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Antihyperglycemic Agents and PD Patients: What We Need to Remember

Learning Objectives

1. Learn about antihyperglycemic agents that are currently available for PD patients.
2. Learn about the diabetic management plan for new PD patients.

Outline

- Pathophysiology
- Goals of Therapy
- Treatment Targets
- Pharmaceutical Options & Mechanism of Newer Agents
- PD Patients and Diabetes
- PD Effect on Glucose Test Strips
- Pharmaceutical Considerations in PD Patients
- Insulin Overview
- Case: Diabetes Monitoring and Management in PD Patients

Pathophysiology

Type 1 diabetes (5-10%)

- Insulin deficiency due to autoimmune destruction of pancreatic beta cells

Type 2 diabetes (90%)

- Development of insulin resistance
- Reduction in pancreatic secretion of insulin
- Metabolic syndrome
 - Obesity, hypertension, dyslipidemia

Goals of Therapy

- Establish glycemic control and glycemic targets
- Eliminate clinical symptoms
- Prevent macrovascular and microvascular complications
- Prevent ADRs
- Achieve optimal management of associated risk factors

Diabetes Monitoring and General Targets

- Clinical symptoms
 - Polyuria, polydipsia, weight loss
- Blood glucose targets for most patients:
 - Fasting: **4 - 7 mmol/L**
 - Postprandial: **5 - 10 mmol/L**
 - **5-8 mmol/L if A1c not at target**
 - Stronger predictor of CVS risk and all-cause mortality
- A1C target for *most* patients: **≤7.0%**

Can J Diabetes 2013;37(suppl 1):S1-S212.

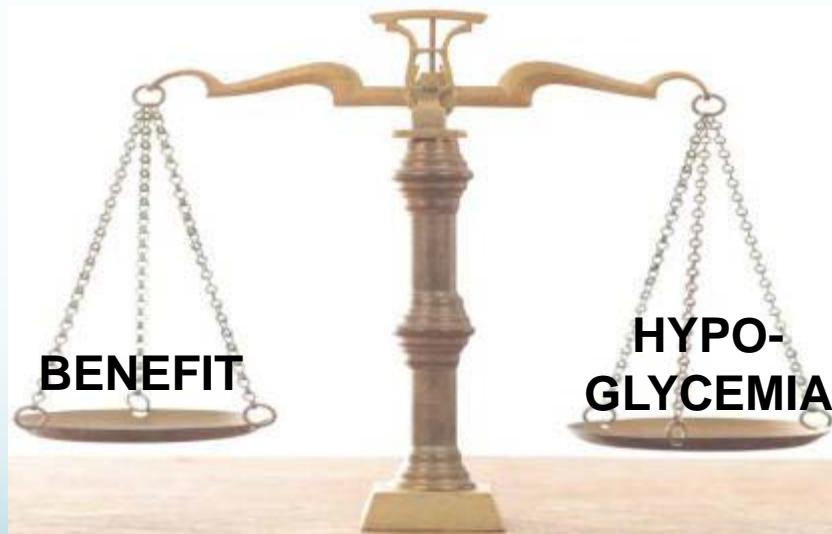
Hanefeld M et al. Diabetologia 1996;39:1577-83.

Ohkubo Y et al. Diabetes Res Clin Pract 1995;28;103-17.

Sorkin JD et al. Diabetes Care 2005;28:2626-32.

Why lower A1C?

- Diagnosis of diabetes: **A1C \geq 6.5%**
- Lower A1C \leq 7% to reduce risk of microvascular and macrovascular complications



Landmark Trials in Diabetes

Intensive vs Standard A1C Targets

Trial	N	Population	Baseline A1C (%)	Final A1C (%)	Outcomes
ACCORD	10,251	Age 62 T2DM High CV risk	8.1	6.4 vs 7.5	<ul style="list-style-type: none"> • ↑ all-cause mortality • ↑ Severe hypoglycemia
ADVANCE	11,140	Age 66 T2DM Hx of CV disease	7.5	6.5 vs 7.3	<ul style="list-style-type: none"> • ↓ microvasc. events • ↓ ESRD • ↑ Severe hypoglycemia
VADT	1791	Age 60 T2DM 40% CAD Hx	≥7.5	6.9 vs 8.4	<ul style="list-style-type: none"> • ↓ albuminuria • NSS: CV event, death, microvasc complications • ↑ SAE

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Duckworth W et al. N Engl J Med 2009;360:129-39.

