BCND – New Therapies in Type 2 Diabetes

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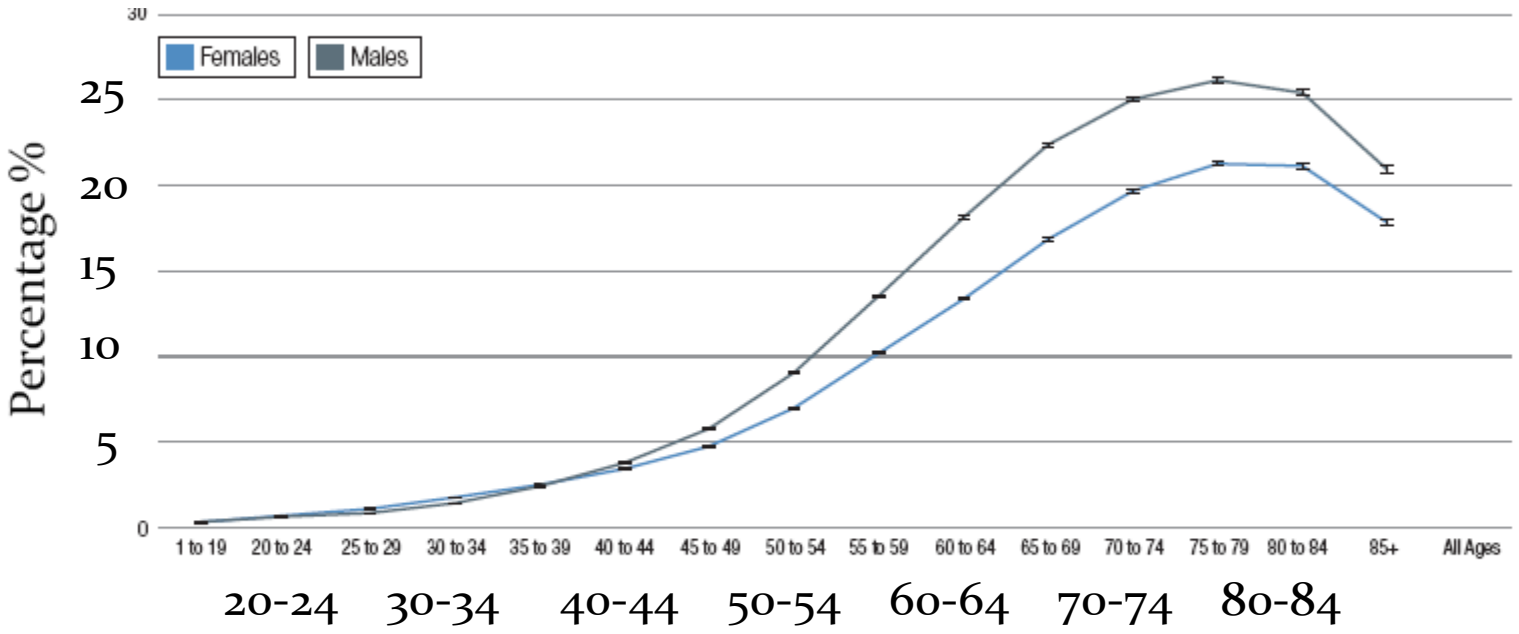
Objectives

- At the end of the talk, the participants will be able to:
- 1. Identify the increasing prevalence of type 2 diabetes and its impact on the burden of renal disease.
- 2. Identify the factors which impact the accuracy of A1c in renal patients.
- 3. Apply the latest evidence to determine an appropriate glycemic target for their patients
- 4. Discuss new treatments for type 2 diabetes

Questions

Diabetes in Canada

Diabetes prevalence rises dramatically with age

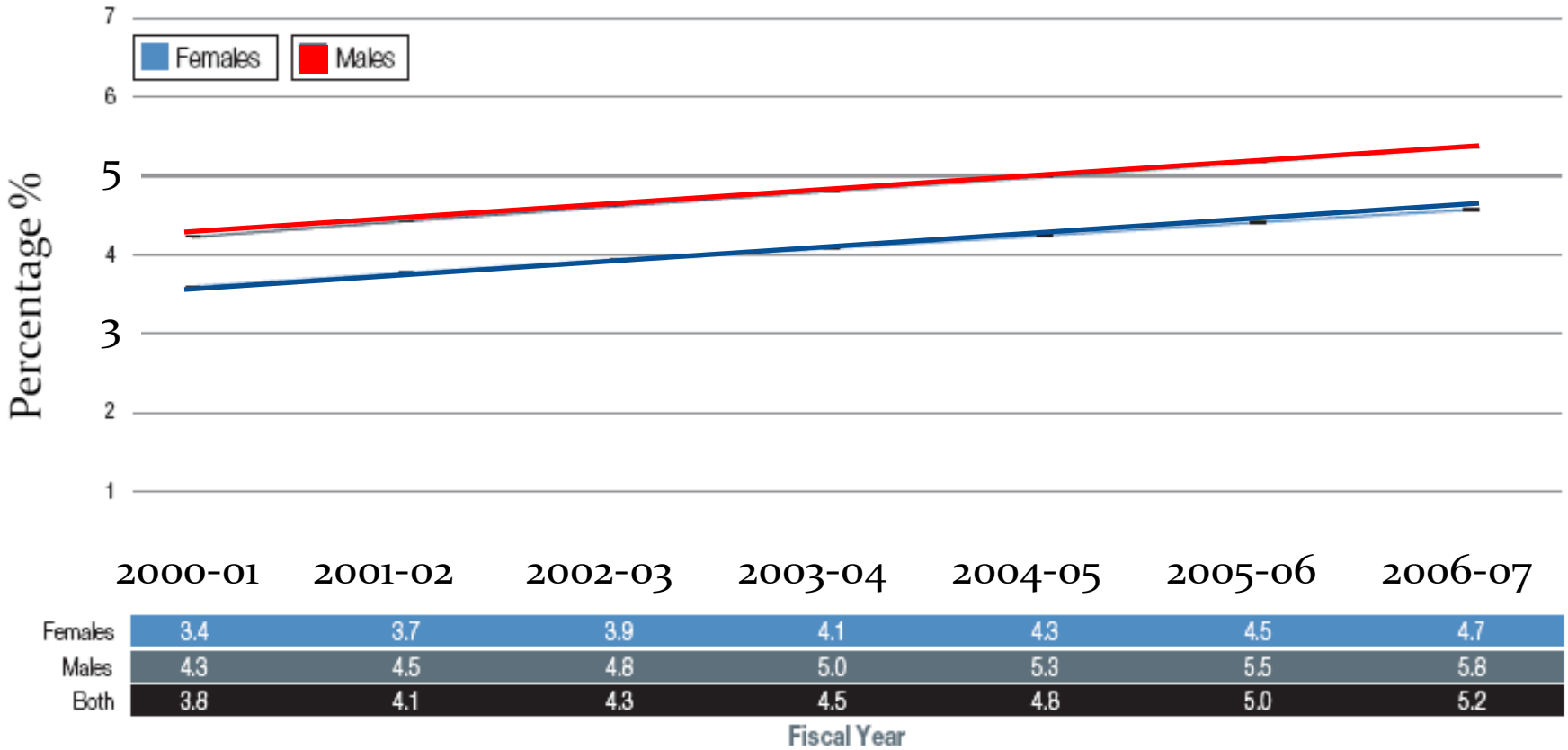


Report from the National Diabetes Surveillance System 2009.

Diabetes in Canada

F

Age-adjusted diabetes prevalence is steadily increasing



	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07
Females	3.4	3.7	3.9	4.1	4.3	4.5	4.7
Males	4.3	4.5	4.8	5.0	5.3	5.5	5.8
Both	3.8	4.1	4.3	4.5	4.8	5.0	5.2

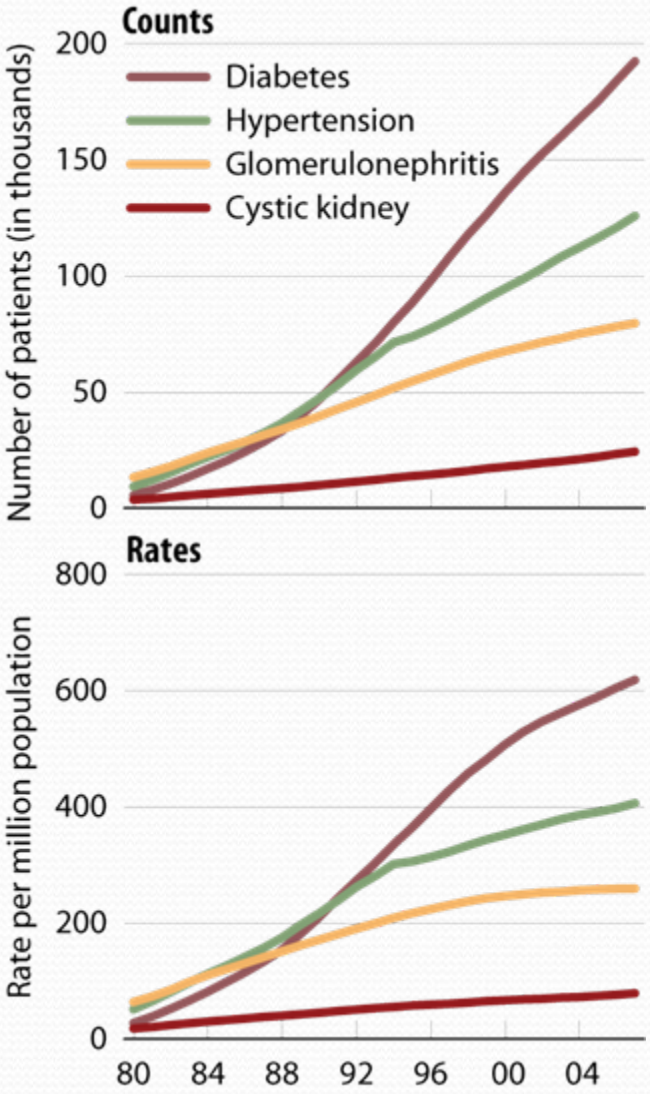
Report from the National Diabetes Surveillance System 2009.

