Oral Agents in Type 2 DM

CME Away

India & Sri Lanka

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Richard A. Bebb MD, ABIM, FRCPC
Consultant Endocrinologist
Medical Subspecialty Institute
Cleveland Clinic Abu Dhabi

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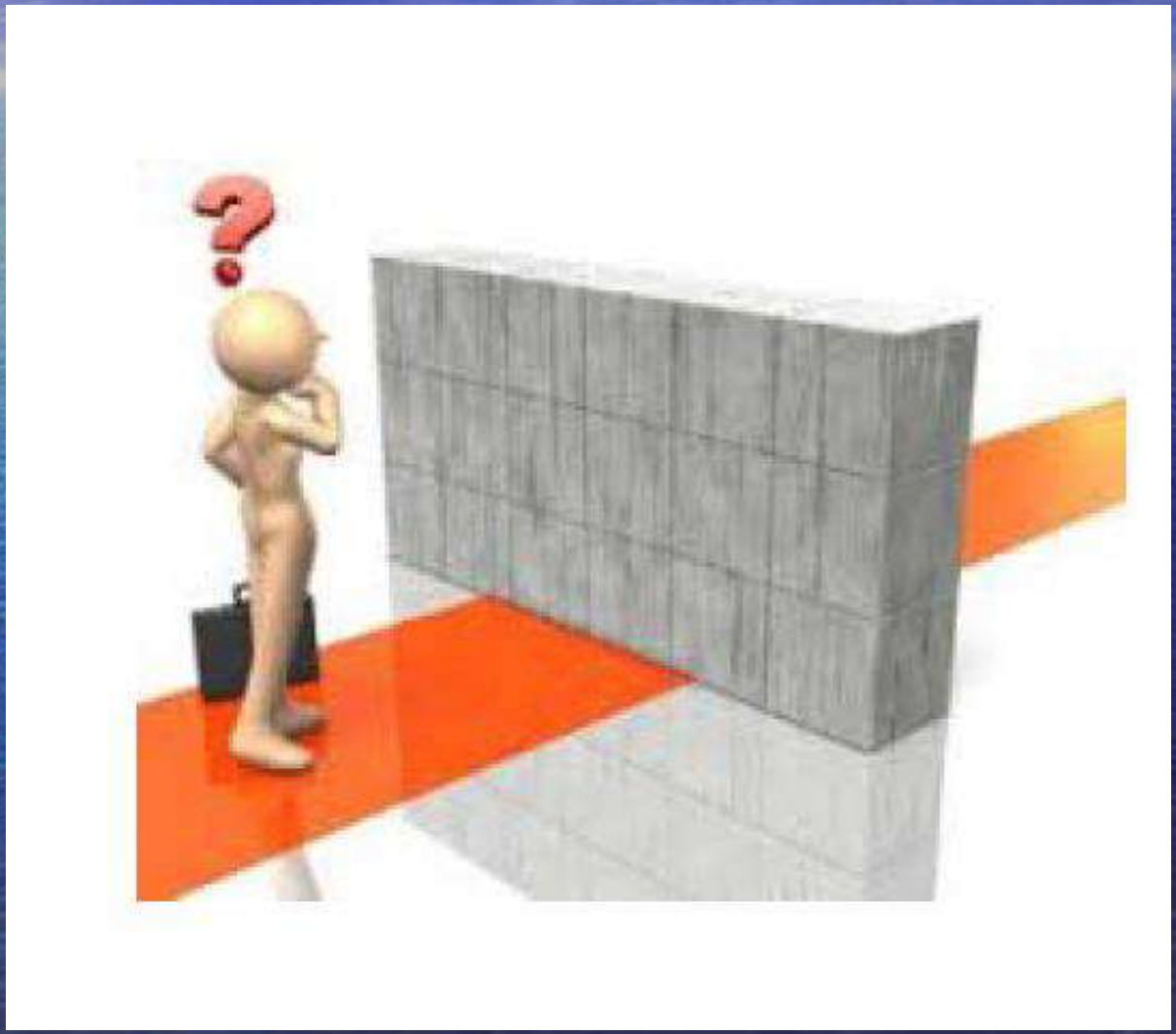
Barriers To Change



Disclosure of Commercial Support

- **This program has not received financial support, or in-kind support, from any Pharmaceutical Company.**

- **<u>Potential for conflict(s) of interest</u>:**
  - **None to declare**

Faculty/Presenter Disclosure

- **Faculty: Richard Bebb**
- **Relationships with commercial interests:**
  - **None to report**

Learning Objectives:

- Review oral agents for diabetes
- Metformin is still a key medication
- Use drugs with CVD outcome data
- Review Diabetes Guidelines
- Issues specific to the Elderly

Case 1: 63 yr male

- FBG 6.2 & 6.8 mmol/L (111 & 122 mg/dl)
- BP 135/85
- A1c 6.8%
- Family history of premature CAD

He has which condition?

1) Impaired fasting glucose
2) Diabetes
3) Impaired glucose tolerance
4) Pre-diabetes

ADA Diagnosis of Diabetes

1) FPG > 6.9 mmol/l (8 hr fast)
   (126 mg/dl)
2) 2hr glucose post 75g OGTT >11.1mmol/L
   (200 mg/dl)
3) Symptomatic hyperglycemia or hyperglycemic crisis with random glucose >11.1mmol/L
   (200 mg/dl)
4) HgbA1c >6.4%
   (using NGSP certified standardized A1c measurement)
   (Increased risk for DM with A1c 5.7-6.4%)

Criteria 1 & 4 should be confirmed by repeat testing, unless unequivocal hyperglycemia
ADA 2018 Clinical Guidelines

Case 1:

- referred to DM education program
  - Diet advise, exercise prescription, SMBG
- HgA1c drops to 6.0%
- 18 months later HgbA1c 7.8%

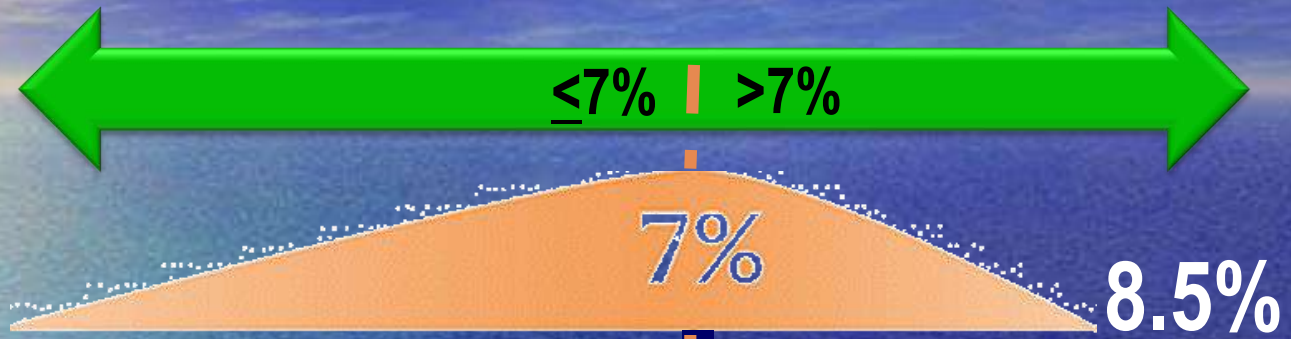
What are our targets?

	A1C (%)	FPG/preprandial PG (mmol/L)	2-hour postprandial PG (mmol/L)
Type 1 and type 2 Diabetes	**≤ 7.0**	4.0 – 7.0 (72-126 mg/dl)	5.0 – 10.0 (90 -180 mg/dl) (5.0 – 8.0 if A1C targets not being met)

- Goals individualized based on:
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness

ADA & CDA Guidelines

Individualizing A1C Goals



Most Patients with T1DM and T2DM

A1C ≤6.5% may be considered in some patients with T2DM to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia

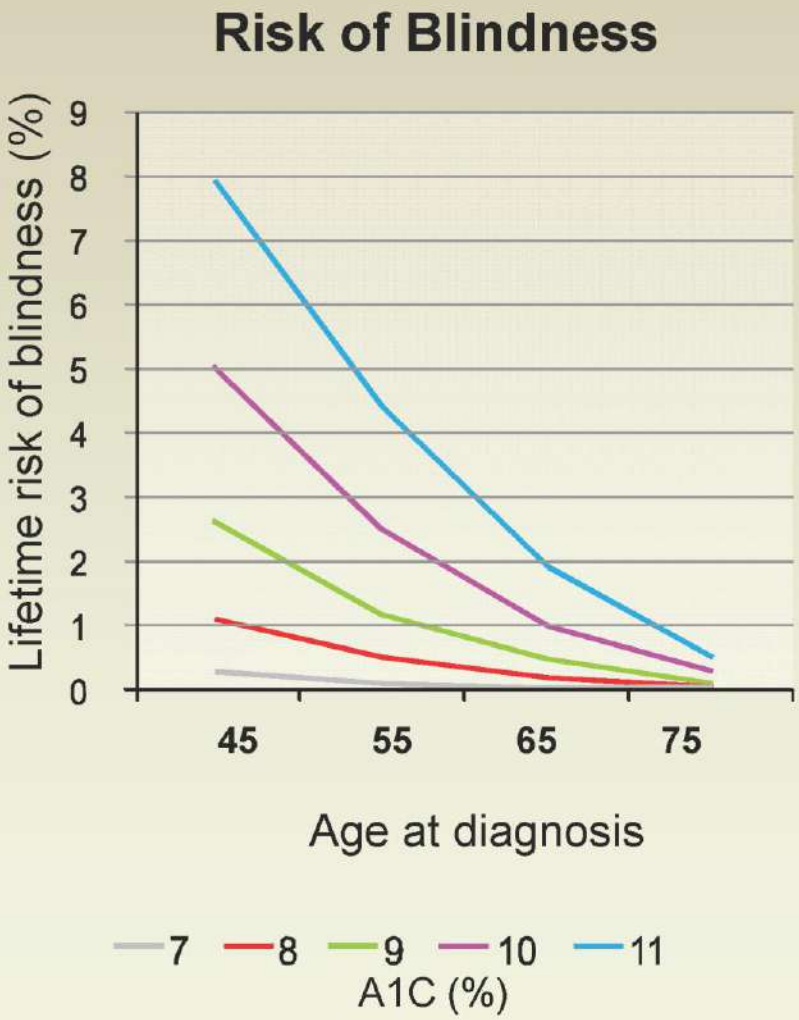
Consider A1C 7.1-8.5% if:

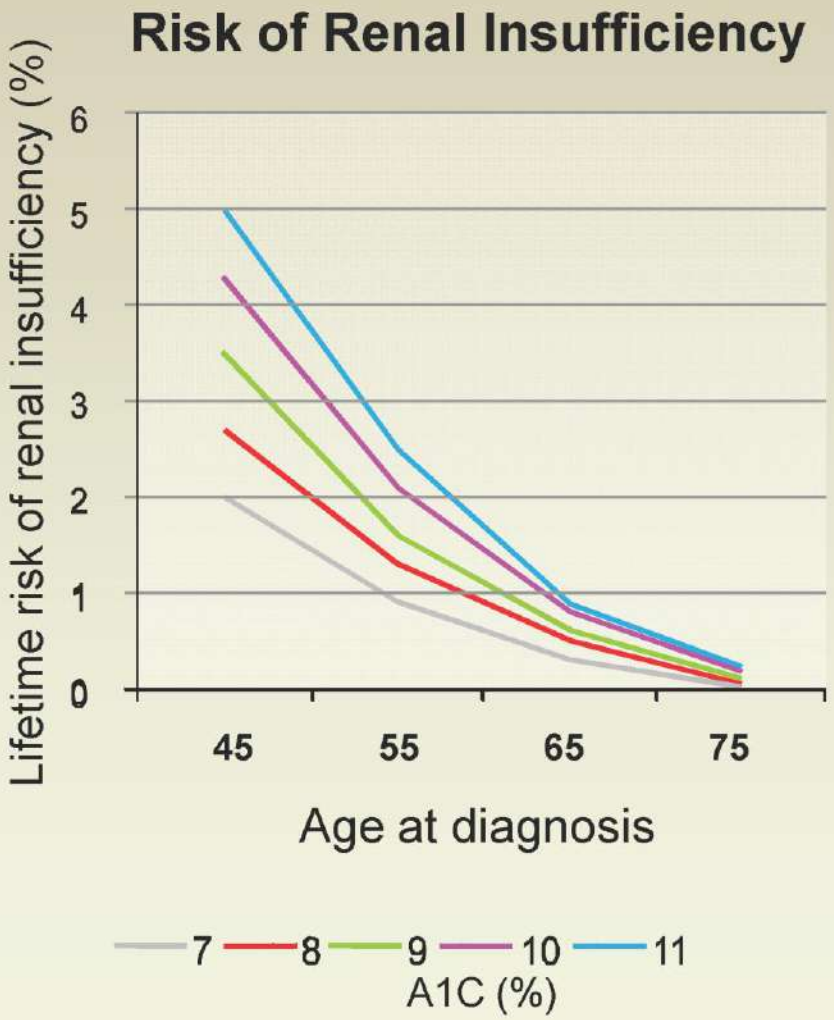
- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom it is difficult to achieve an A1C ≤7.0%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy

Adapted from Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Can J Diabetes 2013;37:S1-S212.

