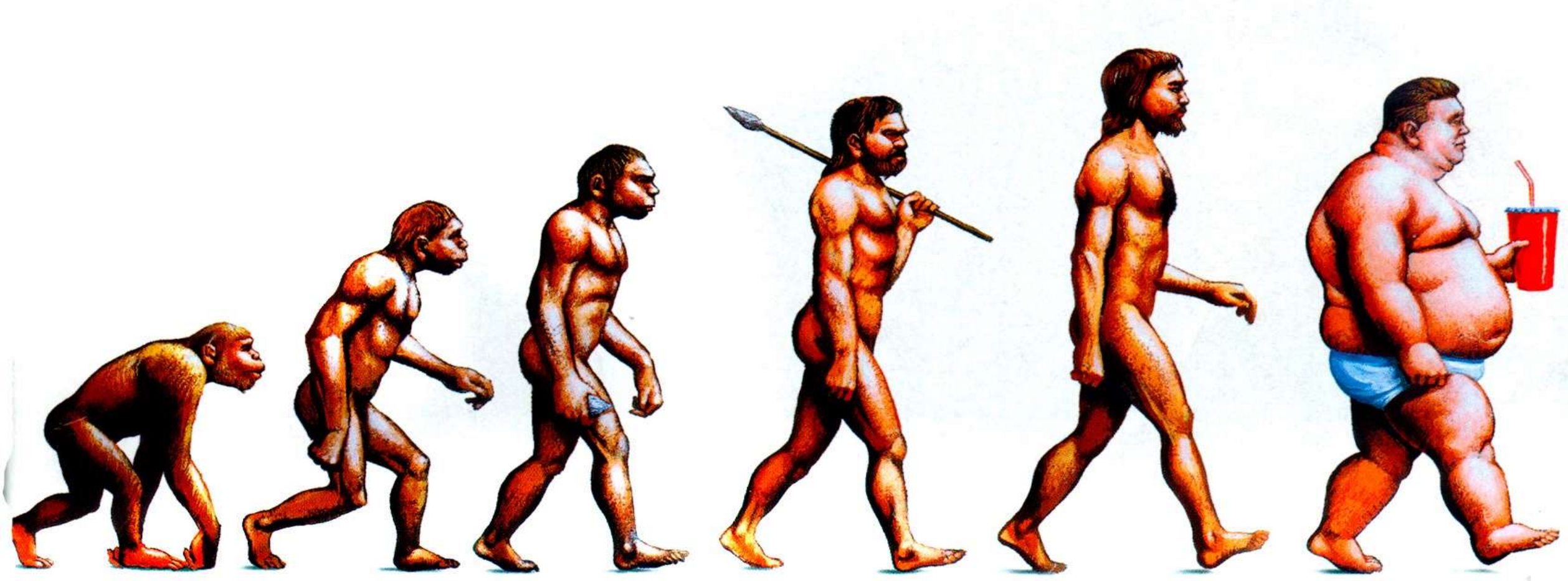
- ORAL AGENT FAILURE AND GLP1 FAILURE TO REACH GOALS
- WHERE DO WE GO FROM HERE

The shape of things to come



key objectivies

- UNDERSTAND HOW TO DEFINE ORAL and INGECTABLE AGENT FAILURES
- understand benefit of QUADRUPLE oral agents vs insulin
- understand where GLP-1 agonists fit in vs insulin

Achieving A1C Target Requires Lowering of Both FPG and PPG

A1C = **Fasting glucose** + **Postprandial glucose**

FPG influenced by:

- Hepatic glucose production
- Hepatic sensitivity to insulin

PPG influenced by:

- Preprandial glucose
- Glucose load from meal
- Incretin levels
- Insulin secretion
- Insulin sensitivity in peripheral tissues

International Diabetes Foundation. *Diabetes Atlas*. 3rd edition. Available at: http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf.

CASE PRESENTATION

- 46 YEAR OLD MALE
- TYPE 2 DIABETES FOR 5 YEARS
- TRADITIONAL MEDS; METORMIN; GLYBERIDE
- A1C STILL 8; WHAT NEXT

TURNING POINT
IF WITH TWO DRUGS NOT AT GOAL

- 1) ADD A THIRD ORAL AGENT
- 2) ADD INSULIN ONCE PER DAY
- 3) ADD GLP-1 INJECTABLE
- 4) ADD MDI INSULIN THERAPY

common terminology

- secretagogues
- biguanides
- dpp4 inhibitors
- glp1 agonists
- slgt2 inhibitors
- tzd
- alphaglucosidase inhibitors
- basal insulin
- basal plus
- mdi

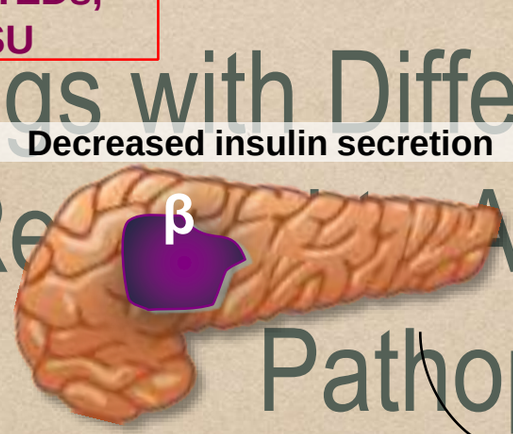
The ominous octet[1-3]

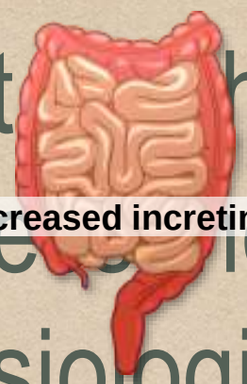
GLP-1 RA; DPP4i;

GLP-1 RA; TZDs, DPP4i, SU

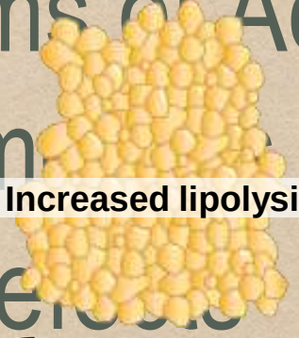
TZDs

Decreased insulin secretion





Decreased incretin effect

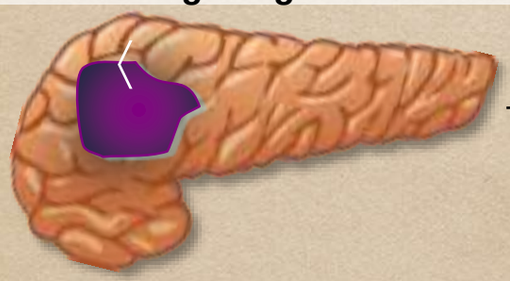


Increased lipolysis

SGLT2 inhibitors

GLP-1 RA; DPP4i

Increased glucagon secretion



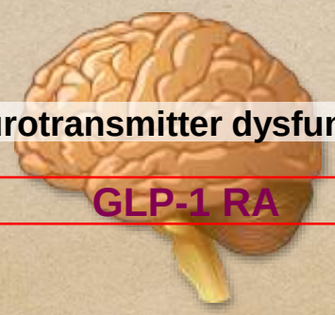
Hyperglycemia

Increased glucose reabsorption

Metformin, TZDs, GLP-1 RA

Increased HGP

Neurotransmitter dysfunction



GLP-1 RA

Decreased glucose uptake

TZDs, metformin

HGP, hepatic glucose production

Recommended Targets for Glycemic Control

	A1C (%)	FPG or preprandial PG (mmol/L)	2-hour PPG (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)

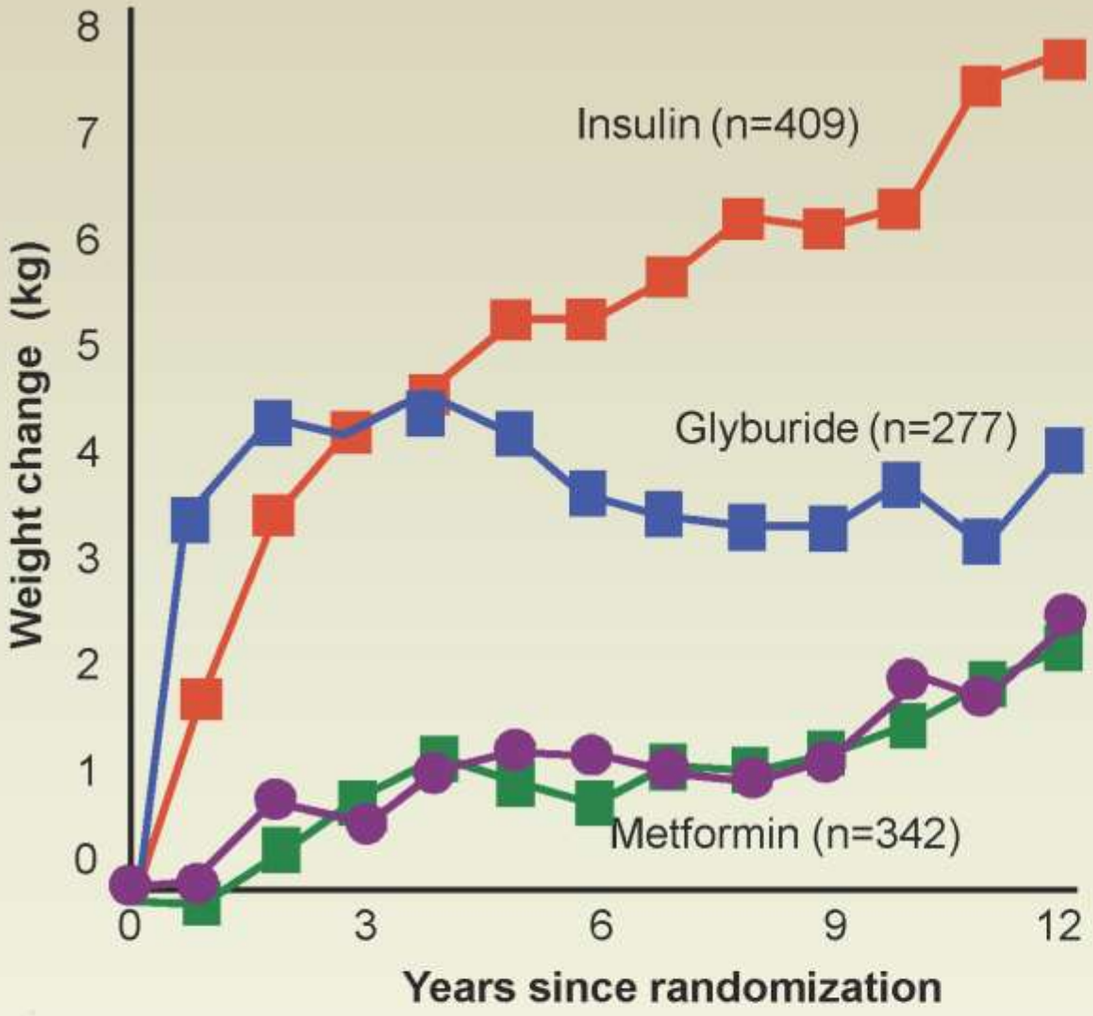
- A target A1C of ≤6.5% may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy, but this must be balanced against the risk of hypoglycemia and increased mortality in patients who are at significantly elevated risk of CVD

FPG = fasting plasma glucose; PG = plasma glucose; PPG = postprandial plasma glucose; CVD = cardiovascular disease

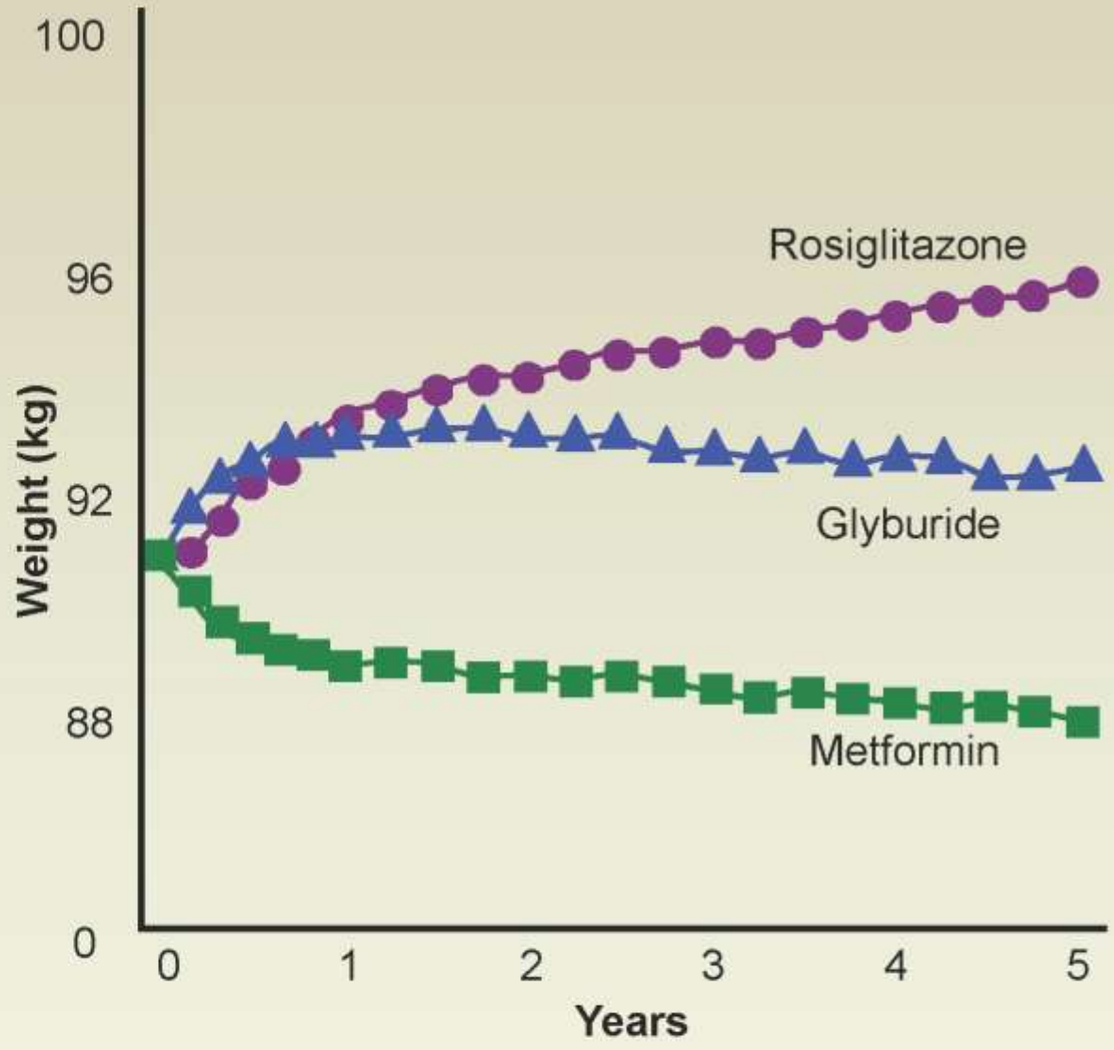
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008; 32(suppl 1):S1-201.