Diabetes in Canada

- Every year 120,000 Canadians will be diagnosed with diabetes
- 2.5 Million Canadians are currently affected by the disease
- Adjusted for age, the prevalence is increasing by 6% per year.

Report from the National Diabetes Surveillance System 2009.

Diabetes continues to be the leading cause of ESRD



December 31 point prevalent ESRD patients; rates adjusted for age, gender, & race.

USRDS 2009 ADR

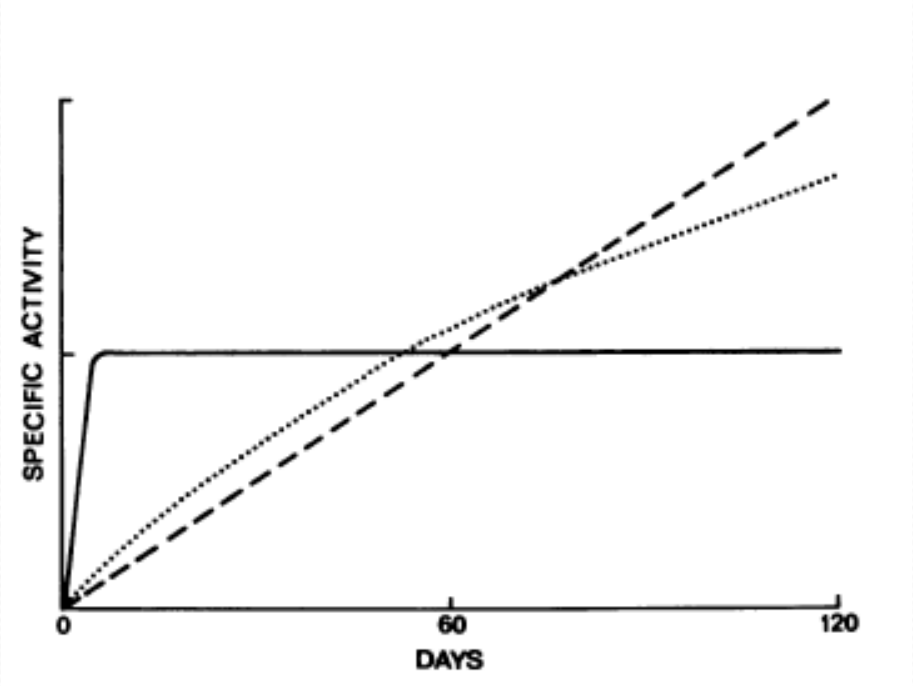
A1c in renal disease:

Useful marker or false reassurance?

Hemoglobin A1c

- Several types of hemoglobin in humans
  - 90% exists as Hb A.
  - After production – glucose can be added to HbA to create a HbA1c molecule
  - Glucose is added over the lifecycle of the RBC (~120 days)

Glycation of hemoglobin occurs over life-cycle of RBC at a relatively constant rate

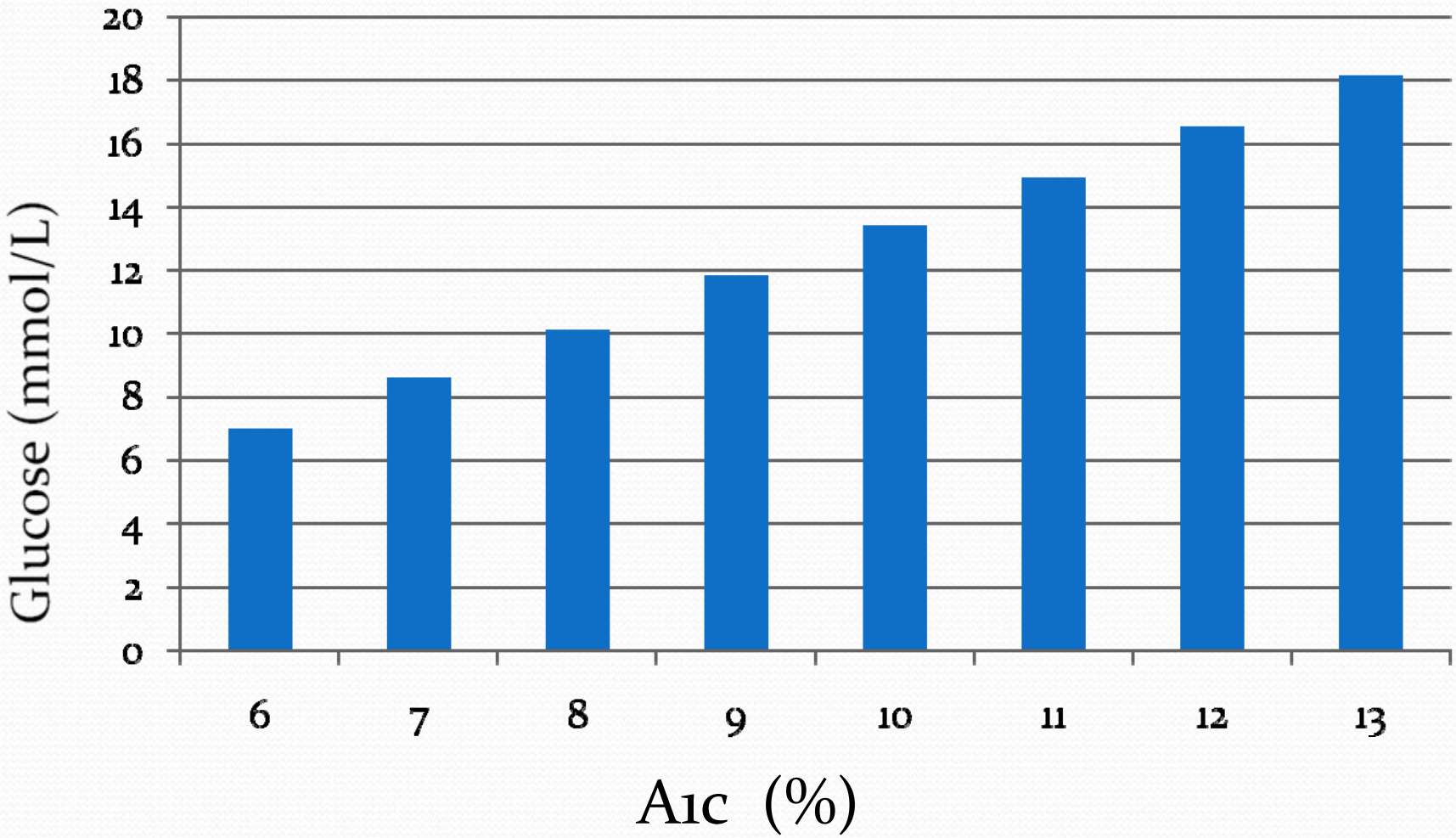


Bunn HF. J of Clin Invest. 1976. 1652-1659

A1c

- Rate of glycation is dependent on the concentration of glucose present in the RBC

Average Glucose by A1c



Nathan DM. Diabetes Care 2008

Factors which lower A1c

- Increased RBC turnover
  - Hemoglobinopathies, hemolysis, bleeding
- Iron replacement therapy
- Salicylate therapy
- Alcoholism
- Transfusions
- Erythropoietin therapy
- Chronic Dialysis

Tarim, O. Pediatrics International. 1999.
Ziemer, DC. Ann Int Med. 2010
Brown JN. Pharmacotherapy 2009.
Freedman, BI. Perit Dial Int. 2010

Factors which increase A1c

- Uremia
- Iron, B12, or folate deficiency
- African-american ethnicity
- Chronic Dialysis

Weykamp CW. Clin Chem. 1999
Tarim, O. Pediatrics International. 1999.
Ziemer, DC. Ann Int Med. 2010.
Wang X. J Endo Invest 2004.

My take

- The A1c may be inaccurate for a number of reasons in renal failure
- Always have the patient check their glucose levels by fingerstick and correlate with A1c
- If readings agree, then I tend to follow A1c. If not, I follow glucometer readings.
- In my experience, if A1c isn't going to be accurate, it is falsely low.

