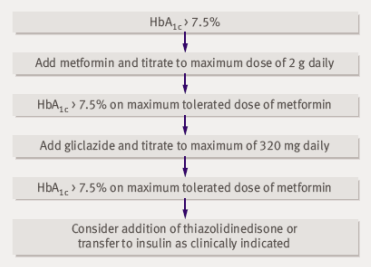
Study Protocol



BMJ 2008;336:1174-77

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Mean A1C Difference Between Groups

Time (months)	Monitoring	Control	P value	Mean difference (95% CI)
0	8.8 (2.1)	8.6 (2.3)	0.68	−0.33 (−0.77 to 0.51)
3	7.2 (1.1)	7.1 (1.2)	0.50	0.18 (−0.47 to 0.23)
6	7.0 (0.9)	7.0 (1.1)	0.82	0.04 (−0.27 to 0.35)
9	6.9 (0.8)	7.1 (1.4)	0.30	0.19 (−0.16 to 0.54)
12	6.9 (0.8)	6.9 (1.2)	0.69	0.07 (−0.25 to 0.38)

BMJ 2008;336:1174-77

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Hypoglycemia

Table 4 | Number of patients who reported hypoglycaemia (total number of hypoglycaemia episodes reported) according to self monitoring and no monitoring (control) of blood glucose

Time (months)	Monitoring	Control
0	1 (3)	0 (0)
3	5 (10)	2 (8)
6	3 (5)	4 (8)
9	5 (9)	1 (6)
12	4 (4)	6 (14)

BMJ 2008;336:1174-77

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Points to consider

- Glycemic control improved rapidly in both groups
- Rigorous treatment algorithm for both groups

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It makes sense to:

- Measure daily at different times of the day initially for 2-4 weeks
  - See how food affects blood glucose levels
  - See how exercise affects blood glucose levels
  - See how _____ affects blood glucose levels
- Okay to back off on measurements and only target the problem readings
- Once problem readings under control
  - q3month A1C check, testing with purpose

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For most adults with type 2 diabetes using oral antidiabetes drugs (without insulin) or no diabetes drugs, the routine use of blood glucose test strips is not recommended.

What does routine mean?

Canadian Optimal Medication Prescribing & Utilization Service. Optimal therapy report: systematic review of use of blood glucose test strips for the management of diabetes mellitus. Canadian Agency for Drugs and Technologies in Health 2009:3(2)

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Clinical Notes:
Given a lack of evidence, the following reflects CERC's clinical opinion and accepted standards of practice:

- **Patients treated with insulin secretagogues may benefit from routine use of SMBG to reduce the risk of hypoglycemia.**
- Other populations that may benefit from SMBG include those:
  - at increased risk of hypoglycemia (e.g., due to a history of severe hypoglycemia or hypoglycemia unawareness, instances of inadequate caloric intake, unforeseen or unplanned physical activity)
  - experiencing acute illness
  - undergoing changes in pharmacotherapy or significant changes in routine
  - with poorly controlled or unstable blood glucose levels
  - who are pregnant or planning a pregnancy.

Canadian Optimal Medication Prescribing & Utilization Service. Optimal therapy report: systematic review of use of blood glucose test strips for the management of diabetes mellitus. Canadian Agency for Drugs and Technologies in Health 2009:3(2)

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Summary of Findings for A1C From Studies Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

Analysis	Number of Studies (Sample Size)	WMD (95% CI) in A1C (%)	I^2 (%)	Quality of Evidence
Evidence from RCTs				
Overall estimate of effect	7 RCTs[4,73-78] (n = 2,270)	-0.25% (-0.36, -0.15)	0	Moderate
Good quality RCTs only	3 RCTs[73,75,77] (n = 1,247)	-0.21% (-0.34, -0.08)	0	High
RCTs in which all subjects used OADs	3 RCTs[73,74,77] (n = 1,628)*	-0.24% (-0.36, -0.11)	0	Moderate
RCT in which all patients use sulfonylureas	1 RCT[73] (n = 610)	-0.24% (-0.43, -0.05)	N/A	High
More intensive education	3 RCT[75-77] (n = 710)	-0.28% (-0.47, -0.08)	17.8	Moderate
Less intensive or unspecified education	5 RCTs[4,73,74,77,78] (n = 1,712)	-0.22% (-0.34, -0.10)	0	Moderate

Canadian Optimal Medication Prescribing & Utilization Service. Optimal therapy report: systematic review of use of blood glucose test strips for the management of diabetes mellitus. Canadian Agency for Drugs and Technologies in Health 2009:3(2)

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- A1C difference of -0.25%
  - (95% CI : -0.36, -0.15)
  - Statistically significant
  - Is this clinically significant?