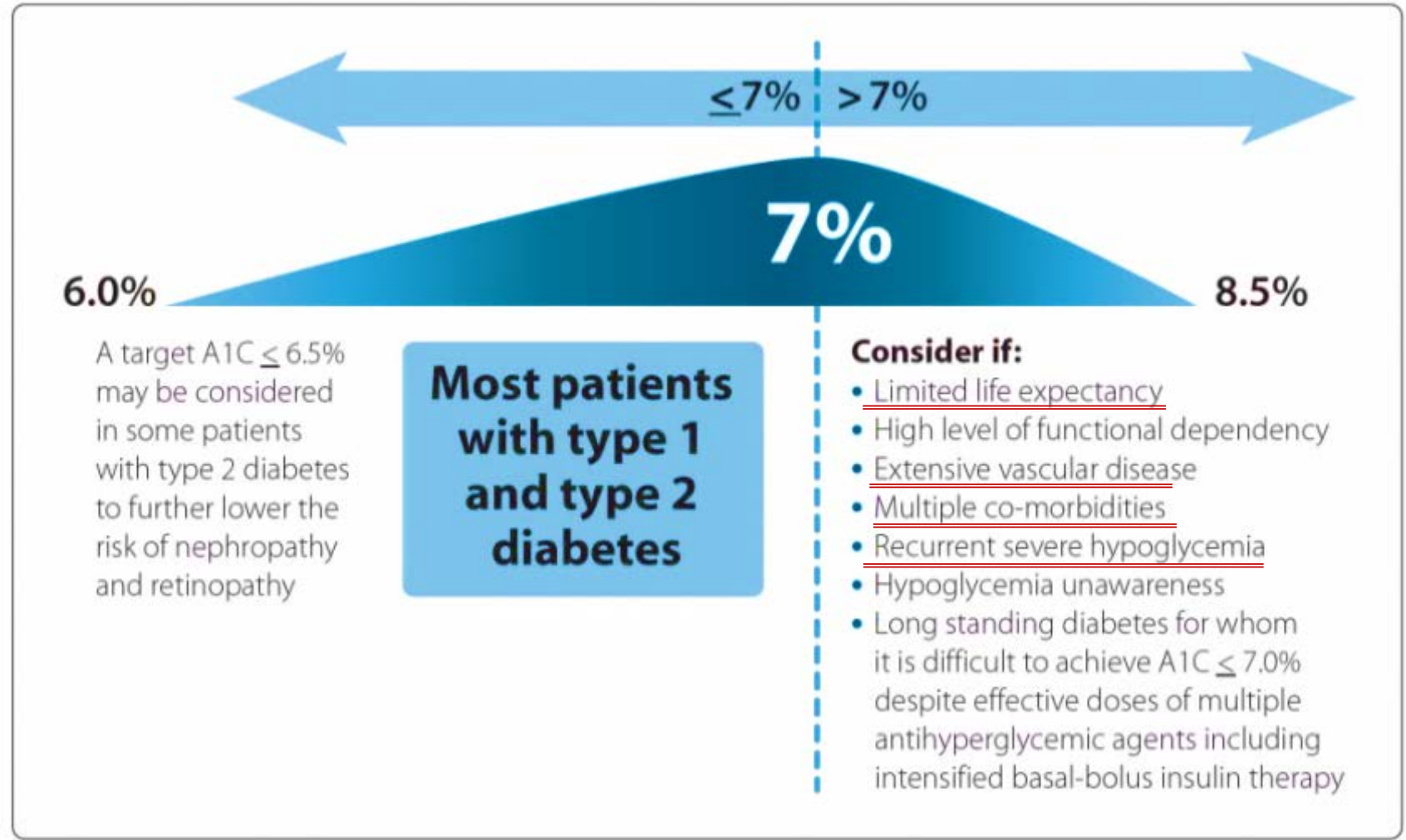
Jensen B et al. RxFiles Drug Comparison Charts - 9th Edition; 2012.

Moritz T et al. N Engl J Med 2009;361:1024-5.

The Action to Control Cardiovascular Risk in Diabetes Study Group. N Eng J Med 2008;358:2545-59.

The ADVANCE Collaborative Group. N Engl J Med 2008;358: 2560-72.

Individualizing A1C Targets



Individualizing A1C Targets

- PD patients
 - Limited life expectancy → A1C 7.5-8.5%
 - Younger / otherwise healthy patients → A1c 6.5 -7.5%
- CDA Tool for individualizing A1C Target:
<http://guidelines.diabetes.ca/BloodGlucoseLowering/A1Ctarget>