Glycemic targets

Part of a multifactorial approach to care for diabetic patients

Steno-2 trial

160 patients

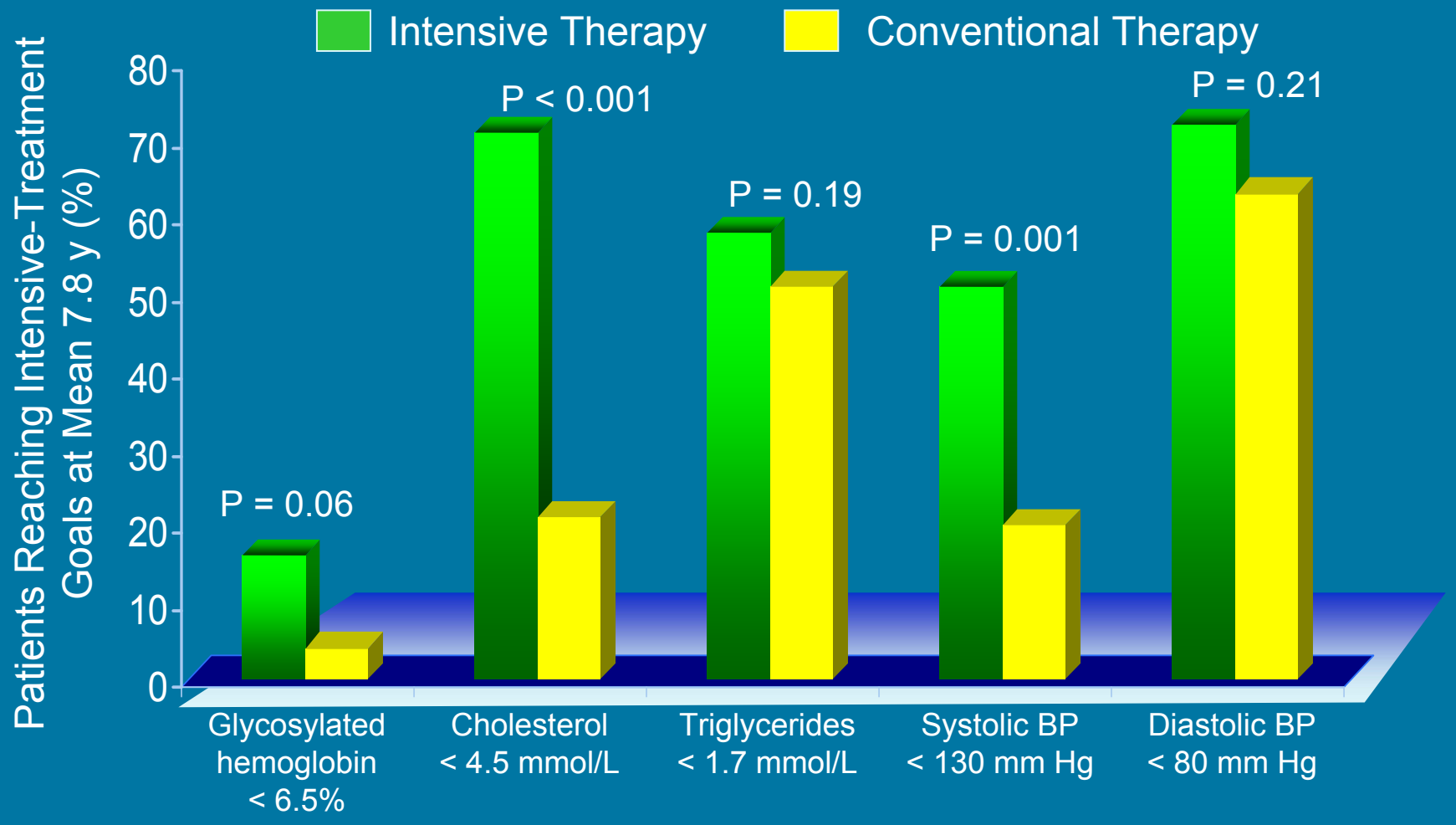
Randomized to conventional vs intensive therapy

Treated for 7.8 years ,followed for 13 years

Gæde P, et al. N Engl J Med 2003;348:383-93.

Steno-2

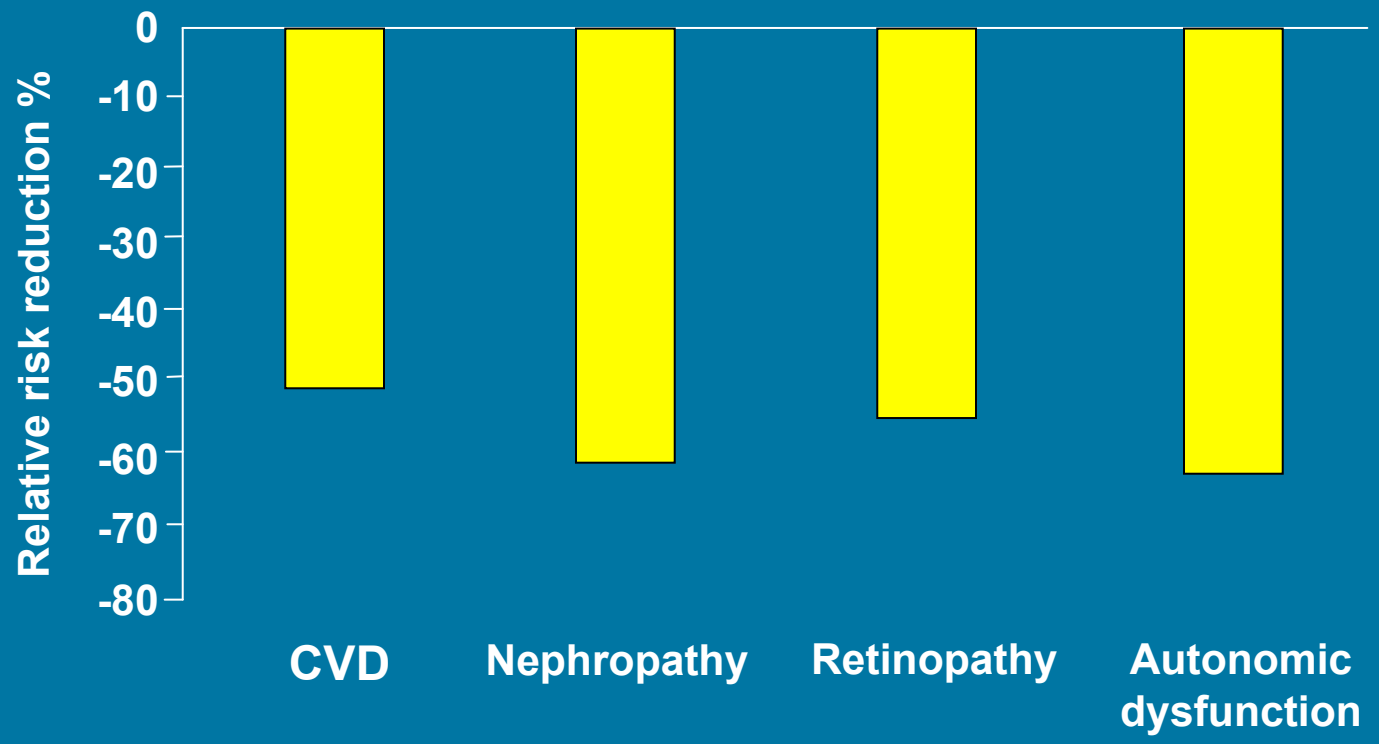
Efficacy of Multiple Risk Factor Intervention in Type 2 Diabetes with Microalbuminuria



Gæde P, et al. N Engl J Med 2003;348:383-93.

Steno-2:
Reduction in CV and Microvascular Disease

Reductions after 7.8 years of intensive vs. conventional treatment

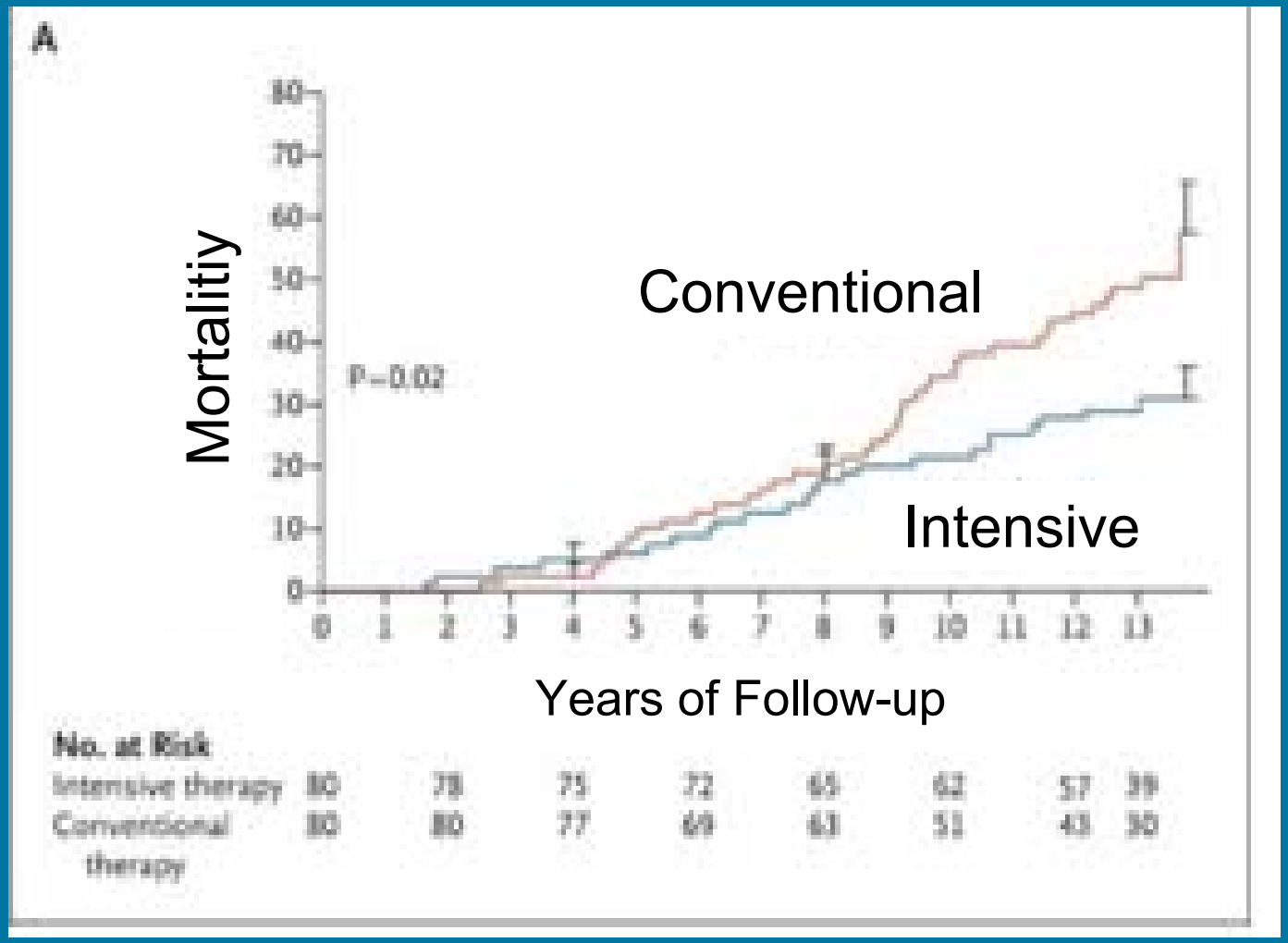


	CVD	Nephropathy	Retinopathy	Autonomic dysfunction
NNT (CI) =	5 (3–19)	4 (3–14)	5 (3–35)	4 (2–9)

NNT: number needed to treat; CI: confidence interval

Gæde P, et al. N Engl J Med 2003;348:383-93.

