Parenteral Agents in Type 2 DM

CME Away

India & Sri Lanka

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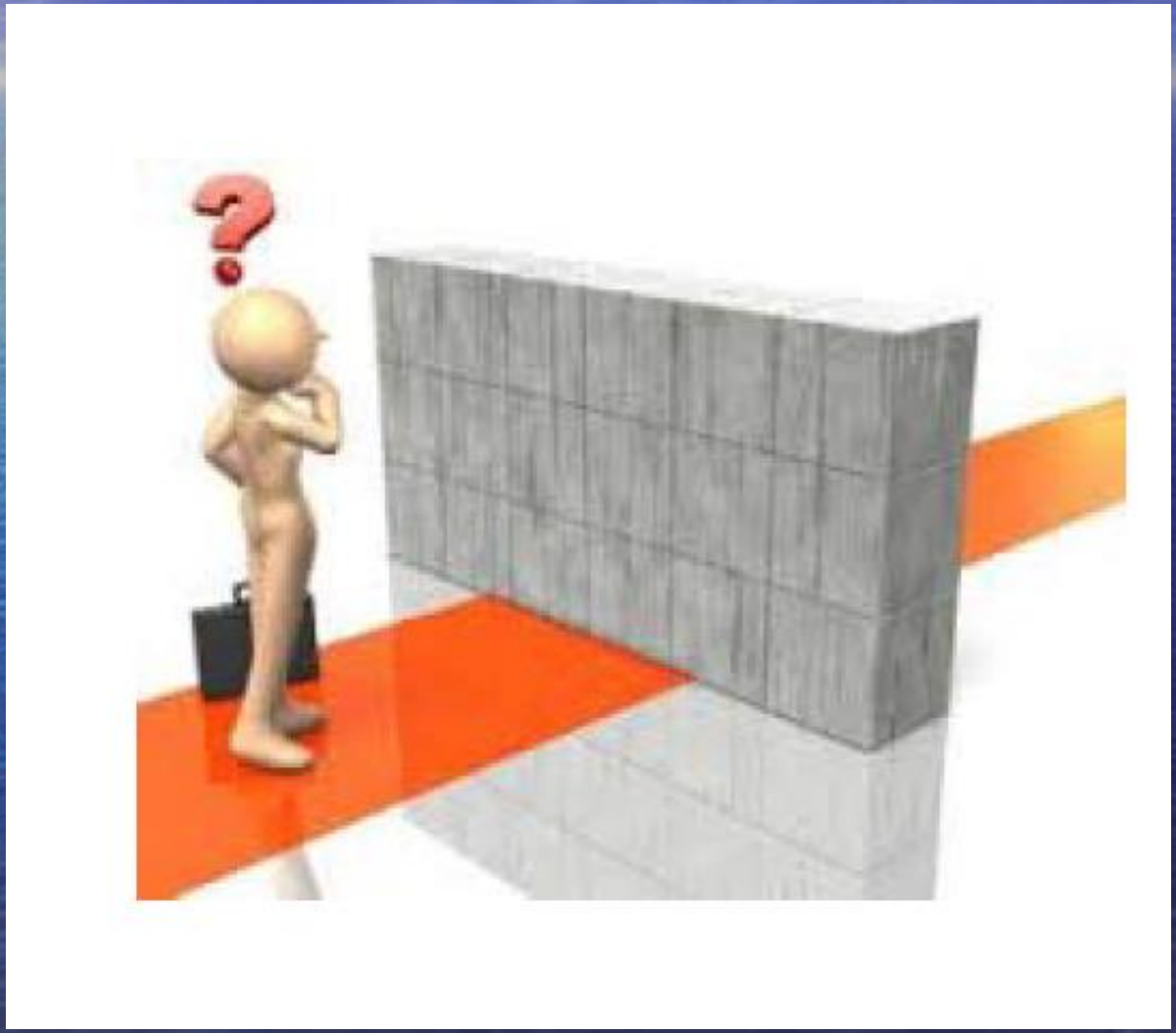
Barriers To Change



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 available & newer insulins
  - Glargine
  - Detemir
  - “Subsequent Entry biologic” Glargine
  - U300 Glargine (Toujou)
  - Degludec
- Review incretin analogue therapy
- Review combination therapy
- Inhaled Insulin

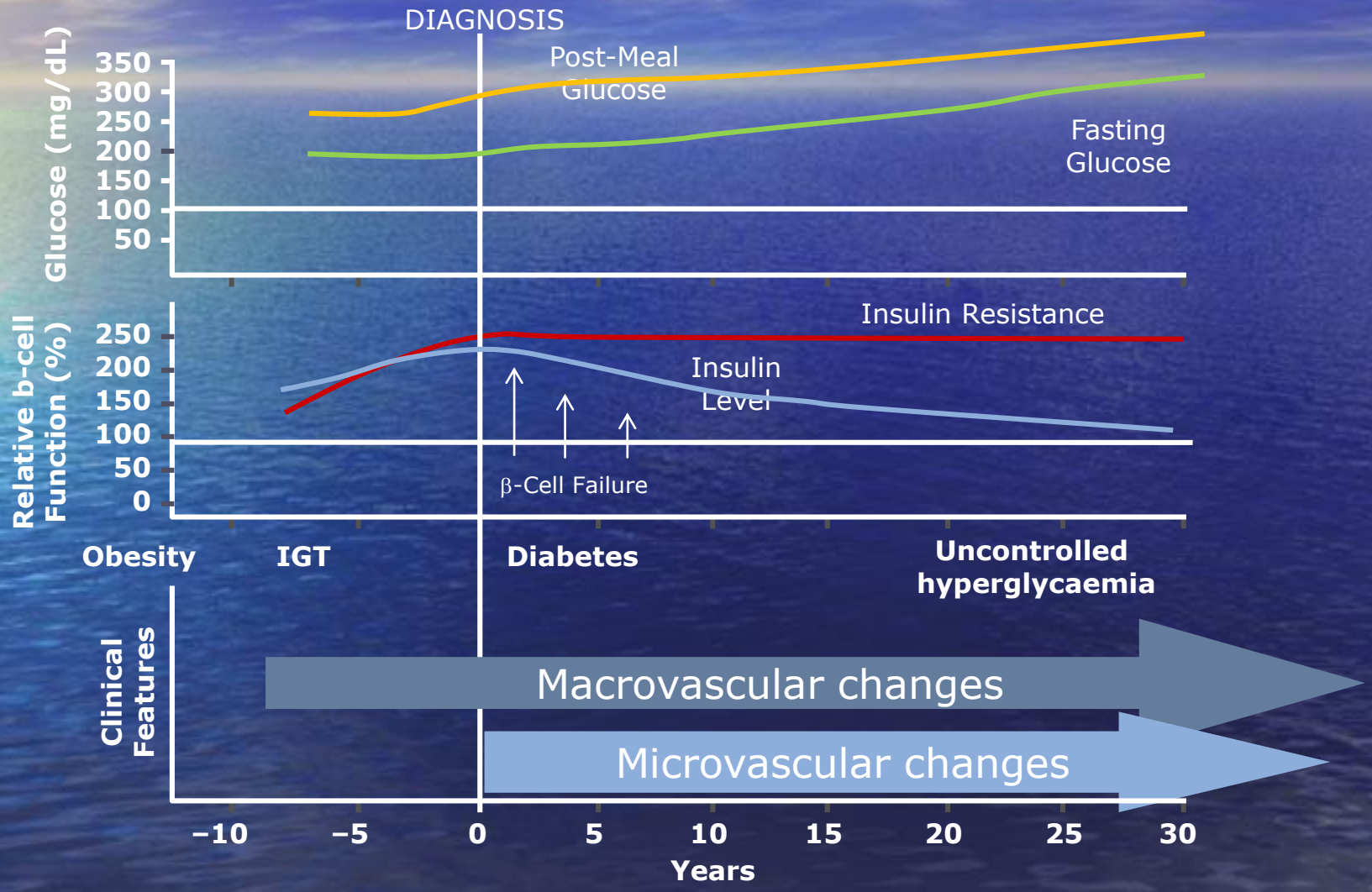
Case 2:

- 56 woman
- Type 2 DM 8 hrs.
- Metformin 1,000 mg po BID,
  Empagliflozin 10 mg po OD,
  Glargine Insulin 48 units sc at HS.
- Fasting glucose range 6.0 – 7.5 mmol (110 – 140 mg/dl)
- HgA1c 8.2

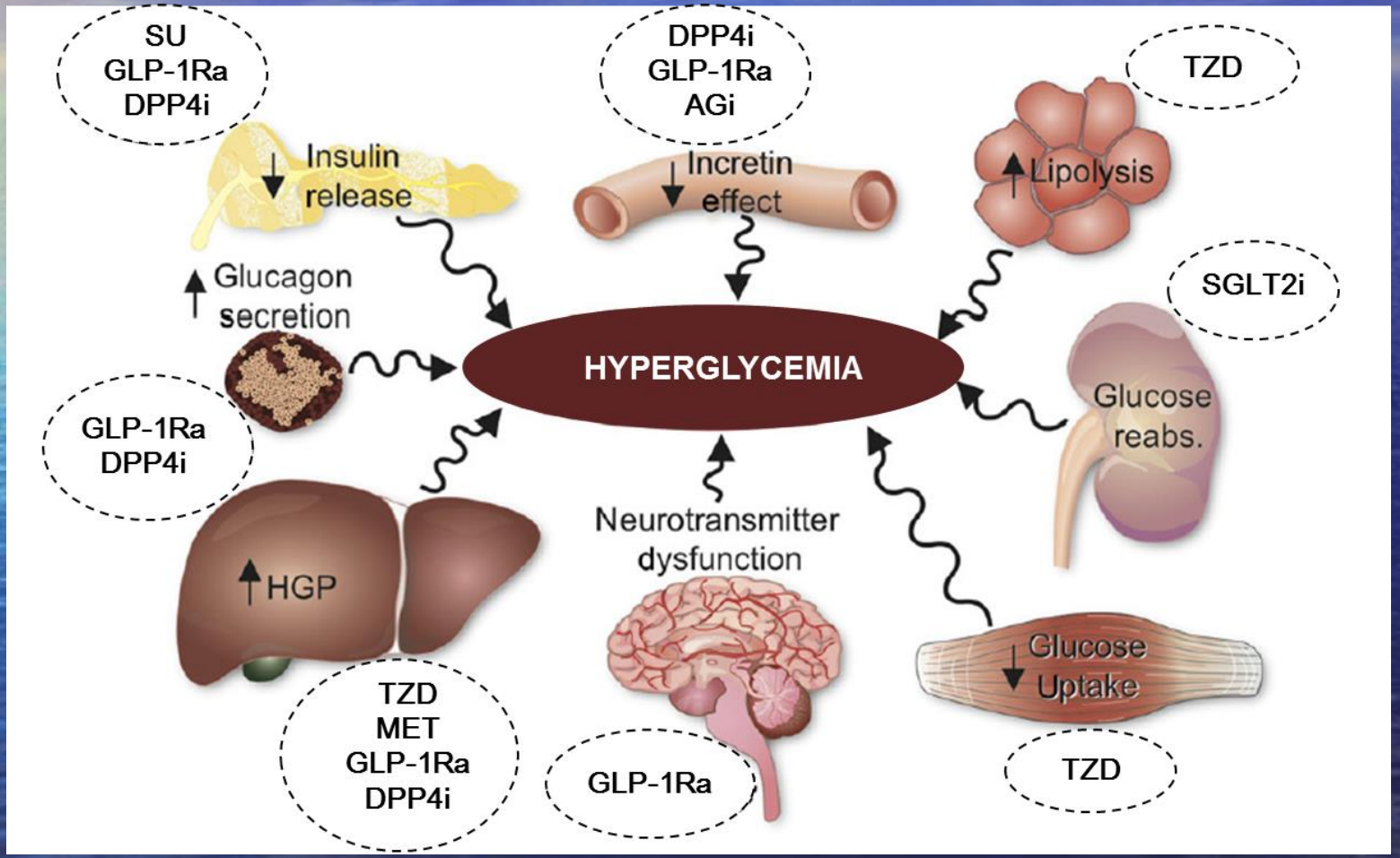
Case 2: What to do next?