A1C and eAG

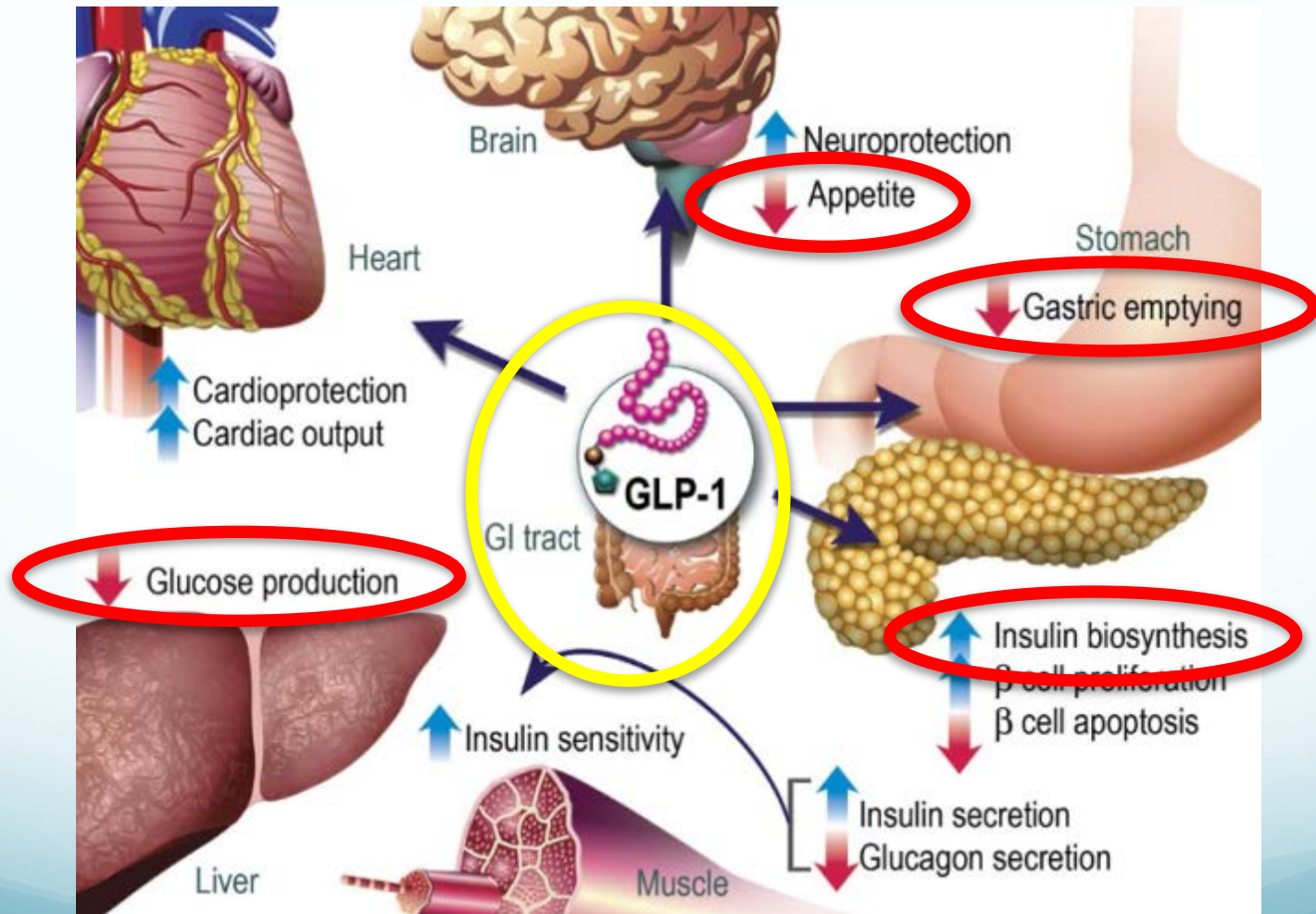
A1C (%)	Estimated Average Glucose (mmol/L)
6	7.0
6.5	7.8
7	8.6
7.5	9.4
8	10.1
8.5	10.9
9	11.8
9.5	12.6
10	13.4

Treatment Options

Drug Class	Example Drugs	A1C Reduction
Biguanide	Metformin	1-1.5%
Insulin secretagogues <ul style="list-style-type: none"> • Sulfonylureas (SU) • Meglitinides (GTN) 	SU: gliclazide, glimepiride, glyburide GTN: nateglinide, repaglinide	SU: 0.8% MG: 0.7%
α -glucosidase inhibitor	Acarbose	0.6%
DPP4-inhibitors	Sitagliptin, saxagliptin, linagliptin	0.7%
GLP-1 receptor agonists	Exenatide, liraglutide	1%
Thiazolidinediones	Pioglitazone, rosiglitazone	0.8%
Insulin	Various	0.9-1.1%