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How Has My Practice Changed?

- Old practice (based on 2003 guidelines)
  - Measure daily at different times of day OR
  - Measure q2-3 days
    - Measure pre and 2hr post meals
- Current practice
  - Individualizing
  - Okay to not measure
    - challenging

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Hypoglycemia

- When does hypoglycemia occur?
  - During first month of therapy
  - During dosage increases
  - Missed, delayed meals
  - Renal function decline

www.diabetes.ca

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Canadian Diabetes Association Briefing Document

- Group 1–not on any medications or low hypoglycemia risk medications
  - 15 strips per month
- Group 2–on medications with higher risk of hypoglycemia
  - 30 strips per month
- Special authority
  - For special clinical circumstances

http://www.diabetes.ca/documents/for-professionals/CJD--Sept_2011--SMBG.pdf

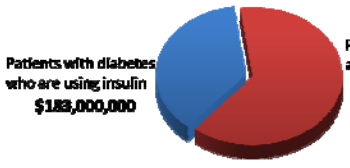
Table 1. Pharmacotherapy: risk of hypoglycemia

Pharmacotherapy with a lower risk of hypoglycemia (Group 1)	Pharmacotherapy with a higher risk of hypoglycemia (Group 2)
• Metformin • Acarbose • Pioglitazone, rosiglitazone • Saxagliptin, sitagliptin • Liraglutide, exenatide	• Gliclazide, glimepiride • Glyburide • Nateglinide, repaglinide • Chlorpropamide, tolbutamide

Cost of Self-Monitoring of Blood Glucose in: Canada

Total Spending in Canadian Publicly and Privately Funded Drug Plans on Blood Glucose Test Strips Exceeded:

$500 Million* in 2010



The following results were prepared by analysts from Brogan Inc., a unit of IMS, PharmaStat®, Public and Private Drug Plans Databases, 2000-2011, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

A1c can now be used to diagnose diabetes

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

http://www.diabetes.ca/documents/for-professionals/CJD--July_2011--FULL.pdf

Table 1. Factors that can affect A1C (adapted from 11)

Factor	Increased A1C	Decreased A1C	Variable change in A1C
Erythropoiesis	Iron deficiency ← B12 deficiency Decreased erythropoiesis ←	Use of erythropoietin, iron or B12 Reticulocytosis ↖ Chronic liver disease	
Altered hemoglobin			Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants
Glycation	Alcoholism Chronic renal failure ← Decreased erythrocyte pH	Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH	
Erythrocyte destruction	**Increased erythrocyte lifespan:** Splenectomy	**Decreased erythrocyte lifespan:** Chronic renal failure ← Hemoglobinopathies Splenomegaly Rheumatoid arthritis Antiretrovirals Ribavirin Dapsone	
Assays	Hyperbilirubinemia Carbamylated hemoglobin ← Alcoholism Large doses of aspirin Chronic opiate use	Hypertriglyceridemia	Hemoglobinopathies

http://www.diabetes.ca/documents/for-professionals/CJD--July_2011--FULL.pdf

Table 1. Glycemia-Related Issues in Chronic Kidney Disease

Glucose metabolism and pharmacokinetics
- Increased risk of hyperglycemia
  - Increased production and use of glucose[25]
  - Impaired glucose disposal[25]
  - Increased insulin resistance[26]
- Increased risk of hypoglycemia
  - Impaired renal gluconeogenesis[25,27]
  - Decreased clearance of insulin[28-30]
  - Decreased clearance of oral hypoglycemic agents

Monitoring of glycemic control
- Falsely increased hemoglobin A_{1c}
  - Carbamylation of erythrocytes interfering with hemoglobin A_{1c} assay[31]
- Falsely decreased hemoglobin A_{1c}
  - Increased erythrocyte turnover (reduced life span)[32]
  - Use of erythropoietin[33]

American Journal of Kidney Diseases, Vol 50, No 5 (November), 2007: pp 865-879

Target A1c

- Shift in thinking based on available evidence
- Individualize targets

Case

- 57 y.o. male with Type 2 diabetes
- New diagnosis
- No other comorbidities
- A1c = 8.7%
- ACR = normal
- BP = 129/79 mm Hg
- LDL = 2.5 mmol/L
- Chol/HDL = 3.9
- No medications

Target A1c

- What should it be?

  ≤ 6.0%
  ≤ 6.5%
  ≤ 7%
  7-7.9%

- Why the debate?