1) Increase Glargine to 55 units a day
2) Add repaglinide at mealtime
3) Add prandial lispro insulin
4) Add liraglutide 1.2 mg sc every am
5) Add pioglitazone 15 mg per day
6) Add linagliptin 5 mg po daily
7) Switch to Degludec 60 units a day

Natural Progression of Type 2 Diabetes

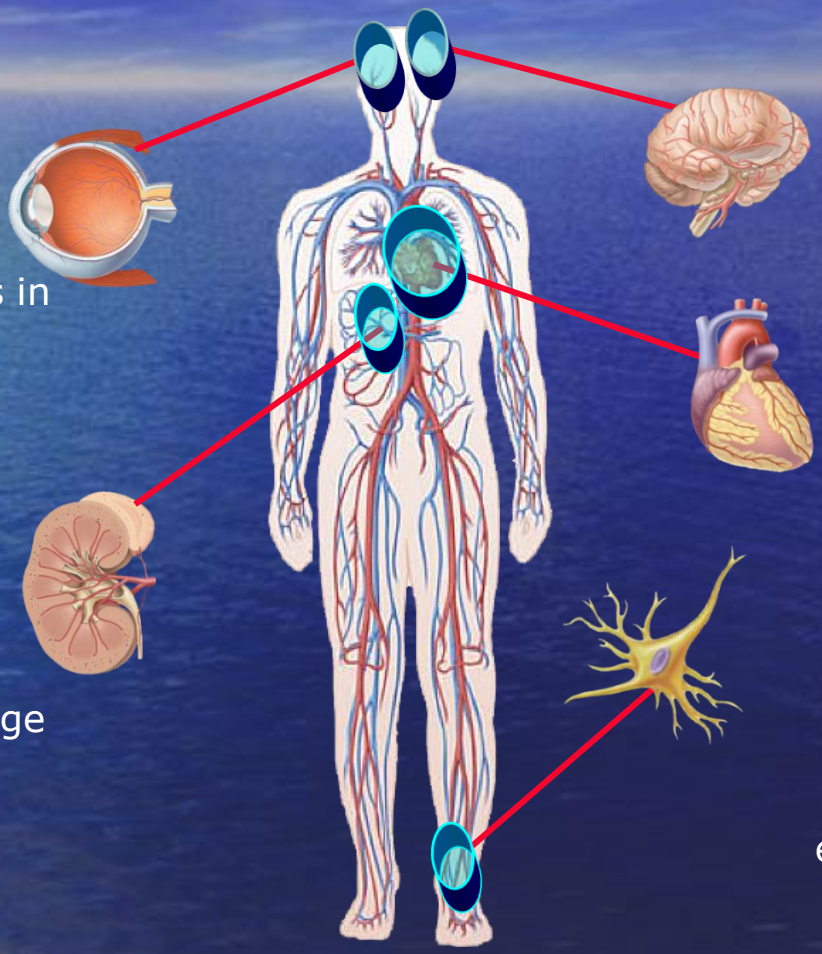


Therapeutic Targets in different Organs to reduce Hyperglycemia



Adapted from Ferrannini and Defronzo. 2015 Eur Heart Journal
doi: 10.1093/eurheartj/ehv239

Diabetes Continues to be Associated with Significant Morbidity



Diabetic Retinopathy

Leading cause of blindness in working-age adults[1]

Diabetic Nephropathy

Leading cause of end-stage renal disease[2]

Stroke

2- to 4-fold increase in cardiovascular mortality and stroke[3]

Cardiovascular Disease

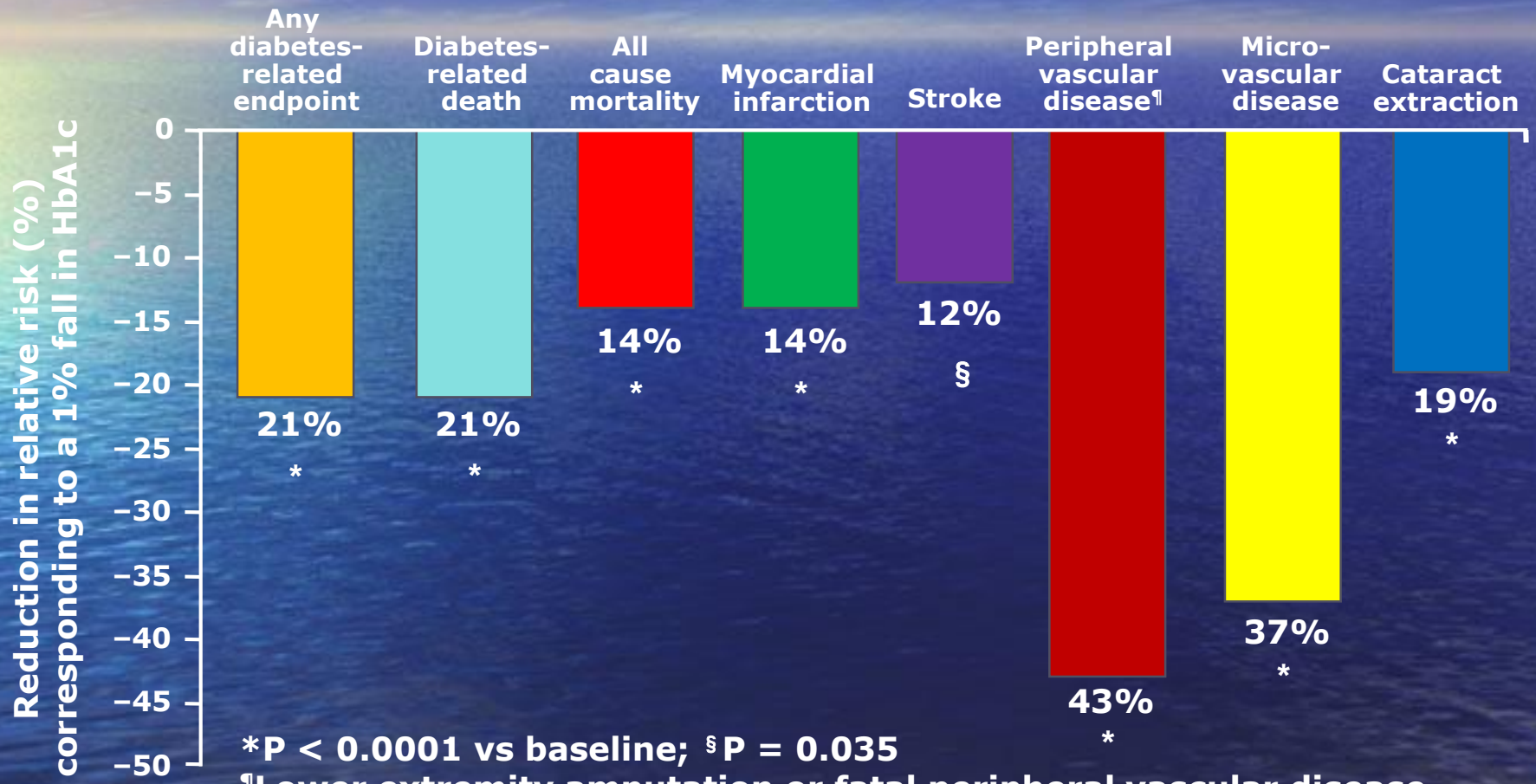
8/10 diabetic patients die from CV events[4]

Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations[5]

1. Fong DS, et al. *Diabetes Care*. 2003; 26 [Suppl. 1]:S99–S102. 2. Molitch ME, et al. *Diabetes Care*. 2003; 26 [Suppl.1]:S94–S98.
3. Kannel WB, et al. *Am Heart J.* 1990; 120:672–676. 4. Gray RP & Yudkin JS. In *Textbook of Diabetes*. 1997.
5. Mayfield JA, et al. *Diabetes Care*. 2003;26 [Suppl. 1]:S78–S79.

UKPDS: Improving Glycemic Control Reduces the Risk of Diabetic Complications



*P < 0.0001 vs baseline; §P = 0.035

¶Lower extremity amputation or fatal peripheral vascular disease

Adapted from Stratton IM, et al. UKPDS 35. BMJ 2000; 321:405–412.

Insulins: The long and the short of it

- The *very* long and smooth
  - *Glargine*
  - *Detemir*
  - *U300* Glargine (Toujeo)
  - Subsequent biologic entry Glargine
  - Degludec

- The *very* short and sharp
  - Inhaled insulin

When to Stop Titrating Basal Insulin and Consider Prandial Control Options

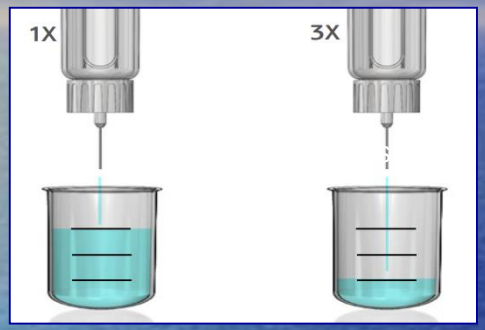
The individual is not meeting glycemic targets on basal insulin[1-4]
and:

- **HbA1C still not at goal with 0.5 units/kg/d of daily basal insulin[3]**
- **HbA1c elevated despite normal FPG with basal insulin[2,3]**
- **FPG with basal insulin is within targeted range, but PPG is persistently above goal[3,4]**
- **Further increases in basal insulin result in hypoglycemia[3]**

1. Skyler JS. In: Lebovitz HE, ed. *Therapy for Diabetes Mellitus and Related Disorders*. Alexandria, VA: ADA, Inc.; 2004:207-223.
2. American Diabetes Association. *Practical Insulin: A Handbook for Prescribing Providers*. 3rd ed. 2011:1-68.
3. Inzucchi S, et al. *Diabetes Care*. 2012;35:1364-1379.
4. Davidson MB, et al. *Endocr Pract*. 2011;17:395-403.

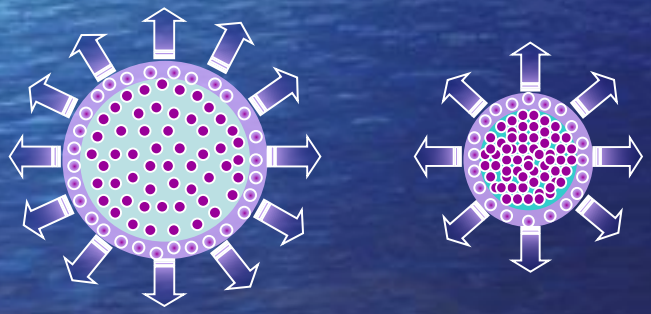
U300 Glargine(TOUJEO) has prolonged , and “flatter” profile vs U100 Glargine

1 **Reduction of volume by 2/3**



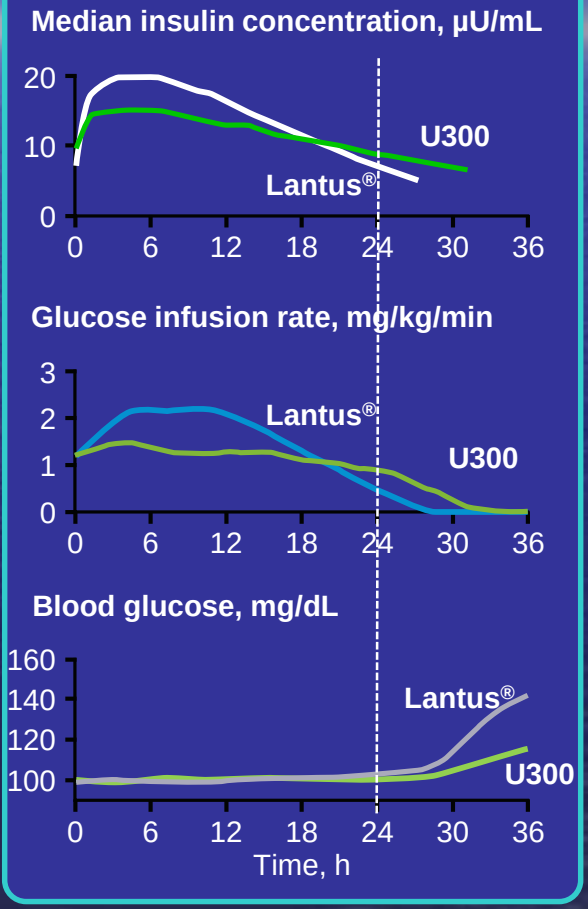
U100 U300

2 **Reduction of depot surface area by 1/2**



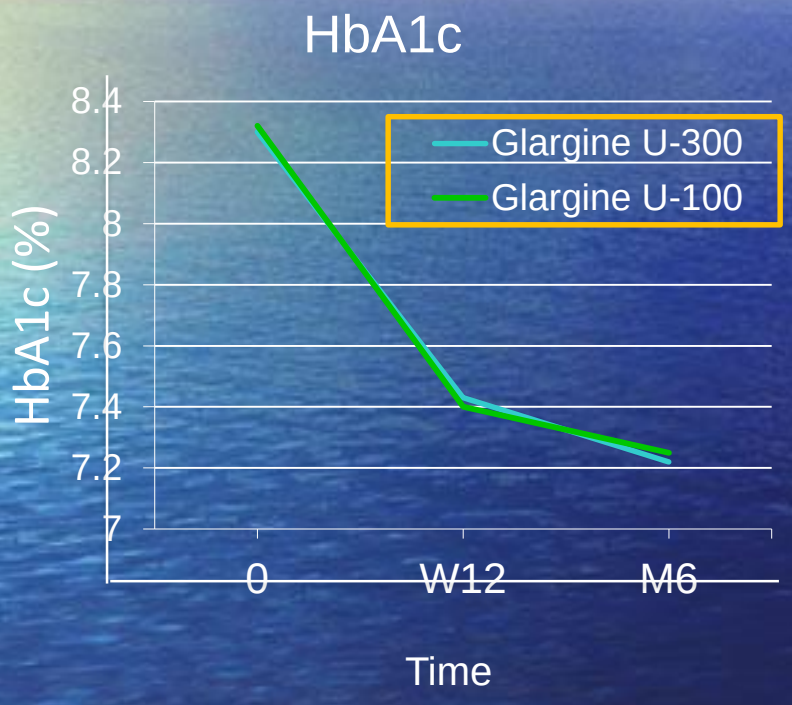
U100 U300

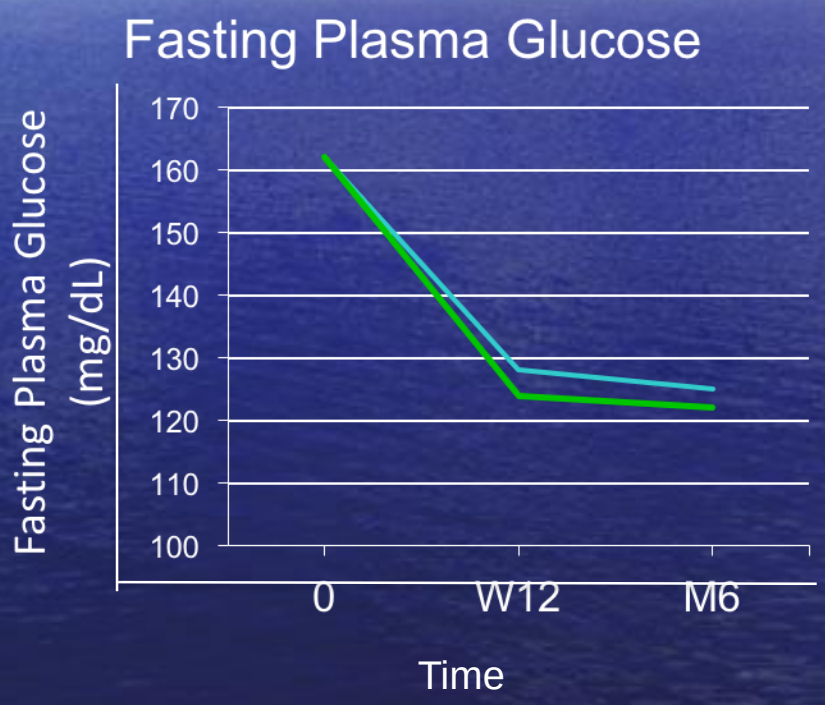
3 **More constant PK/PD profile**



Jax T et al. Poster presented at EASD 2013; Abstract 1029.