Mechanism of Newer Agents

DPP-4 Inhibitors and GLP-1 Receptor Agonists

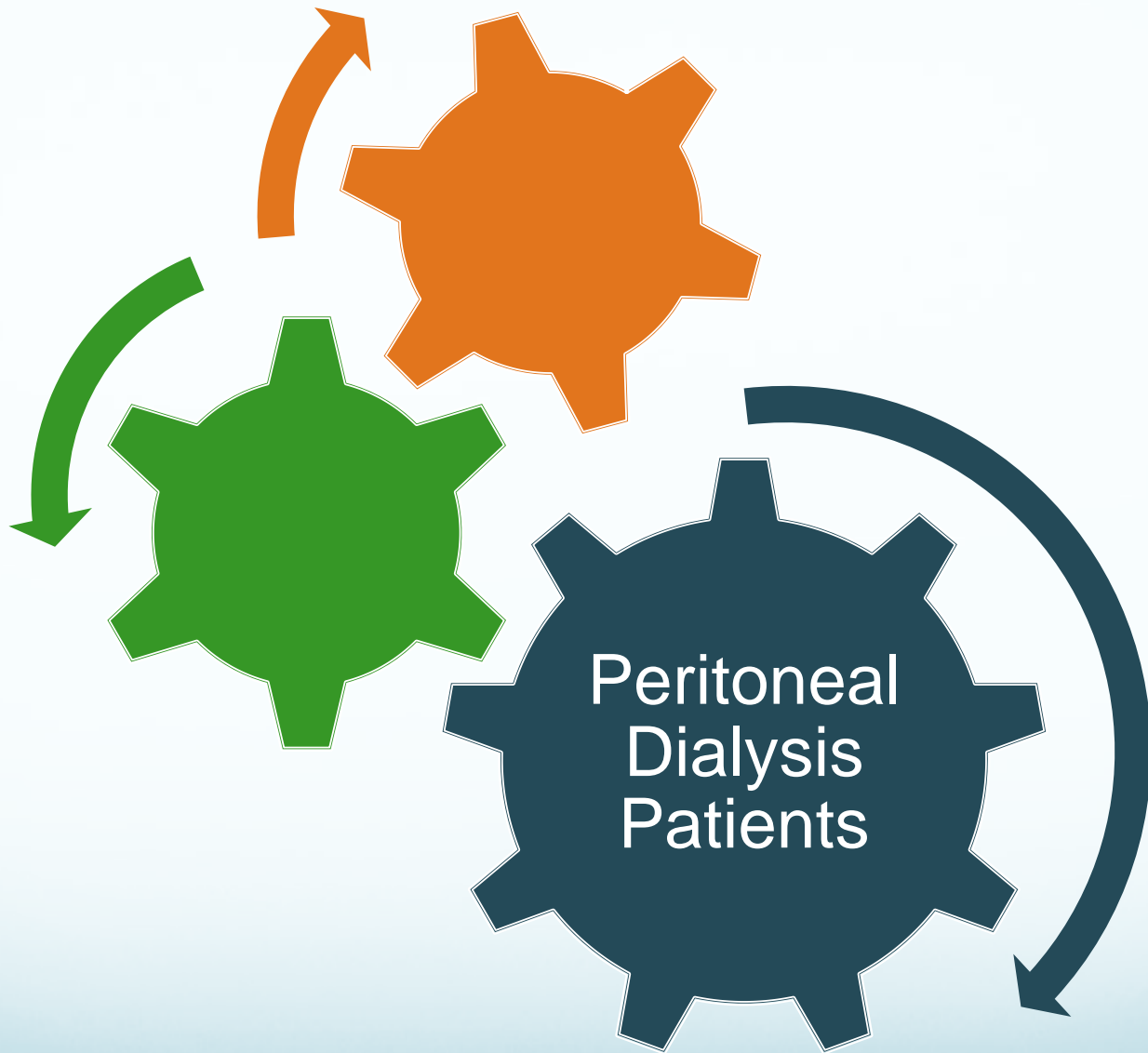


Approach to Therapy in Type 2 Diabetes Mellitus

General Population

- Initial therapy depends on A1C
- In general:





Glycemic Control

↓ Renal function...

- ↓ Renal gluconeogenesis
- ↓ Insulin clearance

Uremia/toxins...

- ↓ Insulin secretion due to metabolic acidosis, vitamin D deficiency and hyperparathyroidism
 - ↓ Peripheral tissue sensitivity to insulin
- ➔ Unpredictable blood glucose profile

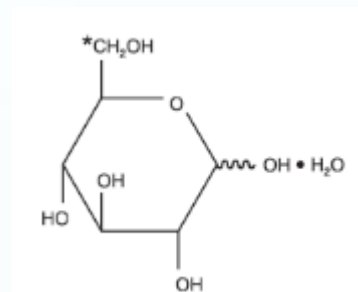
Hemoglobin A1c

- Hemoglobin A1c estimates the % of glycosolated hemoglobin
 - ↑ blood urea nitrogen leads to formation of carbamylated hemoglobin → overestimation
 - Chronic anemia/iron deficiency, shorter RBC life-span, recent blood transfusion, ESA therapy (ie. Aranesp[®], Eprex[®]) → underestimation
- ➔ Practically, still reasonable to utilize as-is

PD Solutions and Blood Glucose

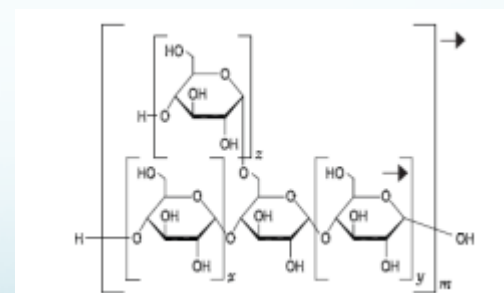
Dextrose (glucose) based dialysate solution:

- Dianeal 1.5%, 2.5%, 4.25%
- Rapidly absorbed via diffusion with greatest absorption rate at beginning of dwell



Icodextrin (glucose polymer) based dialysate solution:

- Extraneal 7.5%
- Broken down into glucose and other oligosaccharides such as **maltose**, maltotriose, and maltotetraose



Glucose Monitoring Test Strip Technologies

- GDH-PQQ (glucose dehydrogenase enzyme with coenzyme pyrroloquinolinequinone)
 - Result *falsely elevated* by ≥ 3 **mmol/L** by icodextrin metabolite, maltose
 - Inappropriate therapy adjustment, unrecognized hypoglycemia
- Other types of test strip not affected by maltose:
 - GO (glucose oxidase) e.g., *OneTouch*
 - GDH-NAD (nicotinamide-adenine dinucleotide) e.g., *Precision*
 - GDH-FAD (flavin-adenine dinucleotide) e.g., *Contour*
 - Modified GDH-PQQ

FDA Warning: Test Strips (Aug

Roche Diagnostics:

ACCU-CHEK Comfort Curve test strips, for use with:

- ACCU-CHEK Inform meters [model 2001201]
- ACCU-CHEK Complete meters [models 200 and 250]
- ACCU-CHEK Advantage meters [models 888, 831, 850, and 768]
- ACCU-CHEK Voicemate meters [model 0009221]

ACCU-CHEK Aviva test strips, for use with:

- ACCU-CHEK Aviva meters [models 525, 535, and 555]

ACCU-CHEK Compact test strips, for use with:

- ACCU-CHEK Compact meters [model GF]
- ACCU-CHEK Compact Plus meters [models GP and GT]

ACCU-CHEK Go test strips

- ACCU-CHEK Go meters [model GJ]

ACCU-CHEK Active test strips

- ACCU-CHEK Active meters [models GG and GN]

Abbot

Freest

Freest

Home Diagnostics:

TRUEtest test strips

- TRUEresult meters
- TRUE2go meters

Smiths Medical:

Abbott Diabetes Care Freestyle test strips, for use with:

- CoZmonitor blood glucose module (for use with the Deltec Cozmo Insulin Pump)

Insulet:





Abbott Diabetes Care Freestyle test strips, for use with:

- OmniPod Insulin Management System

Some companies may have changed their strip technology since 2009.