Most Antihyperglycemic Treatments Lead to Increases in Weight Over Time

UKPDS: up to 8 kg in 12 years



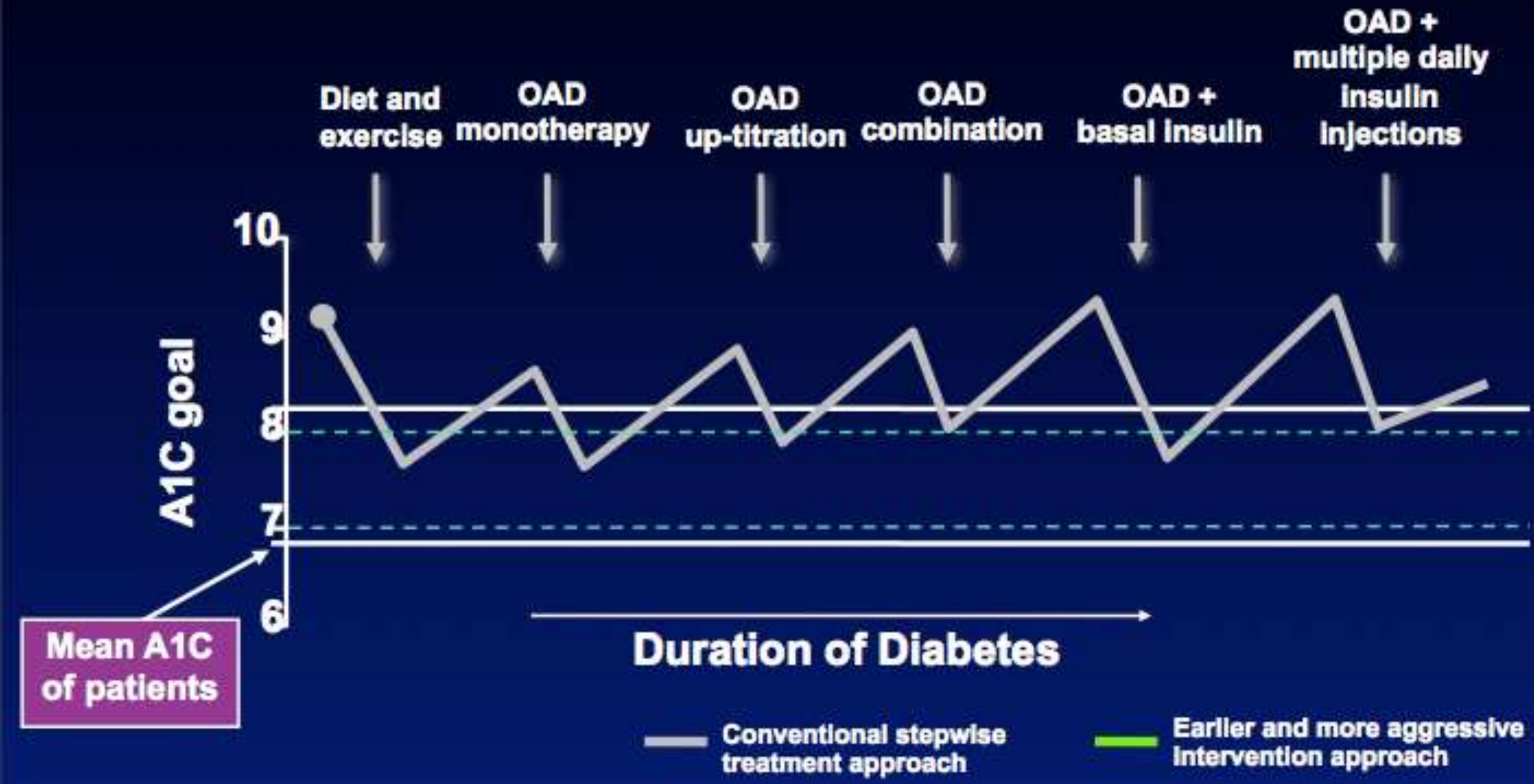
ADOPT: up to 4.8 kg in 5 years



ADOPT = A Diabetes Outcome Progression Trial

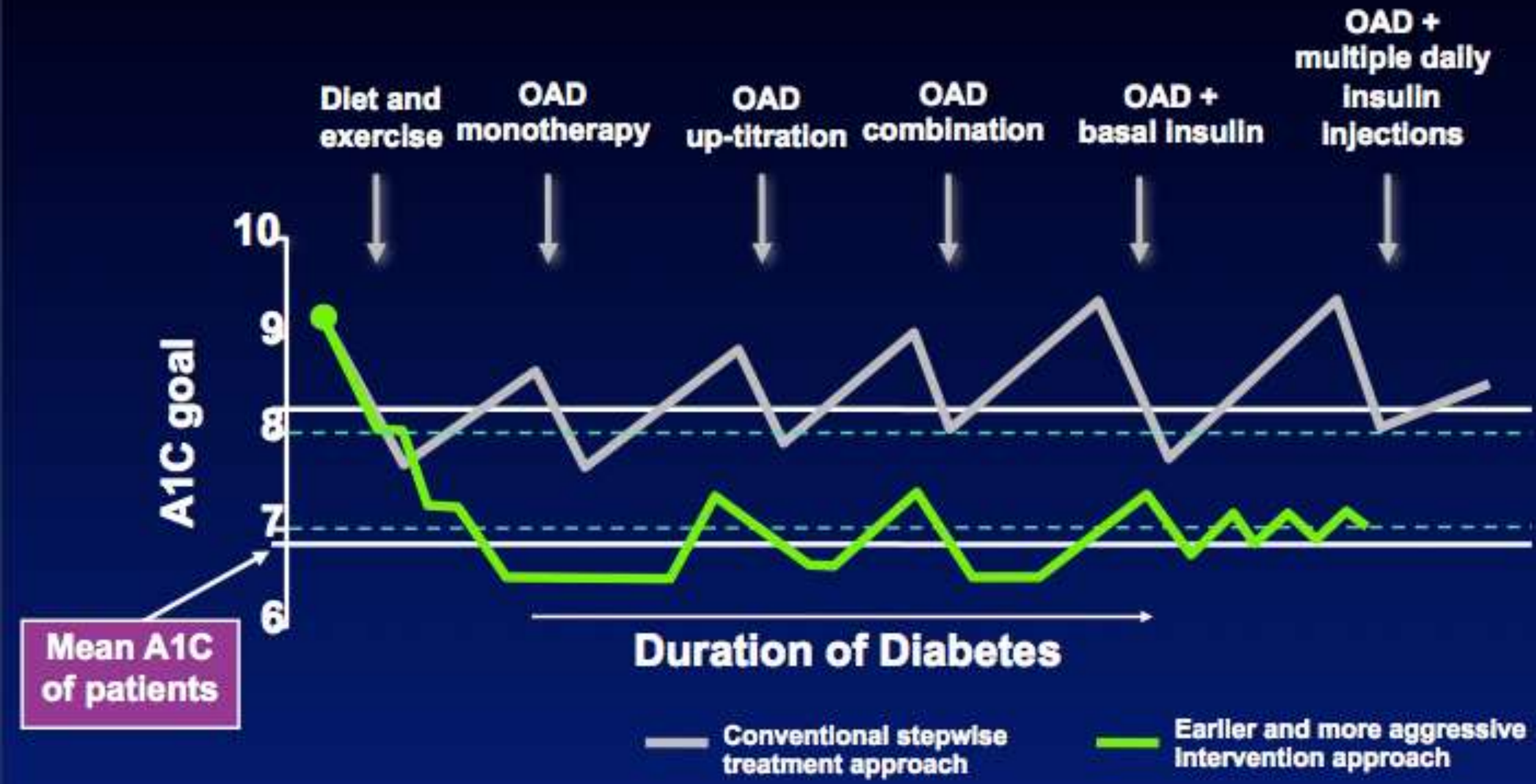
Kahn SE *et al. N Engl J Med* 2006; 355:2427-43; UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:854-65.

Earlier Use of Combination Therapy May Improve Treating to Target Compared With Conventional Therapy: Published Conceptual Approach



OAD = oral antidiabetic agent.
Adapted from: Campbell IW. Br J Cardiol 2000; 7(10):625-31.
Del Prato S, et al. Int J Clin Pract 2005; 59:1345-55.

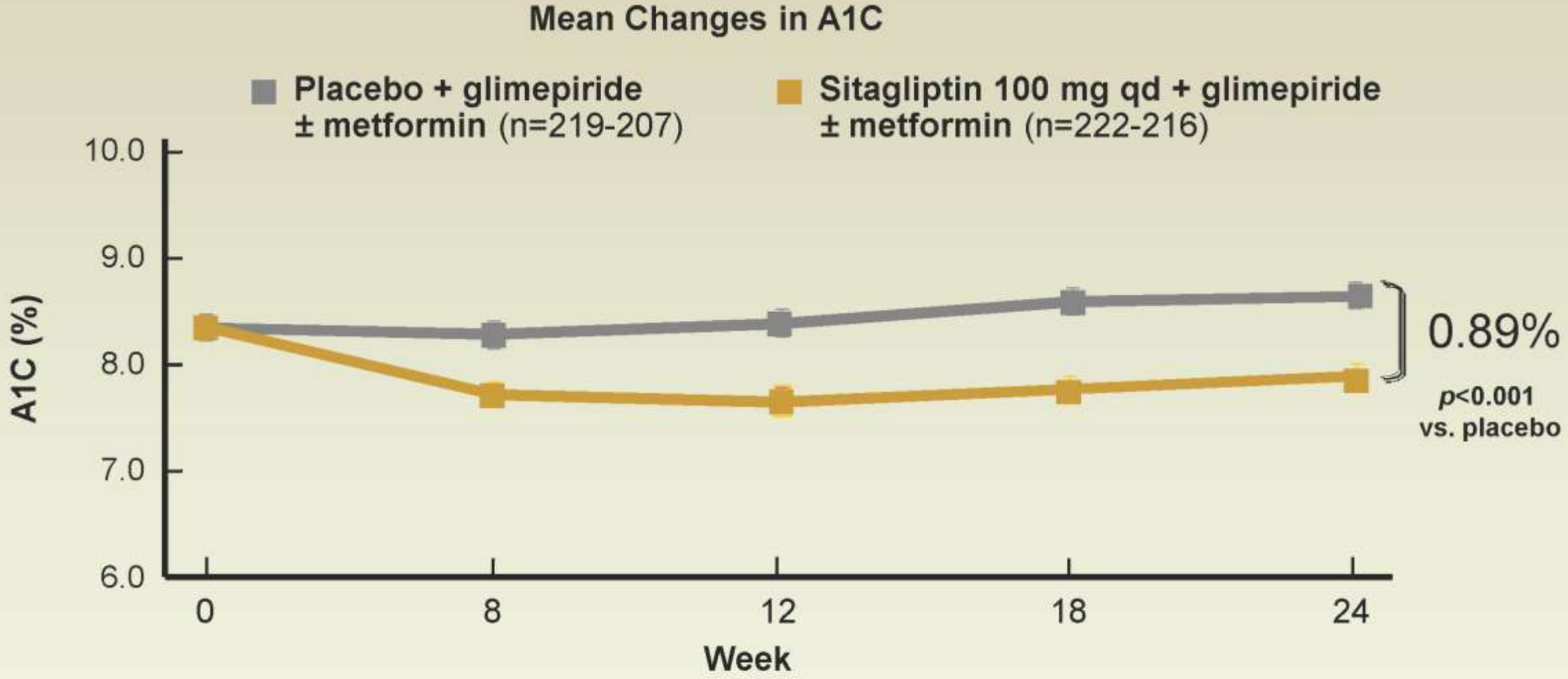
Earlier Use of Combination Therapy May Improve Treating to Target Compared With Conventional Therapy: Published Conceptual Approach



OAD = oral antidiabetic agent.
Adapted from: Campbell IW. Br J Cardiol 2000; 7(10):625-31.
Del Prato S, et al. Int J Clin Pract 2005; 59:1345-55.

Triple Combination Therapy: Sitagliptin, Metformin and Glimepiride

Significant reductions in baseline A1C compared to placebo when added to metformin and glimepiride.



Clinical trial assessing the efficacy and safety of a 24-week treatment with sitagliptin in patients with type 2 diabetes who had inadequate glycemic control (A1C ≥7.5% and ≤10.5%) while on glimepiride alone or in combination with metformin. After a screening, diet/exercise run-in and drug wash-off period, a glimepiride ± metformin dose titration/stabilization period and a 2-week, single-blind placebo run-in, 441 patients were randomized to receive the addition of sitagliptin 100 mg qd or placebo for 24 weeks.
Adapted from: Hermansen K *et al. Diabetes Obes Metab* 2007; 9:733-45.