Insulin Glargine U-300 vs U-100: Glycemic Efficacy

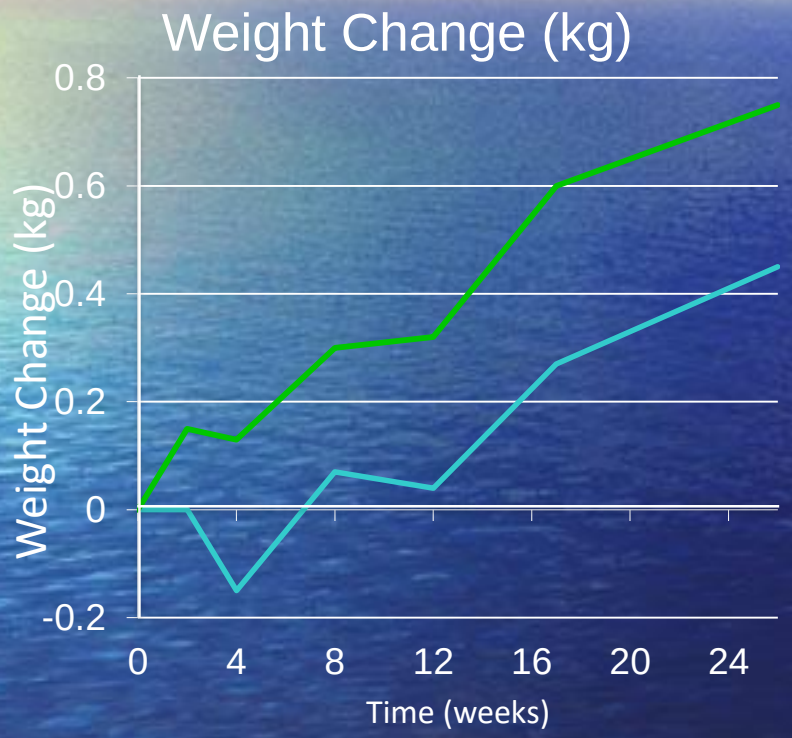


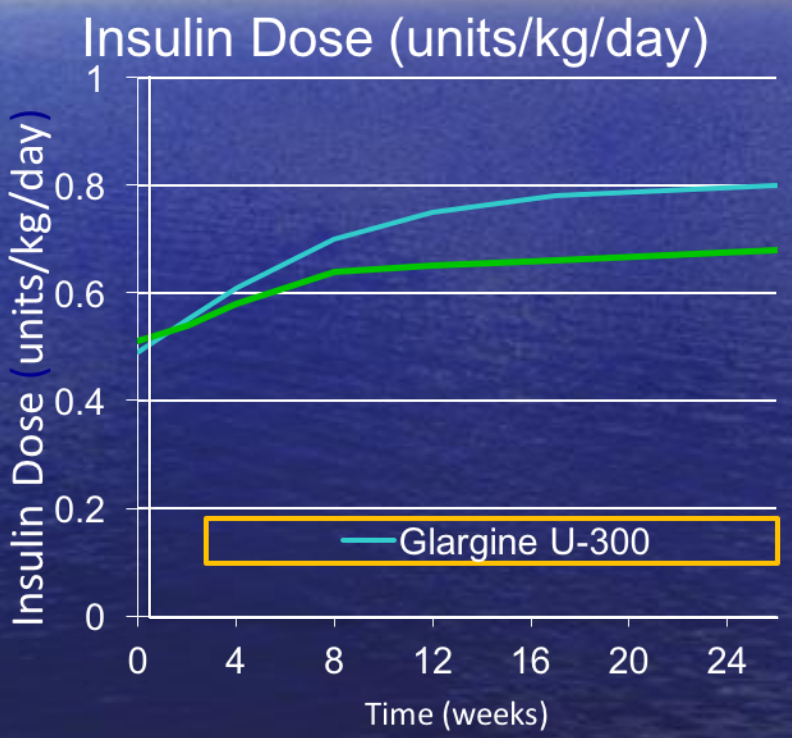


Meta-Analysis of EDITION 1, 2, 3; N=2496

Ritzel R, et al. *Diabetes Obes Metab*. 2015;17(9):859-867

Insulin Glargine U-300 vs U-100: Other Outcomes



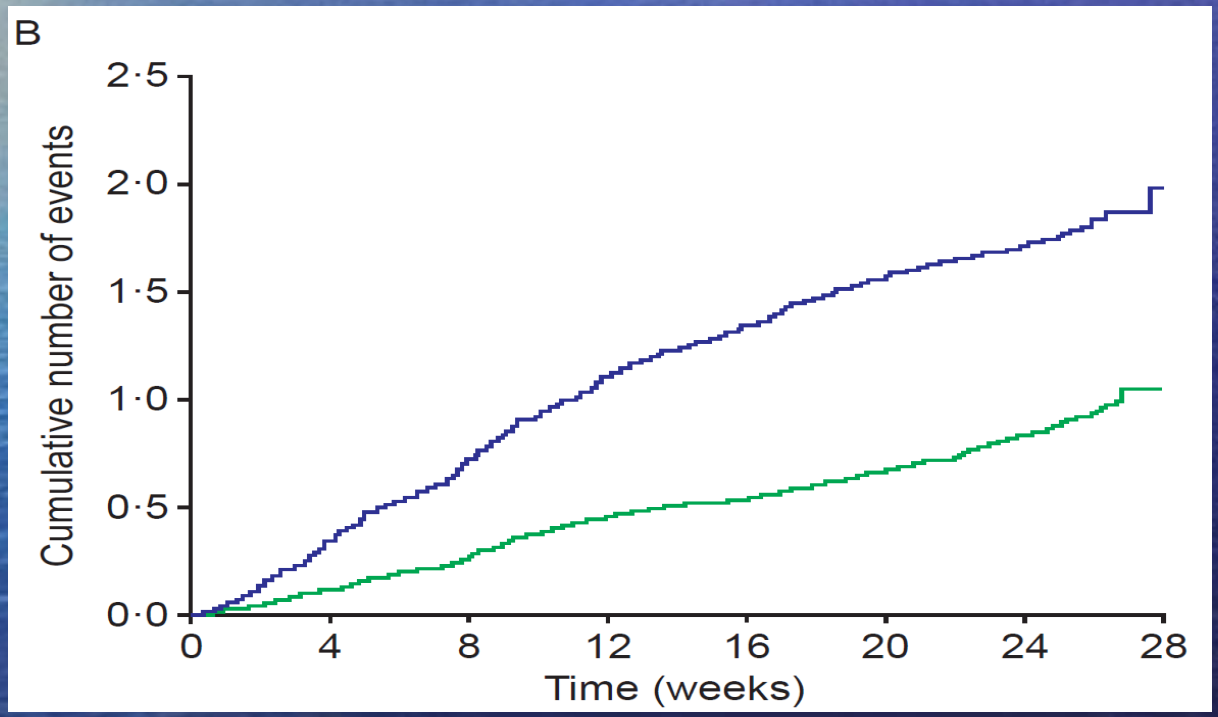


Meta-Analysis of EDITION 1, 2, 3; N=2496

Ritzel R, et al. *Diabetes Obes Metab*. 2015;17(9):859-867

Insulin Glargine U-300 vs U-100: Hypoglycemia

Cumulative mean number of *nocturnal* severe or confirmed (≤70 mg/dL) events/participant



Patients with T2DM using basal insulin + oral agent(s) (N=811)

48% lower with U-300
***P*=0.001**

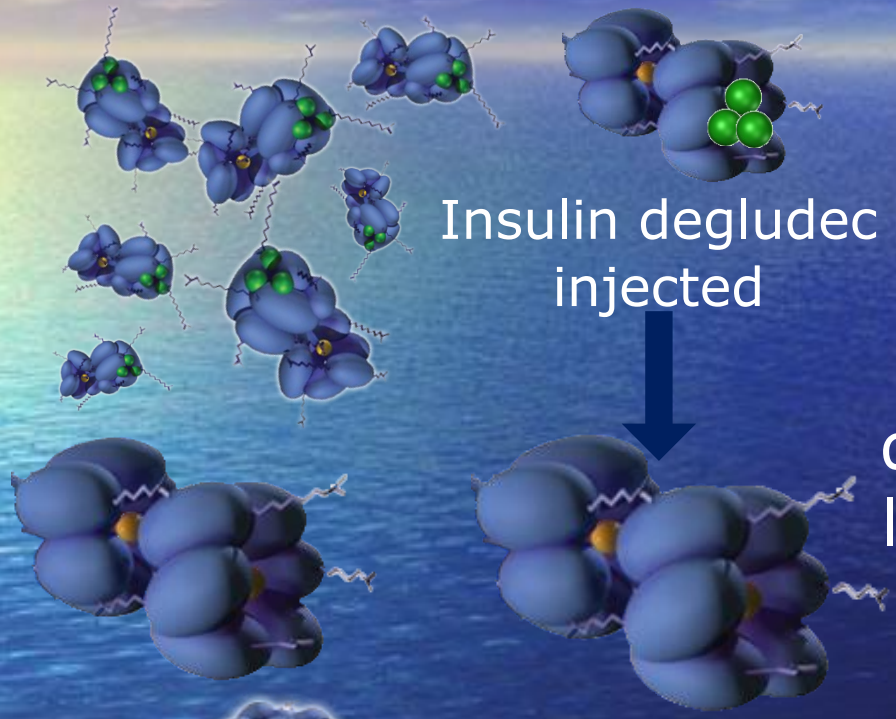
Difference mostly up to 12 wk

Yki-Jarvinen H, et al. *Diabetes Care*. 2014;37:3235-3243.

What is a “subsequent entry biologic”??

- a biologic product similar to an approved biologic
- other terms used include:
  "similar biological medicinal products" in the European Union and "follow-on protein products" in the United States
- Subsequent entry glargine is essentially the same insulin at a lower cost

Insulin degludec from solution to subcutaneous depot



Insulin degludec injected

Phenol Zn^{2+}

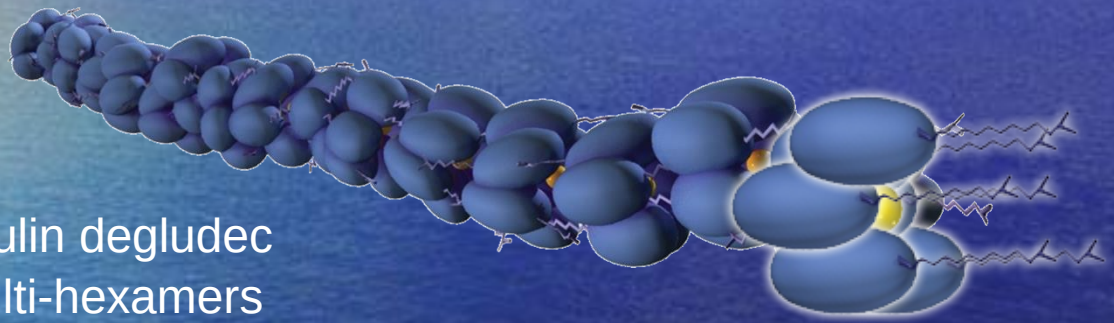
As phenol from the vehicle diffuses degludec hexamers link up via single side-chain contacts