Adjusting Targets & Therapy for the Elderly

Risk of Diabetes Complications by A1C and Age at Diagnosis





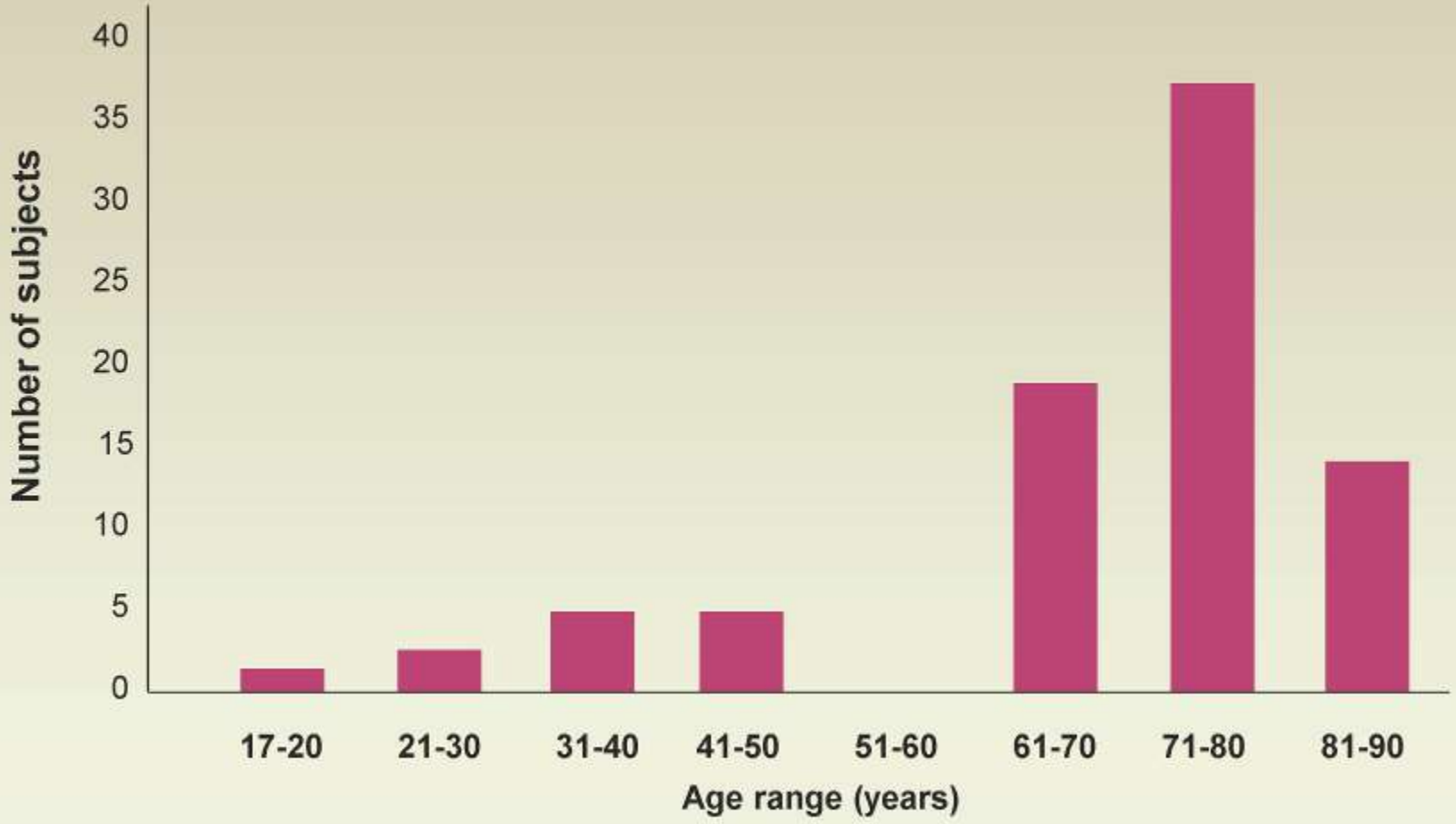
Vijan S *et al. Ann Intern Med* 1997; 127:788-95.

Frequency of Emergency Room Visits for Hypoglycemia by Age

Emergency Room Visits (USA) for Hypoglycemia According to Patient Age, 1993-2005				
	n	Total estimated number of cases (95% CI)	Rate per 1,000 subjects for diabetic pop. (95% CI)	Rate per 1,000 visits at the emergency (95% CI)
Total	1,303	4,960 (4,460, 5,460)	34 (30, 37)	3.7 (3.4, 4.1)
Age (years)				
<45	401	1,550 (1,330, 1,780)	62 (53, 71)	1.7 (1.5, 2.0)
0-19	78	359 (229, 489)	–	0.9 (0.6, 1.2)
20-44	323	1,200 (1,020, 1,370)	–	2.3 (2.0, 2.7)
45-64	364	1,230 (1,060, 1,400)	19 (17, 22)	5.5 (4.7, 6.2)
65-74	219	845 (698, 991)	25 (20, 29)	10 (8.5, 12)
≥75	319	1,330 (1,090, 1,580)	54 (44, 64)	12 (9.4, 14)

Note: this table represents data gathered from the American National Hospital Ambulatory Medical Care between 1993 and 2005.
USA = United States of America; CI = confidence interval
Ginde AA *et al. Diabetes Care* 2008; 31:511-3.

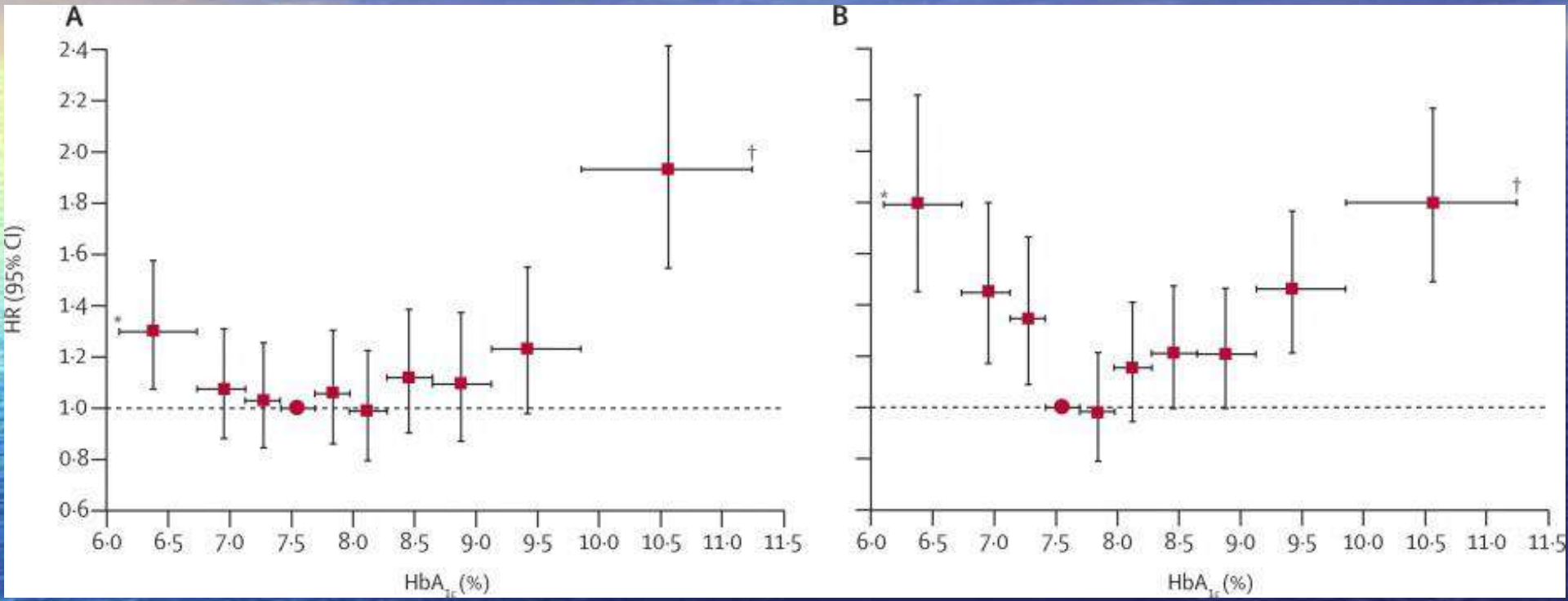
Drug-Induced Hypoglycemic Coma Is More Common in Elderly People with Type 2 Diabetes



Retrospective medical record review of individuals with diabetes who were admitted with drug-induced hypoglycemic coma or developed drug-induced hypoglycemic coma during hospitalization.

Ben-Ami H *et al. Arch Intern Med* 1999; 159:281-4.

Relationship between A1c and Mortality



Currie C, *Lancet* 2010; 375:481-489

Case1: Progression

- Metformin 500 mg po BID
- HgbA1c drops to 7.1%
- 6 months later HgbA1c increased to 7.6%

Was Metformin the correct first medication for him?

1) Yes
2) No
3) He should have been started on Combination Therapy
4) Not sure

Metformin:

- UKPDS: 36% Reduction in all cause mortality in overweight Type 2 (effect persisted for 8.5 yrs post trial)
- Rousel et al 2010: 19,691 pts with DM & CVD:
  eGFR 30 – 60; 36% reduction of all cause mortality
  CHF; 40% reduction of all cause mortality

UKPDS

Arch Intern Med. 2010 Nov 22;170(21):1892-9. doi: 10.1001/archinternmed.2010.409

Metformin Then and Now:

- Old recommendations:

  Metformin contraindicated if creatinine > 1.5 in men, or > 1.4 in women

- New Recommendations:

  eGFR > 45: OK to use metformin.

  eGFR 30 to 45 OK to continue, starting not recommended.

  eGFR < 30 contraindicated

Take home Pearl: Dose reduce – try not to discontinue

Metformin Use with IV Dye

- Previously: prior to any study requiring dye hold for 48 hours
- Now: hold and re-assess eGFR in 48 hours *only* if…
  - eGFR <60
  - Hx of liver disease
  - Hx of heart failure
  - Hx of alcoholism
  - Intra-arterial iodinated contrast
- eGFR >60 plus none of the above?

No need to hold metformin!

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

Appendix Table 6. All-Cause Mortality Using Reference 20

Group	OR (95% CI)	Patients, *n*
No metformin	1.0 (reference)	$n_0 = 2937$
Metformin	OR = 0.52 (0.37–0.71)	$n_1 = 1530$

OR = odds ratio.

Ann Intern Med. 2017;166(3):191-200. doi:10.7326/M16-1901

Clinical Outcomes of Metformin Use in Populations With Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease: A Systematic Review

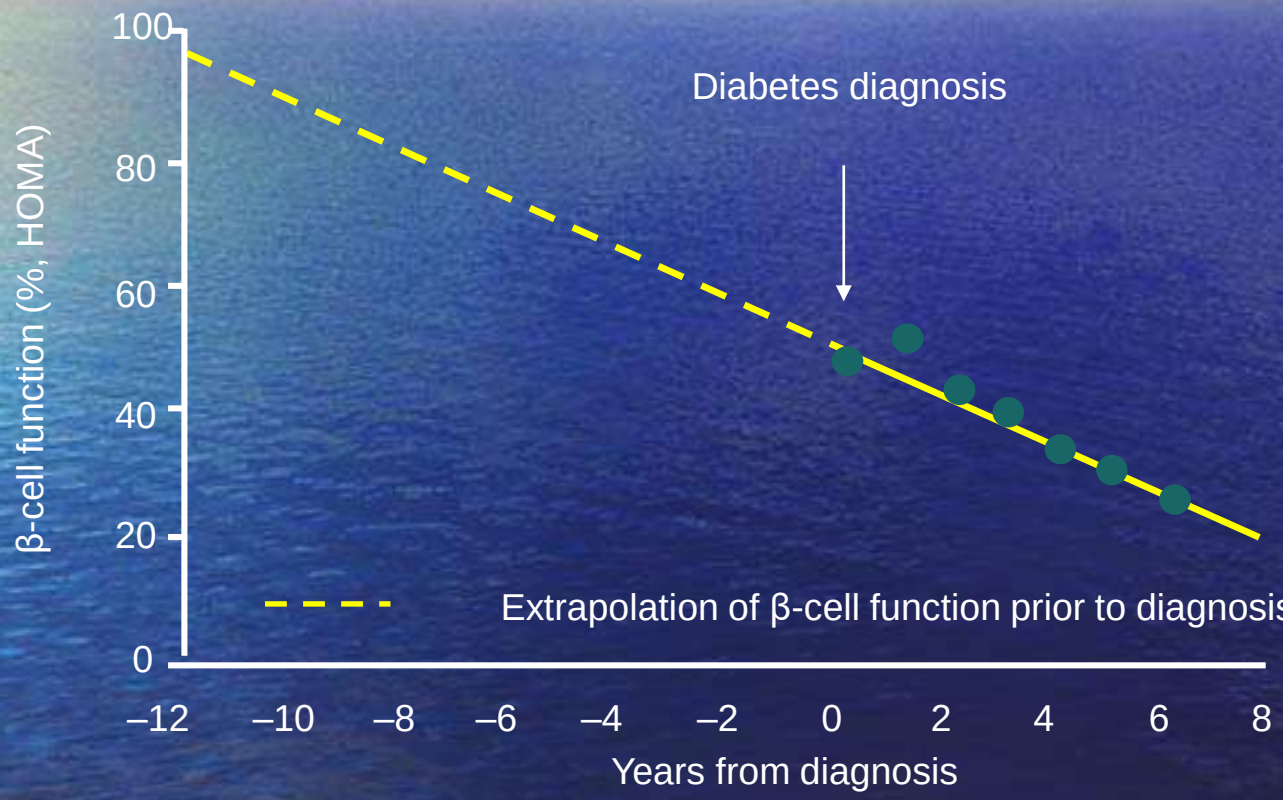
Appendix Table 5. All-Cause Mortality Using Reference 18

Group	HR (95% CI)	Patients, *n*
Sulfonylurea monotherapy	1.0 (reference)	$n_0 = 3615$
Metformin monotherapy	$HR_1 = 0.85$ (0.75–0.98)	$n_1 = 688$
Metformin + sulfonylurea	$HR_2 = 0.89$ (0.82–0.96)	$n_2 = 1549$

HR = hazard ratio.