CASE CONTINUES

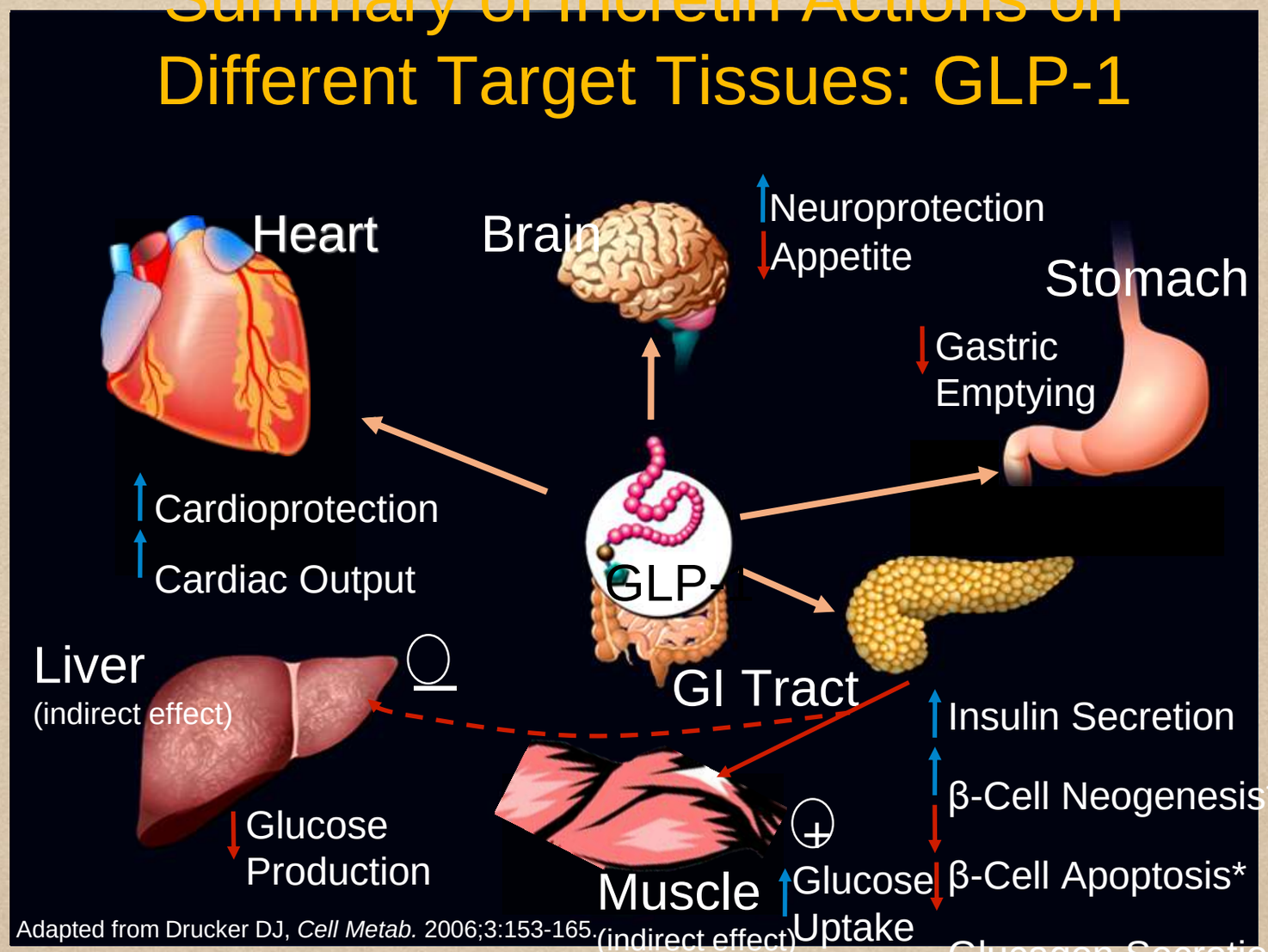
- HIS BMI IS 35 AND WANTS TO LOSE
- WEIGHT
- OPTIONS; INSULIN; SGLT2; OR GLP1


trulicity
trulicity


VICTOZA


OZEMPIC
(semaglutide) injection
-0-

Summary of Incretin Actions on Different Target Tissues: GLP-1

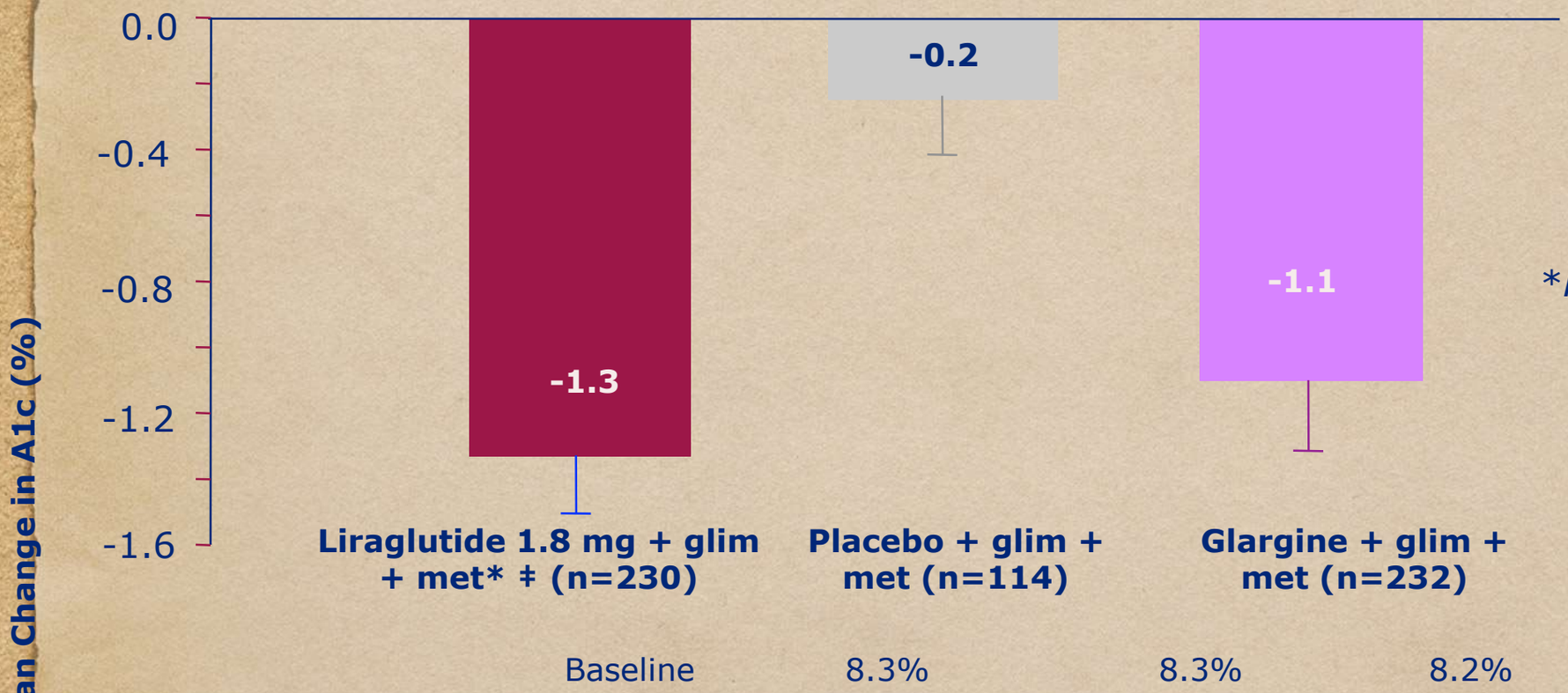


Adapted from Drucker DJ, *Cell Metab.* 2006;3:153-165.

* pre-clinical data

Change in A1C From Baseline: Combination with Two OADs

Combination with SU/metformin



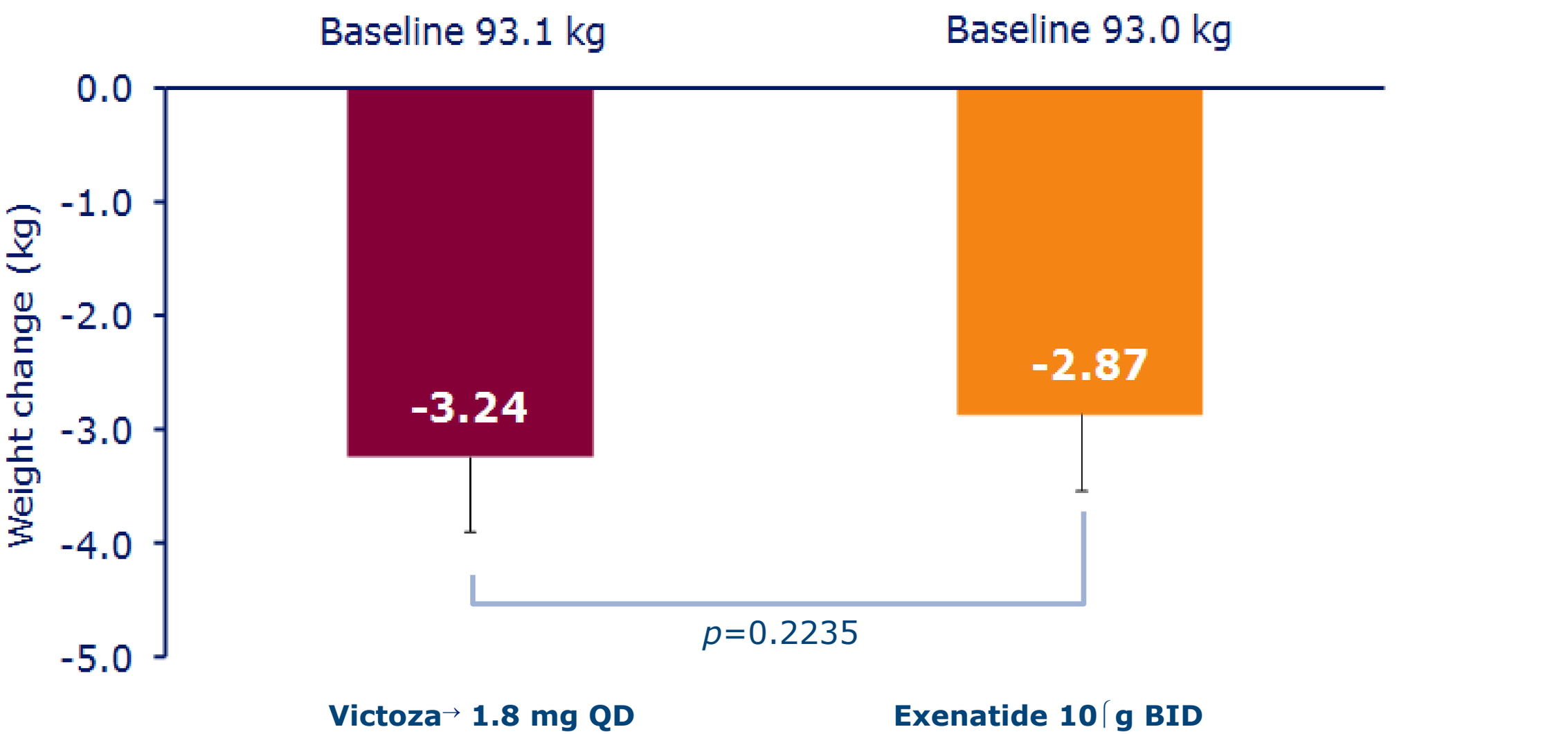
*P <.0001 vs placebo; ‡p=.0015 vs glargine

53% of liraglutide 1.8 mg patients reached the target A1C of <7.0% vs. **46%** for glargine (p=0.0139)

Results based on intention-to-treat population (exposed to at least one dose).
Russell-Jones et al. *Diabetologia*. 2009;52:2046-55. (LEAD-5)

Victoza® + MET and/or SU had a similar effect on body weight vs. exenatide + MET and/or SU

Mean change in body weight through week 26



MET=metformin; SU=sulphonylurea; QD=once a day; BID=twice a day

Buse JB et al. *Lancet* 2009:374;39-47.

Pr VICTOZA® liraglutide

CASE CONTUES

- TRIED GLP1 AGONIST
- COULD NOT TOLERATE
- WHAT ABOUT SGLT2 INHIBITOR

SGLT2 Inhibitors : Dosage and administration

Canagliflozin

Starting dose
100 mg

Dose could be increase if well tolerated to **300 mg** and require additional glycemic control.

Dapagliflozin

Starting dose
5 mg

Dose could be increased if well tolerated to **10 mg.**

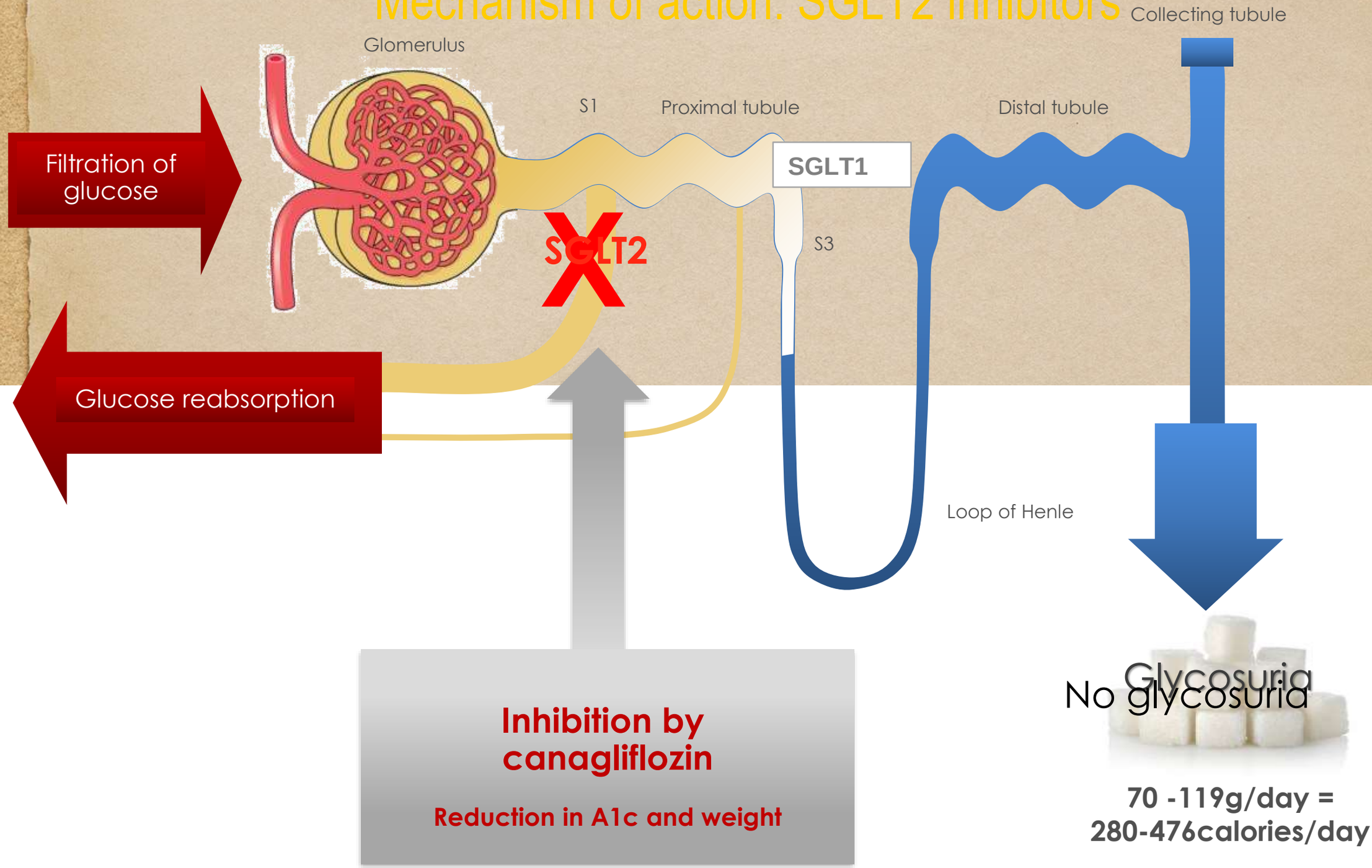
Empagliflozin

Starting dose
10 mg

Dose could be increase if well tolerated to **25 mg** and require additional glycemic control.