Long multi-hexamers assemble

Insulin degludec: slow release following injection

Subcutaneous depot

Zn^{2+}

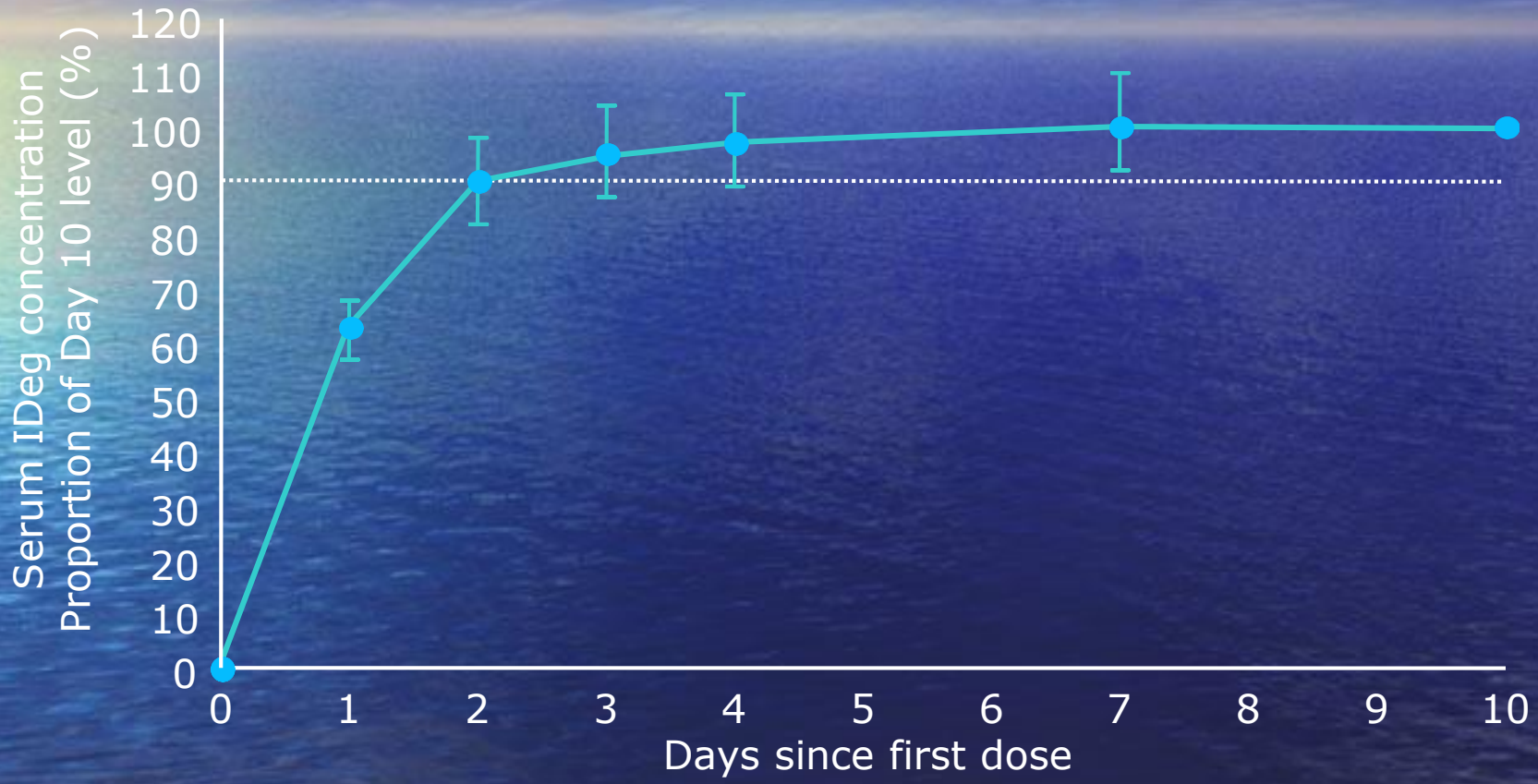


Insulin degludec multi-hexamers

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation

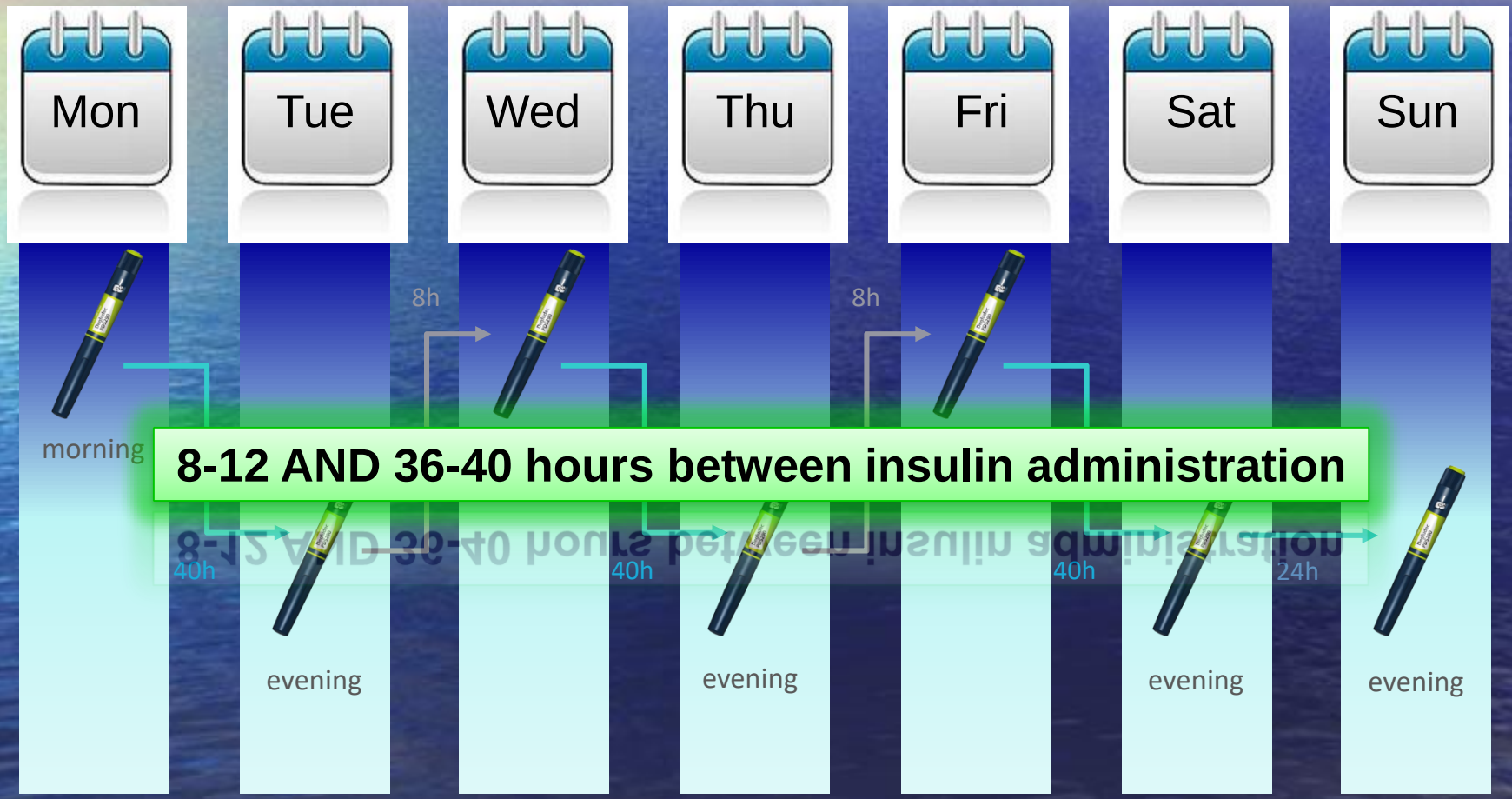
Insulin degludec steady state is reached within 2–3 days of once-daily dosing



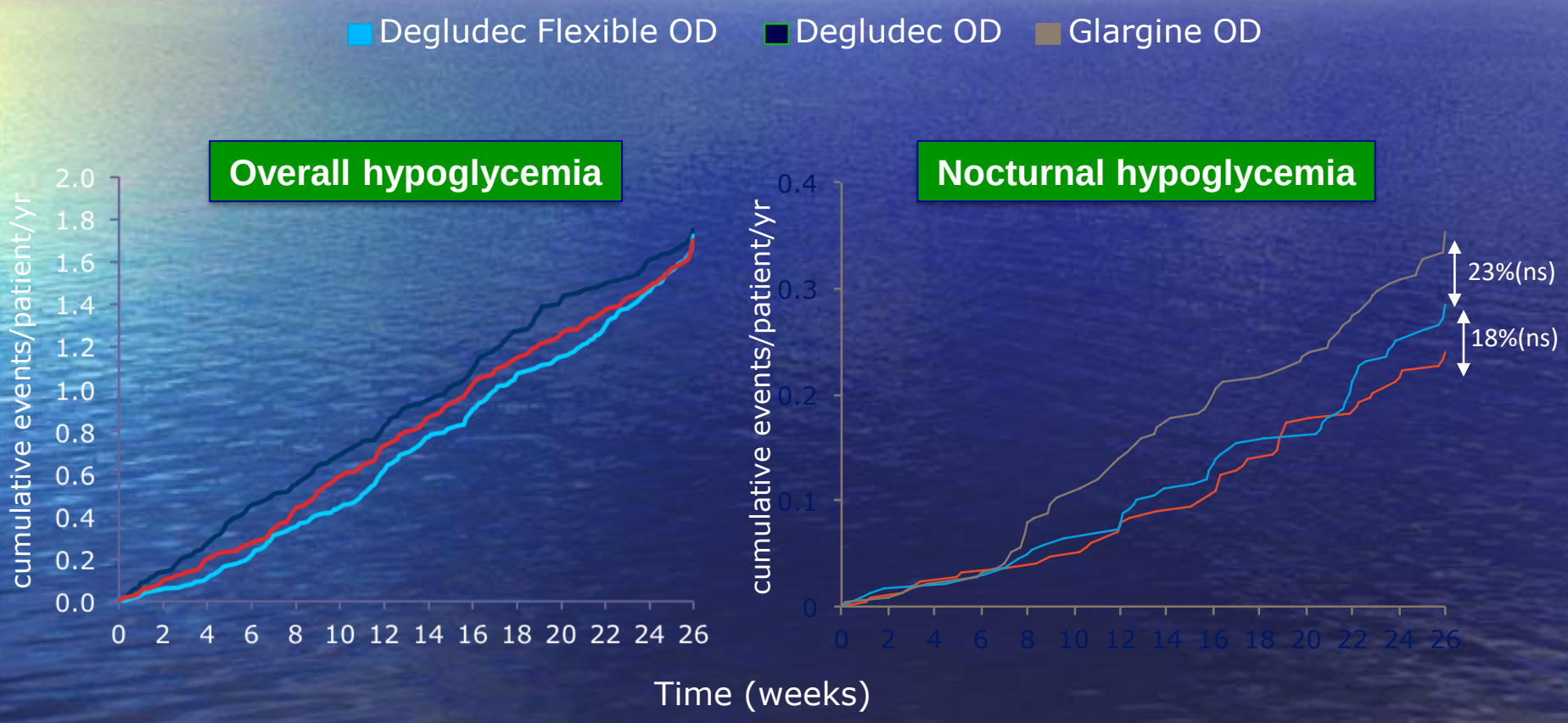
Relative serum IDeg trough concentrations during initiation of once-daily (0.4 U/kg) dosing in patients with T1DM

Heise T *et al. IDF 2011 21st World Congress Abstract Book.* IDF: Dubai, 2011; Poster 1453

Timing of flexible insulin **degludec** administration

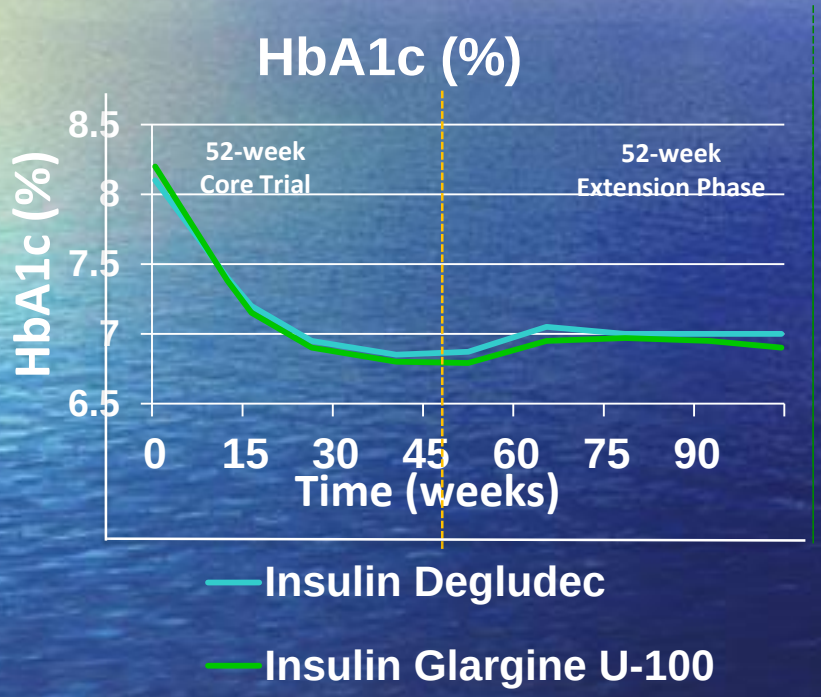


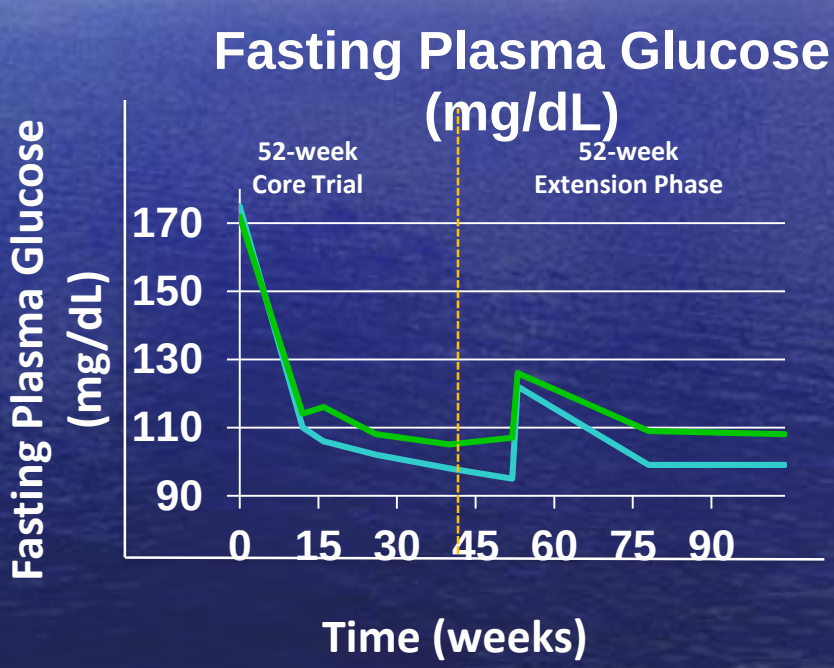
No difference in hypoglycemia between flexible degludec and fixed dosing



Birkeland *et al.* IDF 2011:P-1443; Bain *et al.* IDF 2011:O-0508; Birkeland *et al. Diabetologia* 2011;54(suppl. 1):S423; Atkin *et al. Diabetologia* 2011;54(suppl. 1):S53; Meneghini *et al. Diabetes* 2011;60(suppl. 1A):LB10 (NN1250-3668)