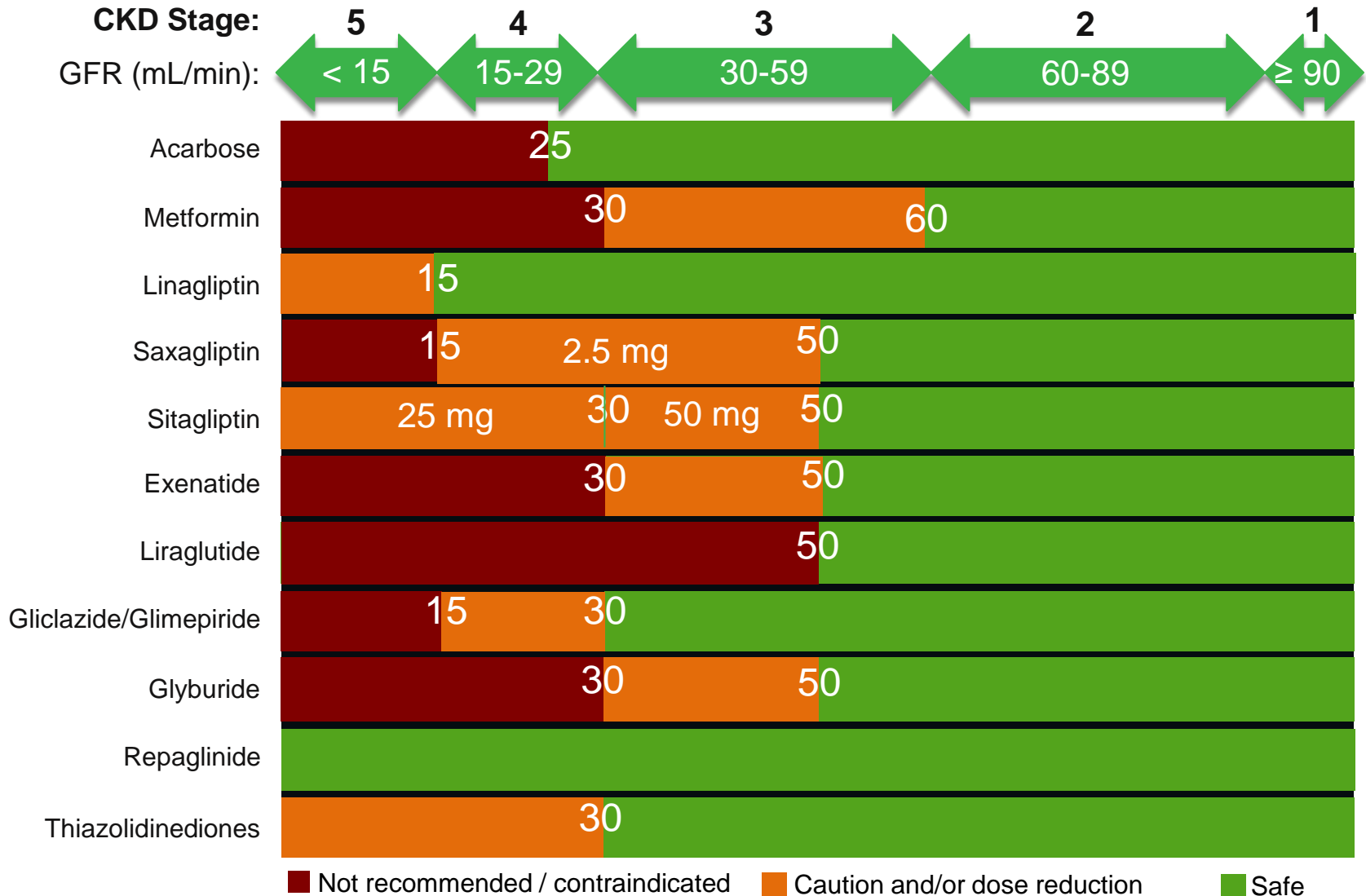
Note: this is not an exhaustive list.

Acceptable Meters & Test Strips

Acceptable Meters	Test Strips	Pictures of Test Strips
<p>OneTouch® (LifeScan)</p> <ul style="list-style-type: none"> Ultra, Ultra2, UltraMini, UltraSmart 	<p>OneTouch Ultra test strips</p>	
<p>FreeStyle® (Abbott)</p> <ul style="list-style-type: none"> Lite 	<p>FreeStyle Lite ZipWik test strips (yellow vial)</p>	
<p>Ascensia® (Bayer)</p> <ul style="list-style-type: none"> Contour 	<p>Ascensia Contour test strips</p>	
<p>Precision Xtra® (Abbott)</p> <ul style="list-style-type: none"> Precision Xtra 	<p>Precision Xtra test strips</p>	

Other acceptable meters/test strips:
 I-Test™, Nova MAX®, Oracle®, TRUEtrack™

Antihyperglycemic Agents and Renal Function



Adapted from: Product Monographs as of March 1, 2013; CDA Guidelines 2008; and Yale JF. J Am Soc Nephrol 2005; 16:S7-S10.
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Considerations for PD patients