Ann Intern Med. 2017;166(3):191-200. doi:10.7326/M16-1901

ß-cell function declines over time



Lebovitz HE. *Diabetes Reviews* 1999;7:139
UKPDS Group. *Diabetes* 1995;44:1249

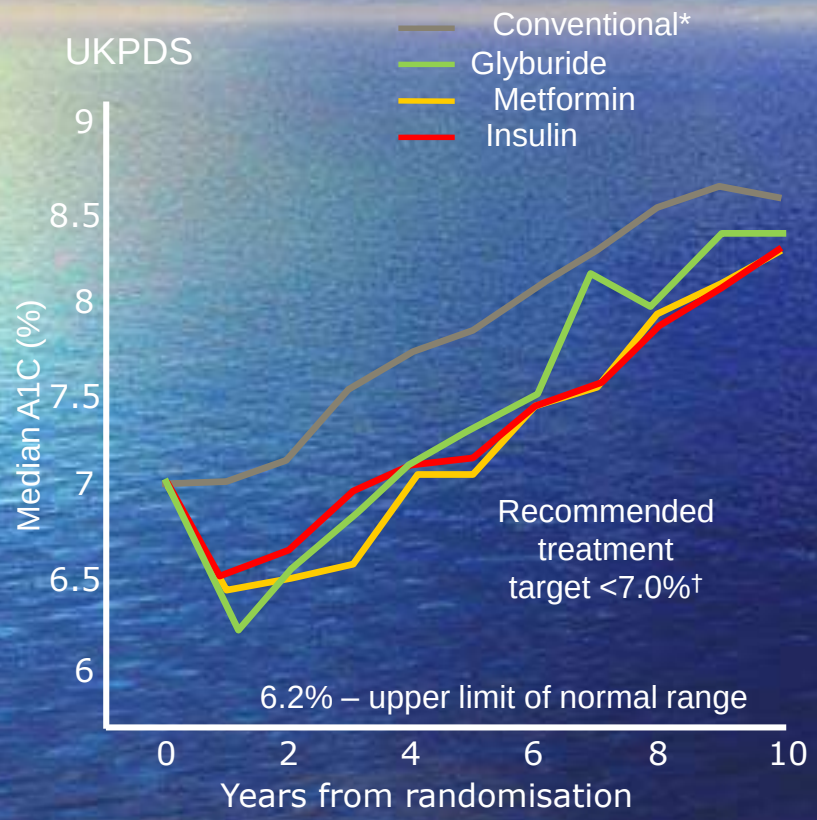
HOMA = homeostasis model assessment

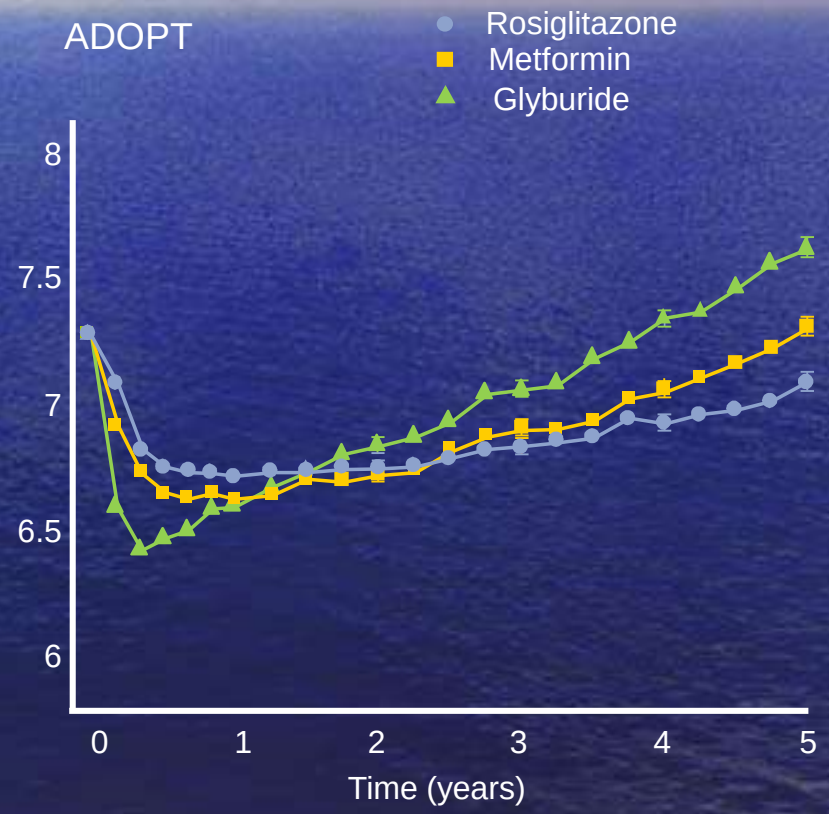
Diabetes and Insulin

If we all live to 150 yrs of age…….

1) 50% of us will have diabetes
2) 100% of us will have diabetes
3) 100% of us will have diabetes and be on insulin
4) The government will still be promising tax relief “next year”

Glycemic control deteriorates over time

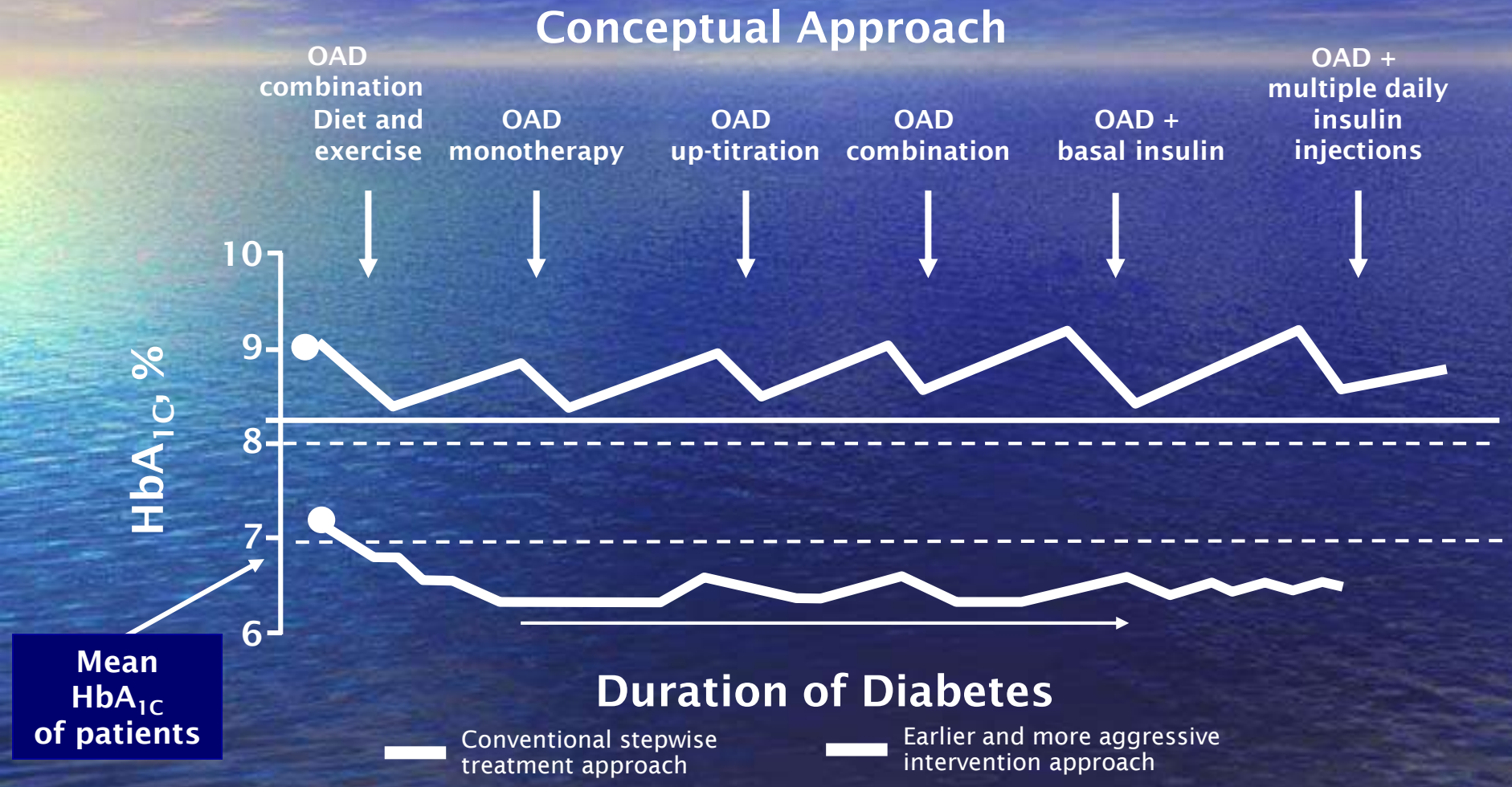




*Diet initially then sulphonylureas, insulin and/or metformin if FPG>15 mmol/L; †ADA clinical practice recommendations.
UKPDS 34, n=1704

UKPDS 34. *Lancet* 1998:352:854–65; Kahn *et al* (ADOPT). *NEJM* 2006;355(23):2427–43. A1C=HbA1C; ADA=American Diabetes Association; ADOPT=A Diabetes Outcome Progression Trial; FPG=Fasting Plasma Glucose; UKPDS=United Kingdom Prospective Diabetes Study.

Earlier and More Aggressive Intervention May Improve Patients' Chances of Reaching Goals



OAD=oral antidiabetic agent.

Adapted from Del Prato S et al. Int J Clin Pract. 2005;59(11):1345-1355.

Managing the Patient with Diabetes

LIFESTYLE

AT DIAGNOSIS OF TYPE 2 DIABETES

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C < 8.5%	A1C ≥ 8.5%	Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)	**Start metformin immediately**	Initiate insulin +/- metformin
Start / Increase metformin	Consider initial combination with another antihyperglycemic agent	

If not at glycemic targets

Add an agent best suited to the individual:

Patient Characteristics

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obesity
- Comorbidities (renal, cardiac, hepatic)
- Preferences & access to treatment
- Other

Agent Characteristics

- BG lowering efficacy and durability
- Risk of inducing hypoglycemia
- Effect on weight
- Contraindications & side-effects
- Cost and coverage
- Other

Adapted from Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Can J Diabetes 2013;37 S1-S212.

If not at target

↓

- Add another drug from a different class; or
- Add bedtime basal insulin to other agent(s); or
- Intensify insulin regimen

↓

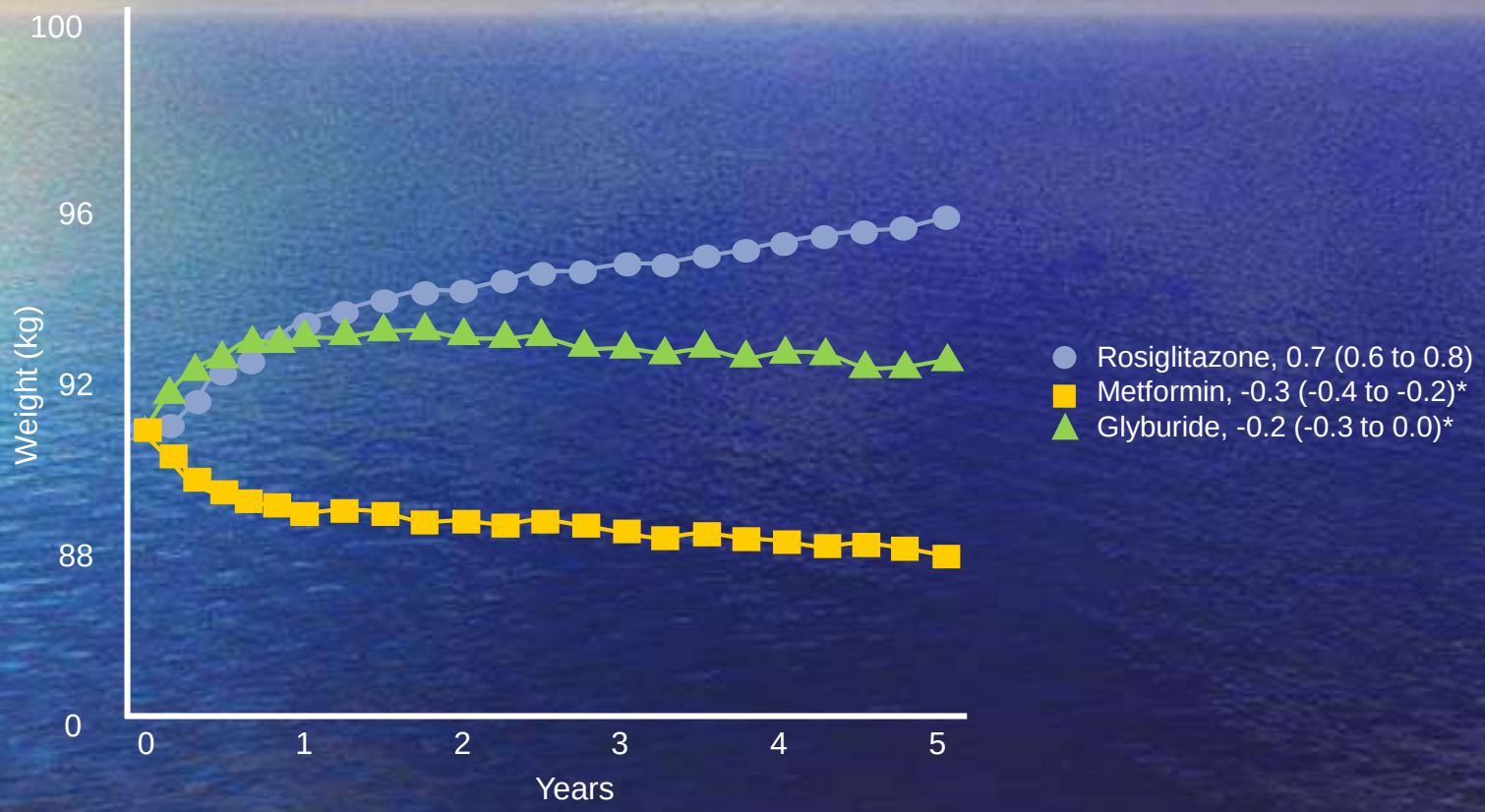
Timely adjustments to and/or addition of antihyperglycemic agents Should be made to attain target A1c within 6 to 12 months

What to do next?