Mortality at 13 years



Gaede P et al. N Engl J Med 2008;358:580-591

Number Needed to Treat

- To prevent 1 death 5
- To prevent 1 cardiovascular event 3
- To prevent 1 microvascular complication 3

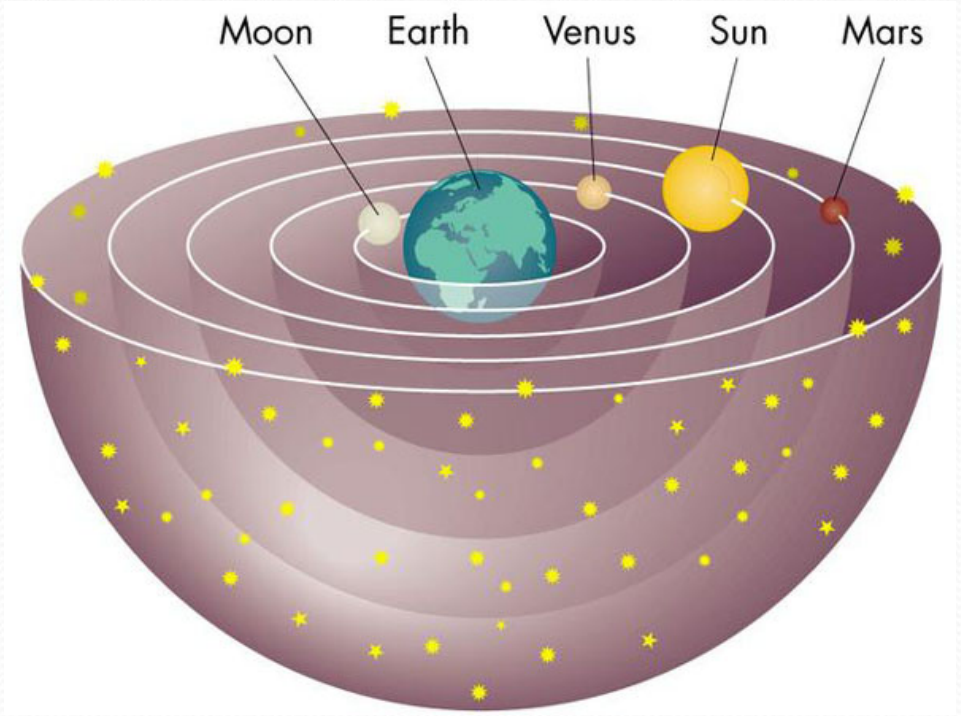
Steno-2 shows the importance of aggressive risk factor management

- Glucose
- Lipids
- Hypertension

- All important targets.

Newer evidence

Long-held beliefs



Long-held beliefs

- An A1c of 7% is good 6% must be better
- Lower glucose reduces heart disease
- Lower glucose reduces microvascular complications

Long-held beliefs – refuted in 2008

- A1c target of 6.0% may not be better than 7.0%
- Lower glucose targets don't lower macrovascular complications* (in the short term)

- Lower A1c levels reduces microvascular complications
  - At least this stayed true

ADVANCE

The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

ADVANCE

- 11140 patients randomized to A1c of 6.5% vs usual care
- DM2
- >55 + macrovascular disease, microvascular disease, or one other risk factor

The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

Randomized glucose lowering strategies

Intensive control arm

- Gliclazide MR (sulfonylurea) in all participants
- Unrestricted additional therapy to achieve target $HbA_{1c} \leq 6.5\%$

Standard control arm

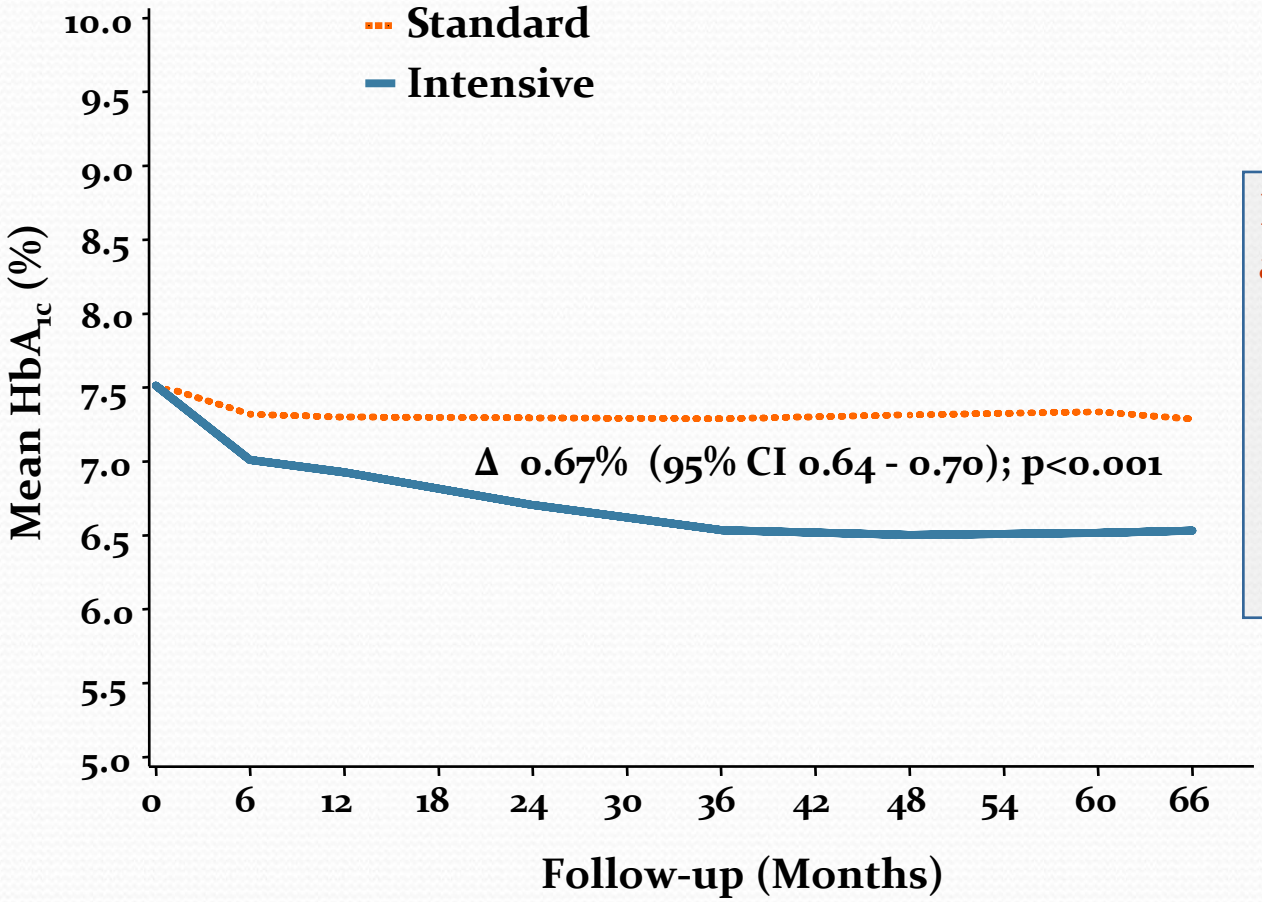
- Sulfonylurea other than Gliclazide MR
- Unrestricted additional therapy according to standard local guidelines

All other treatment

- At discretion of treating physician

The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

Hemoglobin A_{1c}



Mean HbA_{1c} at final visit

7.3 %

6.5%

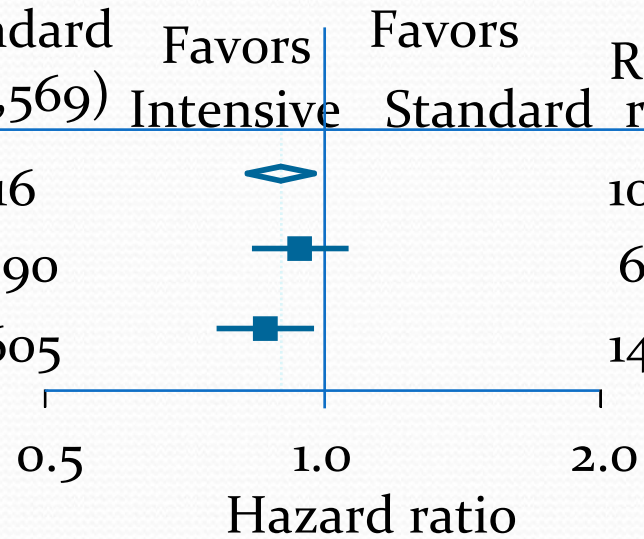
The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

Primary outcomes

Major macro or microvascular event

Number of patients with event

	Intensive (n=5,571)	Standard (n=5,569)	Relative risk reduction
Combined macro+micro	1009	1116	10% (2 to 18)
Macrovascular	557	590	6% (-6 to 16)
Microvascular	526	605	14% (3 to 23)