Drug Class	Example Drugs	Considerations
Biguanide	Metformin	Lactic acidosis
Insulin secretagogues <ul style="list-style-type: none"> • Sulfonylureas (SU) • Meglitinides (GTN) 	SU: gliclazide/glimepiride, glyburide GTN: repaglinide	Risk of hypoglycemia, Clinical experiences with gliclazide in PD patients.
α -glucosidase inhibitor	Acarbose	Limited clinical experience in ESRD patients
DPP4-inhibitors	Sitagliptin, saxagliptin, linagliptin	Limited clinical experience in ESRD patients
GLP-1 receptor agonists	Exenatide, liraglutide	Limited clinical experience in ESRD patients
Thiazolidinediones	Pioglitazone, rosiglitazone	Comorbidities (ie. CHF) and risk of volume overload, \uparrow mortality

Can J Diabetes 2013;37(suppl 1):S1-S212.

Jensen B et al. RxFiles Drug Comparison Charts - 9th Edition; 2012.

KDOQI. Am J Kidney Dis. 2012;60(5):850-886.

Why Not Metformin?

- Excreted unchanged via urine; circulation time prolonged in ESRD
 - Caution if eGFR < 60ml/min
 - Contraindicated if eGFR < 30ml/min
- Metformin Associated Lactic Acidosis (MALA)
 - High anion gap metabolic acidosis
 - Incidence rare (9-47 cases per 100,000 person-years)
 - Mortality rate: 11-45%
- Risk factors: altered renal function, CHF, dehydration, hepatic and respiratory failure, concomitant medications (NSAIDs, ACEI, furosemide, antiretrovirals)

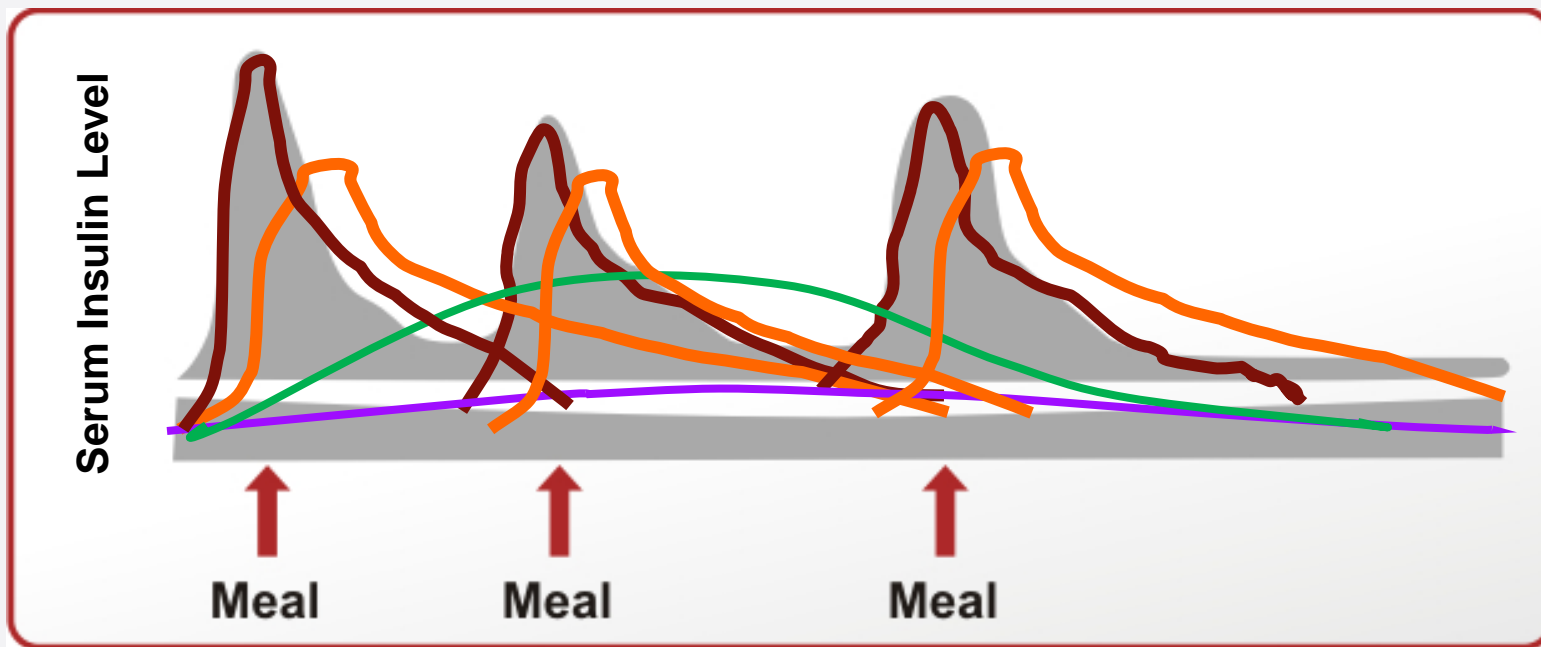
What Are We Left With?