1. Improve lifestyle
2. Increase metformin to 1g TID
3. Add glyburide 2.5mg BID
4. Add pioglitazone 30mg QD
5. Add acarbose 50mg TID
6. Add sitagliptin 100mg QD
7. Add glargine 10 units SC Qhs
8. Add liraglutide 1.2 mg sc Qam
9. Add empagliflozin 10 mg QD

Conventional therapies can lead to weight gain

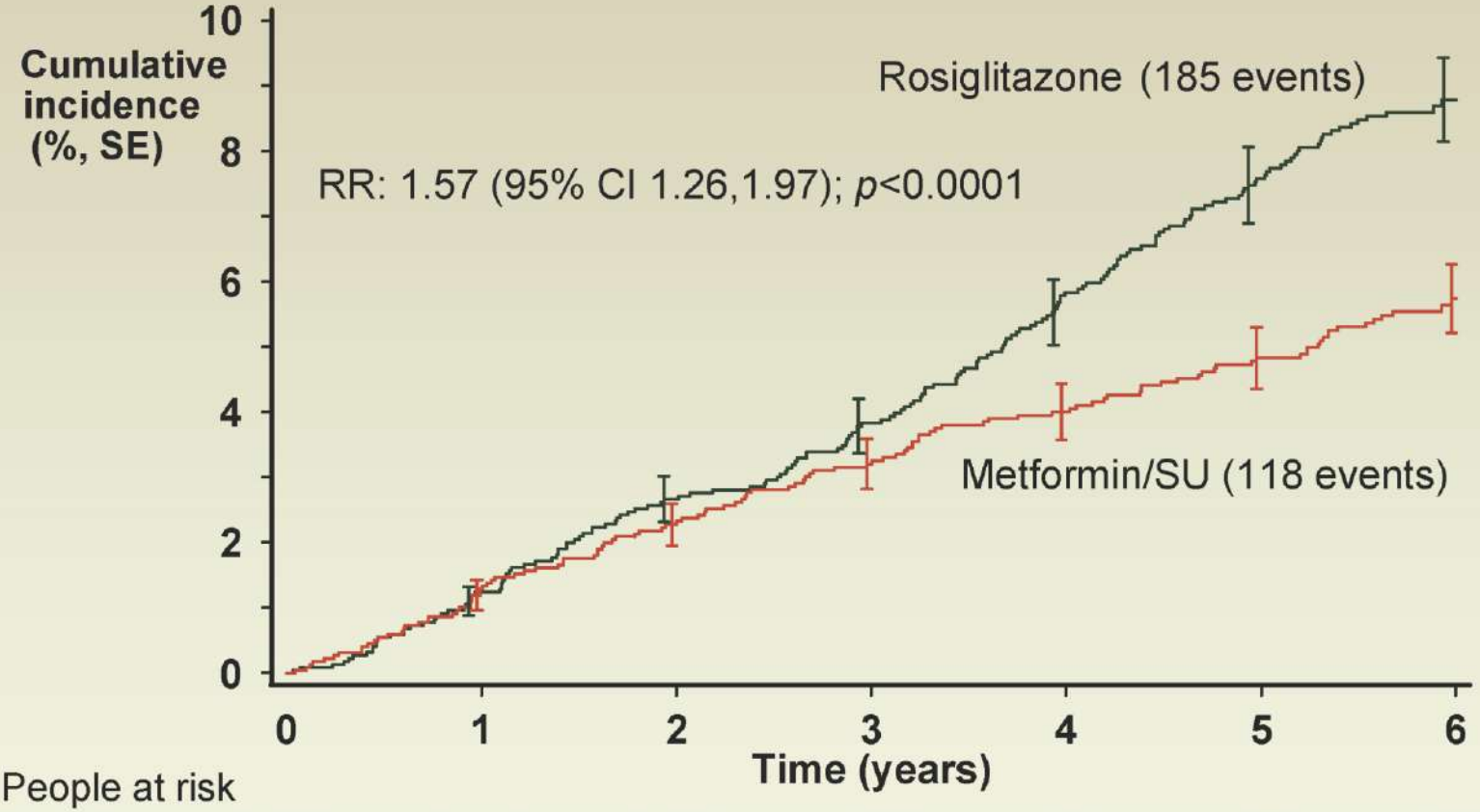
ADOPT: up to 4.8 kg in 5 years



*Significant differences between the rosiglitazone group and the other treatment groups with the Hochberg adjustment

Kahn SE, et al. *NEJM* 2006;355:2427

RECORD: Time to Bone Fracture Event



People at risk							
Rosiglitazone	2,220	2,116	2,031	1,955	1,864	1,778	950
Metformin/SU	2,227	2,123	2,037	1,959	1,888	1,805	958

RECORD = Rosiglitazone Evaluated for Cardiovascular Outcome and Regulation of Glycaemia in Diabetes; SE = standard error; RR = relative risk; SU = sulfonylurea

Home PD *et al. Lancet* 2009; 373:2125-35.

Fractures in Men and Women

	Women			*Men*		
	Rosiglitazone n=1,078	**Control** n=1,075	**Risk ratio***	**Rosiglitazone** n=1,142	**Control** n=1,152	**Risk ratio***
All	124 (154)	68 (78)	1.82	61 (71)	50 (54)	1.23
Upper limb	63 (78)	36 (39)	1.75	23 (24)	19 (19)	1.22
Distal lower limb	47 (49)	16 (17)	2.93	23 (24)	11 (11)	2.11

Number of participants (fractures)

Note: some people had more than one fracture, possibly in different areas.
*Interaction: p=0.1
Home PD *et al. Lancet* 2009; 373:2125-35.

What Are Incretins?

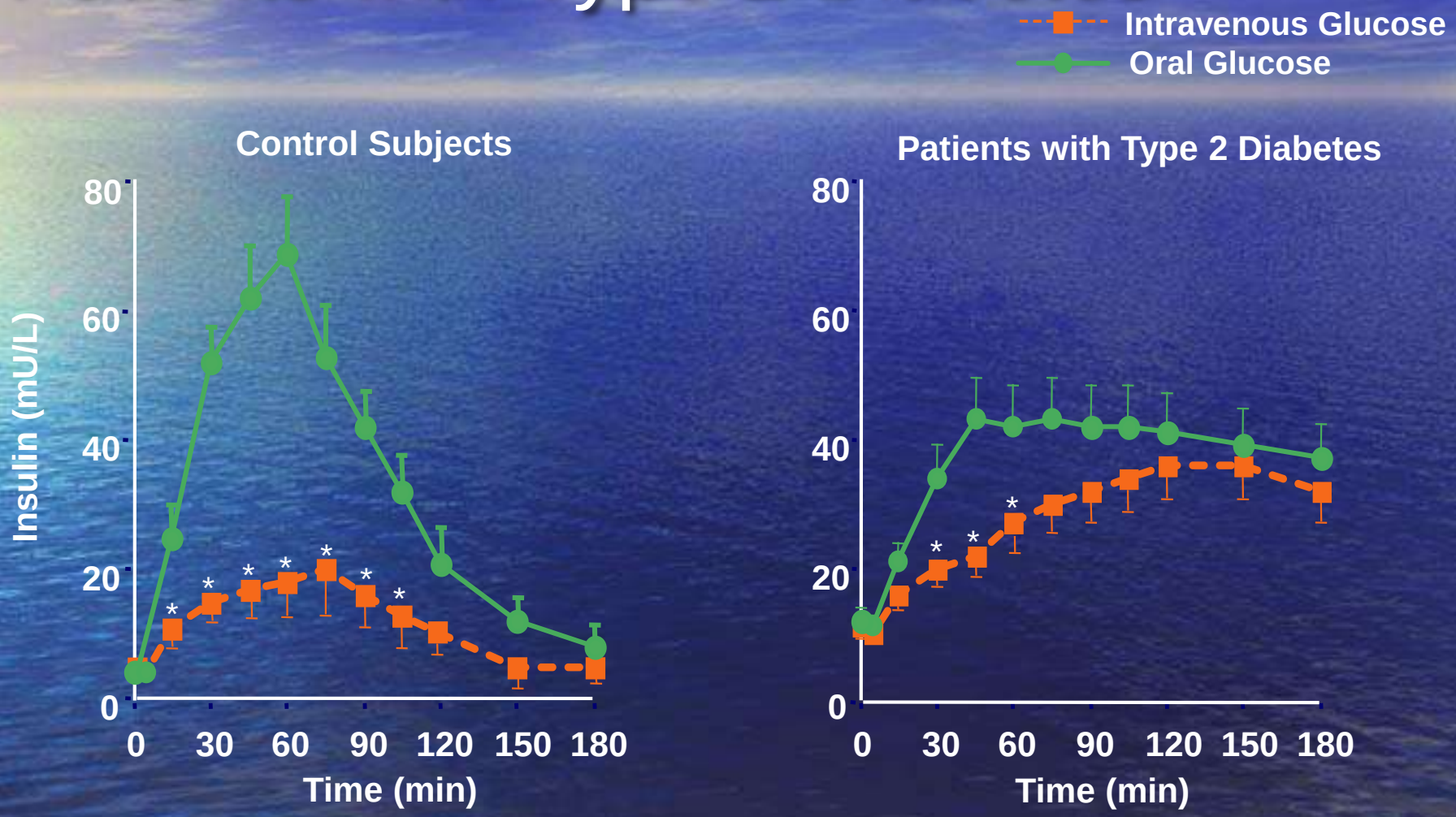
- Gut peptide hormones (GLP-1, GIP)
- Secreted in response to food ingestion
- Stimulate glucose-dependent insulin secretion
- Account for up to 60% of insulin response in healthy subjects

Stedman´s Medical Dictionary, 27th ed, 2000.
Baggio LL, Drucker DJ. *Treat Endocrinol* 2002.
Holst JJ, Gromada J. *Am J Physiol Endocrinol Metab* 2004;287:E199–E206.
Nauck M et al. *Diabetologia*.1986;29:46–52.
Baggio LL, Drucker DJ. *Ann Rev Med* 2006;57:265–281.

Incretin Drugs

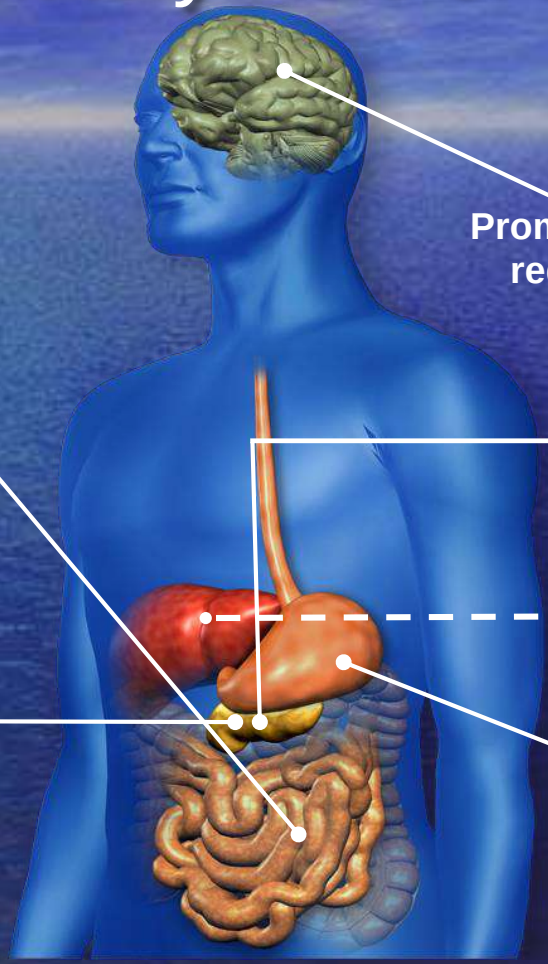
- GLP Agonists
  - Exenatide
  - Liraglutide
  - Semaglutide
  - Albiglutide
  - Taspoglutide
  - Exenatide Lar
  - Lixsenatide
- DPP 4 Inhibitors
  - Vildagliptin
  - Sitagliptin
  - Saxagliptin
  - Alogliptin
  - Linagliptin
  - Dutogliptin
  - metogliptin

The Incretin Effect Is Reduced in Patients with Type 2 Diabetes



Mean ±SE; N=22 (14 patients with T2DM, 8 metabolically healthy control subjects).
*P ≤ 0.05 compared with respective value after oral glucose load (50g/400mL).
Adapted from Nauck MA, et al. *Diabetologia*. 1986;29:46-52.

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload

Promotes satiety and reduces appetite

↑ Beta-cell response

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Beta cells: Enhances glucose-dependent insulin secretion

Stomach: Slows gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553; Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169.

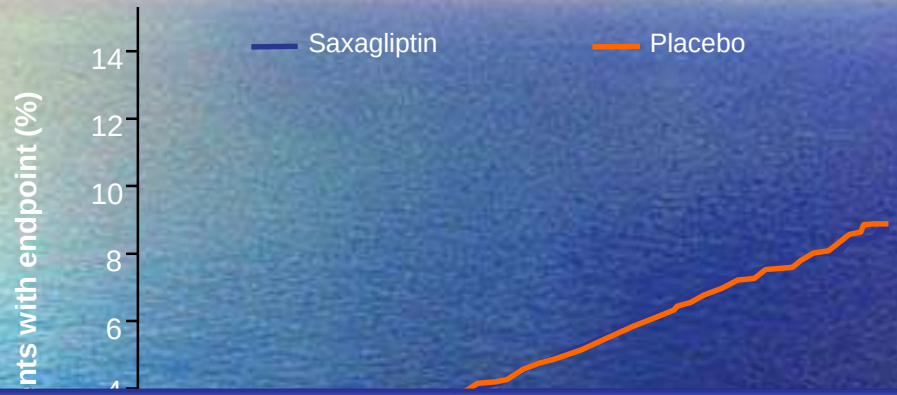
Incretin mimetics and DPP-4 inhibitors: major differences

Properties/effect	Incretin mimetics	DPP-4 inhibitors
Hypoglycaemia	No	No
Maintained counter-regulation by glucagon in hypoglycaemia	Yes	Not tested
Inhibition of gastric emptying	Yes	Marginal
Effect on body weight	Weight loss	Weight neutral
Side effects	Nausea	None observed
Administration	Subcutaneous	Oral

Gallwitz. *Eur Endocr Dis.* 2006

SAVOR-TIMI 53 Primary Endpoint

Composite of CV death, MI, or ischemic stroke



HR (95% CI) = 1.00 (0.89-1.12)
P < 0.001 for non-inferiority
P = 0.99 for superiority

Saxagliptin met the primary endpoint of non-inferiority but not superiority when compared to placebo

Days

No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53.

Scirica BM *et al. N Engl J Med.* 2013;369:1317-26.