Case

	2005	2012
A1C	≤ 7% ≤ 6%	

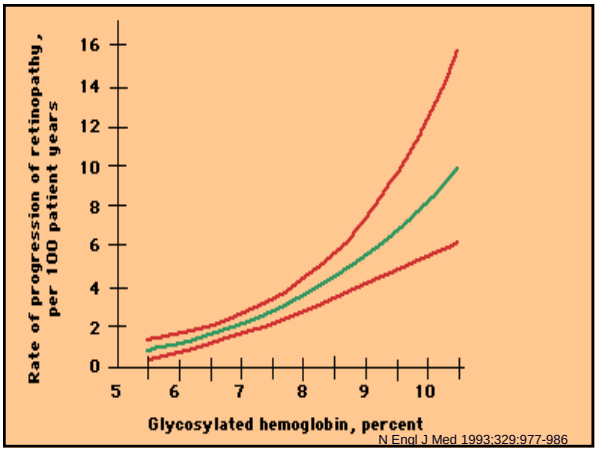
What is the target A1c for a person with diabetes?

- Target A1c =
- 2003 guidelines:
  - If safely achievable then aim for ≤ 6%
  - Not mentioned in latest 2008 guidelines
- A1c in a person without diabetes is =

What is the target A1c for a person with diabetes?

- Note:Aim for ≤ 6% if safely achievable is no longer mentioned, instead
- ≤ 6.5% may be considered
  - To reduce nephropathy
  - Balance this against hypoglycemia, mortality in high CVD risk people

2008 CDA guidelines diabetes.ca



N Engl J Med 1993;329:977-986

UKPDS 33

- Intensive blood glucose control (Type 2)
  - Reduced microvascular complications
  - Did not reduce macrovascular complications
- A1c in intensive group was 7%
- A1c in control group was 7.9%

Lancet 1998;352:837-53

ACCORD Study

- Does intensive diabetes therapy (target A1c <6%) reduce cardiovascular complications?
  - MI, stroke, death from cardiovascular causes
- 65% of deaths are due to cardiovascular causes
- Type 2 diabetes increases heart disease risk 2-4 fold

N Engl J Med 2008;358:2545-59

ACCORD Study

- 10,251 participants
- Intensive A1c target:<6%
- Standard A1c target:7-7.9%
- US and Canada
  - 77 sites
- Age 40-82
- Type 2 diabetes + 2 or more CV risk factors or heart disease
- On average had diabetes for 10 years

ACCORD Study-Stopped

- 18 months early
- Increased risk of death
  - 257/5128 died in intensive arm
  - 203/5123 died in standard arm
  - HR, 1.22; 95% CI, 1.01-1.46; p=0.04

Advance Study

- What is the effect of intensive glucose control on vascular events (both microvascular and macrovascular)?
- A target A1c of 6.5% reduced nephropathy (microvascular) but not macrovascular complications

N Engl J Med 2008;358:2560-2572

Advance Study

- 11, 140 patients
- Intensive A1c target:≤6.5%
- Standard A1c target:dependent on country
- 20 countries
  - Asia, Australia, Europe and North America
- Age ≥ 55
- Type 2 diabetes + micro or macrovascular disease or at least one risk factor for vascular disease
- On average had diabetes for 8 years

Case

- 57 y.o. male with Type 2 diabetes
- New diagnosis
- No other comorbidities
- A1c = 8.7%
- ACR = normal
- BP = 129/79 mm Hg
- LDL = 2.5 mmol/L
- Chol/HDL = 3.9
- No medications

Case

	2005	2012
A1C	≤ 7% ≤ 6%	≤ 7%

What if the patient had limited life expectancy?

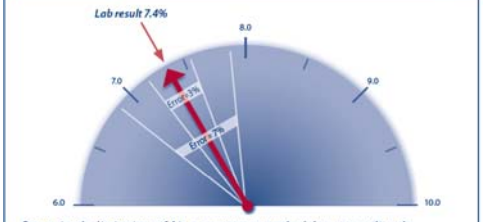
TABLE G-1 Determination of Target HbA_1c Level (1) (2)

1. Determine glycemic control target range using risk stratification criteria
2. Adjust the target according to patient factors
3. Set the target range after discussion with the patient
4. Consider risk of hypoglycemia when recommending a target goal