Insulin Degludec vs Insulin Glargine U-100: Glycemic Efficacy

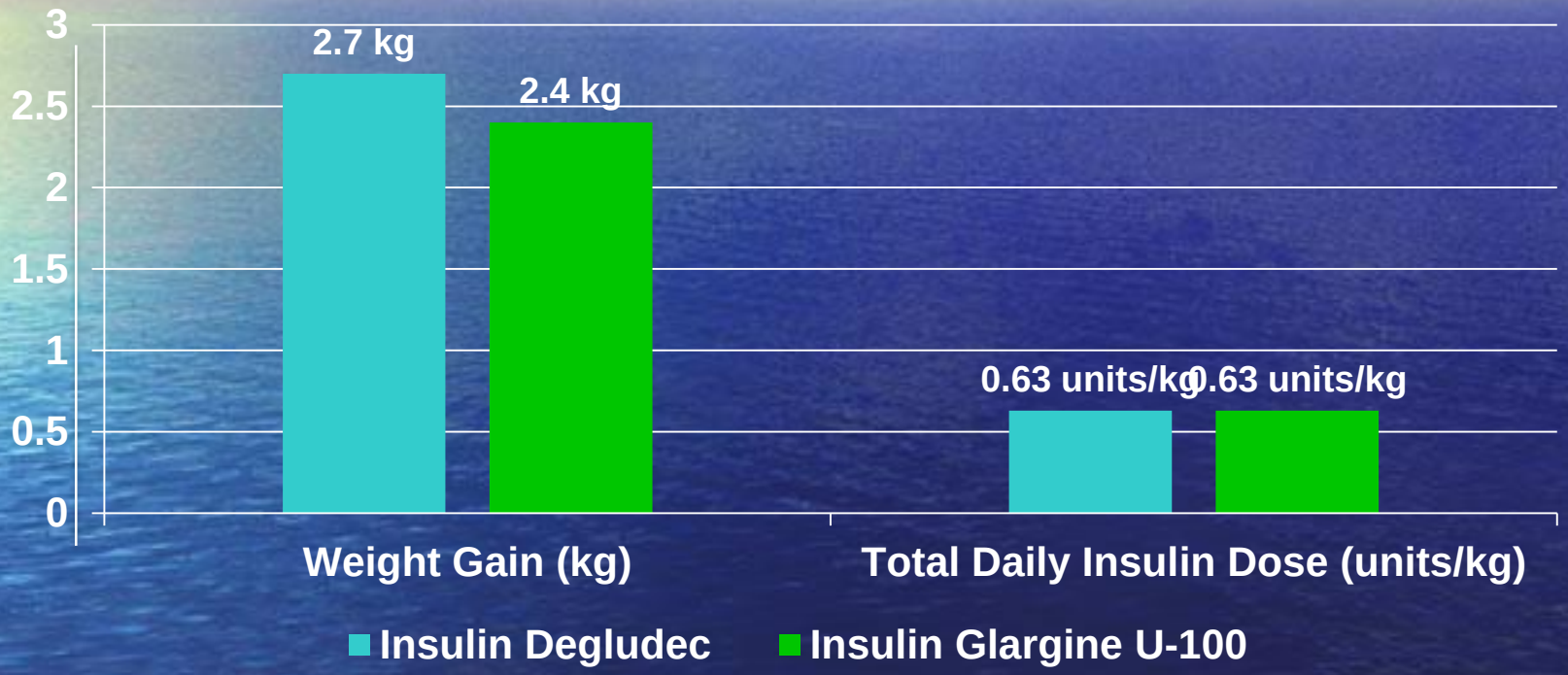




N=725

Rodbard HW, et al. *Diabet Med*. 2013;30:1298-1304.

Insulin Degludec vs Insulin Glargine U-100: Other Outcomes



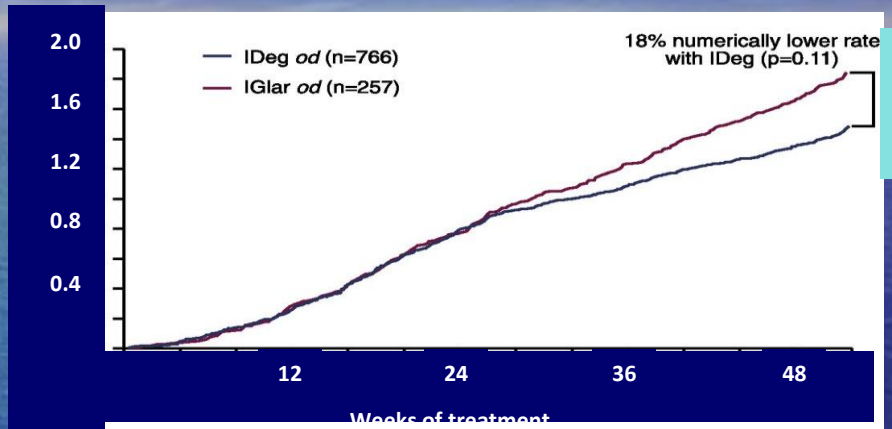
N=1023

Rodbard HW, et al. *Diabet Med*. 2013;30:1298-1304.

Insulin Degludec vs Insulin Glargine U-100

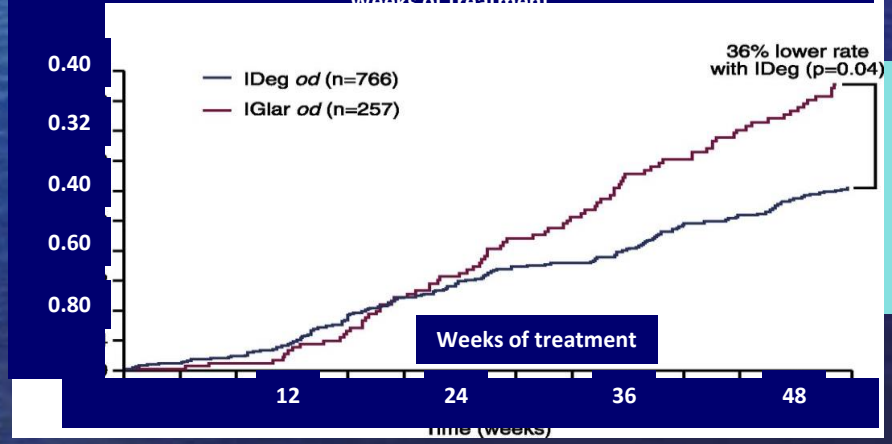
Cumulative hypoglycemic events (confirmed <56 mg/dL)

Anytime events/patient



18% lower with degludec *P*=0.11

Nocturnal events/patient



36% lower with degludec *P*=0.04

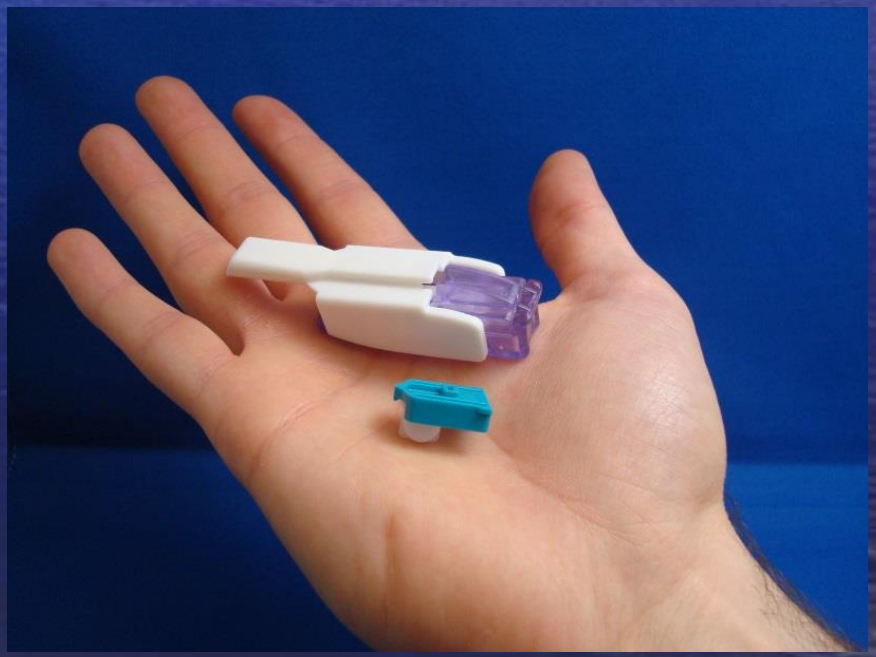
1023 insulin-naïve patients with T2DM

Zinman B, et al. Diabetes Care. 2012;35:2464-2471.

The very short

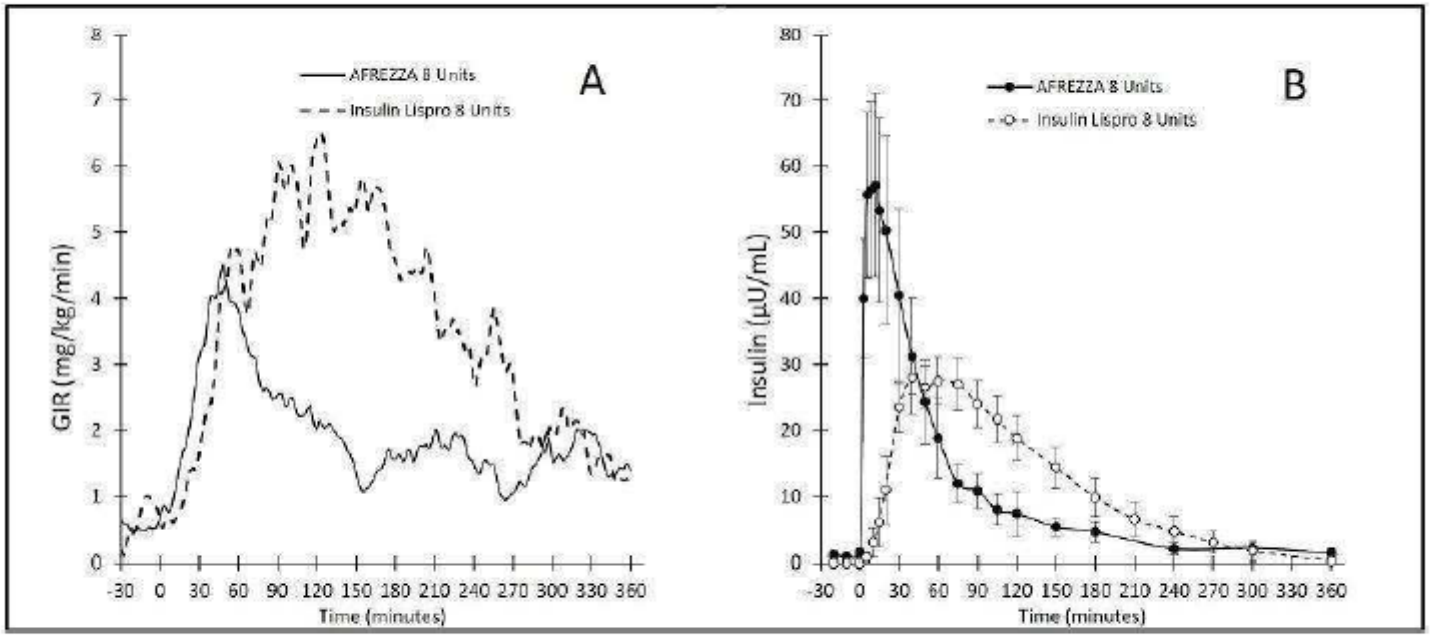
Faster onset
More rapid clearance

afrezza



Does not avoid need for basal insulin injections

Figure 3. Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentrations (B) after Administration of AFREZZA or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients*



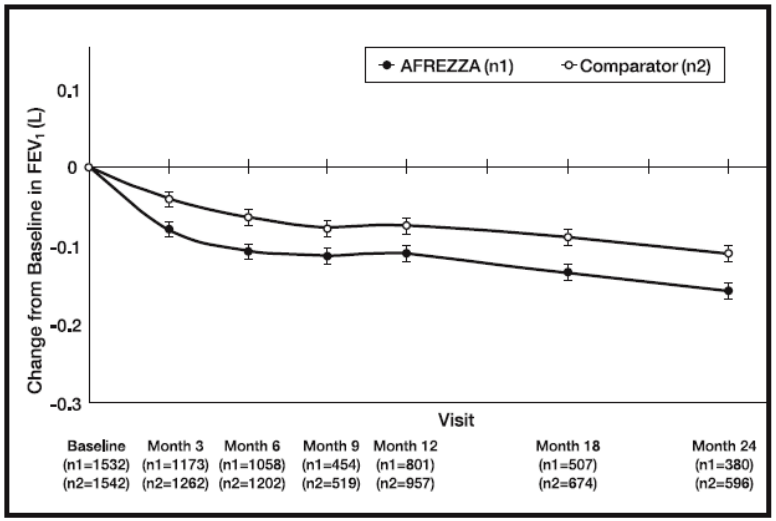
*Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.

Afrezza product monograph: afrezza.com

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. *[see Warnings and Precautions (5.1)]*.
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. *[see Contraindications (4)]*.
- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*.