SAVOR-TIMI 53
Major Secondary Endpoints

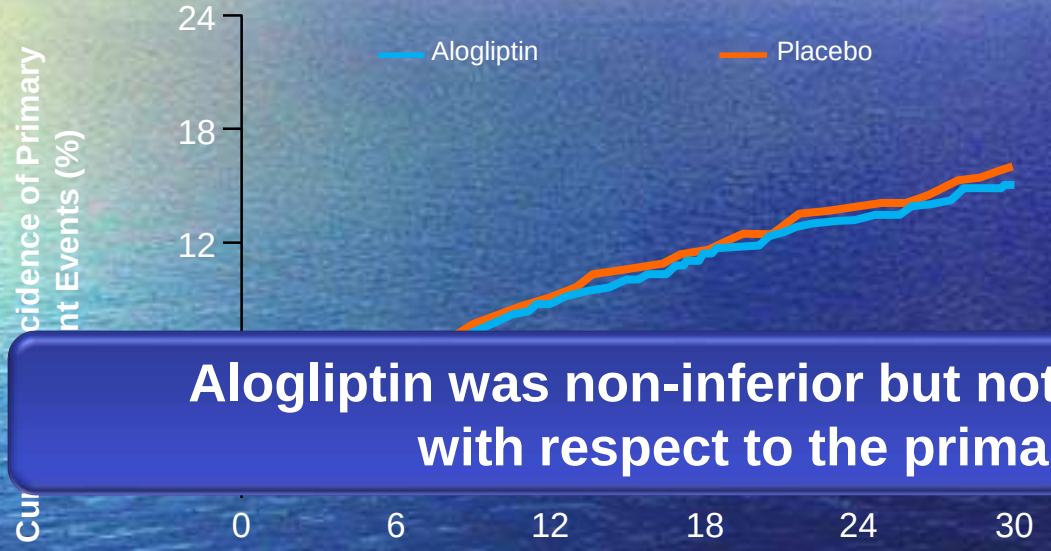
Cardiovascular Endpoints	Placebo (N=8212)	Saxagliptin (N=8280)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Death from cardiovascular causes	260 (2.9)	269 (3.2)	1.03 (0.87–1.22)	0.72
Myocardial infarction	278 (3.4)	265 (3.2)	0.95 (0.80–1.12)	0.52
Ischemic stroke	141 (1.7)	157 (1.9)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	81 (1.0)	97 (1.2)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	228 (2.8)	289 (3.5)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	459 (5.6)	423 (5.2)	0.91 (0.80–1.04)	0.18

CI = confidence interval; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 .

Scirica BM *et al. N Engl J Med*. 2013;369:1317-26.

EXAMINE
Primary Endpoint

Composite of death from CV causes, non-fatal MI, or non-fatal stroke



HR (95% CI) = 0.96 (≤1.16)
P < 0.001 for non-inferiority
P = 0.32 for superiority

Alogliptin was non-inferior but not superior to placebo with respect to the primary endpoint

No. at Risk						
Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

CI = confidence interval; CV =cardiovascular; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome; HR = hazard ratio; MI = myocardial infarction.

White WB *et al. N Engl J Med.* 2013;369:1327-35.

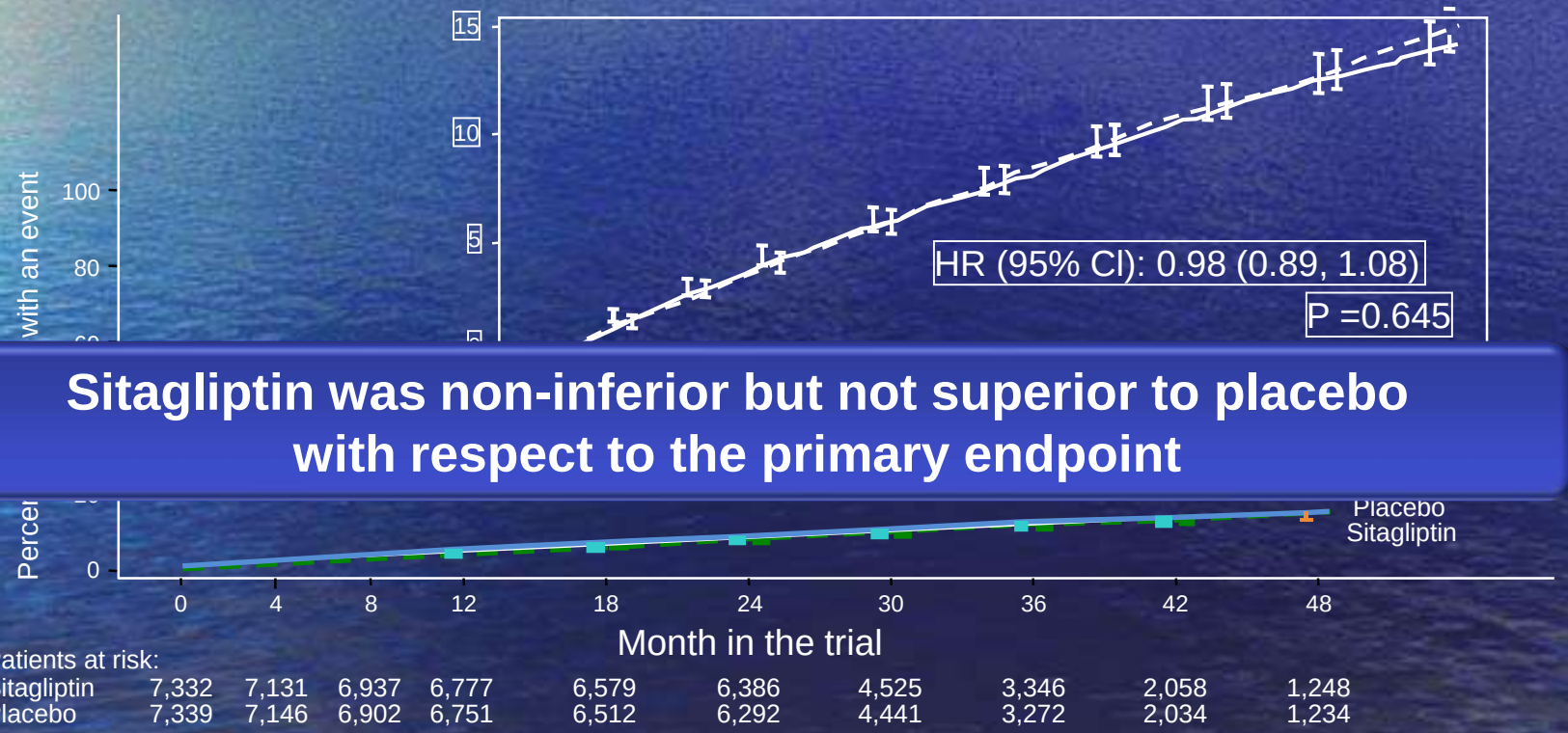
EXAMINE: Major Safety Endpoints

	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Components of primary endpoint				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Non-fatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Non-fatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end-point §	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end-points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21
Hospital admission for heart failure	89 (3.3)	106 (3.9)	1.19 (0.90–1.58)	0.22

*P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.
§ The secondary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a non-fatal primary end-point event.
CI = confidence interval
White WB *et al. N Engl J Med.* 2013;369:1327-35.; Zannad F et al. *Lancet.* 2015;385:2067-76.

TECOS Primary Endpoint

Time from randomization to the first confirmed CV-related death, non-fatal MI, non-fatal stroke, or UA requiring hospitalization



Sitagliptin was non-inferior but not superior to placebo with respect to the primary endpoint

CV = cardiovascular; MI = myocardial infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UA = unstable angina.

Green JB et al. *N Engl J Med.* 2015 doi: 10.1056/NEJMoa1501352.

TECOS
Major Secondary Endpoints

	Placebo (N=7266)	Sitagliptin (N=7250)	Hazard Ratio (95% CI)	P Value
	n (%)			
Secondary end point				
CV death	366 (5.0)	380 (5.2)	1.03 (0.89–1.19)	0.71
Hospitalization for unstable angina	129 (1.8)	116 (1.6)	0.90 (0.70-1.16)	0.42
Fatal or non-fatal MI	316 (4.3)	300 (4.1)	0.95 (0.81-1.11)	0.49
Fatal or non-fatal stroke	183 (2.5)	178 (2.4)	0.97 (0.79-1.19)	0.76
Death from any cause	537 (7.3)	547 (7.5)	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	229 (3.1)	228 (3.1)	1.00 (0.83-1.20)	0.98

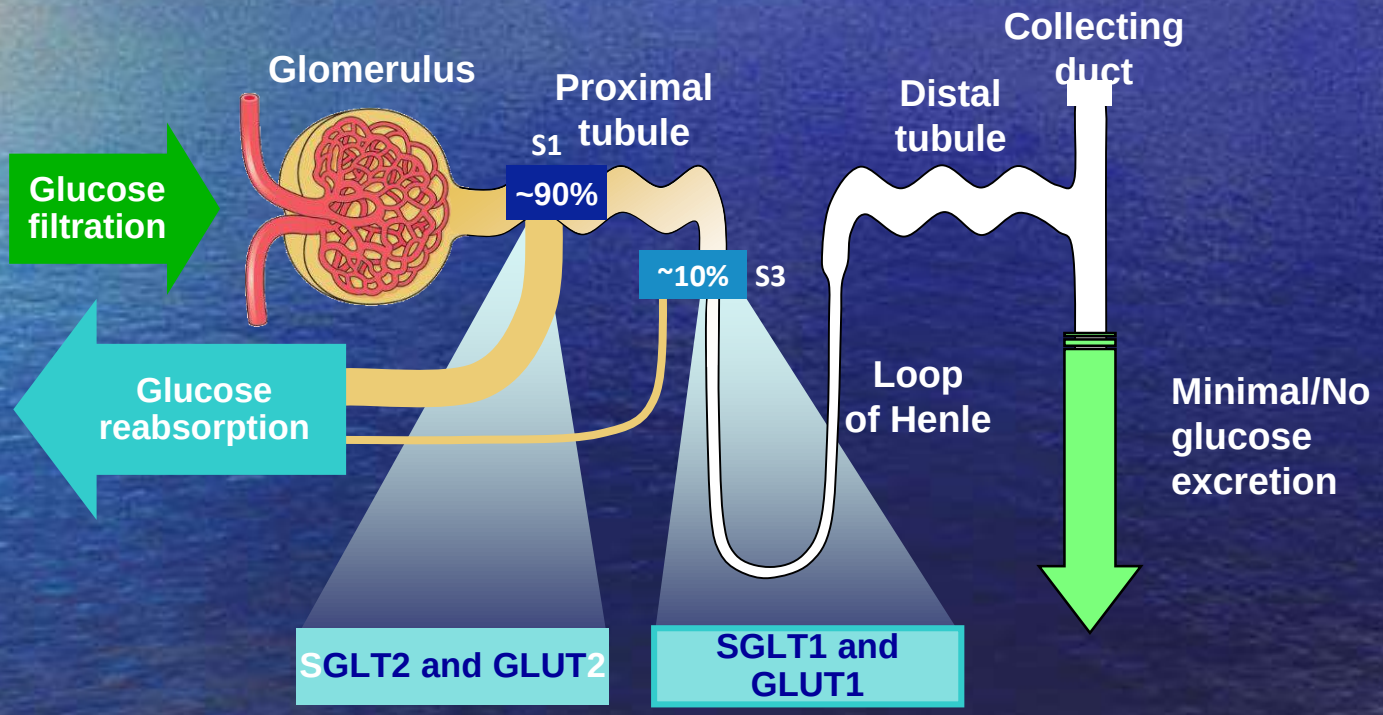
CV = cardiovascular; MI = myocardial infarction; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

Green JB et al. *N Engl J Med.* 2015 doi: 10.1056/NEJMoa1501352.

SGLT2 Inhibitors: Cause glucosuria

SGLT2 Inhibitors: Mechanism of Action

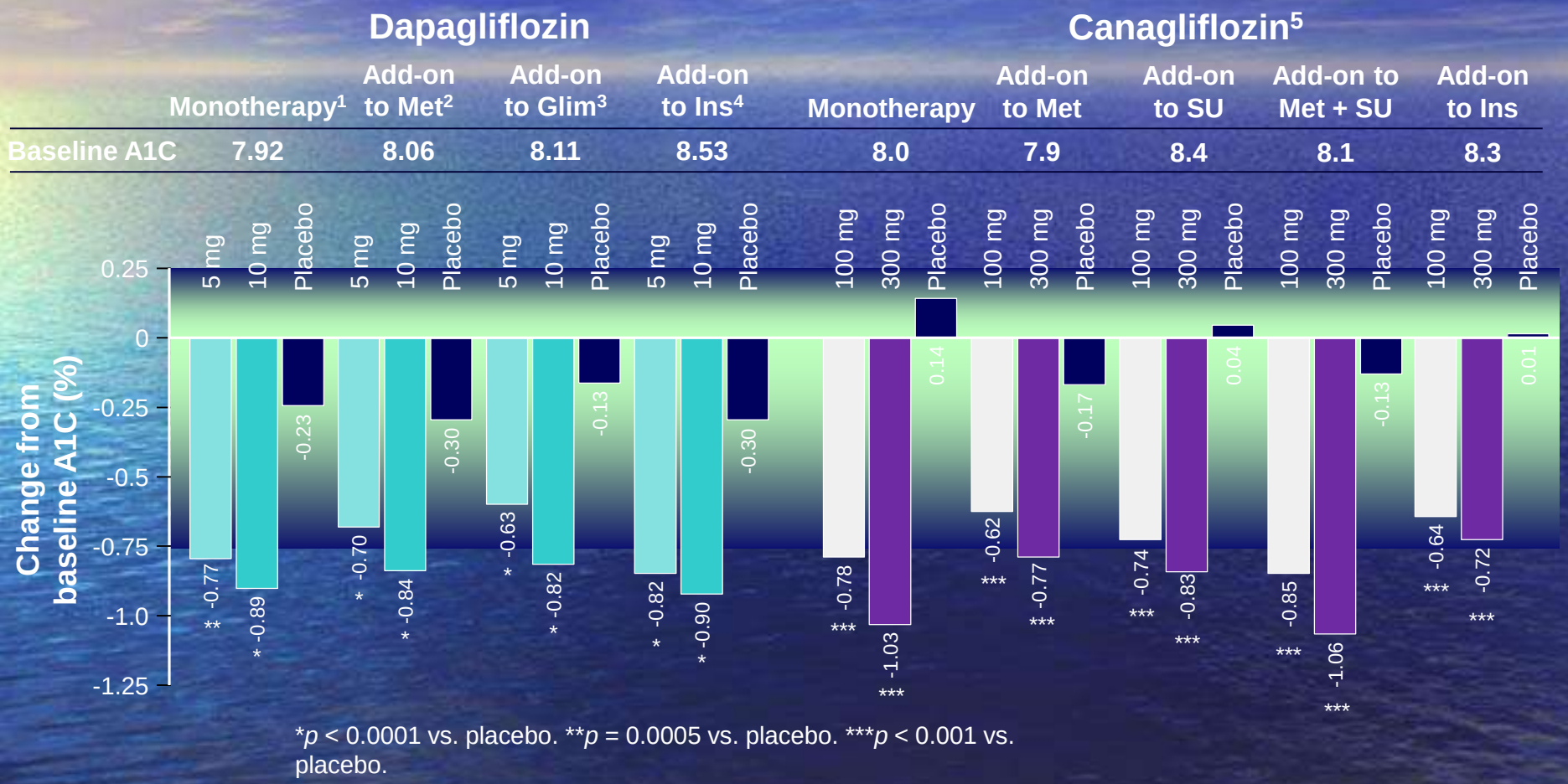
Normal human kidneys reabsorb ~180 g of filtered glucose/day



GLU = facilitative glucose transporter. SGLT = sodium-dependent glucose transporter.