†P=0.013

‡P=0.015

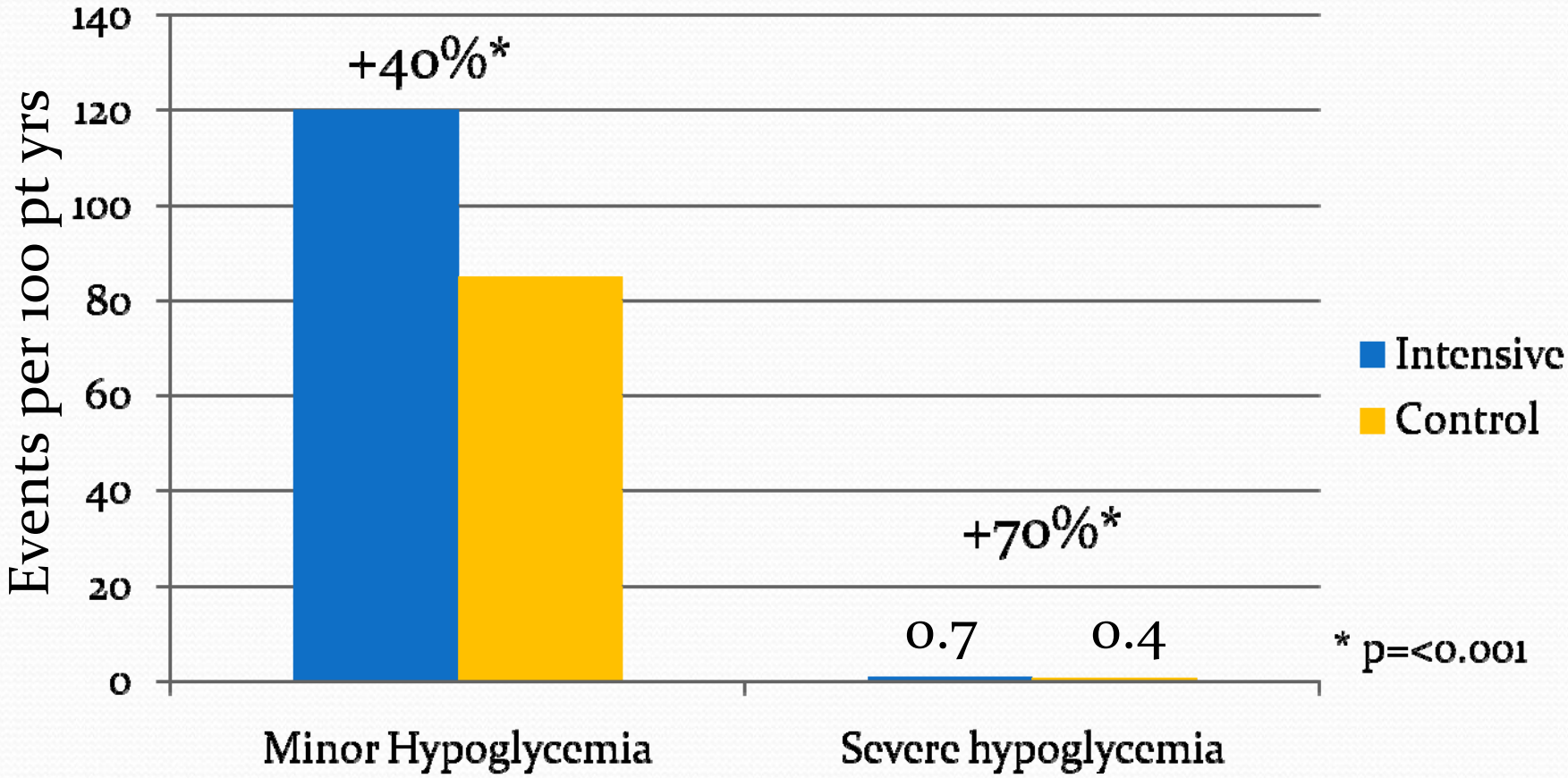
The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

Intensive control reduced microvascular disease

- Hazard Ratio 0.86 (p=0.01)
- Powered exclusively by a reduction in new or worsening nephropathy
- 4.1% vs 5.2% (p=0.006)

The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

But at a cost of increased hypoglycemia



ADVANCE summary

- Targeting an A1c of 6.5% reduced the onset and progression of diabetic nephropathy at a cost of increased hypoglycemia

The ADVANCE Collaborative Group. *N Engl J Med* 2008; 358

Canadian Diabetes Association targets for glycemic control

2003	A1C (%)	FPG/preprandial (mmol/L)	2-h postprandial (mmol/L)
Target for most patients	≤ 7.0	4.0 – 7.0	5.0 – 10.0
Normal range (consider for patients in whom it can be achieved safely)	≤ 6.0	4.0 – 6.0	5.0 – 8.0

2008	A1C (%)	FPG/preprandial (mmol/L)	2-h postprandial (mmol/L)
Type 1 and type 2 Diabetes	**≤ 7.0**	4.0 – 7.0	5.0 – 10.0 (5.0 – 8.0 if A1C targets not being met)

Can J Diabetes. 2008

Recommended targets for glycemic control

- 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.

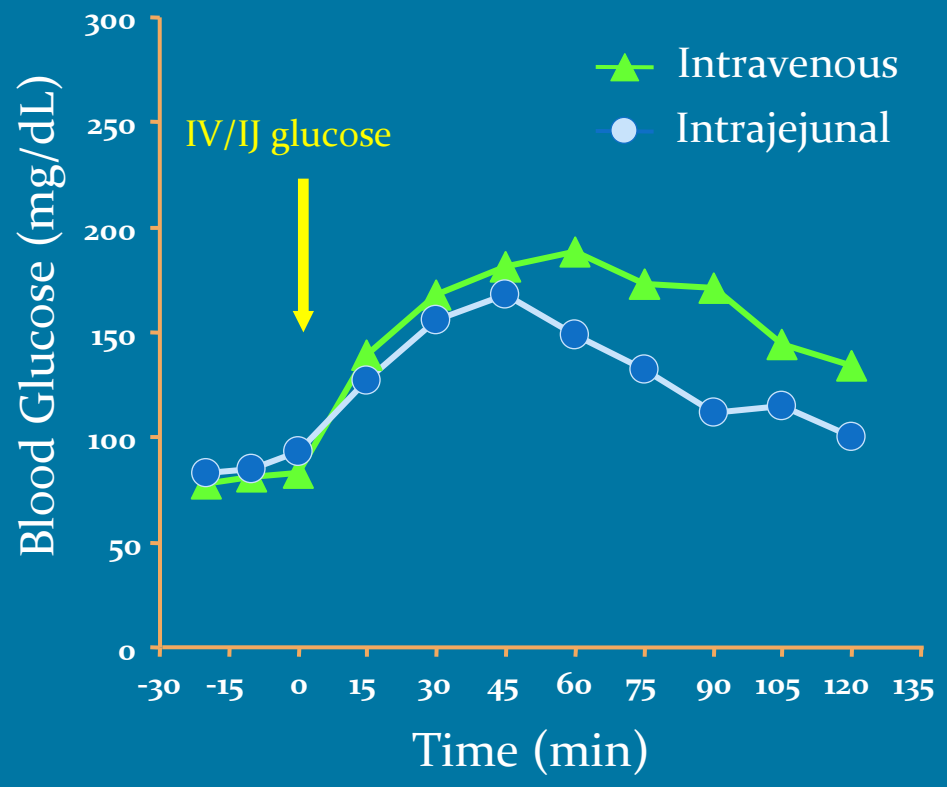
Can J Diabetes. 2008.

Exciting Advances in Diabetes

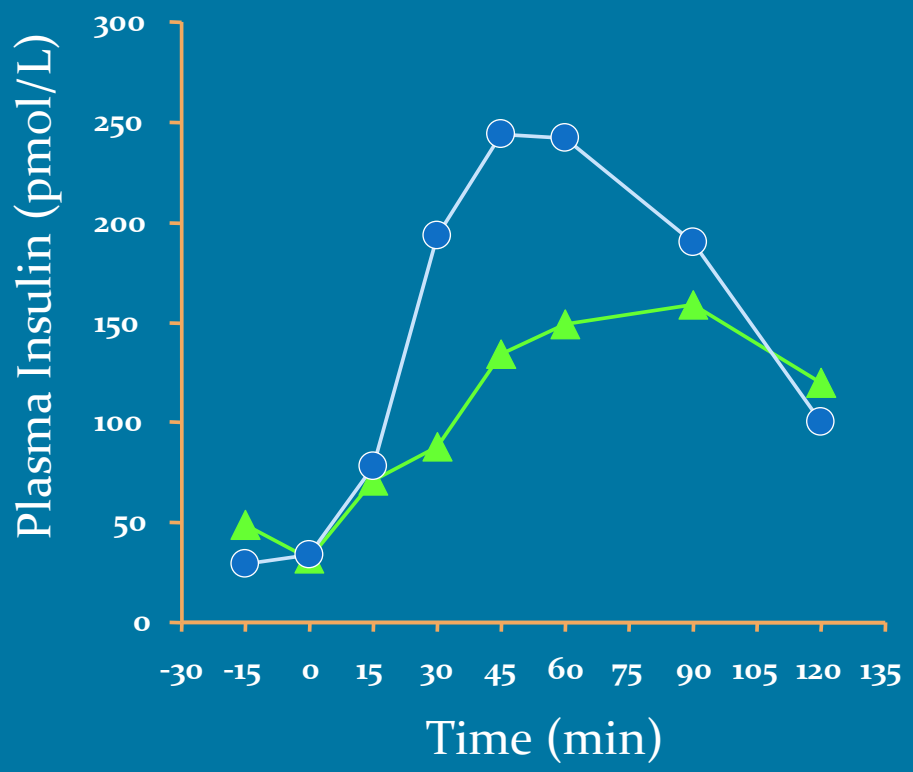
Now Available

A Fundamental Observation: Insulin Secretion is Greater with Oral versus IV Glucose