Monographie d'INVOKANA. Janssen Inc., novembre 2014.
Monographie de FORXIGA. AstraZeneca, décembre 2014.
Monographie de JARDIANCE, Boehringer Ingelheim (Canada) Ltée, juillet 2015

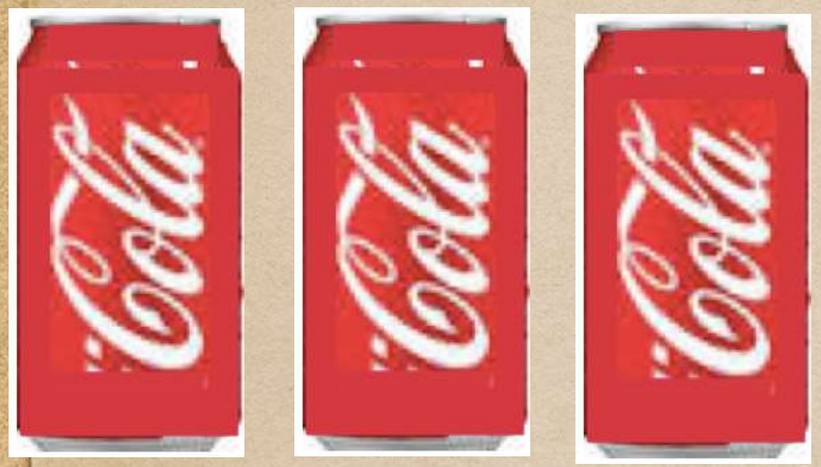
Mechanism of action: SGLT2 inhibitors



SGLT=Sodium/GLucose co-Transporter

Abdul-Ghani MA, DeFronzo, RA. Endocr Pract. 2008;14(6):782-790. Bays H. Curr Med Res Opin. 2009;25(3):671-681.
Product monograph, INVOKANA® (canagliflozin), Janssen Inc., 2014
Product monograph, FORXIGA (dapagliflozin), Astra Zenaca, 2014

Equivalent of 476 kcal?



or

Equivalent physical activity for a 200-lb. person

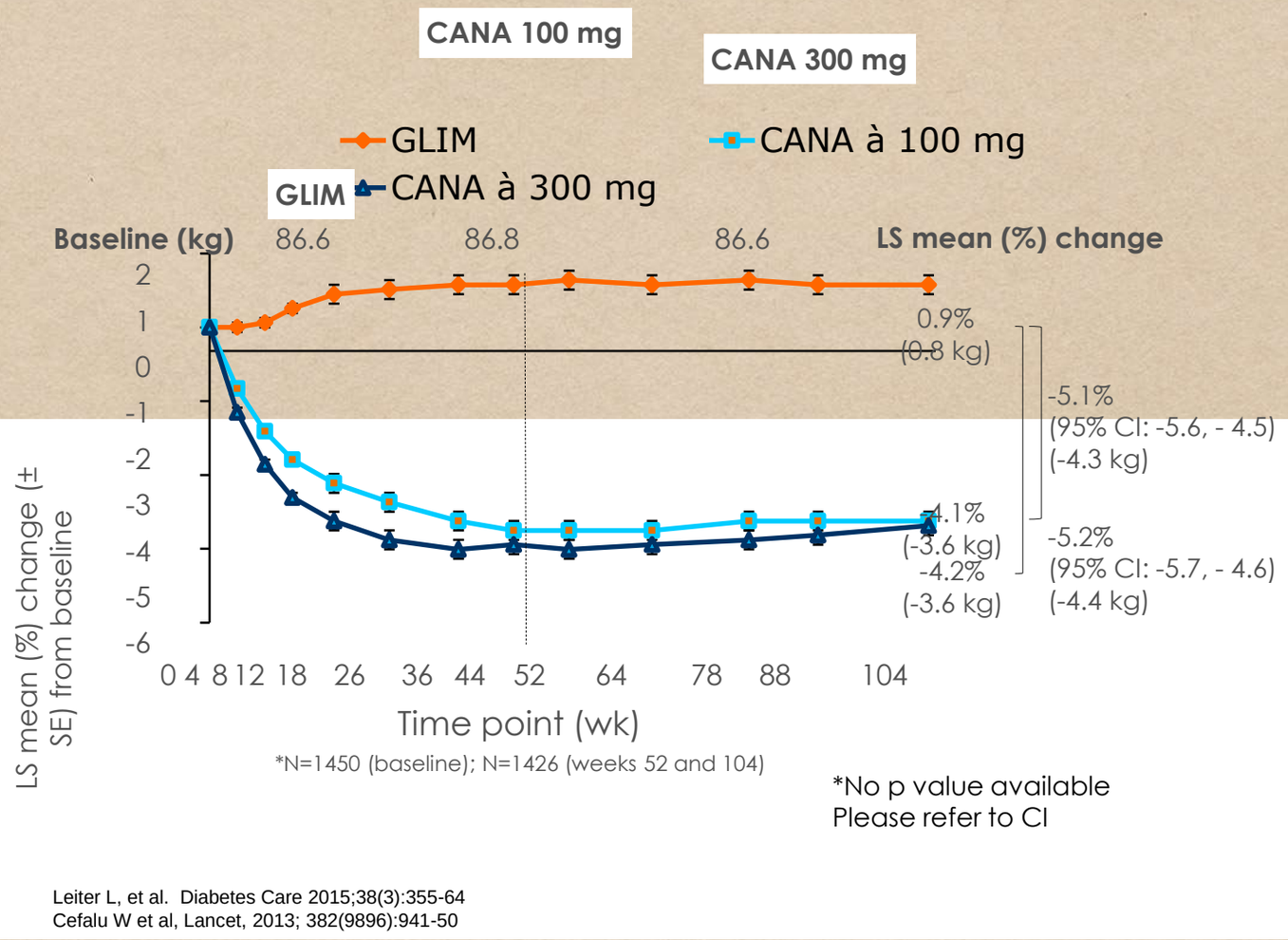
Walking (3 km/hr) for 1.9 hours

9 cookies

43 sugar packs

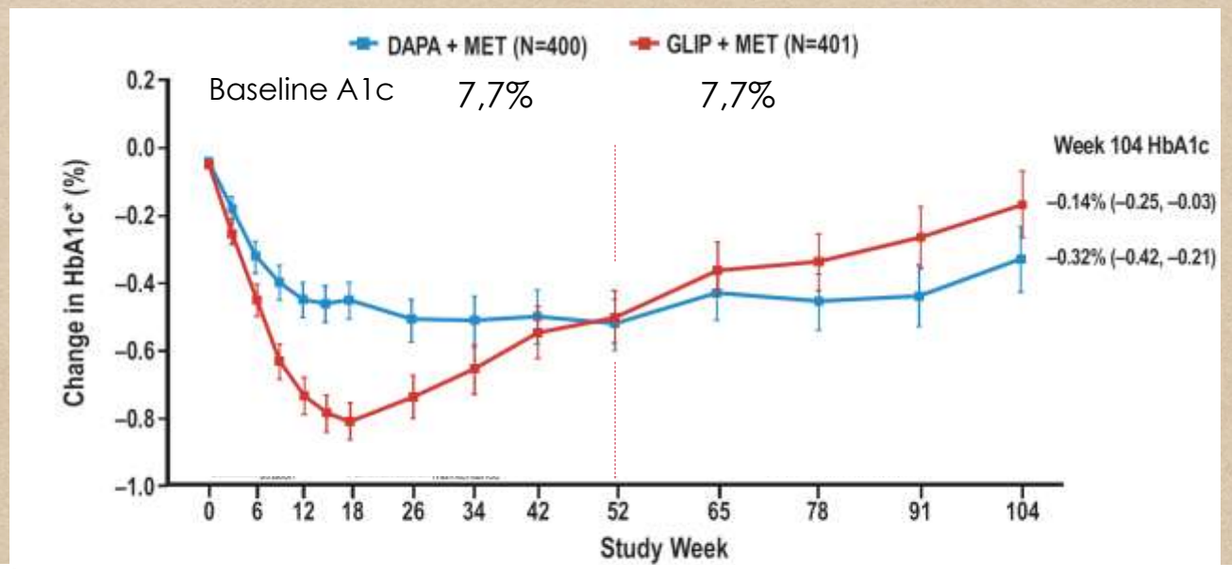
www.calorieking.com

Weight: Comparative data (104 weeks) canagliflozin vs. glimepiride



Leiter L, et al. Diabetes Care 2015;38(3):355-64
Cefalu W et al, Lancet, 2013; 382(9896):941-50

A1C: Comparative data
Dapagliflozin vs glipizide



Difference vs glipizide at 52 weeks:

Dapagliflozin 10mg: -0,52 % (-0,66 à 0.44) statistically non inferior
Glipizide : -0,52 % (-0,66 à 0.44)

Nauck MA et al. Diabetes Obes Metab. 2014 ;16(11):1111-20
Nauck MA,et al. Diabetes Care. 2011 Sep;34(9):2015-22

Antihyperglycemic Medications

Added Therapy	Change in A_{1C} (%)	Change in Weight (kg)	Hypoglycemia Odds Ratio vs placebo
Sulfonylureas	-0,82	2,17	8,86
Meglitinides	-0,71	1,40	10,51
Thiazolidinediones	-0,82	2,46	0,45
Alpha-glucosidase Inhibitors	-0,66 -0.6 to 1.1	-1,01 -2.0- 4.0	0,40 0.6
SGLT2 INHIBITORS			
DPP-4 Inhibitors	-0,69	0,23	1,13
GLP-1 Receptor Agonists	-1,02	-2.8	0,92
Basal Insulin	-1	1,38	4,77

Liu, Sung-Chen et al. Diab Obes & Metab 14:810-820, 2012.

ONGOING PROBLEMS

LOST WEIGHT ON SGLT2
BUT NOW A1C 8.5

Lifestyle Recommendations

- **Exercise**
  - Minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise
  - Perform resistance exercise 3 times per week

In UKPDS, 3 months of non-pharmacological treatment (mostly lifestyle changes) achieved a reduction in body weight of ~5 kg in conjunction with a decrease in A1C of ~2%.

- **Eat well**
  - Follow Canada's Food Guide
  - Maintain regularity in timing and spacing of meals
  - Choose carbohydrates with a low glycemic index more often
  - Sucrose-containing foods can be substituted for other carbohydrates up to a maximum of 10% of total daily energy, provided adequate control of blood glucose and lipids is maintained
  - Consume no more than 7% of total daily energy from saturated fats
  - Limit intake of trans-fatty acids

UKPDS = United Kingdom Prospective Diabetes Study

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008; 32(suppl 1):S1-201; Rydén L *et al. Eur Heart J* 2007; 28:88-136.

Plans to Achieve Target

More aggressive treatment is planned for only half of these patients.	
	Total
Sample	**1,128**
No action	5%
Reinforce lifestyle	79%
More aggressive treatment plans (NET)	56%
• Increase dose oral antihyperglycemic agents	28%
• Add oral antihyperglycemic agents	18%
• Refer to specialist	13%
• Increase insulin dose	10%
• Add insulin	6%

Patients with most recent A1C ≥7.0% who have target A1C.

Harris SB *et al. Diabetes Res Clin Pract* 2005; 70:90-7.

When Oral Medications Are Not Enough

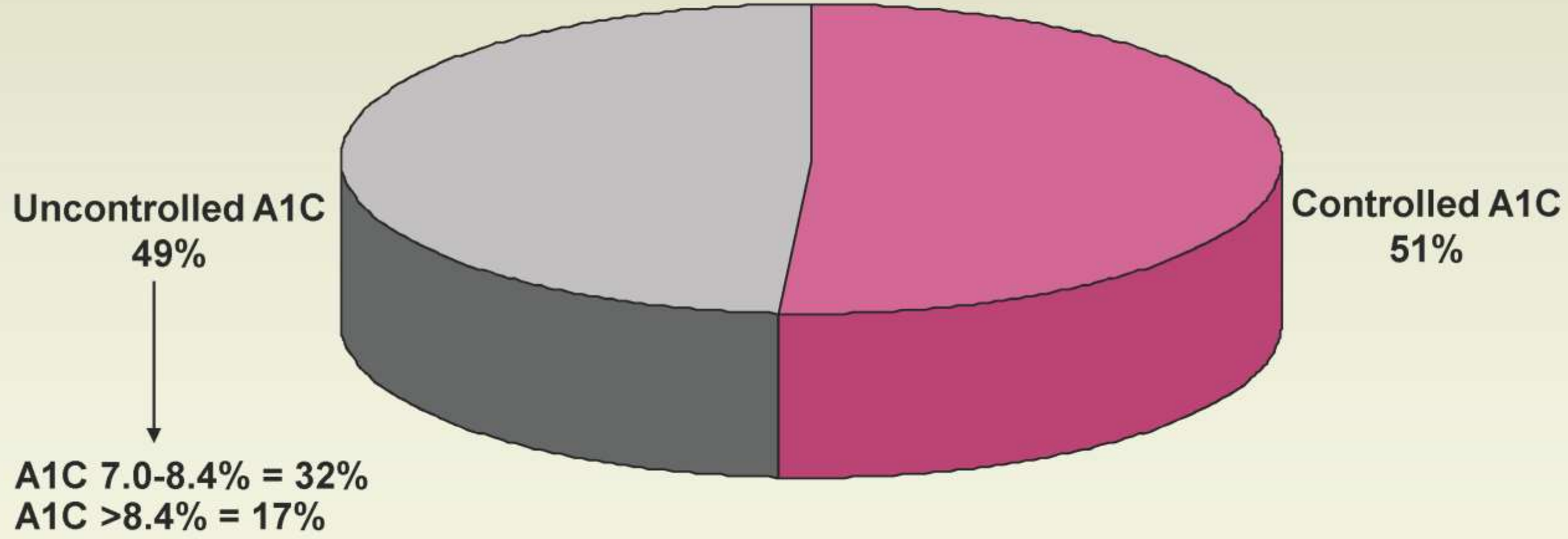
- **Watch for the following signs**
  - Increasing BG levels
  - Elevated A1C
  - Unexplained weight loss
  - Traces of ketonuria
  - Poor energy level
  - Sleep disturbances
  - Polydipsia
- **Next steps**
  - Make a decision to start insulin
  - Offer patient encouragement, not blame

Remind the patient of disease progression…

Inadequate Achievement of Treatment Goals

- 1 in 2 type 2 diabetes patients in Canada are not at target (<7%) → mean A1C = 7.3%

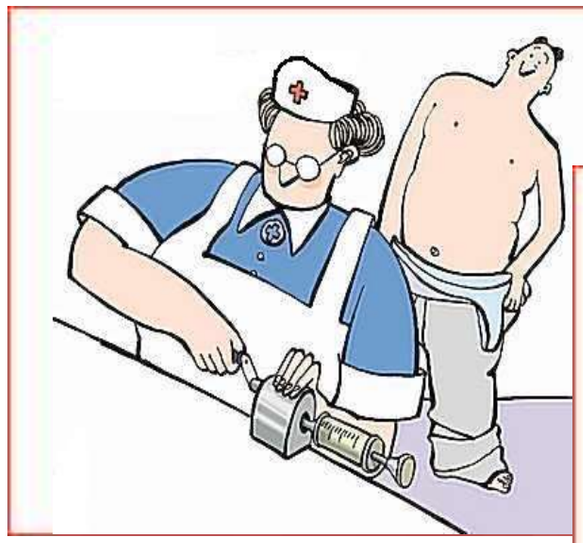
Most Recent A1C Test Results (n=2,337)



Harris SB *et al. Diabetes Res Clin Pract* 2005; 70:90-7.