Adapted from: Abdul-Ghani MA, et al. Endocr Pract 2008; 14(6):782-90. Bays H. Curr Med Res Opin 2009; 25(3):671-81. Wright EM. Am J Physiol Renal Physiol 2001; 280(1):F10-8. Lee YJ, et al. Kidney Int Suppl 2007; 106:S27-35. Han S, et al. Diabetes 2008 ; 57:1723-9.

A1C Reductions Across Continuum of T2DM = 0.6-1.1% from Baseline with Dapa and Cana



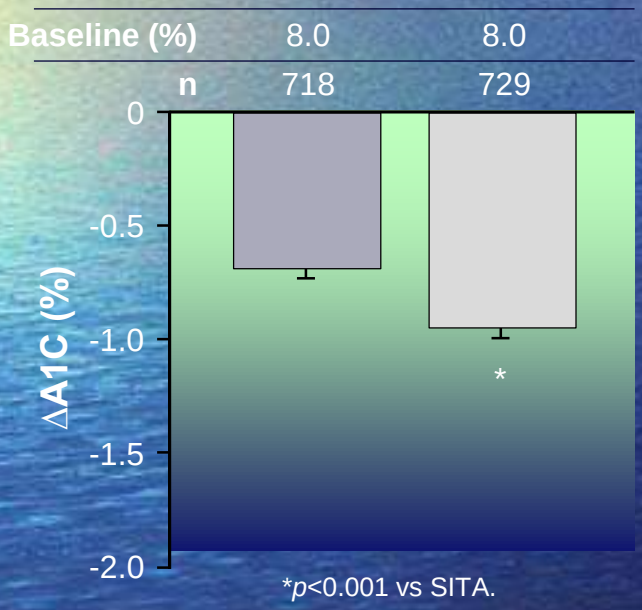
*p < 0.0001 vs. placebo. **p = 0.0005 vs. placebo. ***p < 0.001 vs. placebo.

Bargraph denotes individual trials and is not intended for comparisons between dapagliflozin and canagliflozin.

Ferrannini E, et al. Diabetes Care 2010; 33:2217-24. 2. Bailey CJ, et al. Lancet 2010; 375:2223-33. 3. Strojek K, et al. Diabetes Obes Metab 2011; 13:928-38. 4. Wilding JP, et al. Ann Intern Med. 2012 Mar 20;156(6):405-15. 5. INVOKANA Product Monograph. Janssen Inc., November 2014.

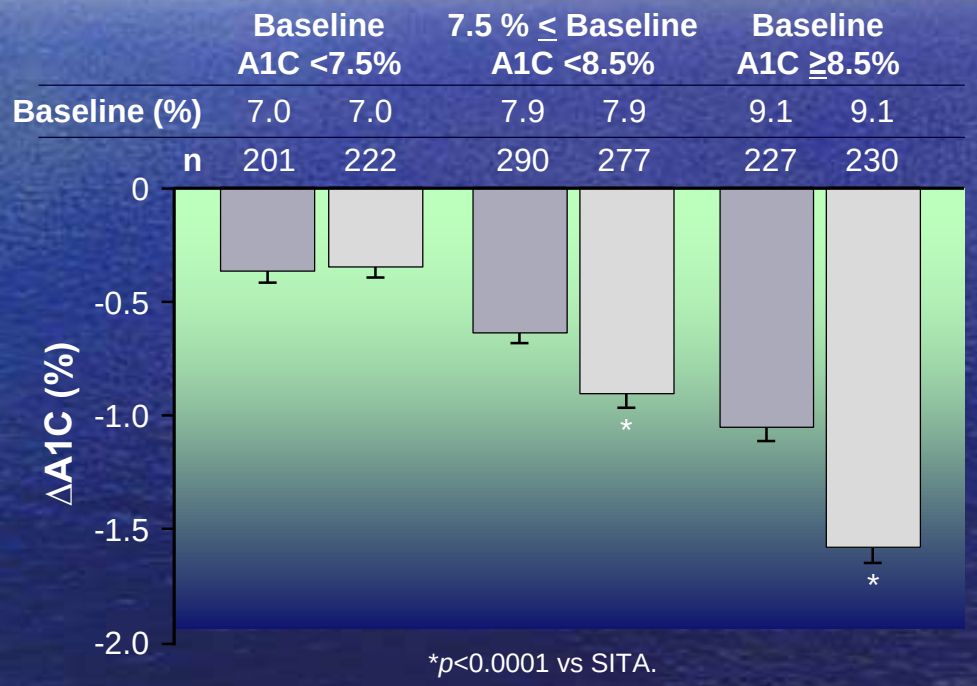
SGLT2i Have Greater A1c Efficacy Than DPP-4i Especially At Higher Baseline A1C

Change in A1C in all patients



*p<0.001 vs SITA.

Efficacy In Subgroups Based On Baseline A1C



*p<0.0001 vs SITA.

SITA 100 mg CANA 300 mg

- CANA 300 mg was more effective than SITA 100 mg in patients with baseline A1C between 7.5% and 8.5% and in patients with baseline A1C ≥ 8.5%

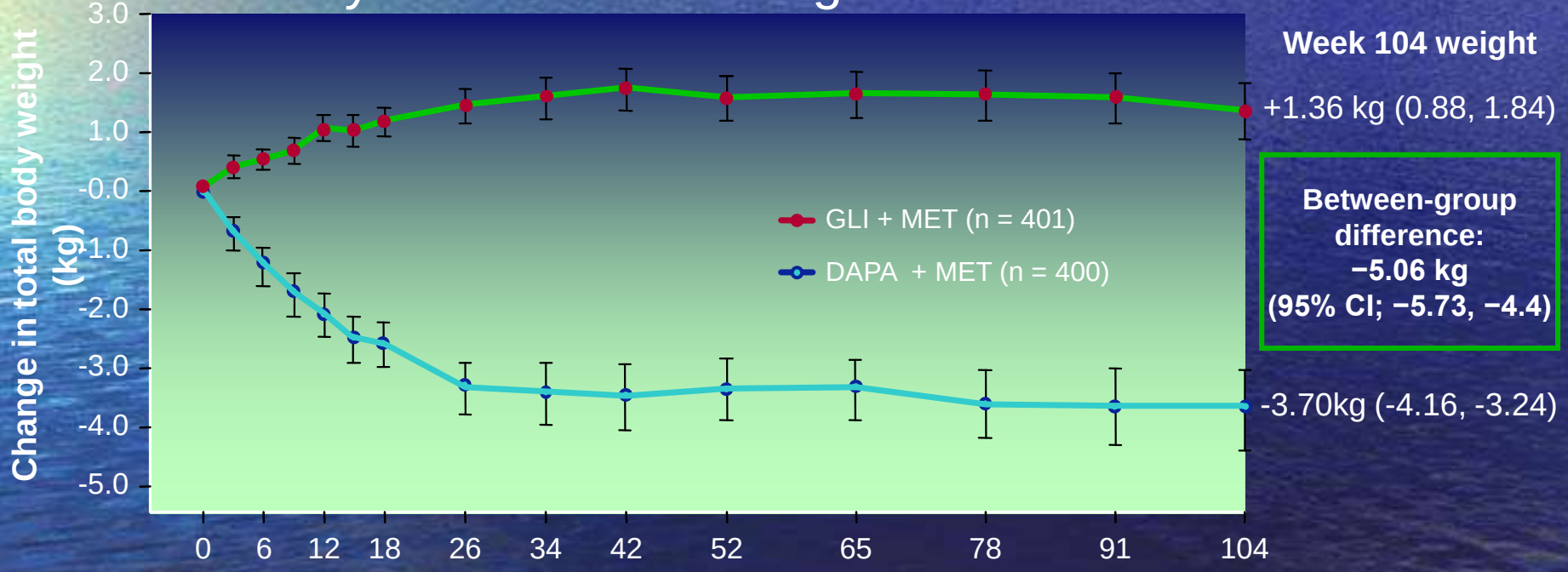
Matthews et al. ADA Poster Presentation June 2014; San Francisco CA (1096-P)

Sustained Body Weight Reduction with Add-on Dapagliflozin vs. Add-on Glipizide* in Patients Taking Metformin (104 weeks)

Baseline weight

DAPA + MET: 88.4 kg

Sulfonylrea + MET: 87.6 kg



Week 104 weight

+1.36 kg (0.88, 1.84)

Between-group difference: −5.06 kg (95% CI; −5.73, −4.4)

-3.70kg (-4.16, -3.24)

Sample size per time point

DAPA + MET	400		369			323				234	
SU + MET	401		361			315				211	

*Glipizide is approved and authorized for use but is not marketed in Canada.

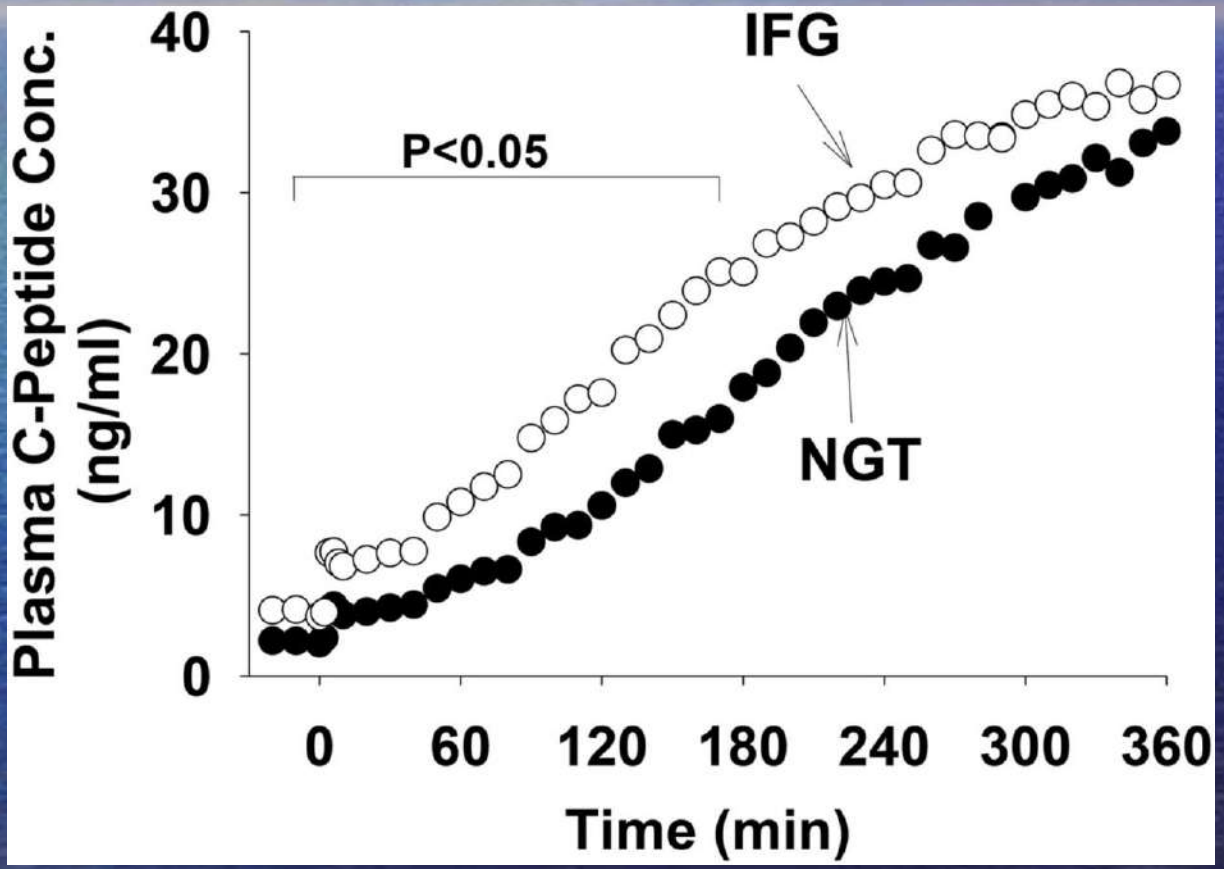
Nauck M, et al. Diabetes Obes Metab 2014; 16(11):1111-20.

Additional Benefits of SGLT2 Inhibitors

Reduction in blood pressure

- BP reduction
  - 3-4 mmHg

Empagliflozin improves beta cell function in patients with IFG



Abdul-Ghani, DeFronzo. *Diabetes*, 2017.

What are the possible adverse effects of SGLT2 inhibition?