- Gliclazide (e.g., Diamicon[®], Diamicon[®] MR, generics)
 - SU with lowest incidence of hypoglycemia
 - Note: fluconazole may increase the serum concentration of sulfonylureas → patient education, close monitoring during course of fluconazole
 - Listed as preferred SU with no dosage adjustment required for dialysis patients in *KDOQI Diabetes Guideline 2012 Update*
 - IR tab: 80mg/tab → 80-320mg PO daily (split total dose > 160mg into BID)
 - MR tab: 30mg/tab, 60mg/tab → 30-120mg PO daily (titrate up 30mg Q2weeks)
- Insulin
 - Can titrate, no dose ceiling
 - Various types and release profiles

Types of Insulin

Insulin Type (trade name)	Onset	Peak	Duration	Timing of injection*
Bolus (prandial) Insulins				
Rapid -acting insulin analogues (<i>clear</i>): <ul style="list-style-type: none"> • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra™) • Insulin lispro (Humalog®) 	10 - 15 min 10 - 15 min 10 - 15 min	1 - 1.5 h 1 - 1.5 h 1 - 2 h	3 - 5 h 3 - 5 h 3.5 - 4.75 h	May be given with 1 or more meals per day. To be given 0 – 15 minutes before meals.
Short -acting insulins (<i>clear</i>): <ul style="list-style-type: none"> • Insulin regular (Humulin®-R) • Insulin regular (Novolin®geToronto) 	30 min	2 - 3 h	6.5 h	May be given with 1 or more meals per day. Should be injected 30 – 45 minutes before the start of the meal.
Basal Insulins				
Intermediate -acting insulins (<i>cloudy</i>): <ul style="list-style-type: none"> • Insulin NPH (Humulin®-N) • Insulin NPH (Novolin®ge NPH) 	1 - 3 h	5 - 8 h	Up to 18 h	Not given at any time specific to meals.
Long -acting basal insulin analogues (<i>clear</i>) <ul style="list-style-type: none"> • Insulin detemir (Levemir®) • Insulin glargine (Lantus®) 	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16 - 24 h)	Not given at any time specific to meals

*adapted from CDA insulin pen start checklist



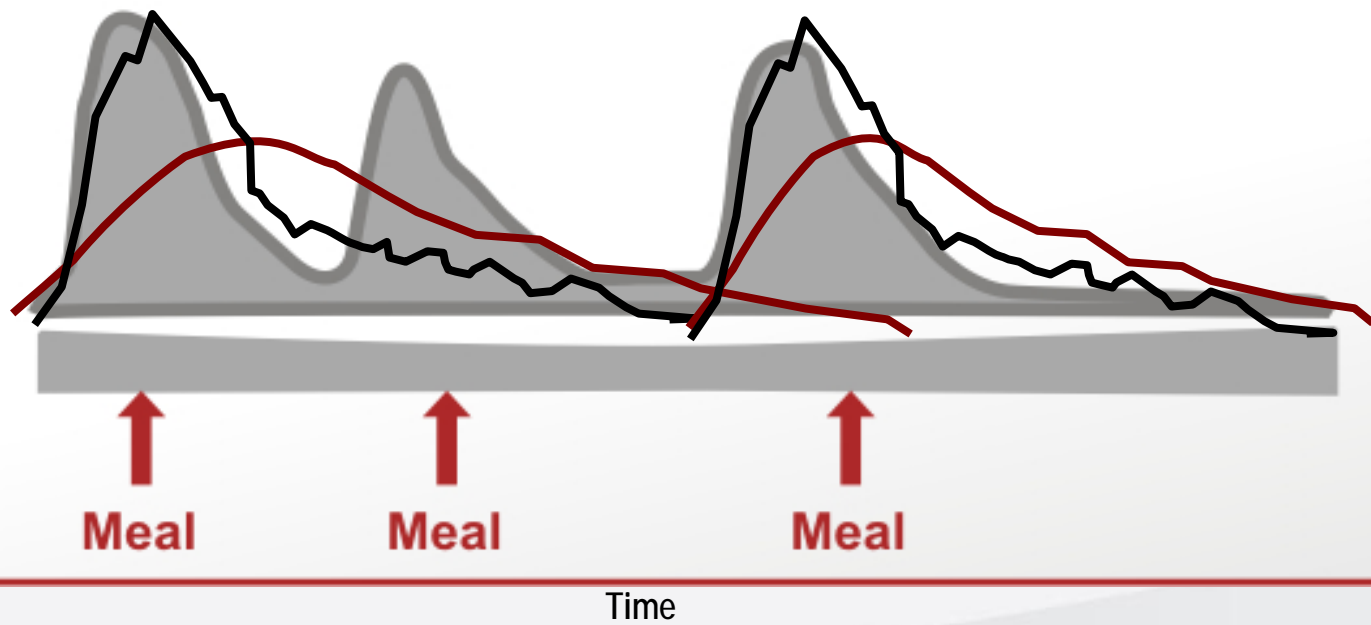
- Human Basal:** Humulin-N, Novolin ge NPH
- Analogue Basal:** Lantus, Levemir
- Human Bolus:** Humulin-R, Novolin ge Toronto
- Analogue Bolus:** Apidra, Humalog, NovoRapid

Types of Insulin (continued)

Insulin Type (trade name)	Time action profile	Timing of injection*
Premixed Insulins		
Premixed regular insulin – NPH (<i>cloudy</i>): <ul style="list-style-type: none"> • 30% insulin regular/ 70% insulin NPH (Humulin® 30/70) • 30% insulin regular/ 70% insulin NPH (Novolin®ge 30/70) • 40% insulin regular/ 60% insulin NPH (Novolin®ge 40/60) • 50% insulin regular/ 50% insulin NPH (Novolin®ge 50/50) 	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)	May be given with one or more meals per day. Should be injected 30 – 45 minutes before meals.
Premixed insulin analogues (<i>cloudy</i>): <ul style="list-style-type: none"> • 30% Insulin aspart/70% insulin aspart protamine crystals (NovoMix® 30) • 25% insulin lispro / 75% insulin lispro protamine (Humalog® Mix25®) • 50% insulin lispro / 50% insulin lispro protamine (Humalog® Mix50®) 		May be given with one or more meals per day. Should be injected 0 – 15 minutes before the start of the meal.