Misperceptions About Insulin Therapy

CASE STUDY

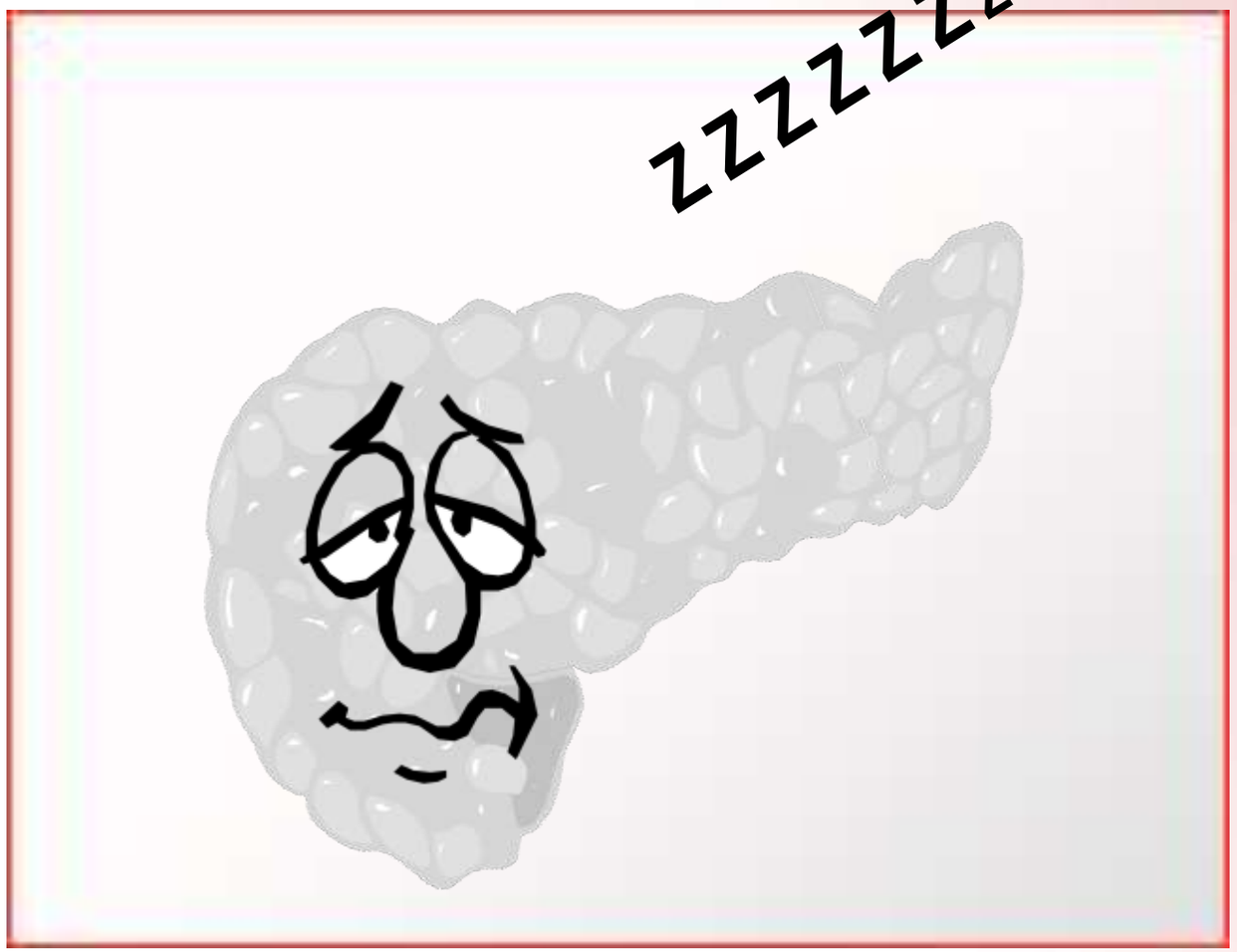



INSULIN
50 Units
10 Units

Improved Technology:
- **disposable**
- **thinner needles**
- **more sanitary**

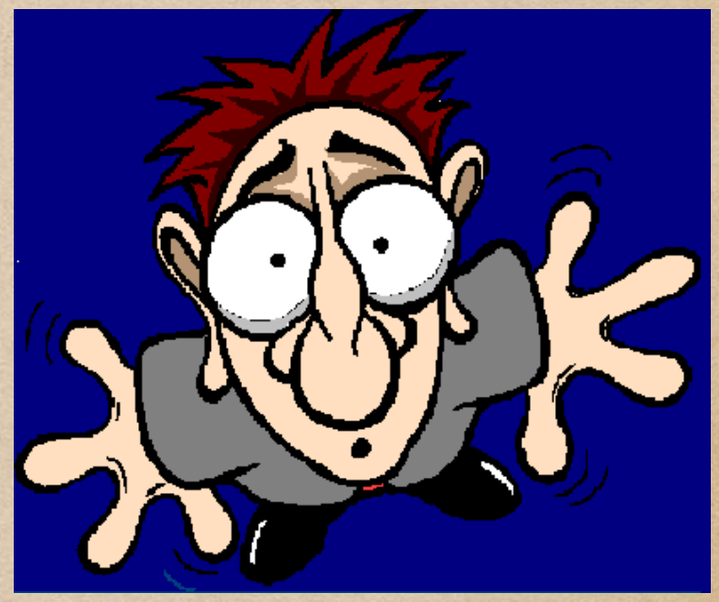
Barriers to the Use of Insulin

A Failing Pancreas is not the Fault of the Patient or Doctor!



A “pooped-out” pancreas

Patient Concerns About Insulin



- Fear of injections
- Perceived significance of need for insulin
- Worries that insulin could worsen diabetes
- Concerns about hypoglycemia
- Complexity of regimens

Indications for insulin therapy

- unexplained recent weight loss (irrespective of the initial weight),
- a short history with severe symptoms,
- the presence of moderate to heavy ketonuria.
- pregnancy

Help Patient Accept and Prepare for Insulin Therapy

- **Address patient concerns**
  - Dispel fear by countering misconceptions
    - Review rationale for insulin use
      - Explain that insulin
        - Can be incorporated into lifestyle
        - Causes only modest weight gain
      - Is a common course of treatment for this progressive disease

- **Promise patient support and close follow-up**
  - Monitoring can prevent hypoglycemia
  - Today's technology can facilitate daily injections and readings

insulins now

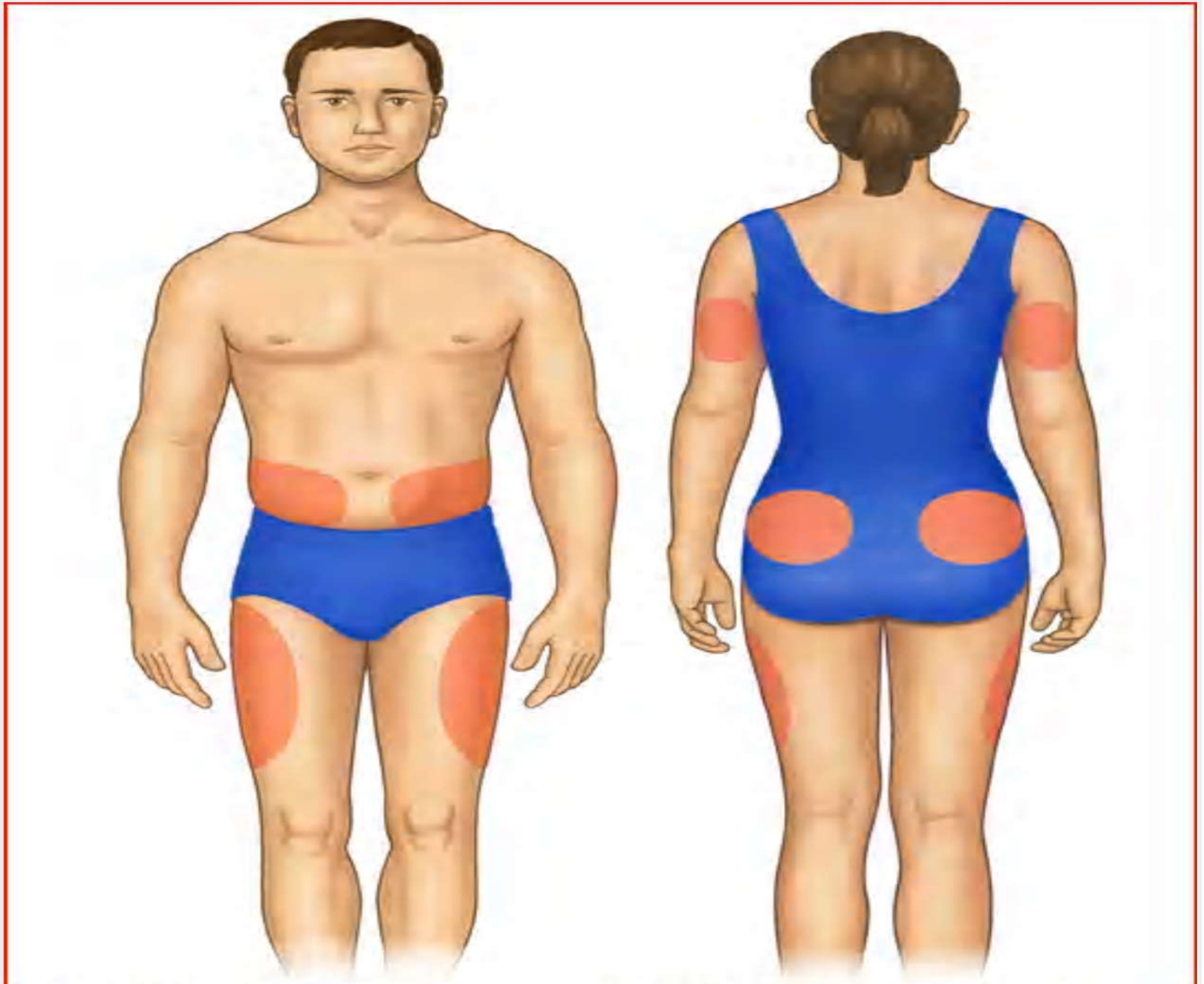
- humulin N
- humulin R
- novolin nph
- novolin toronto
- novorapid
- humalog
- 30/70
- mix 25
- novomix 30
- lantus
- toujeo
- degludec
- levemir

Insulin Injection Devices

Insulin pens

- Faster and easier than syringes
  - Improve patient attitude and adherence
  - Have accurate dosing mechanisms, but inadequate mixing may be a problem

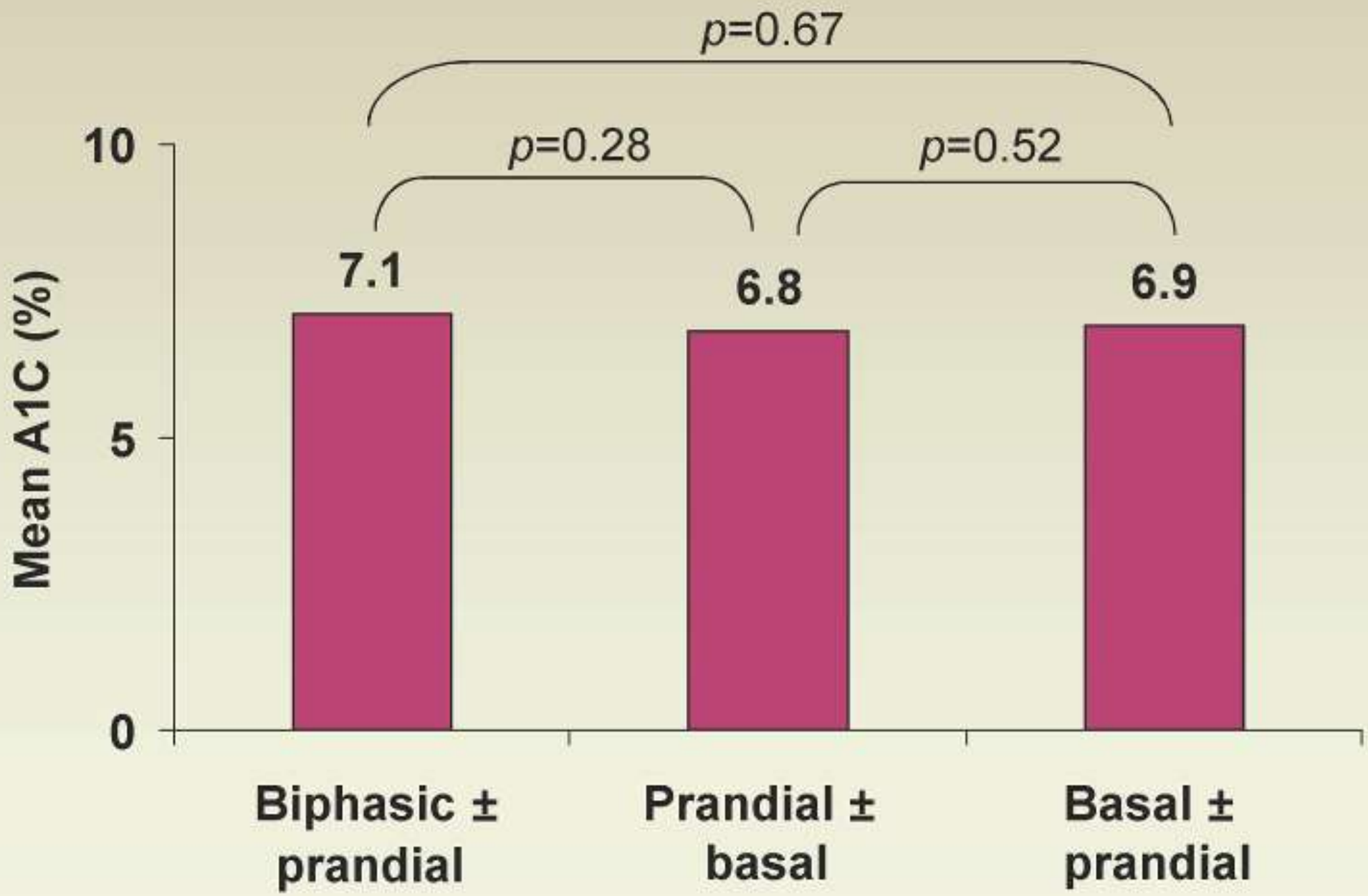
- **Ease of handling**
- **More discrete use**