- Genital Mycotic Infections (GMI)
- Urinary Tract Infections (UTI)
- Volume-related adverse effects

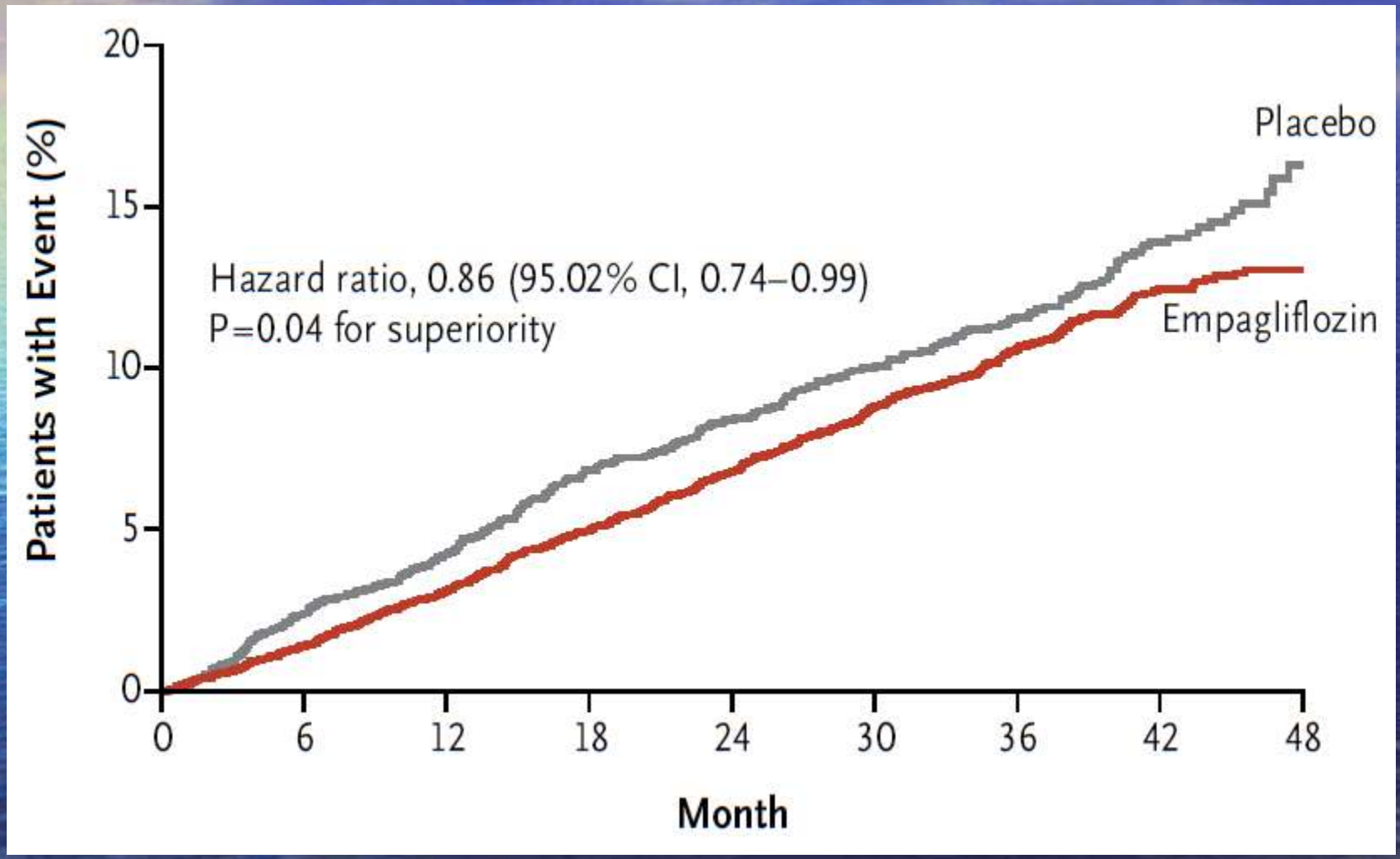
Rare DKA (Beware Latent Type 1)

EMPA-REG

- 7020 pts in RCT for median of 3.1 years
- Lower CV event rate in empagliflozin group (10.5 vs. 12.1%, HR 0.86) with lower rate of death from CV causes and hospitalization for heart failure.
- Long term protection of kidney function.
- Increased rate of genital infections.

N Engl J Med 2015; 373:2117-2128

EMPA-REG CV Outcomes



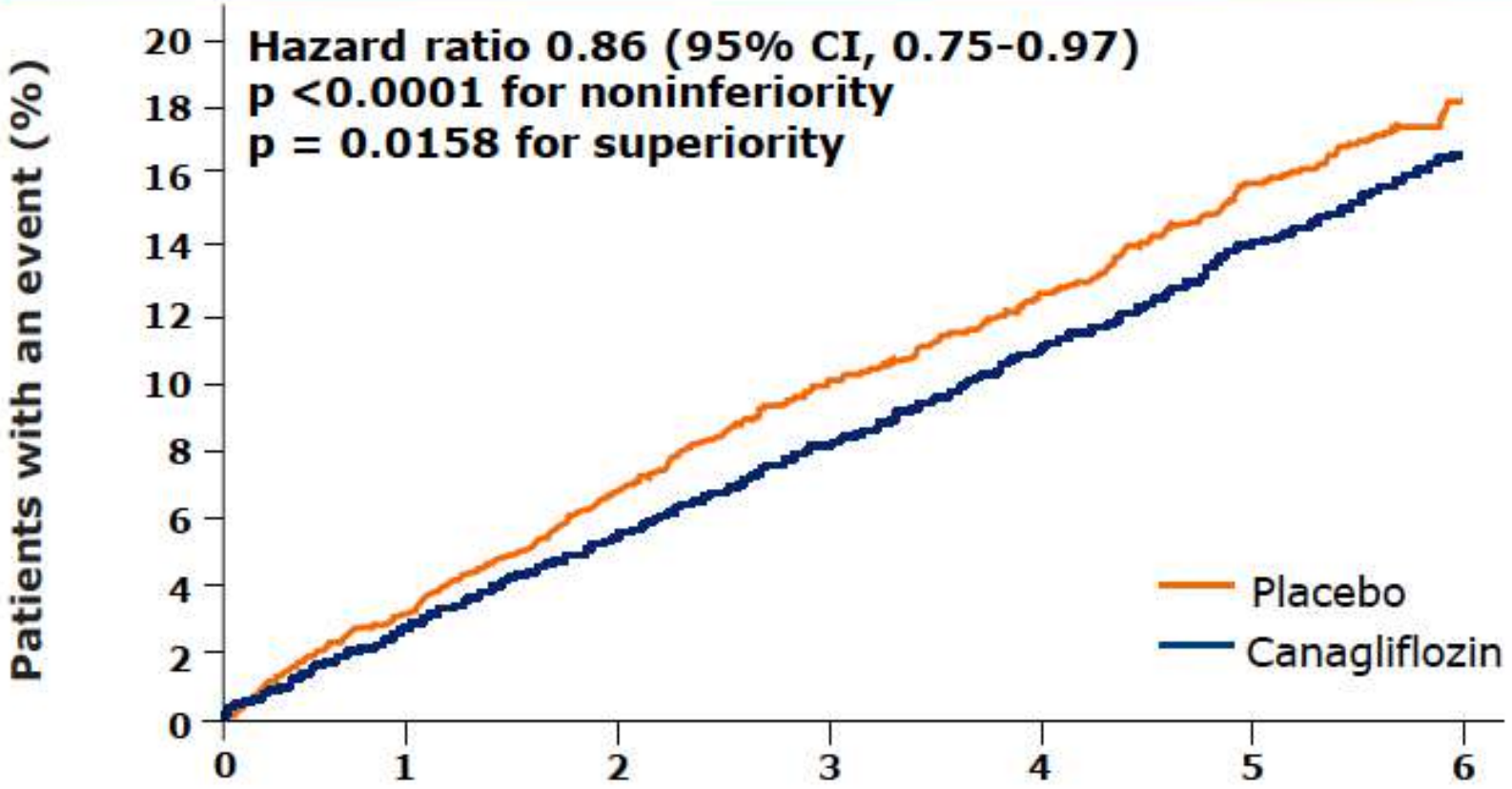
N Engl J Med 2015; 373:2117-2128

CANVAS

- Population: 10,142 DM2 with high CV risk
- Intervention: canagliflozin vs. placebo
- Outcome: CV death, nonfatal MI or stroke at 188 weeks
- Results: 27 vs 31 per 1000 pt-yrs [HR 0.86, P<0.001], reduced progression of albuminuria.
- Note: Higher risk of amputation (6.3 vs 3.4 per 1000 pt-yrs)

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

CANVAS Program

Large CV Outcomes Trials in Diabetes (Non-Insulin)

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pla	pla	pla	sulfonylurea	placebo
N	,500	,400	,000	6,000	8,300
Results	2013	2013	2015	2018	2018

NEUTRAL

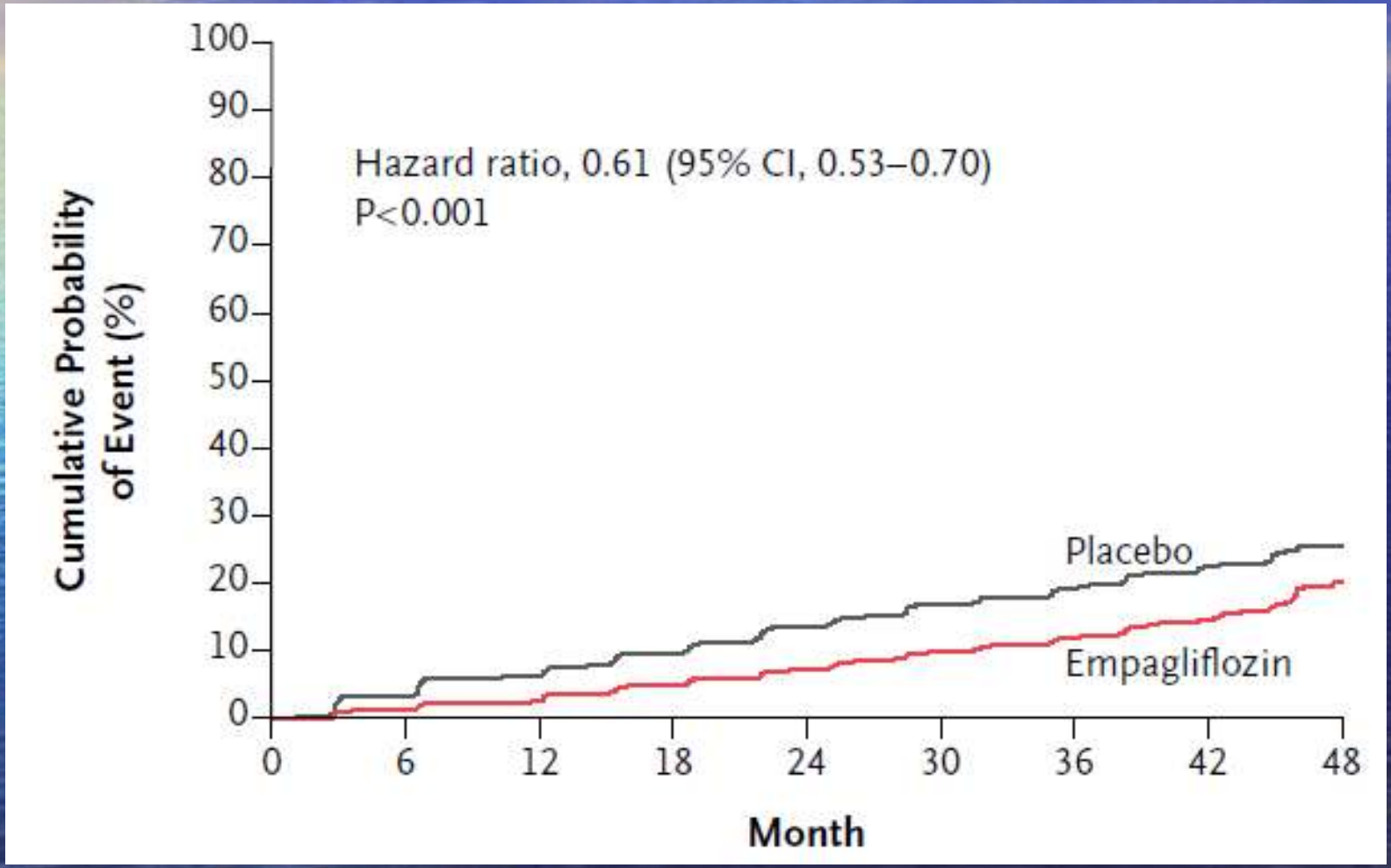
Study	LEADER	ELIXA	USTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	pla	placebo		placebo
N	16,500	,00	6,000	5,400	8,300
Results	2016	2015	2016	2018	2019

NEUTRAL

Study	EMPA-REG	VAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	2015	2017	2019	2020