Major Comorbidity (d) or Physiologic Age	Microvascular Complications		
	Absent or Mild (a)	Moderate (b)	Advanced (c)
Absent >10 years of life expectancy	<7%	<8%	8-9%*
Present (e) 5 to 10 years of life expectancy	<8%	<8%	8-9%*
Marked (f) <5 years of life expectancy	8-9%*	8-9%*	8-9%*

http://www.healthquality.va.gov/diabetes/Final_DM_Pocket_Card_Aug2010.pdf

TABLE G-2 Limitations of A1c Measurement Methodology

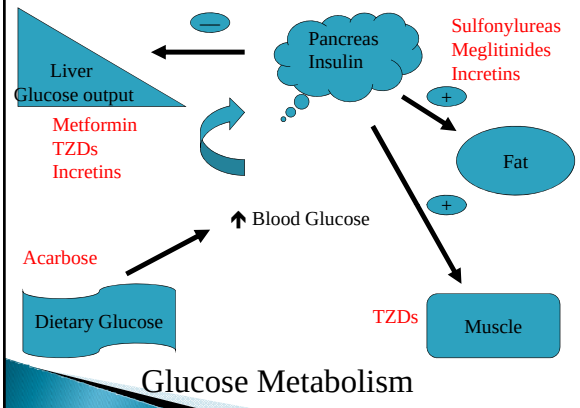


Recognize the limitations of A1c measurement methodology reconciling the diff rences between A1c readings and SMBG on a case-by-case basis. A value of A1c,reported by the lab as 7.4% could be anything between 6.9 and 7.9. The assay has an overall error acceptable for clinical use of 7%. If the overall error of the LAB assay is 3% the range is narrower (7.2 to 7.6)

http://www.healthquality.va.gov/diabetes/Final_DM_Pocket_Card_Aug2010.pdf

Medications

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



Glucose Metabolism

Debate

- Metformin's contraindications should be contraindicated
  - CMAJ 2005;173(5):502-504
- Metformin's contraindications:needed for now
  - CMAJ 2005;173(5):505-507

Reviews/Commentaries/ADA Statements

REVIEW

Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency

Kasia J. Lipska, MD[1]
Clifford J. Bailey, PHD, FRCP[2]
Silvio E. Inzucchi, MD[3]

A common clinical conundrum faces all U.S. practitioners treating patients with type 2 diabetes. Today's U.S. Food and Drug Administration prescribing guidelines for metformin contraindicate its use in men and women with despite multiple trials of intensive glucose control using a variety of glucose-lowering strategies, there is a paucity of data to support specific advantages with other agents on cardiovascular outcomes (5–7).

hepatic gluconeogenesis without raising insulin levels, it rarely leads to significant hypoglycemia when used as a monotherapy (8,11). As a result, metformin is widely considered an ideal first-line agent for the treatment of type 2 diabetes, as recommended by several clinical guidelines (12–14).

In addition to such benefits, metformin reduces the risk of developing diabetes in individuals at high risk for the disease (15) and has been considered as a

DIABETES CARE, VOLUME 34, JUNE 2011

The experience with phenformin resulted in cautious use of metformin in Europe. In the 1980s, the creatinine cut points for contraindication to metformin were considered to be appropriate at 1.4 mg/dL in women and 1.5 mg/dL in men. This was based on the calculated ability to remove 3 g of metformin (an amount slightly beyond the maximum daily U.S. dose) at steady-state levels within 24–48 h. In fact, the ability to comfortably remove the drug extends up to creatinine levels of 1.8–2.0 mg/dL, but the cut points chosen were intentionally set lower to ensure that those patients who may be lost to follow-up and whose creatinine levels increase over time would not be at risk for appreciable drug accumulation.

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, VOLUME 34, JUNE 2011

Benefits of Metformin

- Reduced microvascular complications
- Reduced macrovascular complications
- Reduced death
- Weight loss (neutral)
- Insulin sensitizer
- Cancer prevention?

Sulfonylureas in CKD

- Conflicting information in the literature
- Individualize to your patient
  - Some patients on glyburide will have very high sugars
  - Progressive nature of diabetes vs drug effect
- Outcome studies available
- Hypoglycemia, weight gain

Repaglinide (Gluconorm®)

- ≥ 40 ml/min
  - no dosage adjustment
- 20-39 ml/min
  - start with 0.5mg and adjust based on response
- < 20ml/min
  - no data available

Nateglinide (Starlix®)

- No dosage adjustment required[1]
- Avoid in CKD stage 5[2]

[1]clinicalpharmacology.com
[2]kdoqi guidelines 2007

Repaglinide and Nateglinide

- Useful in people with sulfa allergies and those intolerant to sulfonylureas
- Adverse effects
  - Hypoglycemia
  - Weight gain
- No outcome studies

Acarbose (Glucobay®)