Figure 2. Mean (+/-SE) Change in FEV_1 (Liters) from Baseline for Type 1 and Type 2 Diabetes Patients



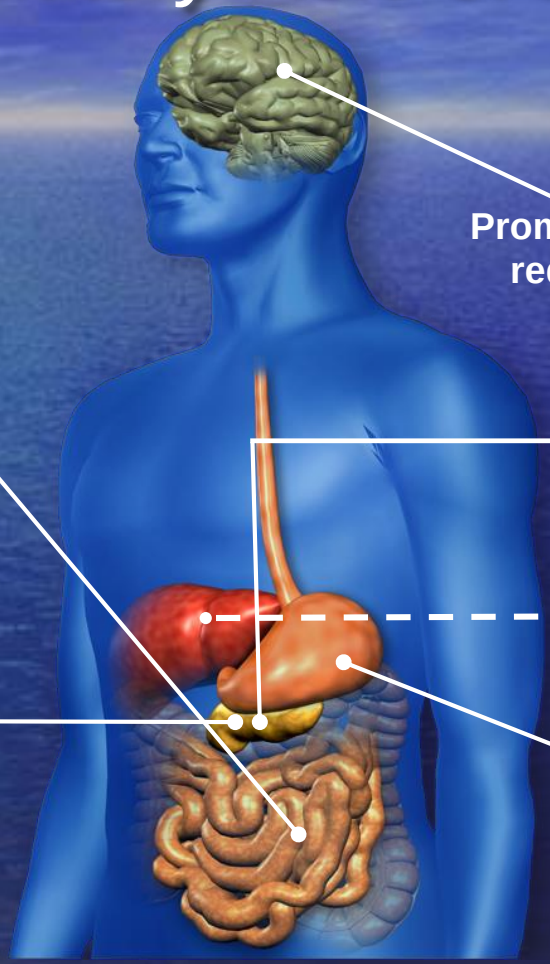
Afrezza product monograph: afrezza.com

The FDA is requiring the following post-marketing studies for Afrezza:

- a clinical trial to evaluate pharmacokinetics, safety and efficacy in pediatric patients;

- a clinical trial to evaluate the potential risk of pulmonary malignancy with Afrezza (this trial will also assess cardiovascular risk and the long-term effect of Afrezza on pulmonary function);

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 Analogue Drugs

- GLP Agonists
  - Exenatide
  - Liraglutide
  - Semaglutide
  - Albiglutide
  - Taspoglutide
  - Exenatide Lar
  - Lixsenatide

Overview of GLP-1 receptor agonists in combination with metformin

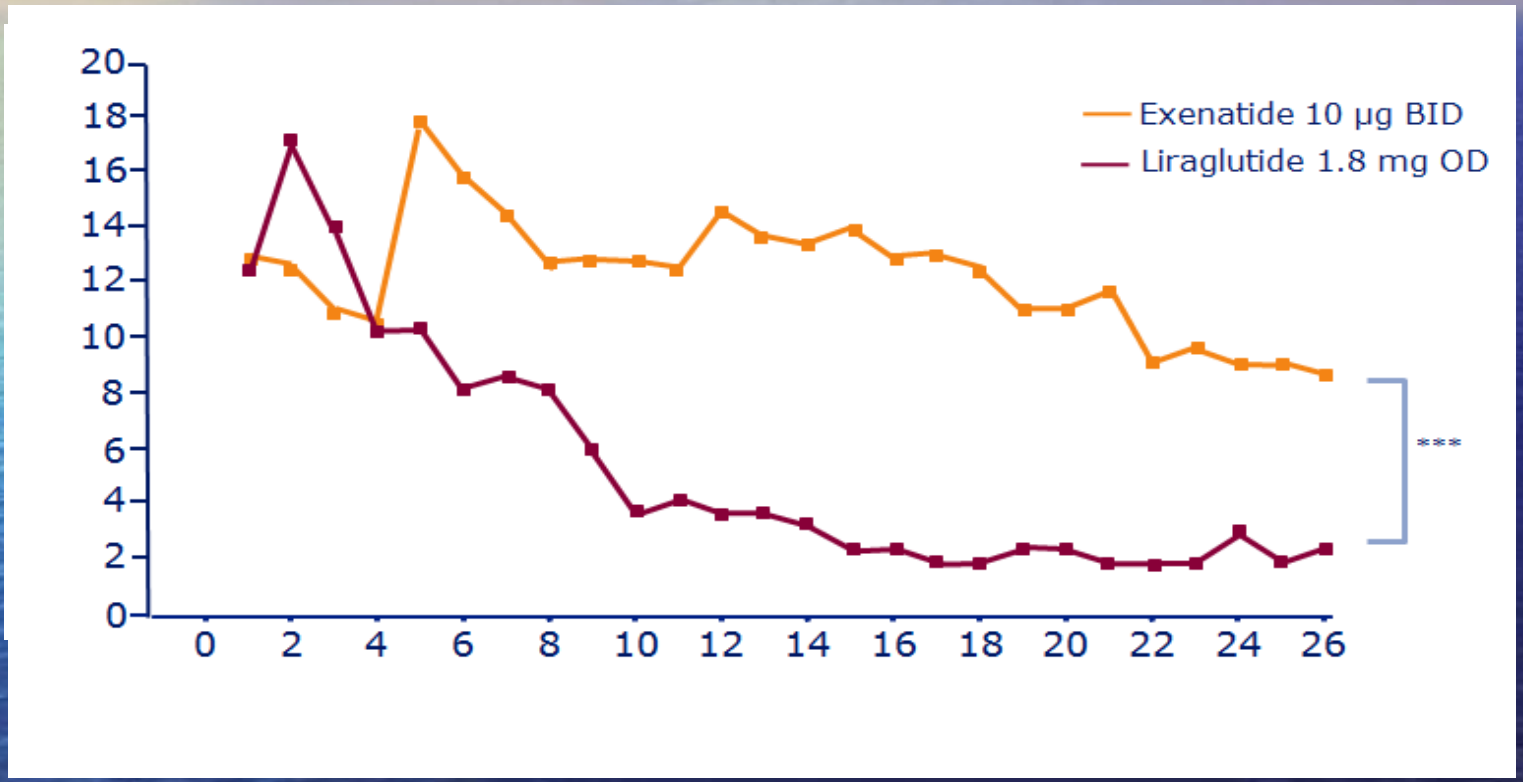
	Baseline A1C	Mean change in A1C	*p*-value
Exenatide[1,2] (5 ug BID)	8.2%	**-0.5%**	$p \leq 0.05$ vs. placebo
Exenatide[1,2] (10 ug BID)	8.3%	**-0.9%**	$p \leq 0.0001$ vs. placebo
Placebo	8.2%	-0.0%	
Liraglutide[3,4] (1.2 mg QD)	8.3%	**-1.0%**	*P*=NS vs. glimepiride
Liraglutide[3,4] (1.8 mg QD)	8.4%	**-1.0%**	
Glimepiride (4 mg)	8.4%	-1.0%	

- Exenatide and liraglutide were associated with weight loss
  (-1.3 to -2.8 kg weight loss vs. -0.2 to +0.1 kg with comparators)

1. Exenatide Canadian Product Monograph, Eli Lilly Canada, 2011; 2. DeFronzo R et al. *Diabetes Care* 2005;28(5):1092-100; 3. Liraglutide Canadian Product Monograph, Novo Nordisk Canada, 2011; 4. Nauck M et al. *Diabetes Care* 2009;32:84-90.

Most commonly reported adverse event with GLP-1 receptor agonists

Proportion of patients reporting nausea through 26 weeks



p<0.0001

Nausea with GLP-1 receptor agonists was mild to moderate and transient in nature.

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

Glucose Dependent Hypoglycemic Effect

Attempted Suicide with Liraglutide Overdose did not induce Hypoglycemia

33 yr female
72 mg liraglutide overdose
No hypoglycemia
GI Side effects

Nakanishi et al Diabetes Res Clin Pract 2013

Safety: Pancreatitis ?

Incidence of pancreatitis (per 1000 patient years)

Nondiabetic patients	Diabetic patients
1.9	**5.6**

Patients with type 2 diabetes have a
2.1-fold higher risk
than the general population.

Garg R et al. *Diabetes Care* 2010;33:2359-54.

Incretins, DPP4 Inhibitors and Pancreatic Malignancy??

- Type 2 patients have increased risk of abdominal cancers (Prostate is exception)
- Metformin decreases the cancer risk
- No proof of Incretin Analogue or DPP4 inhibitors increasing cancer risk

N Engl J Med 2016; 375:311-322July 28, 2016

Liraglutide and Medullary Thyroid Cancer??

1) The concern was C-cell tumors or hyperplasia in rodents
2) In 5 year Leader study no increase in Differentiated Thyroid Cancer.
3) In 5 year Leader study no increase in Medullary Thyroid Cancer.
4) In 5 year Leader study no increase in Calcitonin levels

SO

There is **no justification for a "screening ultrasound"** prior to initiating liraglutide for DM or Obesity – you may well be hurting your patient if you do so

N Engl J Med 2016; 375:311-322July 28, 2016

EXSCEL: Study Design

Key Inclusion Criteria

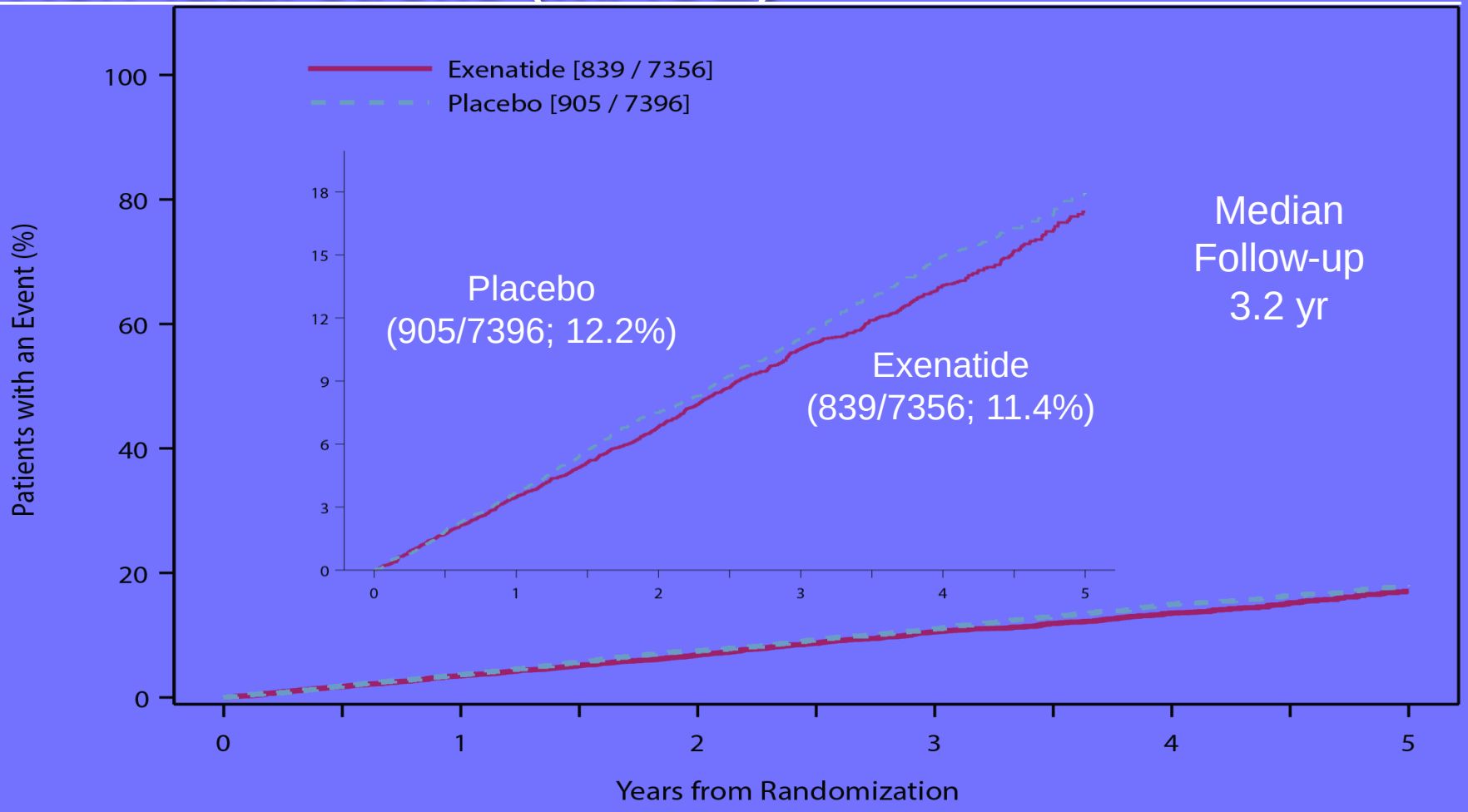
- T2DM, HbA1c 6.5-10%
- Any level of CV risk
- ~70% with prior CV event

Key Exclusion Criteria

- T1DM
- ≥2 episodes severe hypoglycemia
  eGFR <30mL/min/1.73m^2
- Prior pancreatitis

N Engl J Med 2017; 377:1228-1239

Primary Endpoint: CV Death, Non-fatal MI and Non-fatal stroke (MACE)