Blood Glucose

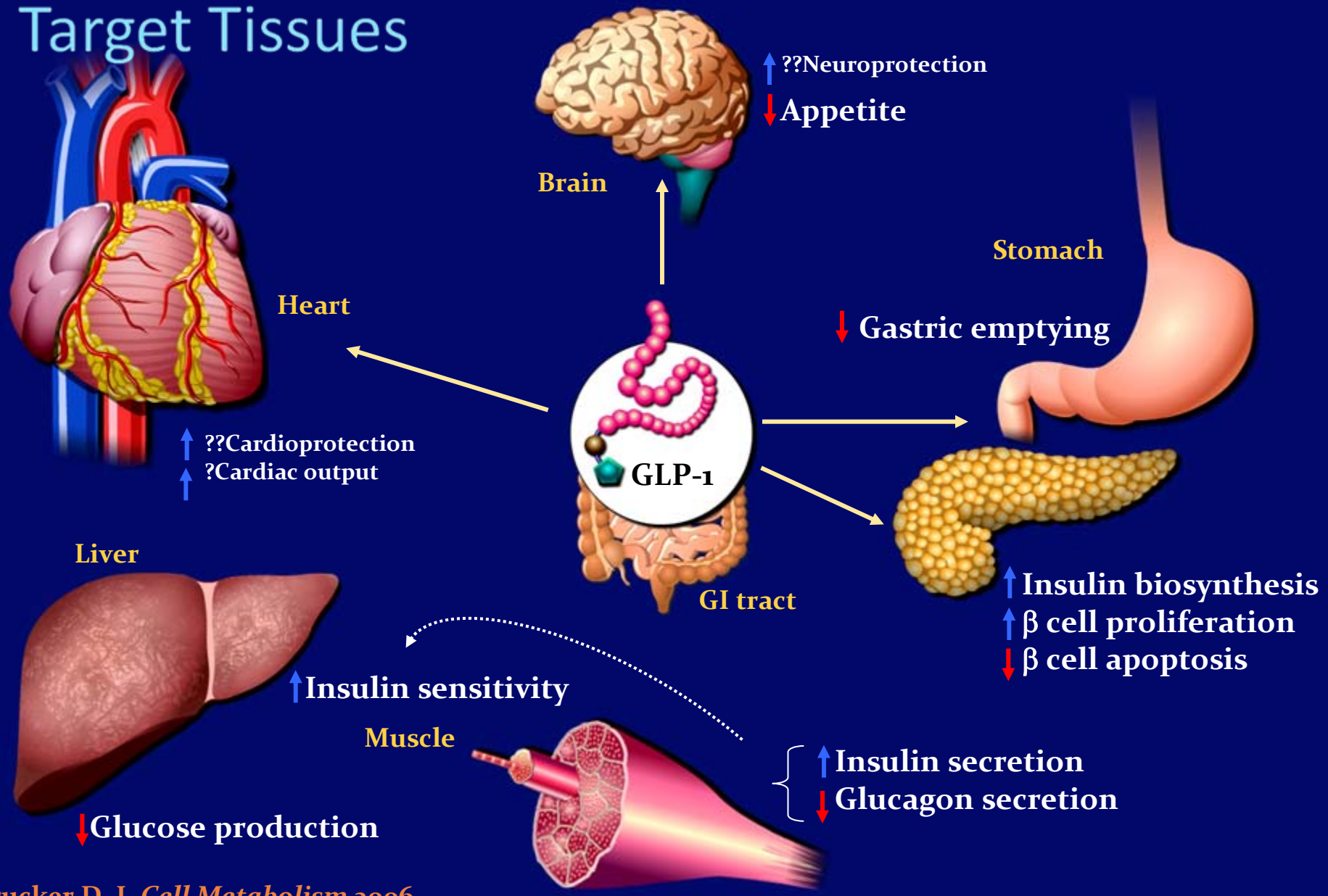


Plasma Insulin



McIntyre N. *Lancet*. 1964 Jul 4;41:20-21. Copyright © 1964.

Summary of Incretin Actions on Different Target Tissues



Drucker D. J. *Cell Metabolism* 2006

Native GLP-1 only has a ½ life of several minutes

Two Strategies

Use an analogue that isn't degraded as quickly

Inhibit the degradation enzyme

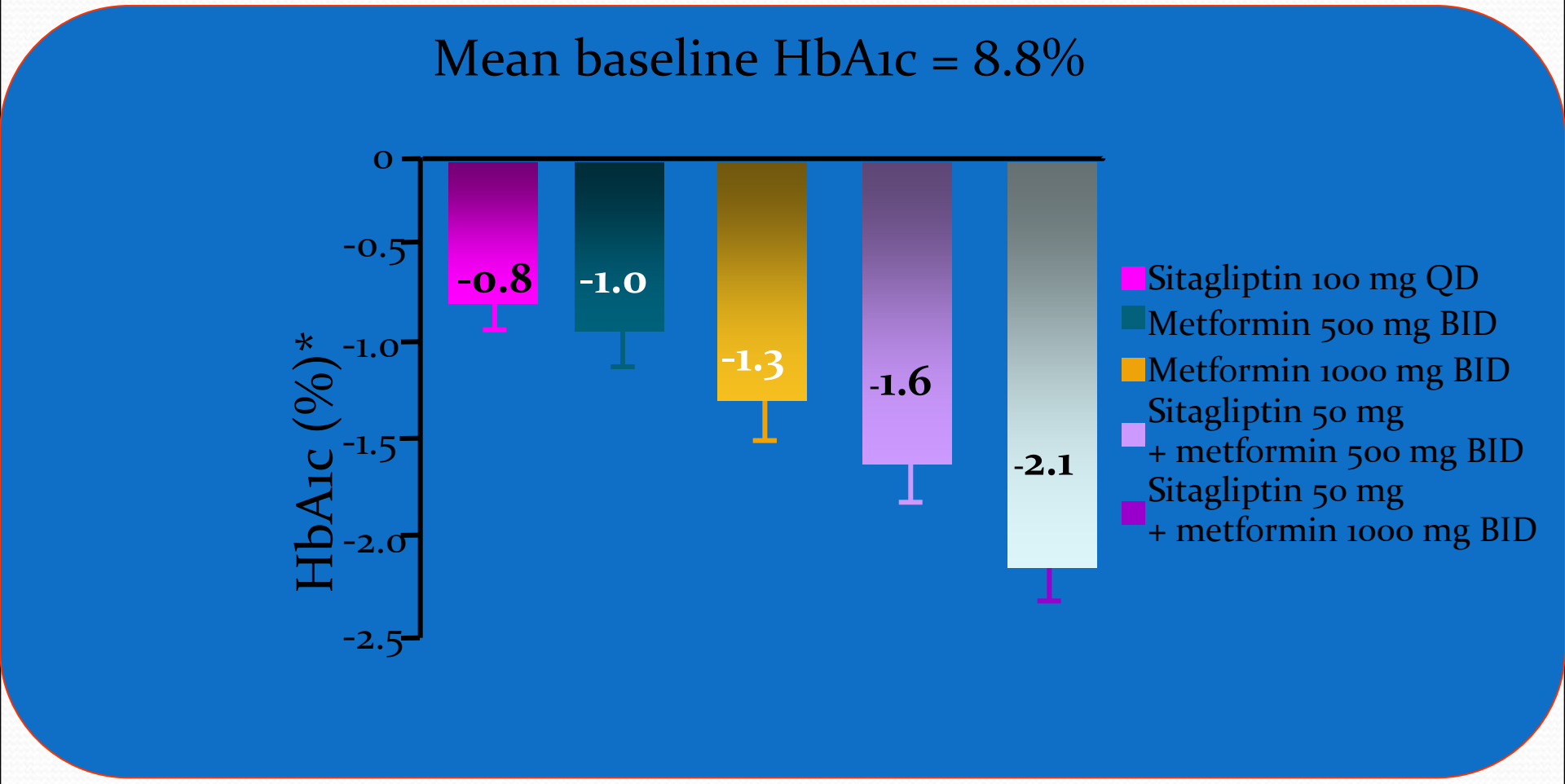
GLP-1 analogues/mimetics

Liraglutide (Victoza)

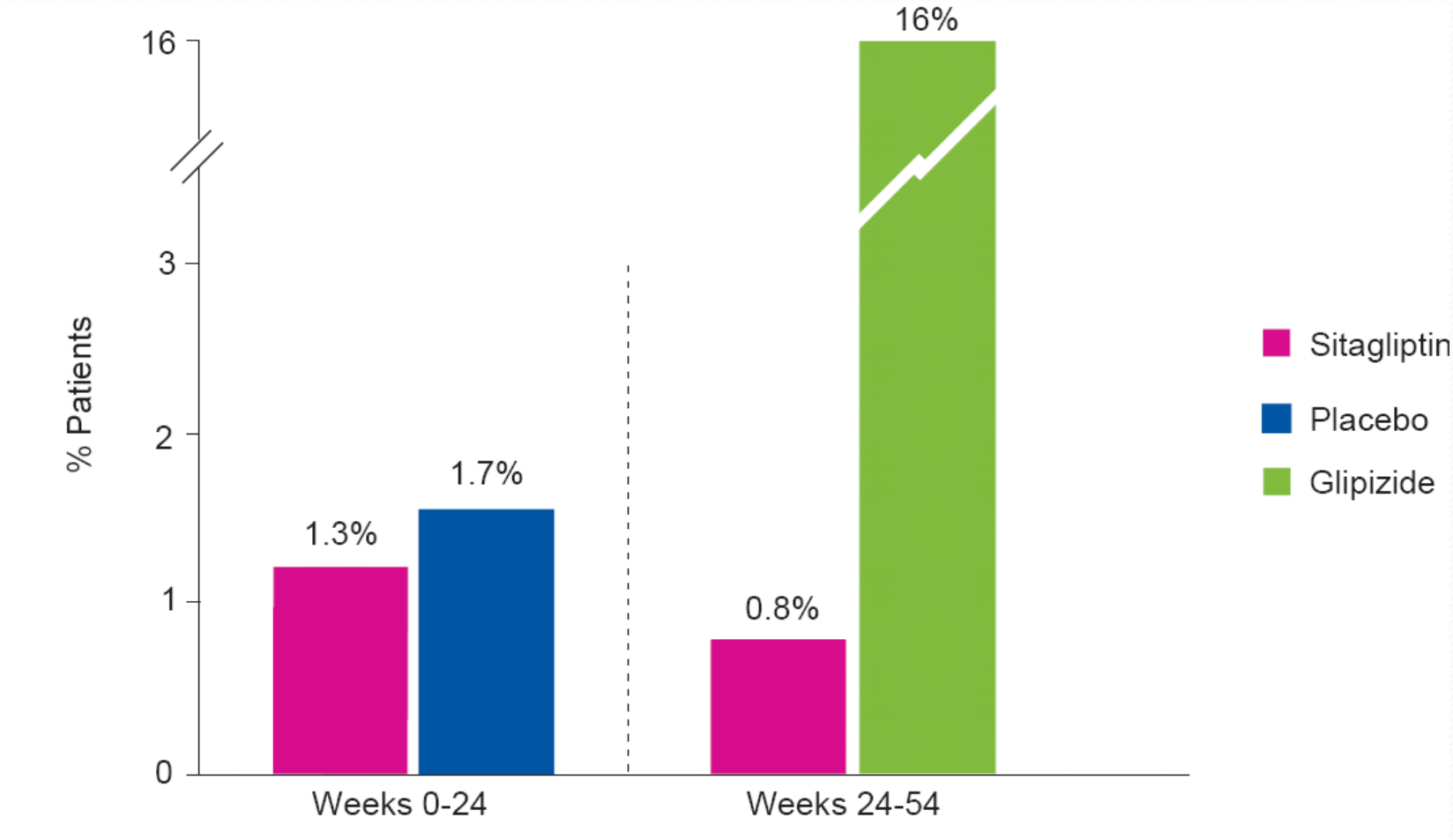
DPP-IV inhibitors

Sitagliptin (Januvia)
Saxagliptin (Onglyza)