- ≥25ml/min
  - No dosage adjustment needed
- < 25ml/min
  - Not studied extensively, not recommended
    - Peak levels are 5-6X higher than in people with eGFR>25ml/min
- 2% of dose is systemically absorbed
- Metabolized within the GI tract, some metabolites are absorbed and one has been shown to have hypoglycemic activity

Hypoglycemia Management (acarbose + hypoglycemic agent)

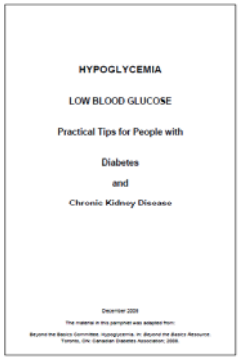
- Treating hypoglycemia
  - do not use:
    - table sugar = sucrose = disaccharide
  - use:
    - 15 g glucose tablets
    - 1 cup milk
    - 1 tablespoon honey

Alpha-Glucosidase Inhibitors

- Acarbose (Glucobay®)
  - reversibly inhibits a variety of enzymes in the small intestine

Complex polysaccharides
Sucrose
→ (Enzymes) → Monosaccharides
↑ Acarbose inhibits

- slows absorption of complex carbohydrates
- lowers post-prandial bG



HYPOGLYCEMIA

LOW BLOOD GLUCOSE

Practical Tips for People with

Diabetes

and

Chronic Kidney Disease

http://www.diabetes.ca/files/for-professionals/hypoglycemia-tool-kidney-disease.pdf

Rosiglitazone (Avandia®)

- No dosage adjustment

Pioglitazone (Actos®)

- No dosage adjustment

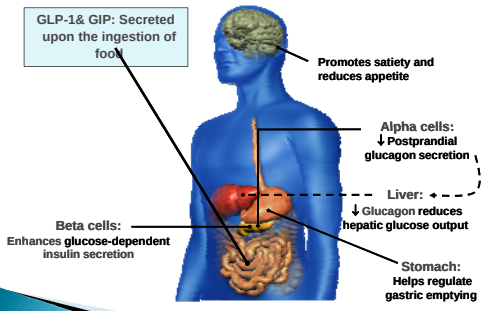
Rosiglitazone Restrictions November 2010

- Applies to Avandia, Avandamet, Avandaryl
- Be aware of the benefits vs risks
- Patients must read the consumer information on rosiglitazone
- Sign informed consent
- Heart problems
  - Heart failure, angina, MI, fluid retention (with or without rapid weight gain)

Incretin Agents

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
- Linagliptin (Trajenta®)
- Liraglutide (Victoza®)
- Exenatide (Byetta®)

Mechanism of Action



Data from Flint A, et al. *J Clin Invest.* [illegible];101:515-520; Data from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia.* [illegible]; Data from Drucker DJ. *Diabetes.* 1998;47:159-169

Sitagliptin (Januvia®) Saxagliptin (Onglyza®) Linagliptin (Trajenta®)

- Oral antihyperglycemic agents
- Weight neutral
- No hypoglycemia (rare)

Sitagliptin-Dose

- 100mg po daily with or without food
- 50mg po daily
  - eGFR 30-50ml/min
- 25mg po daily
  - eGFR <30 ml/min
- 79% excreted unchanged in the urine

Saxagliptin (Onglyza ®) - Dosing

- eGFR > 50ml/min
  - 5mg po daily
- eGFR ≤ 50ml/min
  - 2.5mg po daily

Linagliptin (Trajenta®) - Dosing

- No dosing adjustment

Liraglutide (Victoza®)

- GLP-1 receptor agonist
  - Injectable-subcutaneously
  - Weight loss
  - No hypoglycemia (rare)
  - Store in fridge
  - When using then can keep at room temp x 1 month
  - Start with 0.6mg daily x 1 week to reduce GI symptoms then increase to 1.2mg sc daily
    - Can increase up to 1.8mg sc daily

Liraglutide - Renal Dosing

- Mild renal insufficiency
  - CrCL 50-80mL/min
  - No dose adjustment
- Moderate renal insufficiency
  - CrCL 30-50 mL/min
  - Limited experience
  - Product monograph:do not use
  - Clinical Pharmacology 2000:appears no dosage adjustment needed
- Severe renal insufficiency
  - CrCL <30 mL/min
  - Product monograph:do not use
  - Clinical Pharmacology 2000:appears no dosage adjustment needed

Exenatide (Byetta®)

- Incretin mimetic
- Similar to human hormone, GLP-1
  - Glucagon-like polypeptide-1