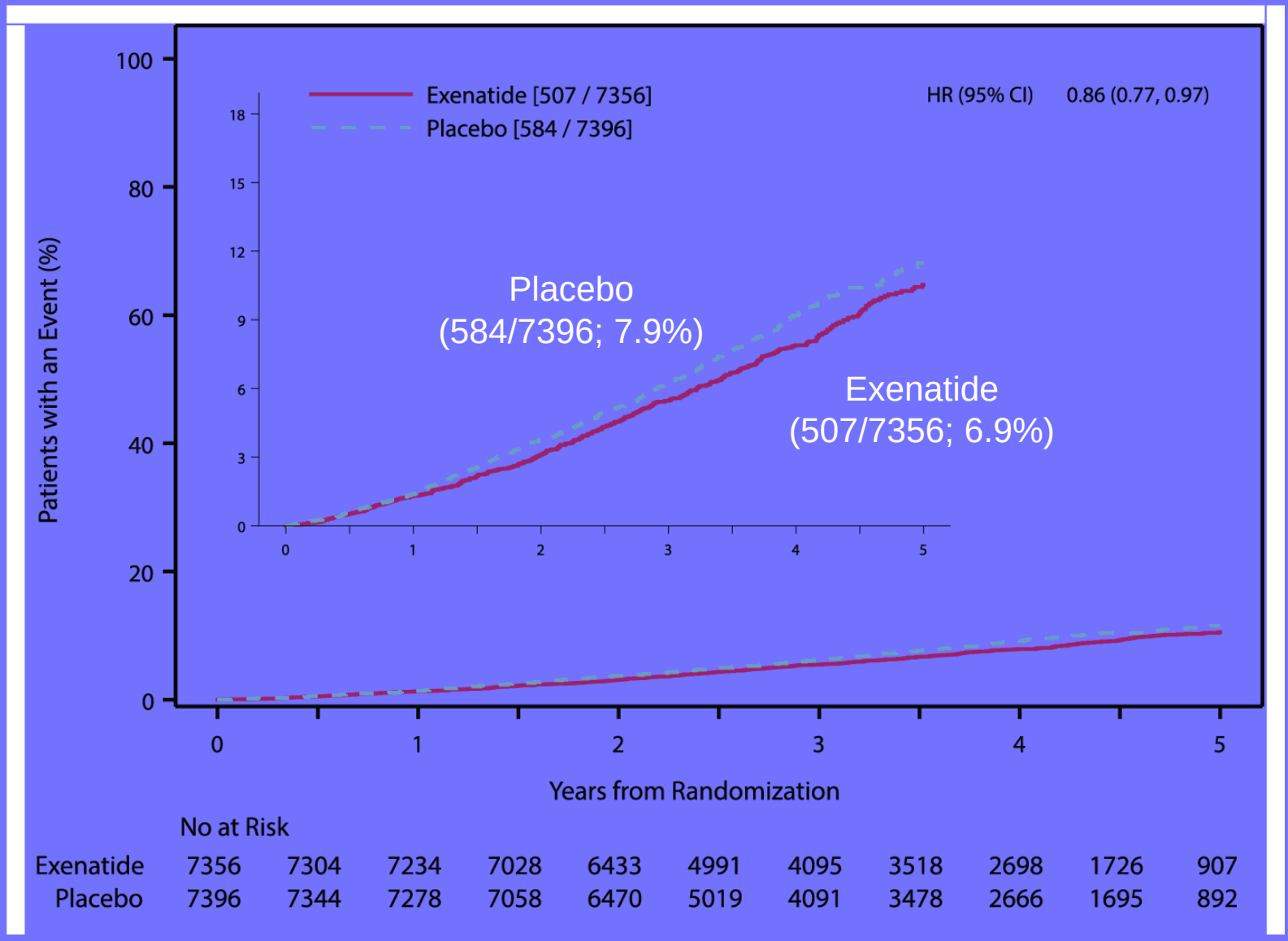


No at Risk

Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

Holman RR, *et al*. *NEJM* 2017;377(13):1228-1239.

All-Cause Mortality

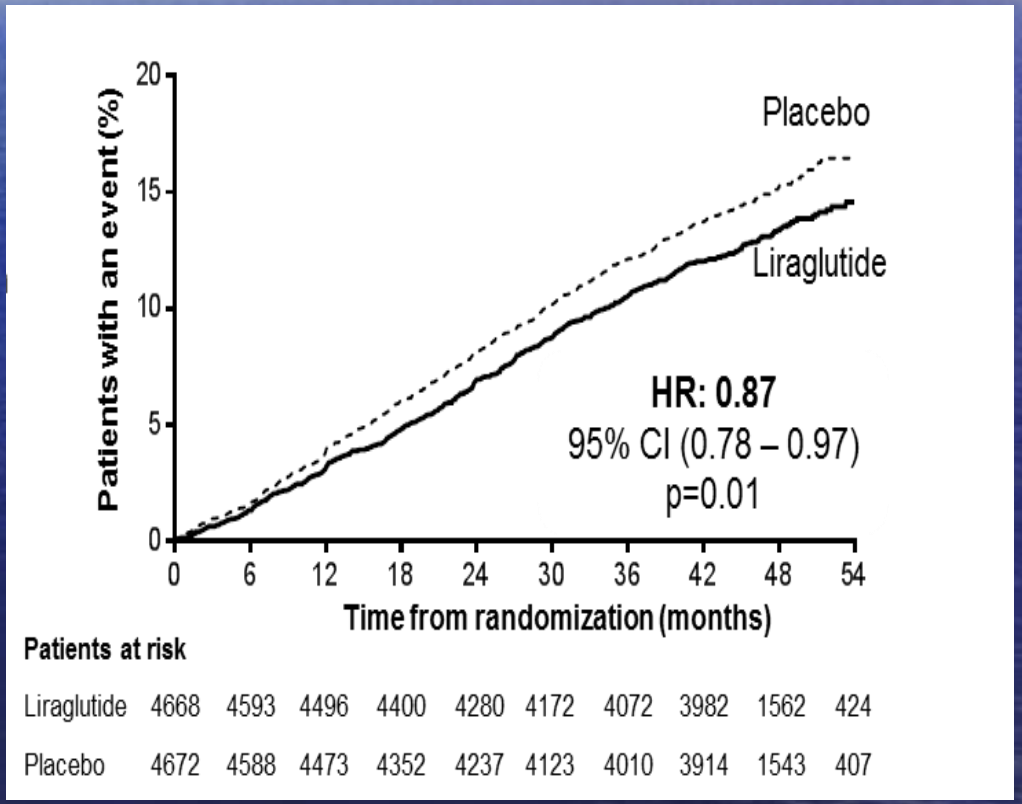


Holman RR, *et al*. *NEJM* 2017;377(13):1228-1239.

LEADER: Primary outcome

9,340 patients with T2DM with CVD or CKD or high risk for CVD were randomized to liraglutide 1.8mg or maximally tolerated dose vs placebo

Primary endpoint
3 point MACE
CV death
Non-fatal MI
Non-fatal CVA



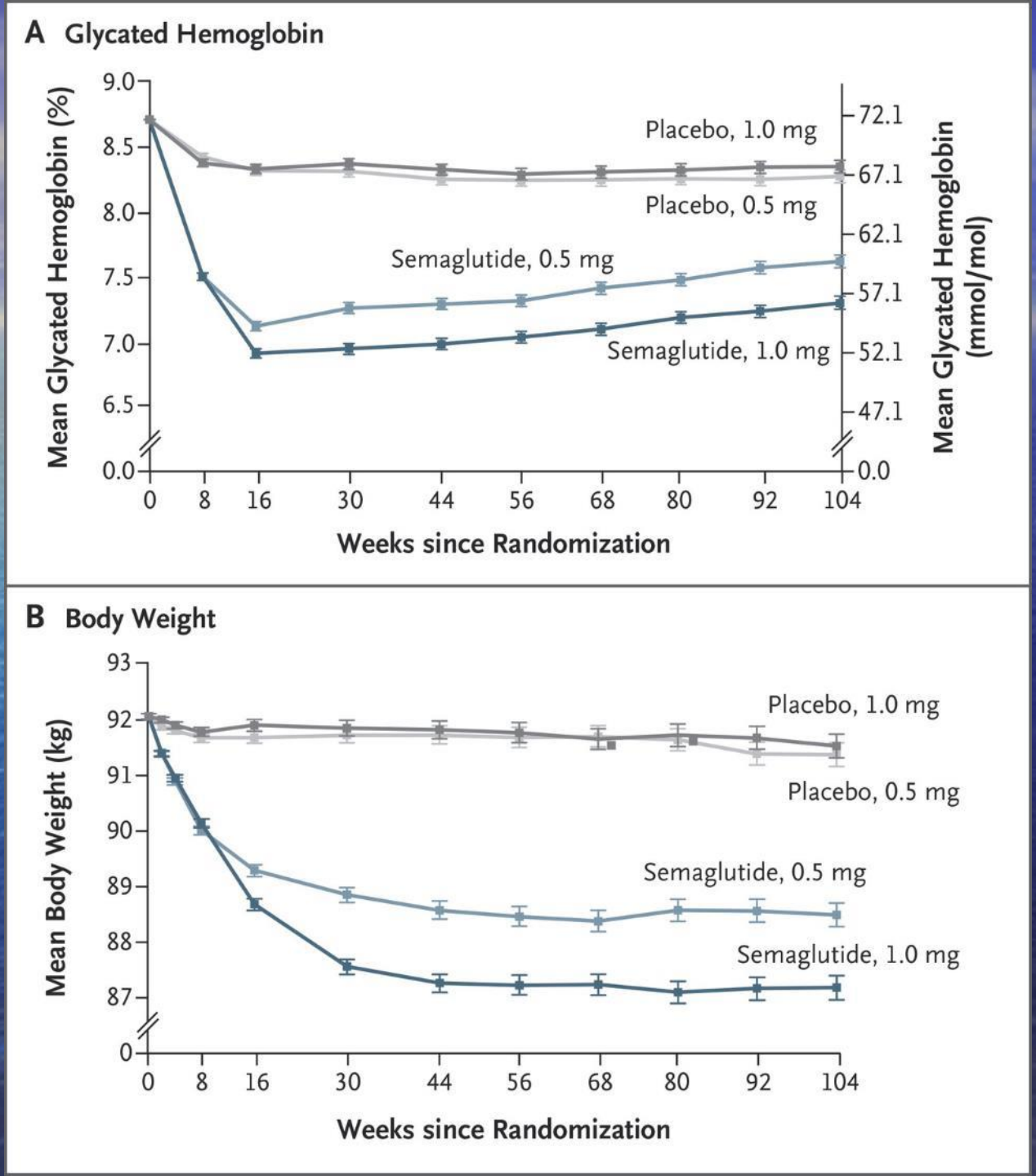
CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

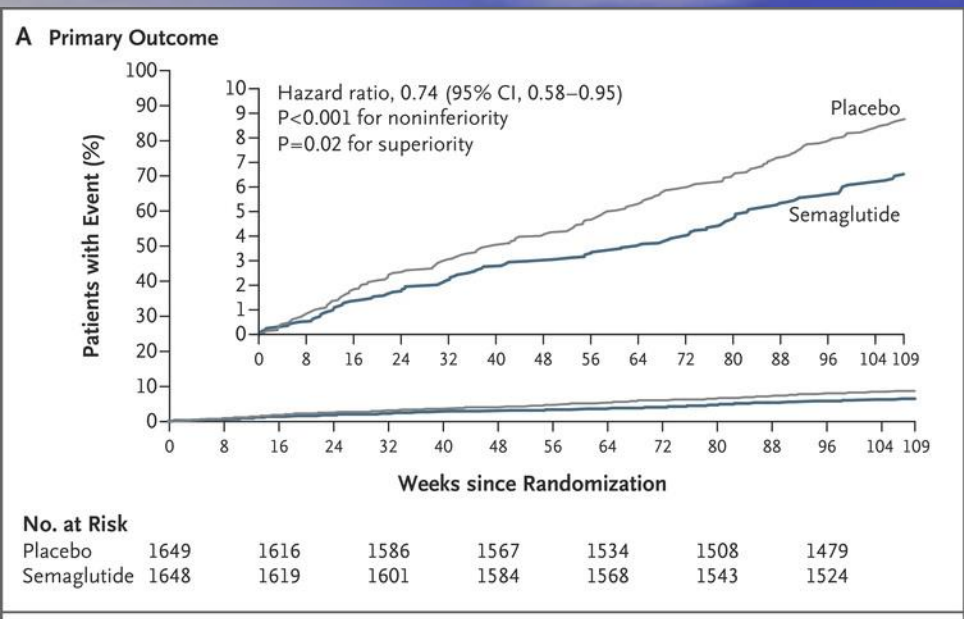
Marso. NEJM June 2016

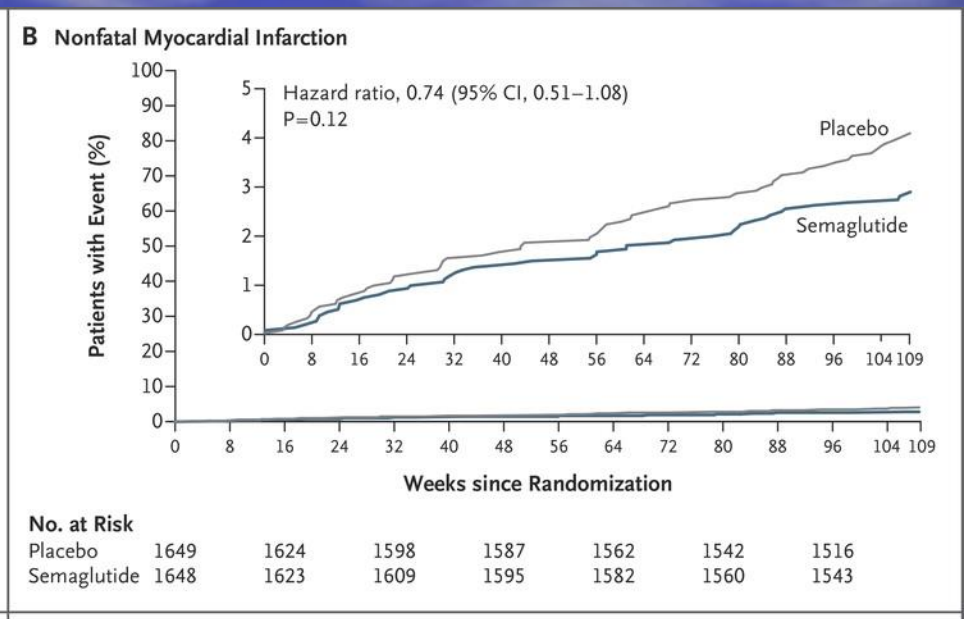
Semaglutide

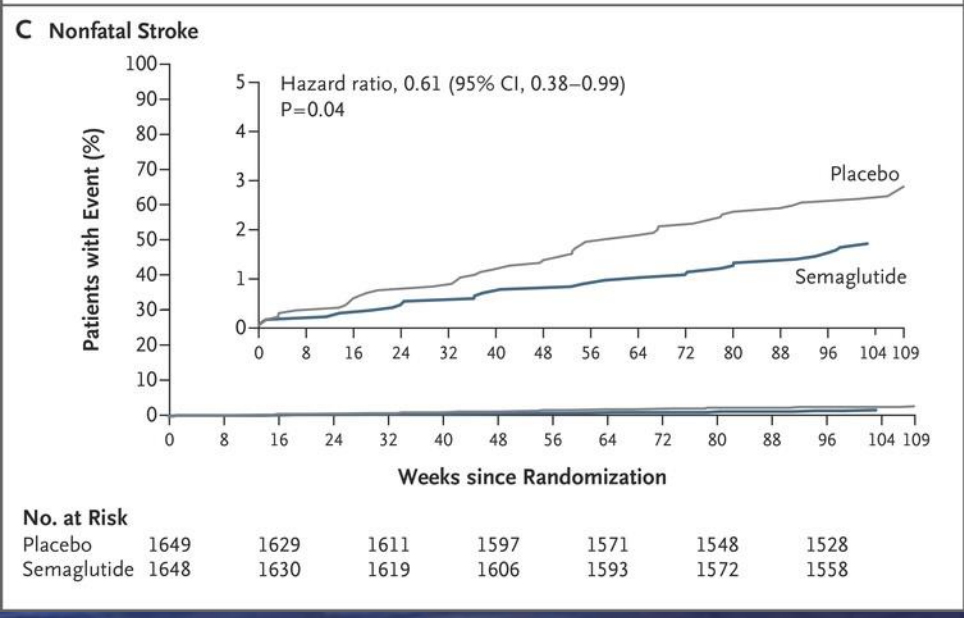
- N=3297 DM2, 83% had CVD/CKD
- Intervention: weekly semaglutide vs placebo
- Outcome: 1st CV death, nonfatal MI or stroke
- Result: 6.6 vs 8.9% [HR 0.74]
- Note: retinopathy risk 3.0 vs. 1.8% [HR 1.76]