DPP-IV inhibition with sitagliptin lowers A1c



Hypoglycemia is rare with DPP-IV inhibitors



Adapted from Karasik A et al., ADA 2007, Abstract 0523-P

DPP-IV side effects

- Similar to placebo
- Partially renally cleared so should have a dose reduction at GFR <50

Two Strategies

Use an analogue that isn't degraded as quickly

Inhibit the degradation enzyme

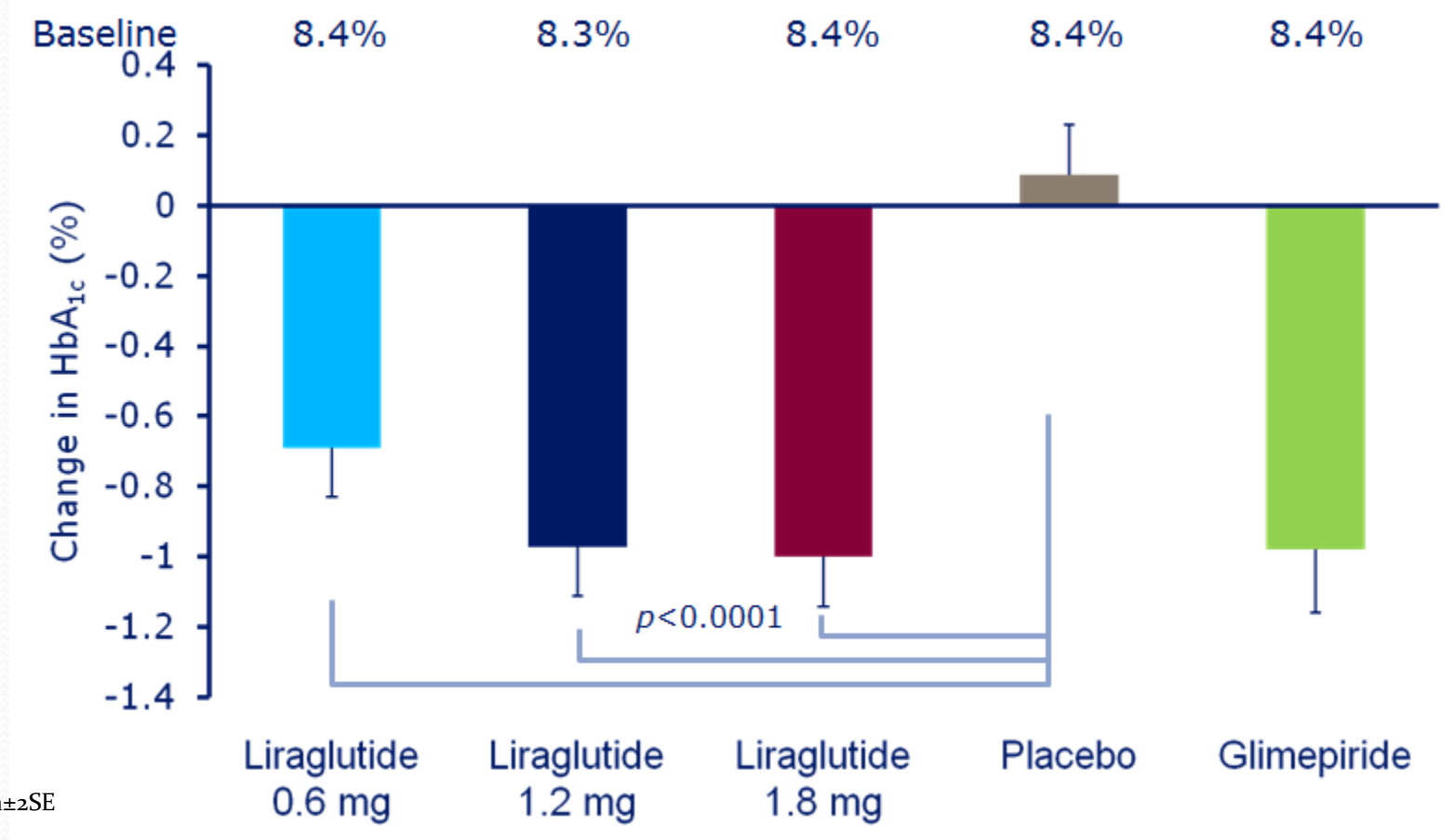
GLP-1 analogues/mimetics

Liraglutide (Victoza)

DPP-IV inhibitors

Sitagliptin (Januvia)
Saxagliptin (Onglyza)

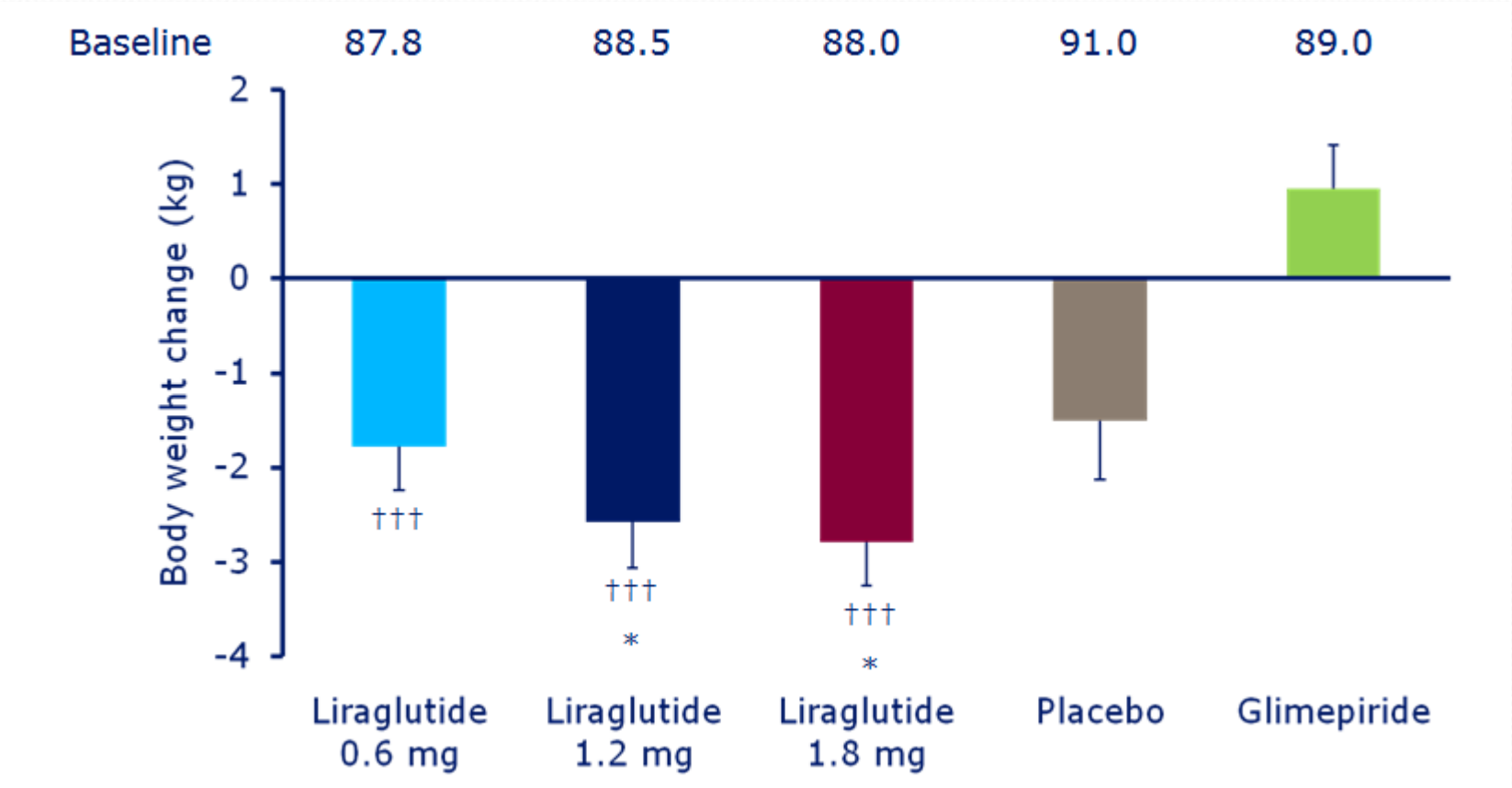
Liraglutide vs Sulfonurea in patient on metformin



Mean±2SE

Nauck *et al. Diabetes Care* 2009;32:84–90 (LEAD-2)