Dosage

- 5 mcg subcutaneously twice daily within 60 minutes of meal (before 2 main meals of the day, at least 6hrs apart)
- Do not administer after a meal
- After one month, can increase to 10 mcg twice daily
- May need to reduce dose of sulfonylurea by 50%

Do not use

- Creatinine clearance < 30 ml/min
- Severe GI disease
  - gastroparesis

Adverse Effects

- Nausea
  - 44% exenatide vs 18% placebo
  - Withdrawal rate 7% vs 3% (placebo)
  - Tends to resolve as therapy is continued
  - Dose dependent
- Pancreatitis
  - Incidence
  - Delayed approval in Canada?
- Anti-exenatide antibody titers
  - Clinical significance unknown

Drug Interactions

- Slows gastric emptying
  - Take medications one hour before injecting exenatide
  - If medication is taken with food, take with snack

Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)

John B Buse, Julio Rosenstock, Gregor Sesti, Wolfgang E Schmidt, Edward Montanya, Joseph H Brett, Marcin Zychma, Lawrence Blonde, for the LEAD-6 Study Group*

Summary

Background Unlike most antihyperglycaemic drugs, glucagon-like peptide-1 (GLP-1) receptor agonists have a glucose-dependent action and promote weight loss. We compared the efficacy and safety of liraglutide, a human GLP-1 analogue, with exenatide, an exendin-based GLP-1 receptor agonist.

Methods Adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulphonylurea, or both, were stratified by previous oral antidiabetic therapy and randomly assigned to receive additional liraglutide 1·8 mg once a day (n=233) or exenatide 10 μg twice a day (n=231) in a 26-week open-label, parallel-group, multinational (15 countries) study. The primary outcome was change in glycosylated haemoglobin (HbA_1). Efficacy analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00513682.

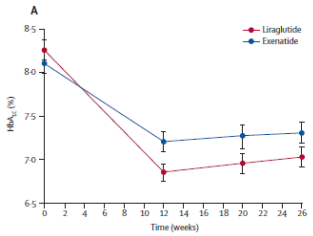
Findings Mean baseline HbA_1 for the study population was 8·2%. Liraglutide reduced mean HbA_1 significantly more than did exenatide [-1·12% [SE 0·08] vs -0·79% [0·08]; estimated treatment difference -0·33; 95% CI -0·47 to -0·18; p<0·0001] and more patients achieved a HbA_1 value of less than 7% (54% vs 43%, respectively; odds ratio 2·02; 95% CI 1·31 to 3·11; p=0·0015). Liraglutide reduced mean fasting plasma glucose more than did exenatide [-1·45 mmol/L [SE 0·20] vs -0·40 mmol/L [0·20]; estimated treatment difference -1·01 mmol/L; 95% CI -1·57 to -0·45; p<0·0001] but postprandial glucose control was less effective after breakfast and dinner. Both drugs promoted similar weight losses (liraglutide -3·24 kg vs exenatide -2·87 kg). Both drugs were well tolerated, but nausea was less persistent (estimated treatment rate ratio 0·448, p<0·0001) and minor hypoglycaemia less frequent with liraglutide than with exenatide (1·93 vs 2·60 events per patient per year; rate ratio 0·55; 95% CI 0·34 to 0·88; p=0·0131; 25·5% vs 33·6% had minor hypoglycaemia). Two patients taking both exenatide and a sulphonylurea had a major hypoglycaemic episode.

Interpretation Liraglutide once a day provided significantly greater improvements in glycaemic control than did exenatide twice a day, and was generally better tolerated. The results suggest that liraglutide might be a treatment option for type 2 diabetes, especially when weight loss and risk of hypoglycaemia are major considerations.

Funding Novo Nordisk A/S.

	Liraglutide 1·8 mg once a day (n=233)	Exenatide 10 μg twice a day (n=231)
Men	114 (49%)	127 (55%)
Age (years)	56·3 (9·8)	57·1 (10·8)
Race		
White	216 (93%)	210 (91%)
Body-mass index (kg/m²)	32·9 (5·5)	32·9 (5·7)
Duration of diabetes (years)	8·5 (6·2)	7·9 (5·9)
Fasting C-peptide (nmol/L)	1·25 (0·56)	1·26 (0·58)
Prestudy antidiabetic treatment		
Metformin and SU combination	145 (62%)	147 (64%)
SU alone	24 (10%)	21 (9%)
Metformin alone	64 (27%)	63 (27%)
HbA_{1c}	8·2% (1·0%)	8·1% (1·0%)

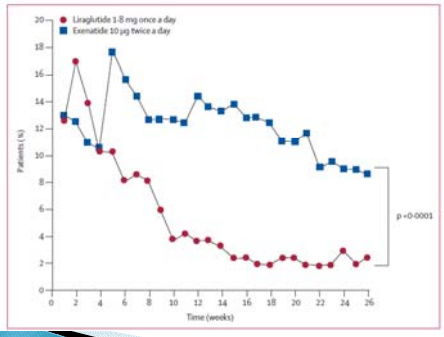
Primary Outcome: Change in A1c



-1.12% vs -0.79%
-0.33%;95% CI -0.47 to -0.18;
p<0.0001

Is this clinically significant?