*adapted from CDA insulin pen start checklist

Serum Insulin Level



- **Human Premixed:** Humulin 30/70, Novolin ge 30/70
- **Analogue Premixed:** Humalog Mix25, NovoMix 30

Insulin Dosing (Basal, Bolus, Correctional)

Initiate Basal Insulin

- Basal insulin (intermediate or long-acting) 5-10 units SC QHS or 0.1-0.2 units/kg SC QHS
- **PD Patients: ↓ dose by 50%: 5 units SC QHS or 0.05-0.1 units/kg SC QHS**

Titrate Basal Insulin

- Titrate basal insulin up by 1 unit SC every 1-2 days until AM AC BG at target

Add Prandial Insulin

- 2-4 units SC qAC or 10% of basal insulin dose qAC
- Discontinue insulin secretagogues

Titrate Prandial Insulin

- Titrate to target
- Correction Factor (“1800 rule”): $100/\text{total daily insulin dose} = \# \text{ of units BG reduced by each additional unit of prandial insulin}$

Drugs that can cause hyperglycemia

- Beta-blockers (atenolol, **metoprolol**, propranolol)
- Corticosteroids (**prednisone**)
- Immunosuppressive agents (sirolimus, **tacrolimus**)
- Interferon alfa
- Isoniazid
- Niacin
- Protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)
- Second-generation antipsychotic agents (clozapine, **olanzapine**, paliperidone, **quetiapine**, **risperidone**)
- Thiazide or loop diuretics (chlorthalidone, **furosemide**, hydrochlorothiazide)

Case Study – Meet George



- 78 y/o male, 83kg
- ESRD secondary to diabetes/HTN
- Consumes normal diet
- Loves to garden and walk around park
- SMBG sometimes
- Will be starting PD because he is suffering from uremic symptoms

Baseline Diabetes Bloodwork and VS:

Random glucose 9.1 HbA1c 8.1% BP 157/96 P 77

What do you think of his blood work?



George's Diabetes Baseline Assessment

What would you like to know more about George and **why**?

- Medical history?
- GP/endocrinologist information?
- Any change in appetite/weight?
- Any change in exercise level?
- Type of glucose meter and test strips?
- Review blood glucose log?
- Current medications?
- Recent changes to medications?



George's Diabetes Assessment

What would you like to know more about George and **why**?

- Medical history? **PMR, CHF (EF 25%), gout, hypothyroidism, insomnia**
- GP/endocrinologist information? **Managed by GP**
- Any change in appetite/weight? **↓ appetite x 2 weeks**
- Any change in exercise level? **↓ energy, ↓ walk/gardening**
- Type of glucose meter and test strips? **Accu-Chek Aviva meter & Aviva test strips**
- Review blood glucose log? **Done randomly, not useful**
- Current medications? ***See next slide***
- Recent changes to medications? **No**

George's Medications



- Metformin 500mg po daily
- Glyburide 5mg po with breakfast
- Pioglitazone 15mg po daily
- Furosemide 40mg po QAM
- Metoprolol 50mg po BID
- Quetiapine 25mg po QHS PRN
- Prednisone 5mg po daily
- Ramipril 10mg po daily
- Calcium acetate 169mg (elemental) po TID CC
- Ferrous sulfate 300mg po QHS
- Aranesp 30 mcg SQ Q2weeks
- Synthroid 88mcg po daily

What are his diabetes medications? Are they appropriate?

What are some drugs that can cause hyperglycemia?

Hypoglycemia?

George's Care Plan



1. Establish glycemic control and glycemic targets
 - What should be his target A1c?
 - What medications can he take for diabetes?
2. Eliminate clinical symptoms
 - Does he have any?
3. Prevent macrovascular and microvascular complications
 - What is his life expectancy? Benefit-risk assessment?
4. Prevent ADRs
 - How can we help him prevent hypoglycemia?
5. Achieve optimal management of associated risk factors such as hypertension and dyslipidemia



George's CAPD & Glycemic Control

1. What PD prescription is George likely to get?
2. What type(s) of dialysate solution?
3. What effect would the exposure to dialysate have on George's blood glucose?
4. When do you expect to see these effects?
5. How should he monitor his blood glucose?
6. What should he tell his family doctor?



George's CCPD & Glycemic Control

1. How is CCPD different from CAPD?
2. What type(s) of dialysate solution?
3. What effect would the exposure to dialysate have on George's blood glucose?
4. When do you expect to see these effects?
5. How should he monitor his blood glucose?
6. What should he tell his family doctor?

In our opinion, there is only one definitive way to accurately assess a Vancouverite's knowledge about diabetes.

Ask him what type of *short-acting insulin* he uses:

Vancouver or Toronto?

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