Major drawback to intensive therapy

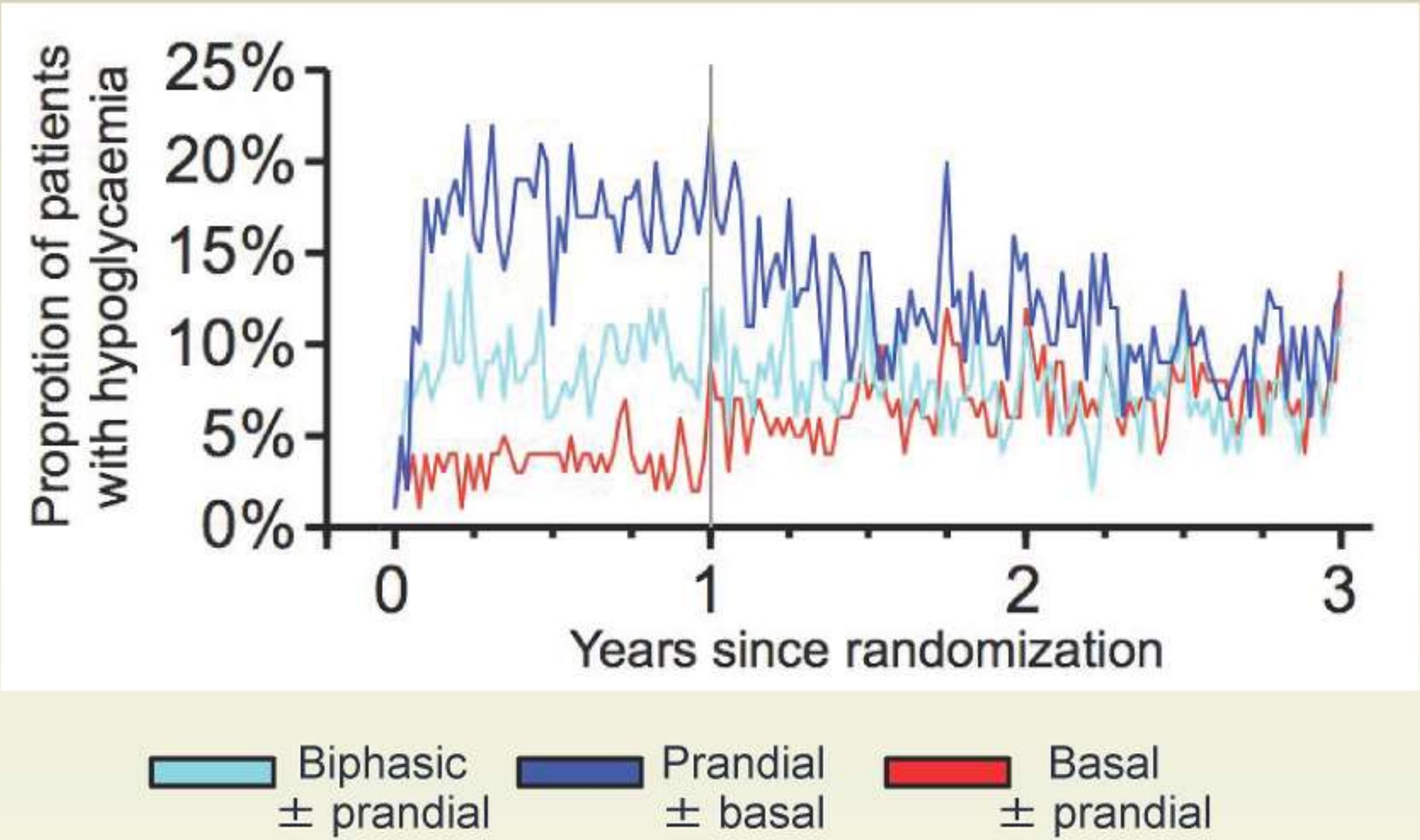
- Cost (three times)
- Weight gain
- Risk of hypoglycemia (three times)

4T Trial Primary Outcome: A1C at 3 Years



Holmann RR *et al. N Engl J Med* 2009; 361:1736-47.

4T Trial: Grade 2 or 3 Hypoglycemia Over 3 Years



Holmann RR *et al. N Engl J Med* 2009; 361:1736-47.

Initiating Insulin: Example of Titration Schedule When Adding Basal or NPH Insulin to Oral Agents

- Insulin should be titrated to achieve target FPG of 4.0-7.0 mmol/L
- Suggested starting dose: 10 units qd at bedtime
- Suggested titration: 1 unit/day until target is reached
  - Dose should not be increased if the individual experiences 2 episodes of hypoglycemia in 1 week or any episode of nocturnal hypoglycemia
- Lower starting dose, slower titration and higher targets may be considered for elderly or normal weight subjects

FPG = fasting plasma glucose

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008; 32(suppl 1):S1-201.

Current A1C levels and use of insulin in Canada

50% — **A1C ≥7.0%**
Average A1C was 7.4%

9.2 y — Mean duration of diabetes (T2DM)

87% — Of patients use antihyperglycemic agents

62% — Of patients on insulin
42% on insulin and ≥1 AHA
19% on insulin alone

A1C: glycated hemoglobin; AHA: antihyperglycemic agent; T2DM: type 2 diabetes mellitus; y: years

1. Leiter LA et al. Type 2 Diabetes Mellitus Management in Canada: Is It Improving?. *Can J Diabetes.* 2013;37:82-89.

Discuss: What to do with other agents
Consider: A1C, weight, hypo, CV, pill burden, etc.

Agents	Stop	No change	Reduce dose
Alpha-glucosidase inhibitor	?	✓	
DPP-4 inhibitor	?	✓	
GLP-1 receptor agonist		✓	
Insulin secretagogue (sulfonylurea)	?		✓
Metformin		✓	
Thiazolidinedione	✓		
Weight-loss agent		✓	
SGLT2 inhibitor		✓	

Basal insulin product options and features

	Brand name	Total units per pen (units)	Maximum dose for injection (units)	In use time (days)	Pre-filled Pen
NPH	Humulin® N 100 U/mL	300	60	28	KwikPen®
Insulin detemir	Levemir® 100 U/mL	300	80	42	FlexTouch®
Insulin glargine	Lantus® 100 U/mL	300	80	28	SoloSTAR®
	Basaglar™ 100 U/mL	300	60	28	KwikPen®
	Toujeo™ 300 U/mL	450	80	42	SoloSTAR®
Insulin degludec	Tresiba® 100 U/mL	300	80	56	FlexTouch®
	Tresiba® 200 U/mL	600	160	56	FlexTouch®

1. Novo Nordisk Canada Inc. Novolin® ge Product Monograph. 2016; 2. Eli Lilly Canada Inc. Humulin® N Product Monograph. 2016; 3. Novo Nordisk Canada Inc. Levemir® Product Monograph; 4. Sanofi-aventis Canada Inc. Lantus® Product Monograph. 2016; 5. Eli Lilly Canada Inc. BASAGLAR™ Product Monograph. 2015; 6. Sanofi-aventis Canada Inc. Toujeo™ Product Monograph. 2015; 7. Novo Nordisk A/S. Tresiba® Summary of Product Characteristics (SmPC). Bagsværd, Denmark. 2015.

Review of newer basal insulin options

H glycemia
- ommon side effect of insulin
- Should be discussed at each visit
- Leads to reluctance to intensify treatment

insulin options
ve differing mechanisms of protraction
- Have a flatter action profile and a longer half-life
- Aim to decrease day-to-day variability to reduce hypo risk

cal profiles
ually efficacious at lowering A1C
- Differ in the prevalence and rate of hypoglycemia
- Available CVOTs demonstrate CV safety

tion and optimization
n be simple
- Individualized to the patient – no dose ceiling
- Flexible dose timing available

Glargine U300 vs. Glargine U100: Reduced hypoglycemia in insulin-naïve patients

Documented hypoglycemia

Lower during full treatment of glargine U300

Driven by titration period

Similar during maintenance of glargine U300

Nocturnal hypoglycemia

Similar during full treatment of glargine U300

Similar during maintenance of glargine U300

Severe hypoglycemia (or <3.0 mmol/L)

Similar during full treatment of glargine U300

Similar during maintenance of glargine U300

Titration period = up to week 9, as dose is being adjusted; Maintenance period = week 9 to end of trial, when dose has typically stabilized; Full treatment period = titration + maintenance

1. Bolli GB et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17(4):386–394.

Degludec vs. Glargine U100: Reduced hypoglycemia in insulin-naïve patients

Overall hypoglycemia

Similar during full treatment of degludec

Similar during maintenance of degludec

Nocturnal hypoglycemia

Lower during full treatment of degludec

Lower during maintenance of degludec

Driven by maintenance period

Severe hypoglycemia

Lower during full treatment of degludec

Lower during maintenance of degludec

Titration period = up to week 16, as dose is being adjusted; Maintenance period = week 16 to end of trial, when dose has typically stabilized; Full treatment period = titration + maintenance

1. Zinman B et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12):2464-2471.

Hypoglycemia is the most common adverse event in insulin therapy, regardless of A1C level

HAT study & IN-HYPO survey in T2DM

Overall hypoglycemia

51.4% experienced in last 30 days

37.3 events per year

Nocturnal hypoglycemia

29.7% experienced in last 4 weeks

12.7 events per year

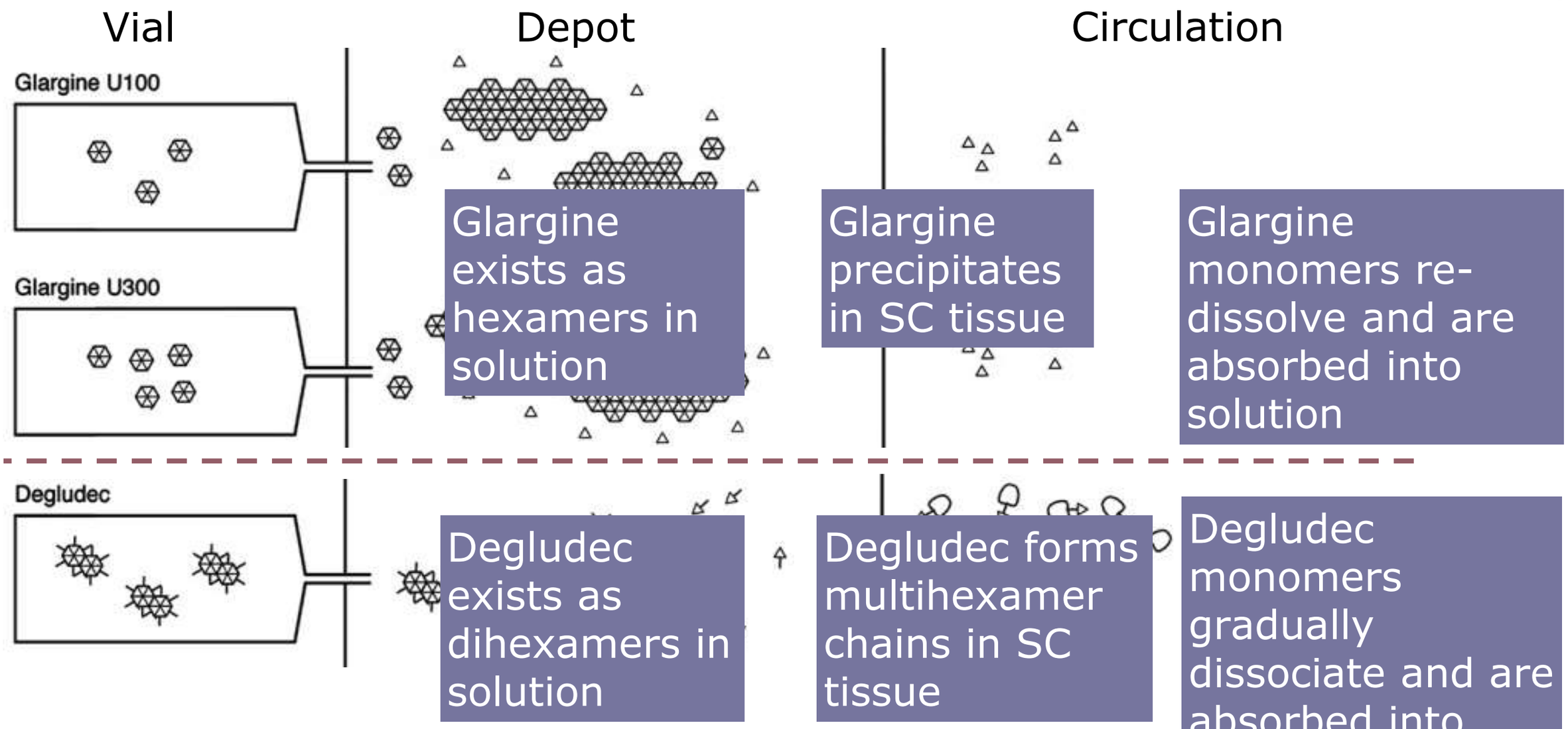
Severe hypoglycemia

37.9% experienced in last year

1.8 events per year

1. Khunti K et al. Rates and predictors of hypoglycemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab.* 2016;18(9):907-915; 2. Reichert SM et al. A Population-based Study on Incidence and Associated Risk Factors for Hypoglycemia in Canada: The InHYPO-DM Study. Presented at: 52nd European Association for the Study of Diabetes (EASD) Annual Meetings; Sept 13-15, 2016; Munich, Germany; 3. Aronson R et al. The Canadian Hypoglycemia Assessment Tool Program: Insights Into Rates and Implications of Hypoglycemia From an Observational Study. *Can J Diabetes*. 2017 [epub ahead of print].

Mechanism of protraction of newer basal insulins



SC: Subcutaneous

1. Heise T et al. Impact of the mode of protraction of basal insulin therapies on their pharmacokinetic and pharmacodynamic p
outcomes. *Diabetes Obes Metab.* 2017;19(1):3–12.