Proportion of patients with an episode of nausea



GLP-mimetics	DPP-IV inhibitors
Nausea, vomiting, diarrhoea, jittery, dizziness, headache, dyspepsia	Upper respiratory tract infection, nasopharyngitis, headache
Hypoglycaemia associated with coexisting sulphonylurea therapy	

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide.

Clinical Medicine 2010 10;5:491-5

What about outcomes?

- **TECOS** (Trial Evaluating Cardiovascular Outcomes With Sitagliptin)
- **EXAMINE** (EXamination of CArdiovascular OutcoMes: AlogliptIN vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome)..
- **SAVOR-TIMI 33** (Saxagliptin in Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus)..
- **EXSCEL** (Exenatide Study of Cardiovascular Event Lowering
- **LEADER** ((Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results).

Clinicaltrials.gov

Incretins in Clinical Trials

Inhibitor	Company
ABT-279, ABT-341	Abbott
ALS 2-0426	Alantos/Servier
BI 1356	Boehringer Ingelheim
Denagliptin	GSK
GRC8200	Glenmark
PSN-9301	OSI
PHX 1149	Phenomix
Saxagliptin	BMS/AstraXeneca
SSR-162369	Sanofi-Aventis
TS-021	Taisho
Alogliptin	Takeda
TA-6666	Tanabe

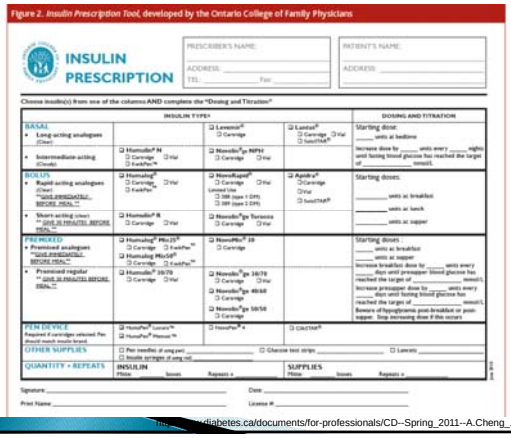
Table 1. Currently available insulins in Canada

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

http://www.diabetes.ca/documents/for-professionals/CD--Spring_2011--A.Cheng_.pdf

GPAC Guidelines

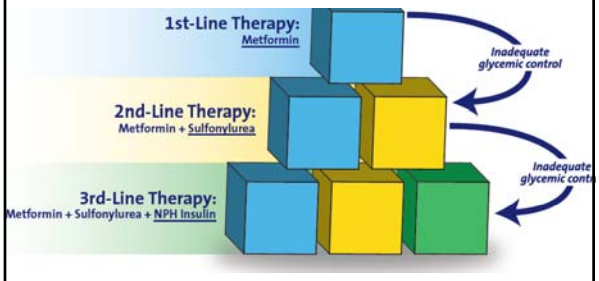
- http://www.bcguidelines.ca/pdf/diabetes_appendix_d.pdf
- List of all available insulins and cost and Pharmacare coverage



http://www.diabetes.ca/documents/for-professionals/CD--Spring_2011--A.Cheng_.pdf

Several Options

- Oral medications + basal insulin
- Combination of basal + bolus insulin
  - +/- oral medications
- Premixed insulin
  - +/- oral medications



If insulin is not an option then sitagliptin can be considered as 3rd line

www.cadth.ca/t2dm

Why Sulfonylureas as 2nd Line?

- All drugs reviewed achieved statistically significant A1c reductions
  - 0.6–1.0%
- Hypoglycemia
  - Severe hypoglycemia:rare
- Most cost effective
- Long term safety data available

http://www.healthguidebc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

Why Insulin as 3rd Line?

- All drugs reviewed achieved statistically significant A1c reductions except for meglitinides and acarbose
  - 0.9–1.2%
- Hypoglycemia was more common
  - Severe hypoglycemia:rare
- Most cost-effective 3rd line drug
- Long term safety known

http://www.healthguidebc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

What about incretins?