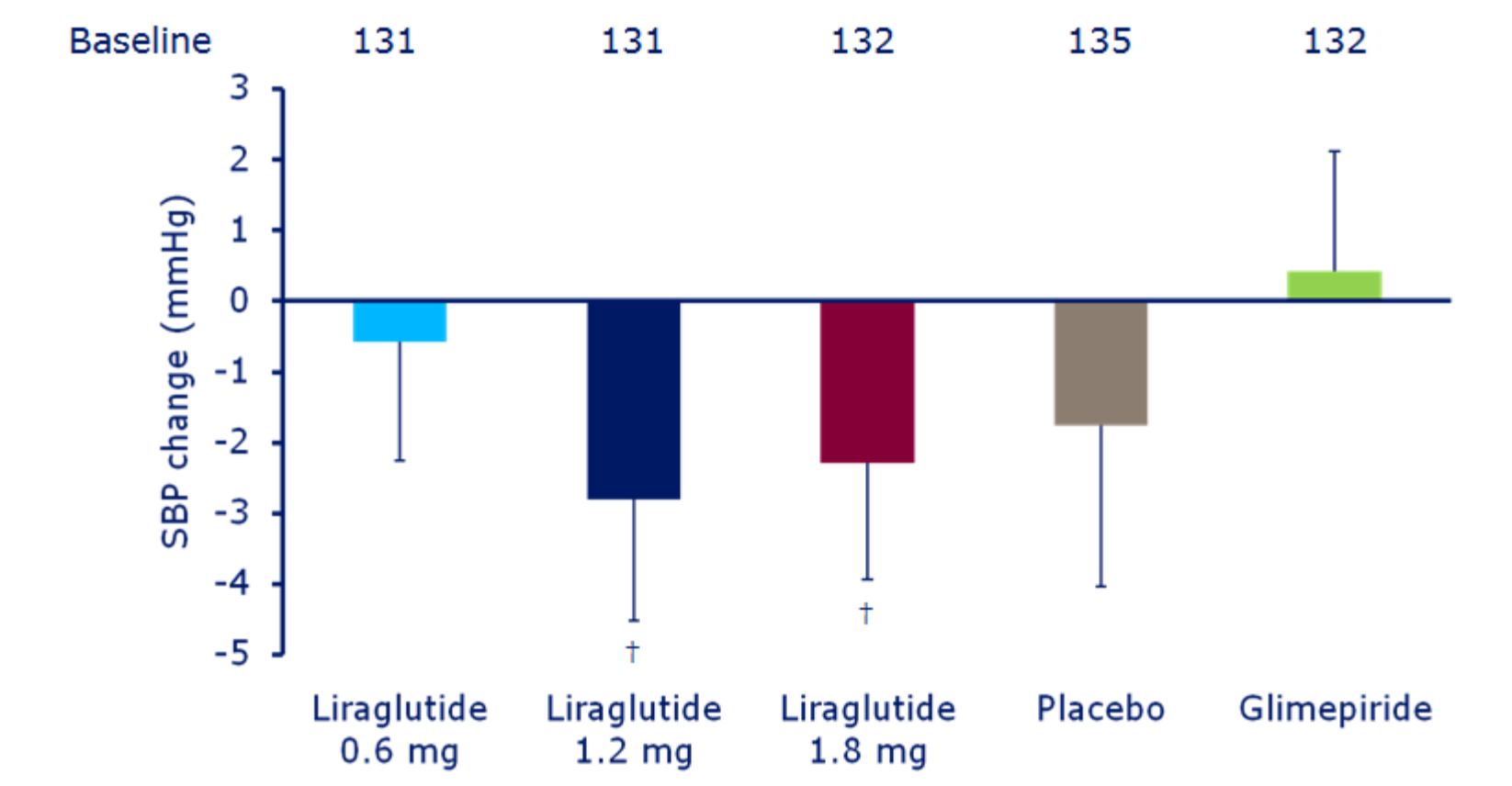
Liraglutide causes weight loss of an average 3kg



*$p<0.05$ versus placebo, †††$p<0.0001$ for treatment difference in changes versus glimepiride

Nauck *et al. Diabetes Care* 2009;32:84–90

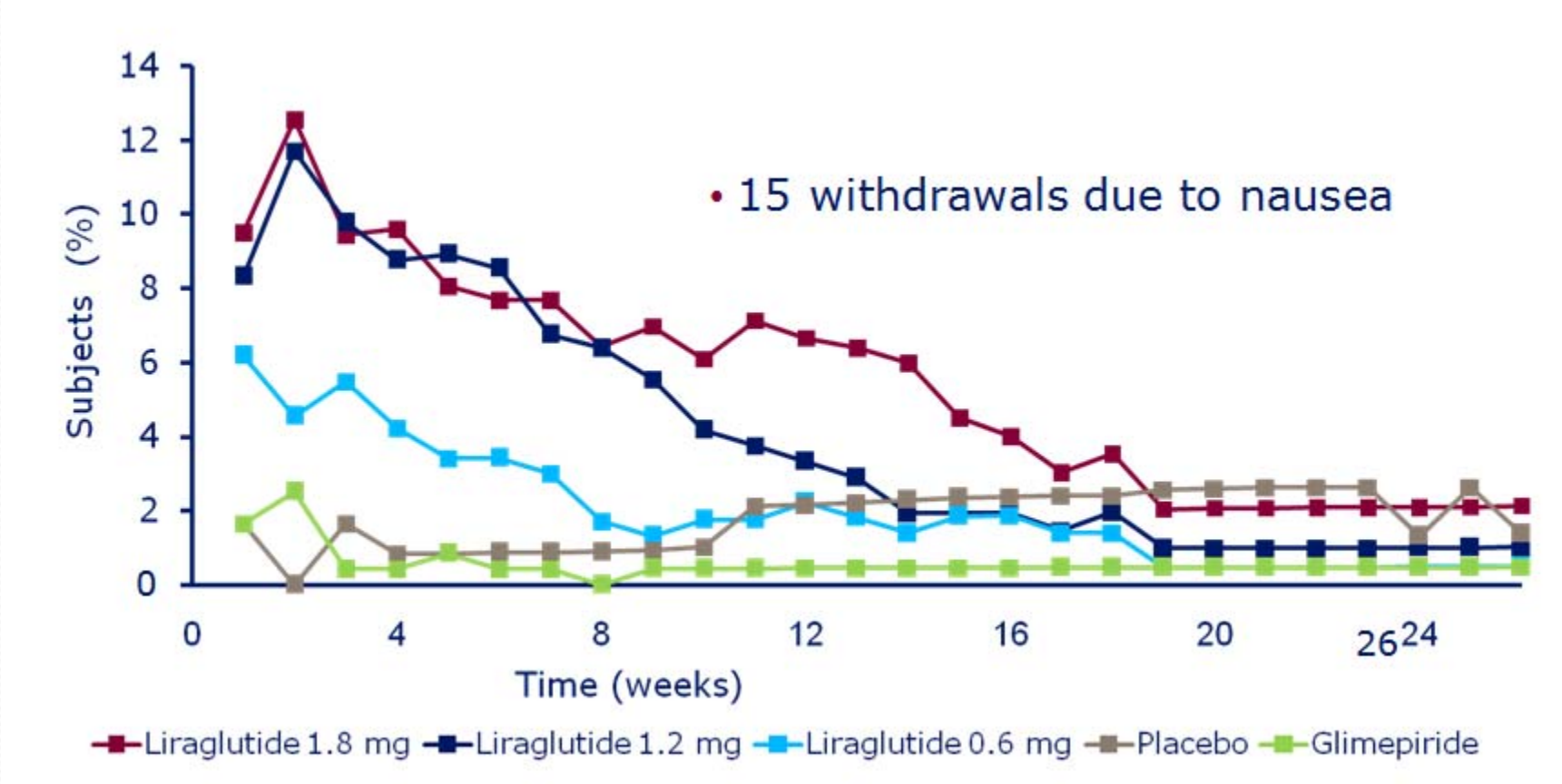
Liraglutide lowers systolic BP by 3mmHg



†$p<0.05$ for liraglutide 1.8 and 1.2 treatment differences in changes vs glimepiride

Nauck *et al. Diabetes Care* 2009;32:84–90

Nausea is more common in patients on liraglutide



Nauck *et al. Diabetes Care* 2009;32:84–90 (LEAD-2)

Liraglutide

- No increase risk of hypoglycemia on its own
- No adjustment for renal disease
- $7 per day

GLP-1 Receptor Agonists Versus DPP-4 Inhibitors

	GLP-1R Agonists	DPP-4 Inhibitors
Administration	Injection	Orally Available
GLP-1 Concentrations	Pharmacological	Physiological
Insulin Secretion	+++	+
Glucagon Inhibition	++	++
Gastric Emptying	Inhibited	+/-
Weight Loss	Yes	No
Blood pressure lowering	Yes	No
Nausea and Vomiting	Yes	No

Exciting Advances in Diabetes

Coming soon

SGLT 2 inhibitors

- Sodium glucose transporter 2
  - Responsible for reabsorption of glucose from the proximal tubule
- System is normally overwhelmed at glucose levels in the low teens = glucosuria
- What if you could make the system spill glucose at a lower threshold?

Dapagliflozin

- In phase 3 trials currently
- 24 week study DM2 on metformin
  - A1c decreased by 0.84%
  - Weight decreased by 2.9kg
  - Systolic BP -5.1mmHg
  - Diastolic BP -1.8mmHg
  - No increase in hypoglycemia

Bailey CJ. Lancet. June 2010

Answers

Summary

- Diabetes remains the leading cause of ESRD and is increasing in prevalence
- A1c levels in renal insufficiency are affected by uremia, dialysis, iron therapy, erythropoietin use.
- A1c should be used in conjunction with capilliary blood glucose testing to assess glycemic control
- Current targets for glycemic control are an A1c <7.0%, 6.5% in patients with nephropathy (if it can be done safely)

Summary

- Several new therapeutic targets are becoming available
- GLP-1 agonists and DPP-IV inhibitors
  - Glucose-dependent insulin release
  - Decrease glucagon release
- SGLT-2 inhibitors
  - Lower renal threshold for glucosuria

Questions?

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