The burden of insulin-induced hypoglycemia

Short-term

- Work and driving performance impaired
- Social, sport and travel activities affected
- Hypothermia
- Cognitive impairment
- Acute morbidity due to increased risk of accidents (e.g., falls) cardiovascular events, cerebrovascular events

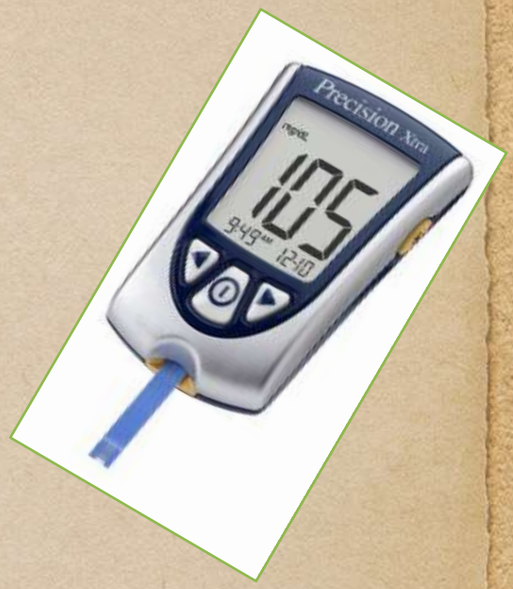
Long-term

- Fear of hypoglycemia
- Restrictions on employment
- Driving restrictions
- Disruptions of personal relationships
- Reduced quality of life
- Possible worsening of diabetic and/or vascular complications
- Cognitive decline

Burden of hypoglycemia can lead to **reluctance to intensify** treatment as necessary

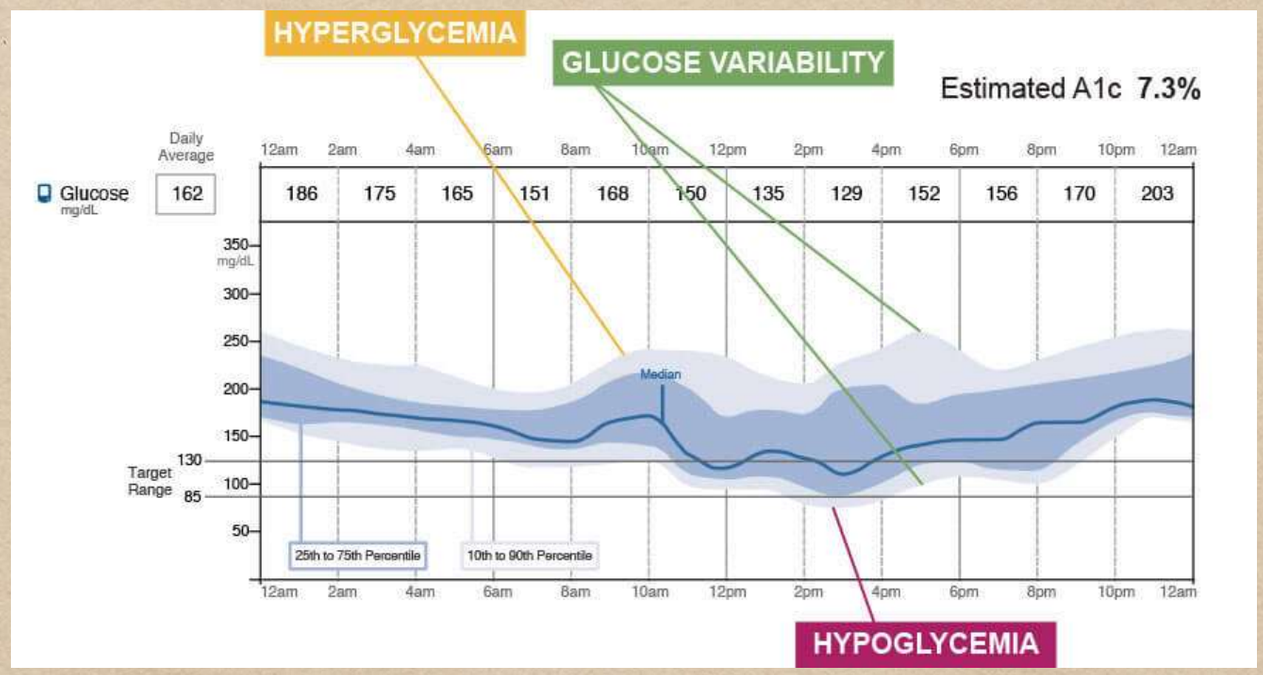
1. Frier BM. Hypoglycemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol*. 2014;10(12):711–722.

Glucose Monitoring




www.jothydev.net
+91 9447040055


Messages
Important
messages
would appear
here
Current glucose
reading
Food note
Grams of food
or serving data
6.2
FreeStyle Libre


HYPERGLYCEMIA
GLUCOSE VARIABILITY
Estimated A1c 7.3%
Daily Average
Glucose mg/dL
162
12am 2am 4am 6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am
186 175 165 151 168 150 135 129 152 156 170 203
350 mg/dL
300
250
200
150
Target Range 130
100
85
50
Median
25th to 75th Percentile
10th to 90th Percentile
12am 2am 4am 6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am
HYPOGLYCEMIA

Example start titration algorithms

	Long-acting basal insulins[1] (glargine, detemir)	Ultra-long-acting[2] (degludec)
Start with	10 units once daily	
Adjust dose	Every day	**Once a week**
Based on	That morning's FPG	
Increase/decrease by	1 unit	**4 units**
Until	FPG target achieved	

REMEMBER: Insulin has no dose ceiling!

1. Canadian Diabetes Association. Appendix 3: Examples of Insulin Initiation and Titration Regimens in People with Type 2 Diabetes. Available at: http://guidelines.diabetes.ca/browse/appendices/appendix3; 2. Philis-Tsimikas A et al. Insulin degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). *Adv Ther.* 2013;30(6):607-622.

Basal insulin analogues vs. NPH: Nocturnal hypoglycemia reduced

Overall hypoglycemia

Similar for insulin analogues vs. NPH

Nocturnal hypoglycemia

For insulin analogues vs. NPH

Why?

Mechanism of protraction

Flatter time-action profile (reduced peak)

+

Increased duration of action (less peak:trough ratio)

+

Lower variability

1. Hannele YJ et al. Less Nocturnal Hypoglycemia and Better Post-Dinner Glucose Control With Bedtime Insulin Glargine Compared With Bedtime NPH Insulin During Insulin Combination Therapy in Type 2 Diabetes. *Diabetes Care.* 2000;23:1130–1136; 2. Philis-Tsimikas A et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther.* 2006;28:1569-1581.

Types of insulin			
Insulin type (trade name)	**Onset**	**Peak**	**Duration**
BOLUS (prandial or mealtime) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra®) • Insulin lispro (Humalog®) U-100 U-200 • Faster-acting insulin aspart (Fiasp®)	 9–20min 10–15min 10–15min 4min	 1–1.5h 1–1.5h 1–2h 0.5-1.5h	 3–5h 3.5–5h 3–4.75h 3-5h
Short-acting insulins (clear) • Insulin regular (Humulin®-R, Novolin® ge Toronto) • Insulin regular U-500 (Entuzity® (U-500)	 30min 15min	 2–3h 4-8h	 6.5h 17-24h
BASAL insulins			
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn (Humulin® N, Novolin® ge NPH)	 1–3h	 5–8h	 Up to 18h
Long-acting insulin (clear) • Insulin detemir (Levemir®) • Insulin glargine U-100 (Lantus®) • Insulin glargine U-300 (Toujeo®) • Insulin glargine biosimilar (Basaglar®) • Insulin degludec U-100, U-200 (Tresiba®)	90min	Not applicable	U-100 glargine 24h, detemir 16–24h U-300 glargine >30h degludec 42h
PREMIXED insulins			
Premixed regular insulin –NPH (cloudy) • Humulin® 30/70 • Novolin® ge 30/70, 40/60, 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)		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (NovoMix® 30) • Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)			

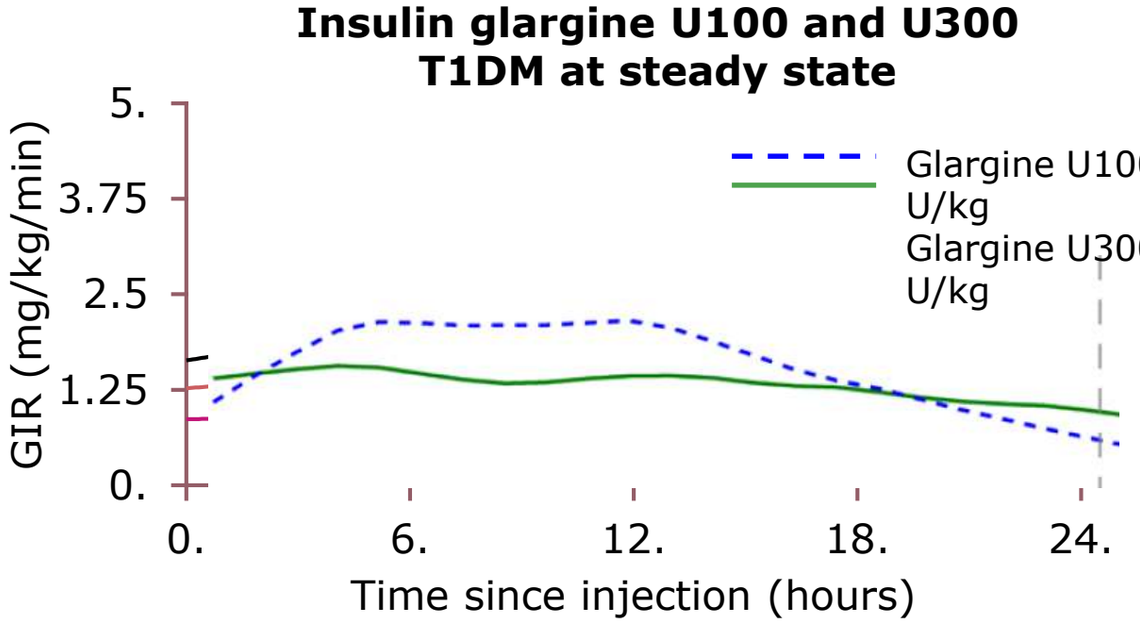
Spot the myth

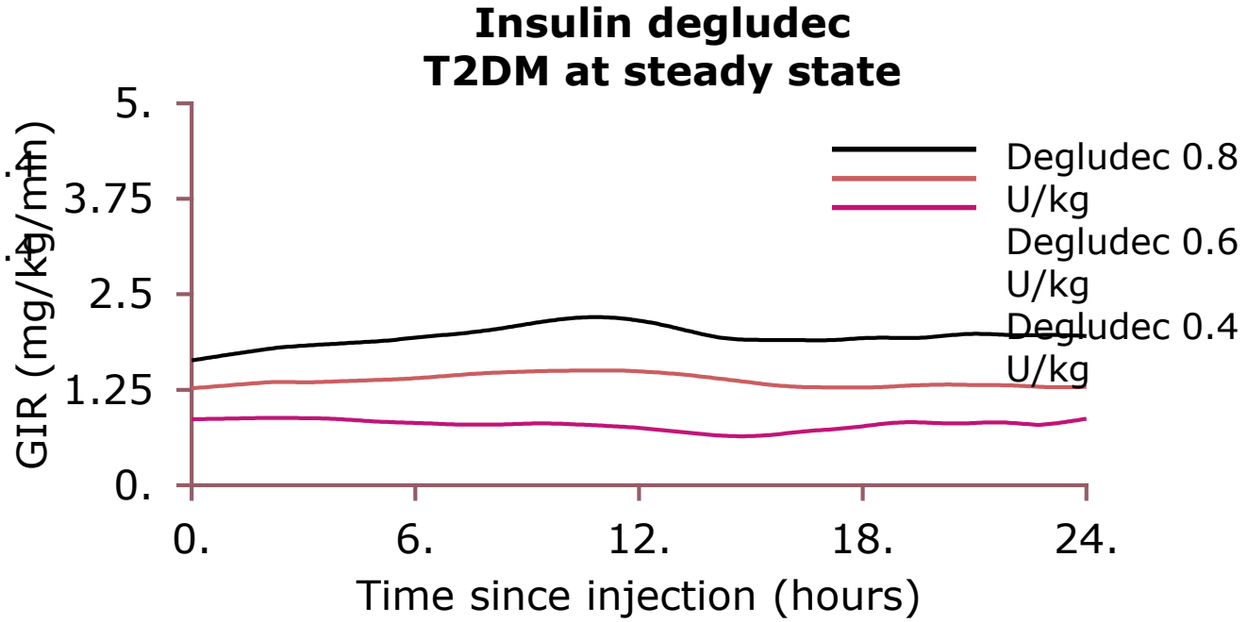
A. All basal insulins are equally efficacious in reducing A1C

B. Basal insulin advances have reduced the frequency of hypoglycemia over time

C. Insulin therapy increases the risk of major cardiovascular events in type 2 diabetes

Flat-action profile and a longer half-life for new basal insulins





$t_{1/2}$	Glargine U100	Glargine U300	Glargine U100	Degludec
Half-life (hours)	13.5	19.0	12.1	25.0

xicol.
Metab.

2012;14:944–950; 3. Heise T et al. Impact of the mode of protraction of basal insulin therapies on their pharmacokinetic and pharmacodynamic properties and resulting clinical outcomes. *Diabetes Obes Metab.* 2017;19(1):3–12.

Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

All people starting insulin should be counseled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (degludec U-100 or U-200, detemir, glargine U-100 or U-300, NPH) added to non-insulin antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L or individualized targets (e.g. 4.0 to 5.5 mmol/L if A1C target ≤7.0% not achieved; higher fasting BG targets may be considered in some people with diabetes where the goal of avoiding hypoglycemia is important, see Chapter 8. Targets for Glycemic Control, p. S42).
- Individuals can be taught self-titration, or titration may be done in conjunction with a health-care provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached. (Degludec should be titrated by 2 units every 3 to 4 days or 4 units once a week).
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal- weight subjects.
- In order to safely titrate insulin, people with diabetes must perform self-monitoring of blood glucose at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Non-insulin antihyperglycemic agents (especially insulin secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Insulin Initiation and Titration Suggestions for Type 2 Diabetes

People starting insulin should be counseled about the prevention, recognition and treatment of hypoglycemia.

The following are suggestions for insulin initiation and titration. Clinical judgment must always be used as the suggestions may not apply to every patient.

Basal Insulin (only) as an add-on to Antihyperglycemic Agents (Basaglar™, Lantus®, Levemir®, Toujeo™, Tresiba®, Humulin® N, Novolin® ge NPH)

- Target fasting blood glucose (BG) of 4-7 mmol/L. The fasting BG target can be changed to 4-5.5 mmol/L if not achieving adequate overall glycemic control.
- Most patients will need 40-50 units at bedtime to achieve target but there is no maximum dose.
- Start at a low dose of 10 units at bedtime (may start at lower dose [0.1 -0.2 units/kg] for lean patients [<50 kg]).
- If using Tresiba®, the dose can be increased by 2-4 units every week until fasting BG target is achieved.
- Patient should gently self-titrate by increasing the dose by 1 unit every 1 night until fasting BG target is achieved.
- If fasting hypoglycemia occurs, the dose of bedtime basal should be reduced.
- Metformin and the secretagogue are usually maintained when basal insulin is added.

Dosing and Titration Example

Starting dose 10 units at bedtime.

Increase dose by 1 unit every 1 night until fasting blood glucose has reached the target of 4-7 mmol/L.