- If NPH insulin is not an option then sitagliptin is available via special authority
- Saxagliptin, Linagliptin, Liraglutide and Exenatide are not benefits at this time

http://www.healthguidebc.ca/pharmacare/pdf/infosheet-on-diabetes-therapy.pdf

Benefits

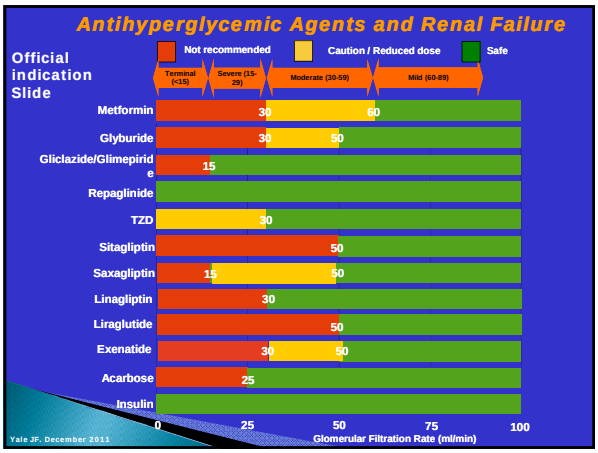
Agent	A1c reduction (%)
Sulfonylureas	1-2
Metformin	1-2
Acarbose	0.5-0.8
Meglitinides*	1-1.5
TZDs	0.5-1.4
Incretins	0.5-1.0
Insulin	Regimen Dependent

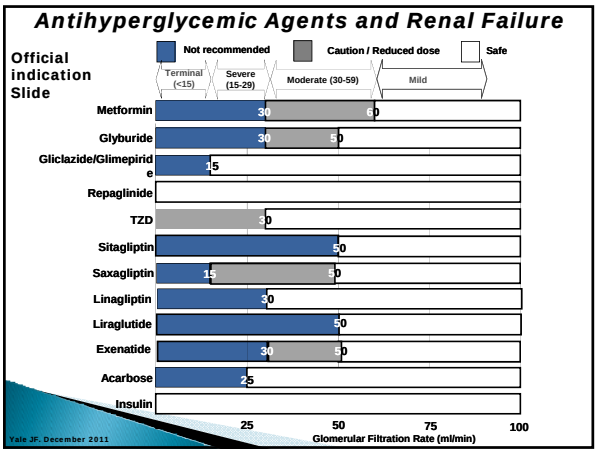
*Repaglinide more effective than nateglinide

Diabetologia 2008;51:8-11
Can Fam Physician 2010;56:639-48

Benefits

Agent	Outcome Studies
Sulfonylureas	Yes
Metformin	Yes
Acarbose	No
Meglitinides	No
TZDs	Yes
Incretins	No
Insulin	Yes


Antihyperglycemic Agents and Renal Failure
Official indication Slide
Not recommended
Caution / Reduced dose
Safe
Terminal (<15)
Severe (15-29)
Moderate (30-59)
Mild (60-89)
Metformin 30 60
Glyburide 30 50
Gliclazide/Glimepiride 15
Repaglinide
TZD 30
Sitagliptin 50
Saxagliptin 15 50
Linagliptin 30
Liraglutide 50
Exenatide 30 50
Acarbose 25
Insulin
0 25 50 75 100
Glomerular Filtration Rate (ml/min)
Yale JF. December 2011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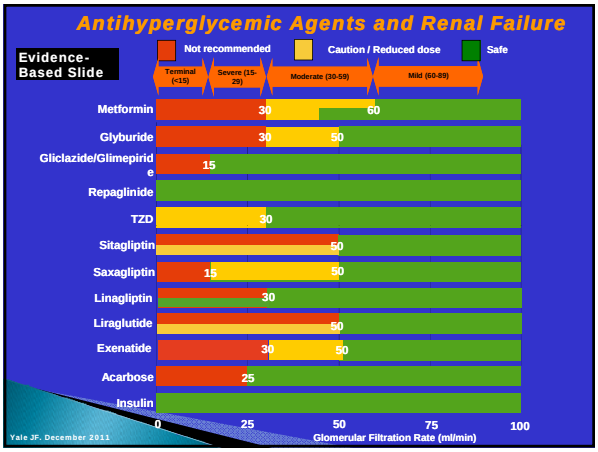
Linagliptin
Liraglutide
Exenatide
Acarbose
Insulin
25 50 75 100
Glomerular Filtration Rate (ml/min)
Yale JF. December 2011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Yale JF. December 2011