EMPA-REG renal outcomes

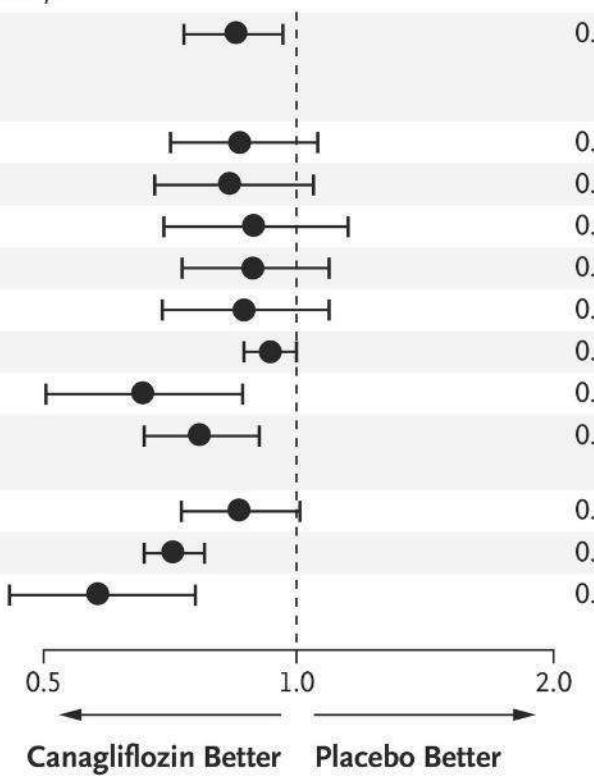
Incident or worsening nephropathy



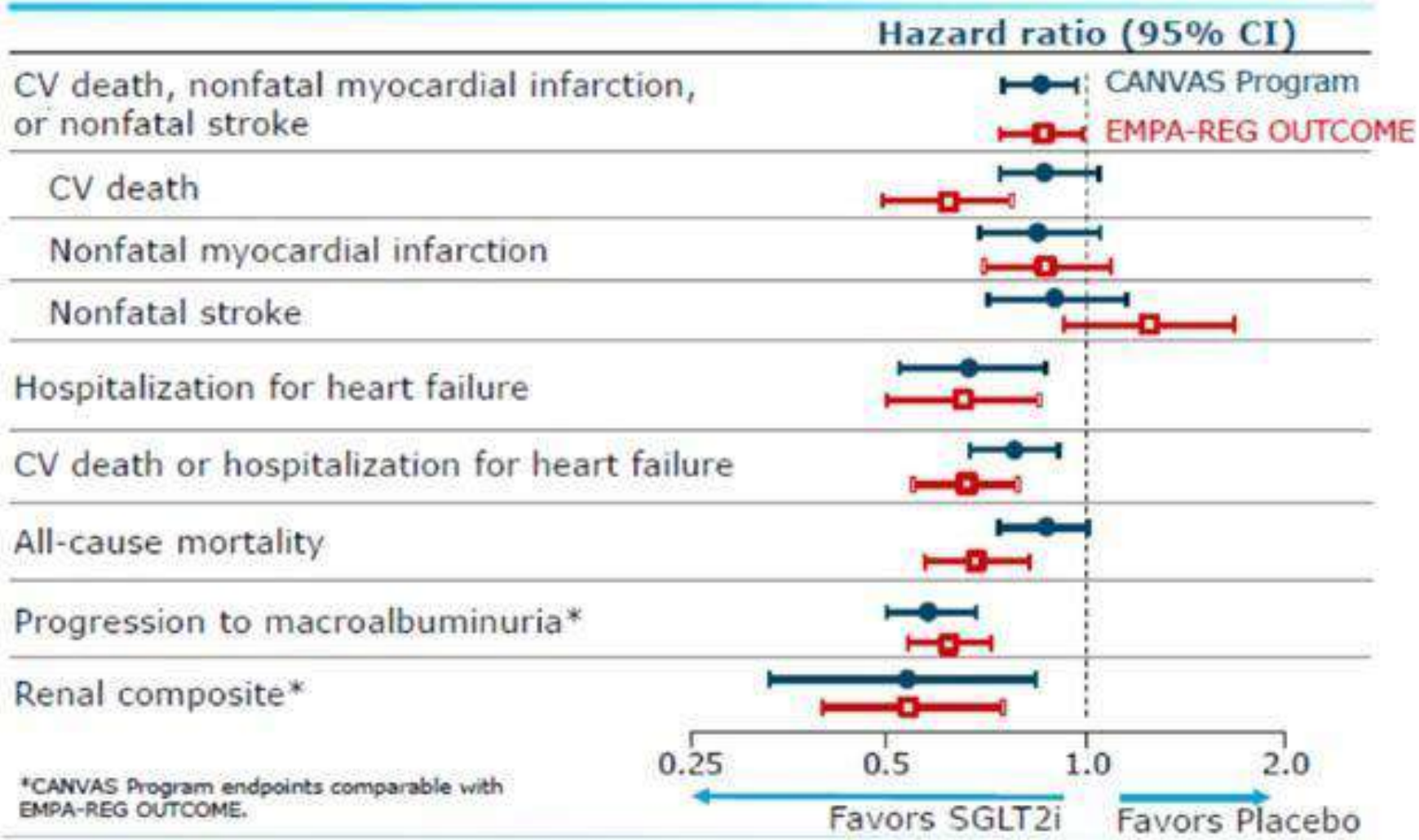
Wanner, NEJM June 2016

Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)

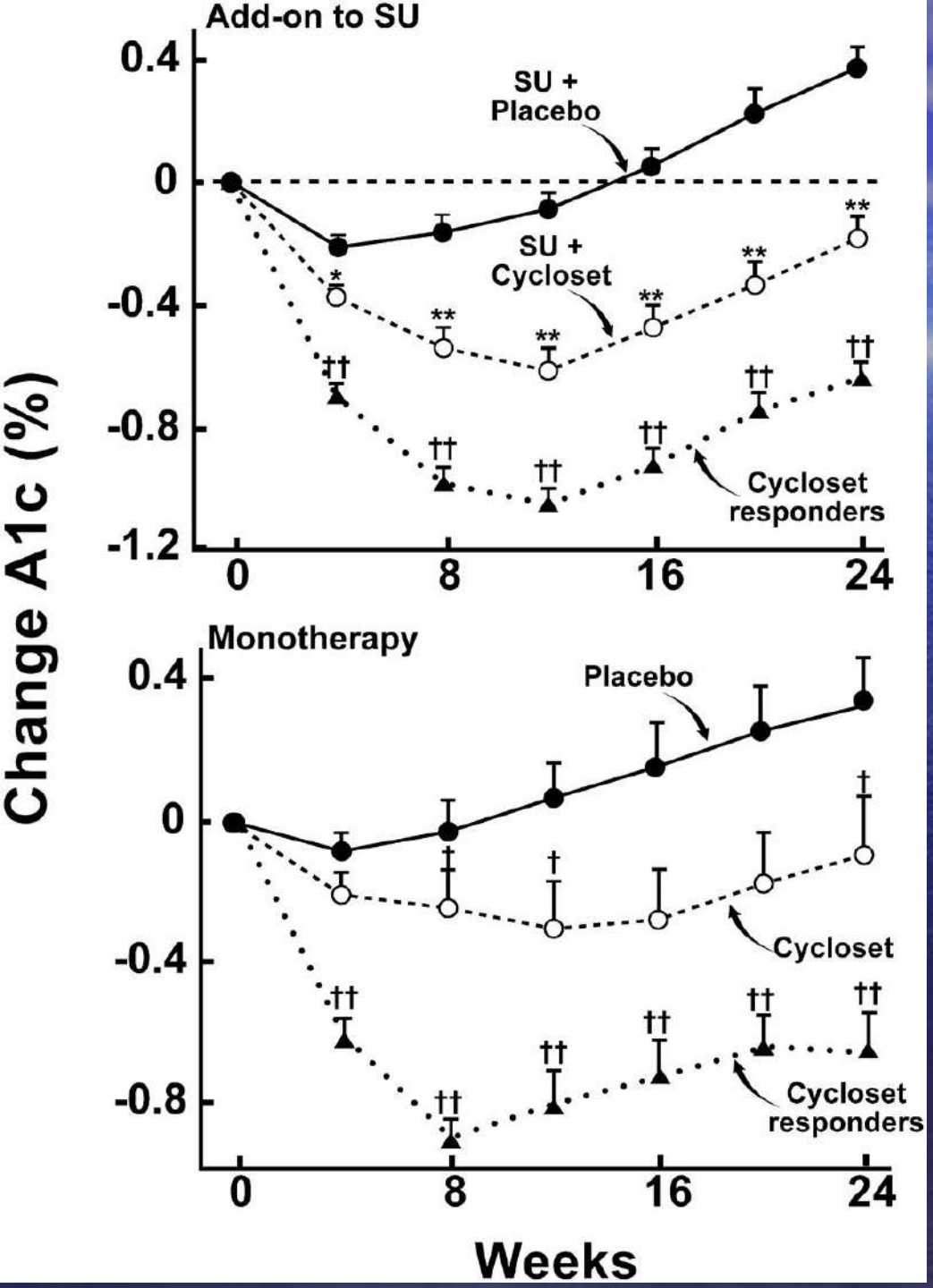


Neal B et al. N Engl J Med 2017;377:644-657


Hazard ratio (95% CI)
CV death, nonfatal myocardial infarction, or nonfatal stroke
CANVAS Program
EMPA-REG OUTCOME
CV death
Nonfatal myocardial infarction
Nonfatal stroke
Hospitalization for heart failure
CV death or hospitalization for heart failure
All-cause mortality
Progression to macroalbuminuria*
Renal composite*
0.25
0.5
1.0
2.0
Favors SGLT2i
Favors Placebo
*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

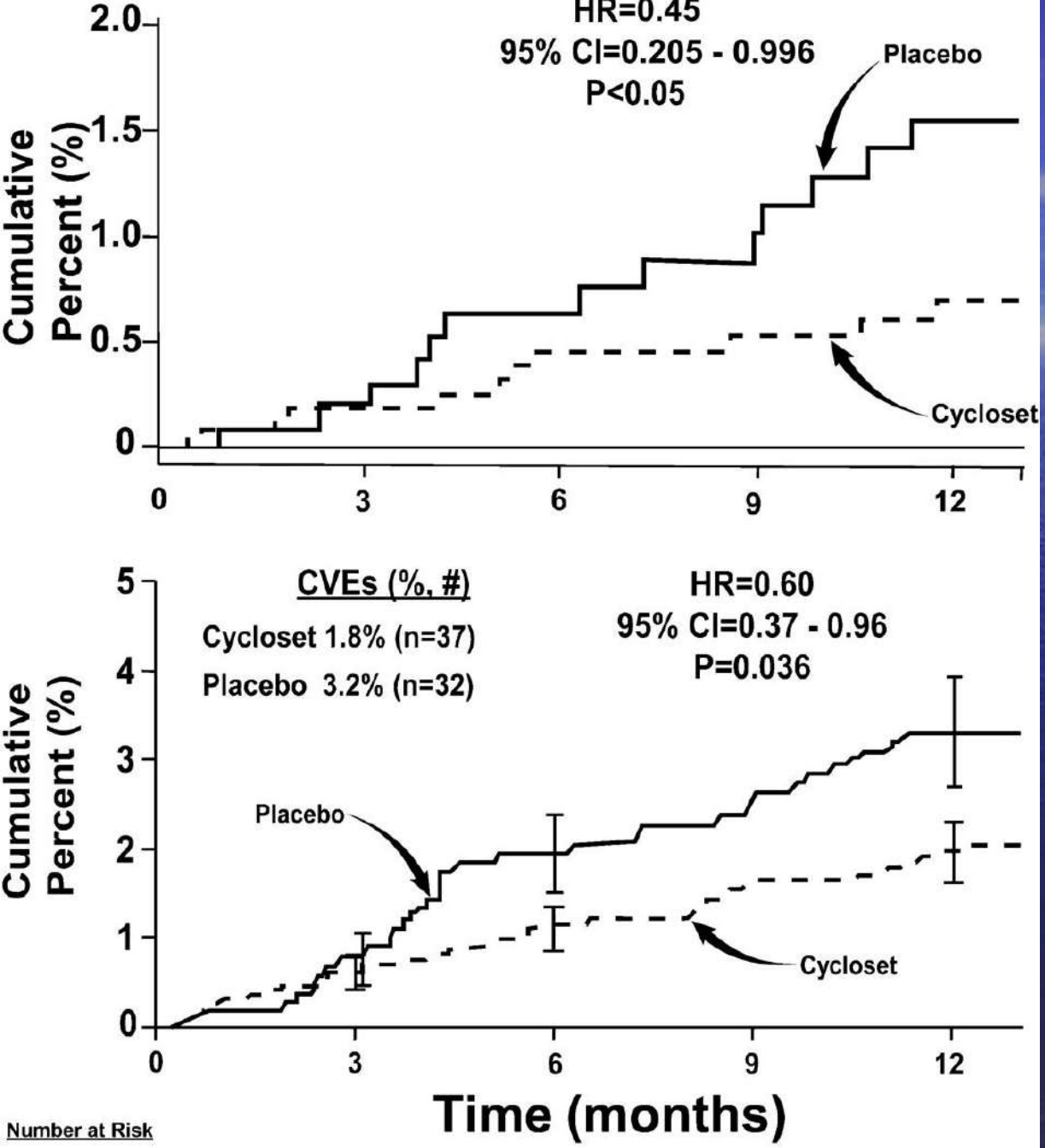
Bromocriptine (0.8 - 4.8 mg OD)

- Decreases PC sugars - mechanism not clear how ? central
- > 10% GI, CNS side effects
- Ergot drug - re: drug interactions
- CYP 3A4 metabolism
- Has CV outcome data
- Has not been well accepted in guidelines



Change in HbA1c in Bromocriptine (0.8 to 4.8 mg OD in am) and placebo-treated diabetic subjects.

Ralph A. DeFronzo
Diabetes Care
2011;34:789-794



Kaplan-Meier plot of time to first cardiovascular (MACE) event (myocardial infarction, stroke, and death) in type 2 diabetic subjects treated with bromocritpine or placebo for 52 weeks

Ralph A. DeFronzo
Diabetes Care 2011;34:789-794

Diabetes Pharmacology

	Efficacy	Hypo risk	Wt change	CV risk lower?
Metformin	+++	0	-	+
SU	++	+	+	0
DPP4	+	0	0	0
TZD	++	0	++	+?
SGLT2	+	0	--	++
GLP1	+++	0	---	++
Insulin	++++	+++	+++	++

Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (*P* value vs placebo)
Antihyperglycemic agents		
Metformin[1]	2.8 years	31% (*P*<0.001)
Acarbose[2]	3.3 years	25% (*P*=0.0015)
Pioglitazone[3]	2.4 years	72% (*P*<0.001)
Rosiglitazone[4]	3.0 years	60% (*P*<0.0001)
Insulin glargine[9]	6 years + follow-up	23% (P=0.014)
Liraglutide, 3.0 mg[8]	3.0 years	66% (*P*<0.0001)
Weight loss interventions		
Orlistat[5]	4 years	37% (*P*=0.0032)
Phentermine/topiramate[6]	2 years	79% (*P*<0.05)
Bariatric surgery[7]	10 years	75% (*P*<0.001)

1. DPP Research Group. *N Engl J Med*. 2002;346:393-403. 2. STOP-NIDDM Trial Research Group. *Lancet*. 2002;359:2072-2077.
3. Defronzo RA, et al. *N Engl J Med.* 2011;364:1104-15. 4. DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.
5. Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161. 6. Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.
7. Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693, 8. le Roux CW,Lancet, 2017. 9. Punthakee Z, ORIGINALE, *Diabetes Care, 2016*

What to do next?

1. Improve lifestyle
2. Increase metformin to 1g TID
3. Add glyburide 2.5mg BID
4. Add pioglitazone 30mg QD
5. Add acarbose 50mg TID
6. Add sitagliptin 100mg QD
7. Add glargine 10 units SC Qhs
8. Add liraglutide 1.2 mg sc Qam
9. Add empagliflozin 10 mg QD