- Typically, insulin secretagogues are stopped and only metformin is continued when bolus (prandial) insulin is added.
- For current basal insulin users, maintain the basal dose and add bolus insulin with each meal at a dose equivalent to 10% of the basal dose. For example, if the patient is on 50 units of basal insulin, add 5 units of bolus insulin with each meal.
- For new insulin users starting a full Basal + Bolus regimen, calculate Total Daily Insulin dose (TDI) as 0.3 to 0.5 units/kg, then distribute as follows:
  - 40% of TDI dose as basal insulin (Lantus®, Levemir®, Toujeo™, Humulin® N, Novolin®ge NPH) at bedtime.
  - 20% of TDI dose as prandial (bolus) insulin prior to each meal.
  - Rapid-acting insulin analogues (Apidra®, Fiasp®, Humalog®, NovoRapid®) should be given 0-10 minutes before eating.
  - Short-acting insulin (Humulin® R, Novolin® ge Toronto) should be given 30 minutes before eating.
- An alternative distribution is 50% basal insulin (at bedtime) and 50% bolus insulin (distributed among the meals of the day).
- Adjust the dose of the basal insulin to achieve the target fasting BG level (usually 4-7 mmol/L).
- Adjust the dose of the bolus (prandial) insulin to achieve postprandial BG levels (usually 5-10 mmol/L) or pre-prandial BG levels for the subsequent meal (usually 4-7 mmol/L).

- TDI = 50 units

Basal insulin = 40% of TDI:
40% x 50 units
- Basal bedtime = 20 units

Bolus insulin = 60% of TDI:
60% x 50 units
- Bolus = 30 units

= 10 units with each meal

Premixed Insulin Before Breakfast and Before Dinner (Humalog® Mix25™, Humalog® Mix50™, NovoMix® 30, Humulin® 30/70, Novolin®ge 30/70)

- Target fasting and pre-supper BG levels of 4-7 mmol/L.
- Most patients with type 2 diabetes will need 40-50 units twice a day to achieve target but there is no maximum dose.
- Start at a low dose of 5 to 10 units twice daily (before breakfast and before supper).
- Patient can gently self-titrate by increasing the breakfast dose by 1 unit every day until the pre-supper BG is at target.
- Patient can gently self-titrate by increasing the supper dose by 1 unit every day until the fasting BG target is at target.
- Beware of hypoglycemia post-breakfast or post-supper. Stop increasing dose if this occurs.
- Premixed analogue insulins (Humalog® Mix25™, Humalog® Mix50™, NovoMix® 30) should be given 0 to 10 minutes before eating.
- Premixed regular insulins (Humulin® 30/70, Novolin® ge 30/70) should be given 30 minutes before eating.
- Continue Metformin and consider stopping secretagogue.

Dosing and Titration Example

10 units ac breakfast , 10 units ac supper.

Increase breakfast dose by 1 unit every 1 day until pre-supper blood glucose has reached the target of 4-7 mmol/L (usual target).

Increase supper dose by 1 unit every 1 day until fasting blood glucose has reached the target of 4-7 mmol/L (usual target).

Selection of Pen Needle

- Forum for Injection Technique (FIT) Canada recommends that 4, 5, and 6mm needles are suitable for all people with diabetes regardless of BMI. In addition, there is no clinical reason for recommending needles longer than 8mm. Initial insulin therapy should start with the shorter needle length (Berard L, et al. FIT Forum for Injection Technique Canada. Recommendations for Best Practice in Injection Technique. October 2011).

CHOOSE AN INSULIN TYPE

CHOOSE A BRAND

DOSING

SEE REVERSE FOR TIPS

tion

n column.

Prescriber's Name:

Addres

Tel:

Patient's Nam

Address:

Tel:

STEP 1: Choose Insulin Type				STEP 2: Dosing and Titration
BASAL **Long-acting analogues** (Clear)	☐ **Basaglar™** ☐ Cartridge ☐ Kwikpen® (prefilled)	☐ **Levemir®** ☐ Cartridge ☐ FlexTouch® (prefilled) ☐ **Tresiba®** ☐ FlexTouch® 100 U/mL (prefilled) ☐ FlexTouch® 200 U/mL (prefilled)	☐ **Lantus®** ☐ Cartridge ☐ Vial ☐ SoloSTAR® (prefilled) ☐ **Toujeo™** ☐ SoloSTAR® (prefilled)	**Starting dose:** _____ units at _____ Increase dose by _____ units every _____ until fasting blood glucose has reached the patient's individual target of _____ mmol/L.
Intermediate-acting (Cloudy)	☐ **Humulin® N** ☐ Cartridge ☐ Vial ☐ Kwikpen® (prefilled)	☐ **Novolin® ge NPH** ☐ Cartridge ☐ Vial		
PRANDIAL (BOLUS) **Rapid-acting analogues** (Clear)	☐ **Humalog®** ☐ Cartridge ☐ Vial ☐ Kwikpen® (prefilled) ☐ **Humalog® 200 units/mL** ☐ Kwikpen® (prefilled)	☐ **Fiasp®** ☐ Cartridge ☐ Vial ☐ FlexTouch® (prefilled) ☐ **NovoRapid®** ☐ Cartridge ☐ Vial ☐ FlexTouch® (prefilled)	☐ **Apidra®** ☐ Cartridge ☐ Vial ☐ SoloSTAR® (prefilled)	**Starting dose:** _____ units ac breakfast _____ units ac lunch _____ units ac supper
Short-acting (Clear) Give 30 minutes before meal.	☐ **Humulin® R** ☐ Cartridge ☐ Vial	☐ **Novolin® ge Toronto** ☐ Cartridge ☐ Vial		
PREMIXED **Premixed analogues** (Cloudy)	☐ **Humalog® Mix25™** ☐ Cartridge ☐ Kwikpen® (prefilled) ☐ **Humalog® Mix50™** ☐ Cartridge ☐ Kwikpen® (prefilled)	☐ **NovoMix® 30** ☐ Cartridge		**Starting doses:** _____ units ac breakfast _____ units ac supper Increase breakfast dose by _____ units every day until pre-supper blood glucose has reached the target of _____ mmol/L. Increase pre-supper dose by _____ units every day until fasting blood glucose has reached the target of _____ mmol/L. Beware of hypoglycemia post-breakfast or post-supper. Stop increasing dose if hypoglycemia occurs.
Premixed regular (Cloudy)	☐ **Humulin® 30/70**	☐ **Novolin® ge 30/70**		

SELECT PEN DEVICE

CHECK OFF SUPPLIES

QUANTITY & REPEATS

PEN DEVICE Required if insulin cartridges selected. Insulin pen should match the insulin brand.	☐ **HumaPen® Savvio™** ☐ **HumaPen LUXURA® HD**	☐ **NovoPen® 4** ☐ **NovoPen Echo®** ☐ **NovoPen® 5**	☐ **ClikSTAR™**
OTHER SUPPLIES	☐ **Pen needles (if using a pen):** Check needle size (refer to back for information): ☐ 4mm ☐ 5mm ☐ 6mm ☐ 8mm **OR** ☐ At discretion of pharmacist ☐ Glucose test strips ☐ Lancets ☐ Insulin Syringe (if using vials) ☐ Glucagon Kit (if applicable) ☐ Ketone Strips (if applicable)		
QUANTITY and REPEATS	**Insulin** Mitte: _____ boxes Repeats x _____		**Supplies** Mitte: _____ boxes Repeats x _____

Signature: Print Name: License #:

SIGN AND DATE

This tool was developed by the Ontario College of Family Physicians and the New Brunswick Diabetes Task Group and was re-produced with permission by Diabetes Canada. Diabetes Canada will keep this tool updated and available at guidelines.diabetes.ca.
Updated December 2017 416584

Type of diabetes: ☐ Type 1 ☐ Type 2 ☐ Other **Date Diagnosed:**

Patient Name:

Comorbidities:
☐ Hypertension ☐ Coronary artery disease ☐ Stroke/TIA
☐ Dyslipidemia ☐ Peripheral arterial disease ☐ Depression/Anxiety
☐ CKD - stage _____ ☐ Other(s):

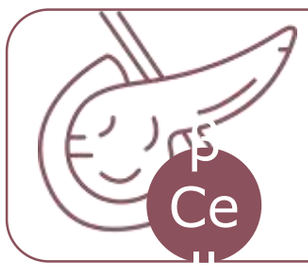
Date of Birth:

		Date:	Date:	Date:
Healthy behaviour interventions	**Weight** (kg) **Height** (cm) **BMI** **Waist circumference** (cm)	Wt _____ Ht _____ BMI _____ WC _____	Wt _____ Ht _____ BMI _____ WC _____	Wt _____ Ht _____ BMI _____ WC _____
	Nutrition			
	Physical Activity (Aerobic 150 mins/week, Resistance 2-3x/week)			
	Smoking Status	☐ Non-smoker ☐ Ex-smoker ☐ Smoker	☐ Non-smoker ☐ Ex-smoker ☐ Smoker	☐ Non-smoker ☐ Ex-smoker ☐ Smoker
Glycemic control	**A1C** (target: ≤7% or _____ %) (Individualize based on patient characteristics and antihyperglycemic medication(s) – see CPG) (q3 months. If at target and stable - q6 months)	Test Date: Result:	Test Date: Result:	Test Date: Result:
	Antihyperglycemic Medication(s) **Drug Name(s)/Dose(s):**			
	Therapy Adherence/Concerns			
	BG Record (targets: premeal: 4-7 mmol/L or _____ mmol/L; 2hr postmeal: 5-10 mmol/L or _____ mmol/L) (Individualize based on ability to achieve A1C target + risk of hypoglycemia) (Annual fasting glucose meter/lab comparison)	Meter/Lab	Meter/Lab	Meter/Lab
	Hypoglycemic Episodes (frequency/pattern/driving risk)			
CV Risk Assessment and Management	**BP** (target <130/80 mm Hg, 3 readings recommended) **Pulse**			
	Antihypertensive(s) **Drug Name(s)/Dose(s):**			
	CVD Symptoms (angina, decreased exercise tolerance, SOB, HF symptoms, claudication)	☐ None ☐ Yes	☐ None ☐ Yes	☐ None ☐ Yes
	Resting ECG, every 3-5 yrs If any: age >40 yrs; duration of diabetes >15 yrs + age >30 years; end organ damage (microvascular, CV); >1 CV risk factor(s)	Date: Report:	Date: Report:	Date: Report:
	Lipids (primary target: LDL <2.0 mmol/L or >50% reduction in LDL, or non-HDL <2.6 mmol/L or apo B <0.8 g/L)	LDL-C non-HDL-C test date:	LDL-C non-HDL-C test date:	LDL-C non-HDL-C test date:
	Lipid-lowering Therapy **Statin +/- 2nd line agent(s)** **Drug Name(s)/Dose(s):** (If any: clinical CVD; age ≥40 yrs; age <40 yrs + 1 of the following: diabetes duration >15 yrs and age >30 yrs; microvascular complications; warrants therapy based on presence of other risk factors according to 2016 CCS Lipid Guidelines)	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:
	ACE inhibitor/ ARB **Drug Name(s)/Dose(s):** If any: clinical CVD; age >55 yrs with an additional CV risk factor or end organ damage (albuminuria, retinopathy, LVH); microvascular complications	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:

		Date:	Date:	Date:
	Antihyperglycemic Agent with Demonstrated CV Outcome Benefit **Drug Name(s)/Dose(s):** (If type 2 DM with clinical CVD not at glycemic target - empagliflozin, liraglutide, canagliflozin)	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:
	Antiplatelet Agent(s) **Drug Name(s)/Dose(s):** (If established CVD; consider if additional CV risk factors)	☐ Not indicated ☐ Yes	☐ Not indicated ☐ Yes	☐ Not indicated ☐ Yes
CKD	**Urine ACR** (normal <2 mg/mmol)	Test Date: Result:	Test Date: Result:	Test Date: Result:
	Serum Creatinine/eGFR	Test Date: Result:	Test Date: Result:	Test Date: Result:
	CKD	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Retinopathy	**Dilated Eye Exam** (type 1 – annually; type 2 – q1-2 years or as recommended by vision care professional)	☐ Date of last visit: ☐ Reminded	☐ Date of last visit: ☐ Reminded	☐ Date of last visit: ☐ Reminded
	Retinopathy	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
	Severity/Therapies			
Neuropathy	**Neuropathy Symptoms** (e.g. pain, paresthesia, GI symptoms, sexual dysfunction)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
	Diabetic Foot Exam (includes 10 g monofilament or 128 Hz tuning fork, structural abnormalities, skin changes, pulses) (annually for screening; every visit if diabetic foot complications) See Appendices 11A, 11B and 12	Sensation _____ Pulses _____ Skin _____ Other _____	Sensation _____ Pulses _____ Skin _____ Other _____	Sensation _____ Pulses _____ Skin _____ Other _____
	Neuropathy	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Mental Health	**Screen for Depression, Anxiety, Other Stressors** (consider use of PHQ-9, GAD-7)	Concerns:	Concerns:	Concerns:
Vaccination	**Influenza** (annual)	☐ No ☐ Yes Reason: Date:	☐ No ☐ Yes Reason: Date:	☐ No ☐ Yes Reason: Date:
	Pneumococcal (once; repeat if >65 yrs)	☐ Yes Date:	☐ No Reason:	
Management Plans	**Patient Goals** **Barriers to Self-management** (e.g. coverage, accessibility, competing demands)			
	Women Contraception/preconception planning			
	Driving Guidelines Reviewed			
	Sick-day Management (advise holding metformin, SGLT2i, SU, ACEi/ARB, diuretic, NSAIDs if inadequate fluid intake and ill			
	Referrals Made			
	Changes to Medications or Other Management			
	Resources provided			
	RECALL (usually q3-4 months)	☐ Appointment given ☐ Noted in recall system	☐ Appointment given ☐ Noted in recall system	☐ Appointment given ☐ Noted in recall system

For additional diabetes management resources, visit **www.guidelines.diabetes.ca.**

Basal insulin effectively lowers blood sugar



Type 2 diabetes is characterized by *insulin resistance* and ongoing decline of *beta-cell function*

UKPDS

Early glycemic control has short- and long-term benefits

↓ microvascular

↓ macrovascular

↑ non-insulin agents = insulin reluctance misconception to delay insulin

Early addition of insulin to oral therapy reduces the risk of complications indefinitely

1. Harper W et al. Pharmacologic Management of type 2 diabetes. *Can J Diabetes.* 2013;37:S61-S68; 2. Yki-Järvinen H et al. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care*. 2000;23(8):1130-1136; 3. Stratton IM et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258) 405-412.; 4. Lovre D et al. Benefits of timely basal insulin control in patients with type 2 diabetes. *J Diabetes Complications.* 2015:29(2):295-301.

Today