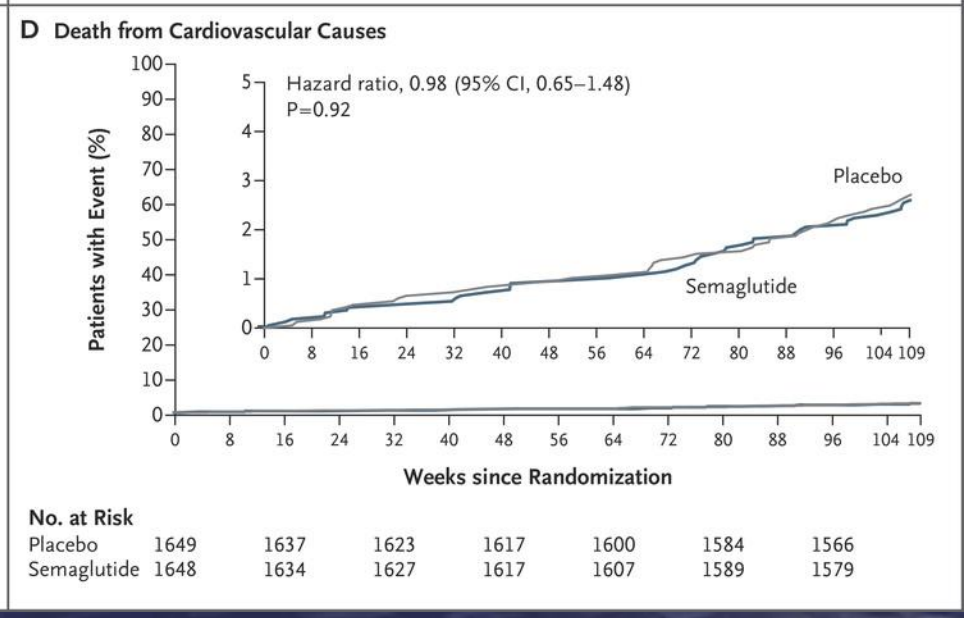
Ref: Marso SP et al. NEJM 2016; 375: 1843


A Glycated Hemoglobin
Mean Glycated Hemoglobin (%)
9.0
8.5
8.0
7.5
7.0
6.5
0.0
72.1
67.1
62.1
57.1
52.1
47.1
0.0
Mean Glycated Hemoglobin (mmol/mol)
Placebo, 1.0 mg
Placebo, 0.5 mg
Semaglutide, 0.5 mg
Semaglutide, 1.0 mg
0
8
16
30
44
56
68
80
92
104
Weeks since Randomization
B Body Weight
Mean Body Weight (kg)
93
92
91
90
89
88
87
0
Placebo, 1.0 mg
Placebo, 0.5 mg
Semaglutide, 0.5 mg
Semaglutide, 1.0 mg
0
8
16
30
44
56
68
80
92
104
Weeks since Randomization

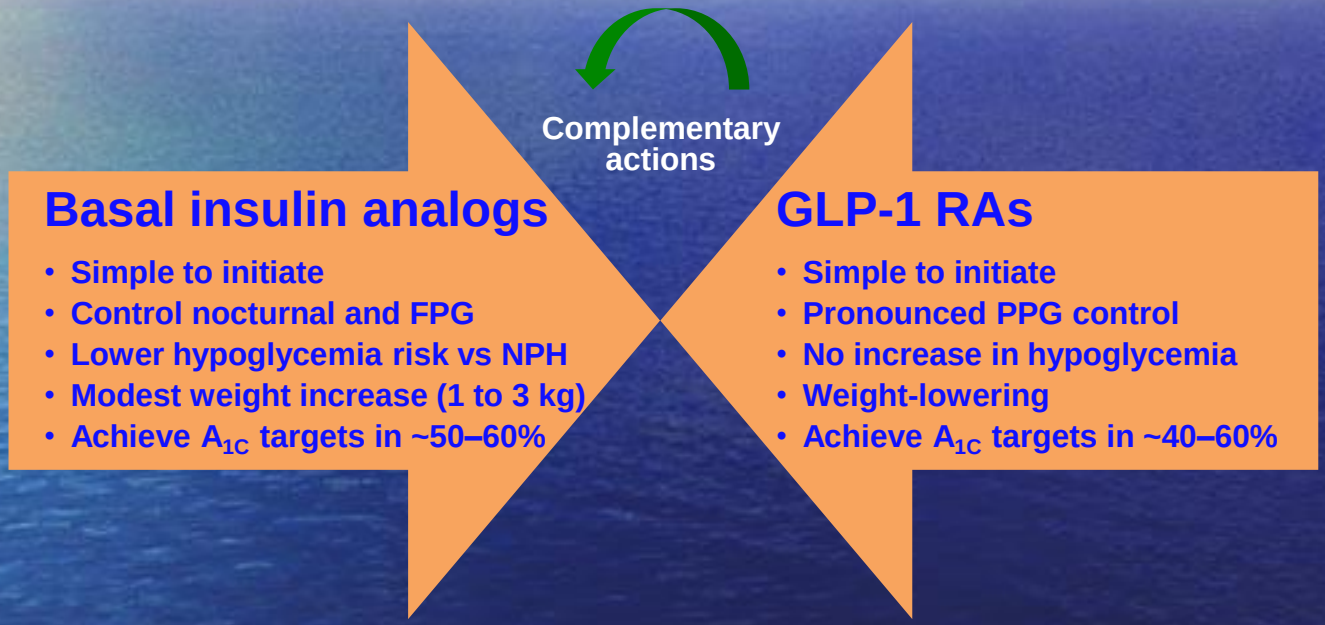

A Primary Outcome
Hazard ratio, 0.74 (95% CI, 0.58–0.95)
P<0.001 for noninferiority
P=0.02 for superiority
Placebo
Semaglutide
Patients with Event (%)
Weeks since Randomization
No. at Risk
Placebo 1649 1616 1586 1567 1534 1508 1479
Semaglutide 1648 1619 1601 1584 1568 1543 1524


B Nonfatal Myocardial Infarction
Hazard ratio, 0.74 (95% CI, 0.51–1.08)
P=0.12
Placebo
Semaglutide
Patients with Event (%)
Weeks since Randomization
No. at Risk
Placebo 1649 1624 1598 1587 1562 1542 1516
Semaglutide 1648 1623 1609 1595 1582 1560 1543


C Nonfatal Stroke
Hazard ratio, 0.61 (95% CI, 0.38–0.99)
P=0.04
Placebo
Semaglutide
Patients with Event (%)
Weeks since Randomization
No. at Risk
Placebo 1649 1629 1611 1597 1571 1548 1528
Semaglutide 1648 1630 1619 1606 1593 1572 1558


D Death from Cardiovascular Causes
Hazard ratio, 0.98 (95% CI, 0.65–1.48)
P=0.92
Placebo
Semaglutide
Patients with Event (%)
Weeks since Randomization
No. at Risk
Placebo 1649 1637 1623 1617 1600 1584 1566
Semaglutide 1648 1634 1627 1617 1607 1589 1579

Combination of Basal Insulin With GLP-1 RA: synergistic and complementary

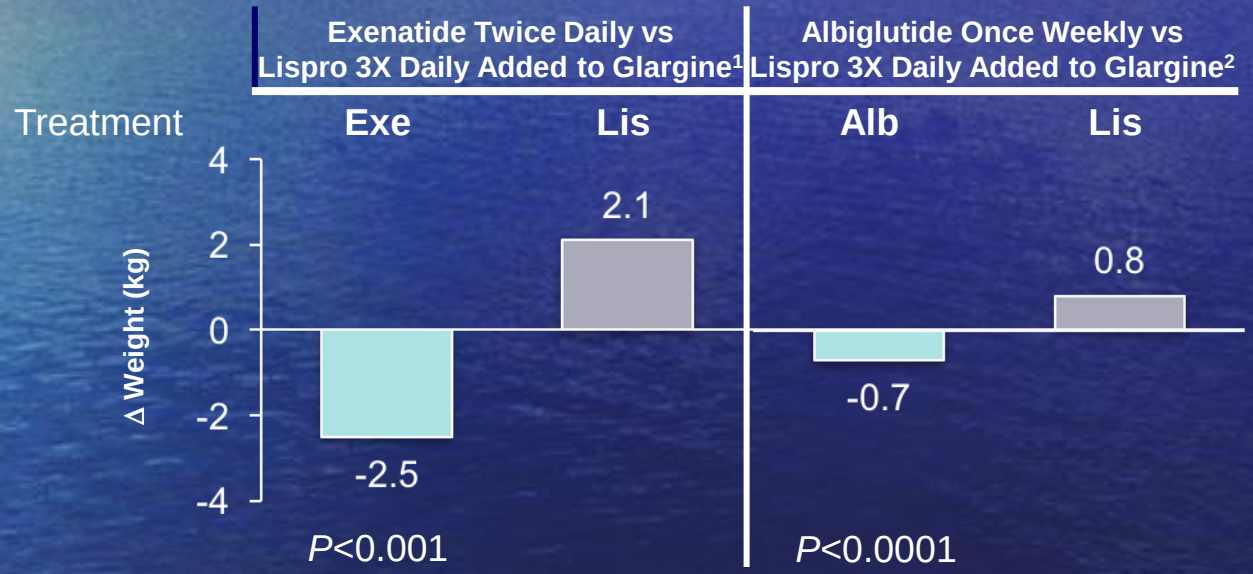


Little S et al. *Diabetes Technol Ther*. 2011:13(suppl 1):S53-S64. Cohen ND et al. *Med J Aust*. 2013;199:246-249. Carris NW et al. *Drugs*. 2014;74:2141-2152.

GLP-1 Receptor Agonists with Basal Insulin

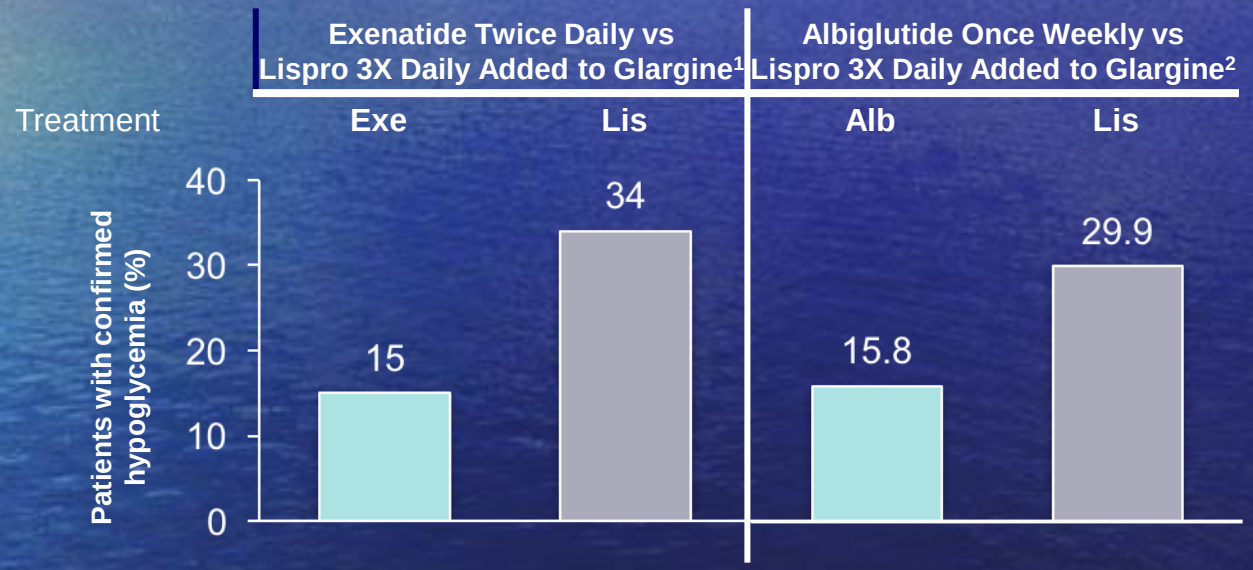
- FDA approved
  - Exenatide BID / weekly
  - Liraglutide
  - Albiglutide (FDA approval 2014 – 2018 withdrawal ? Cost ?Safety)
  - Dulaglutide
  - Lixisenatide
  - Semaglutide
- Fixed dose basal insulin/GLP-1 RA combinations
  - Glargine/lixisenatide 100/33
  - Degludec/liraglutide 100/3.6

Weight Change With GLP-1 Receptor Agonists vs. Prandial Insulin Added to Basal Insulin



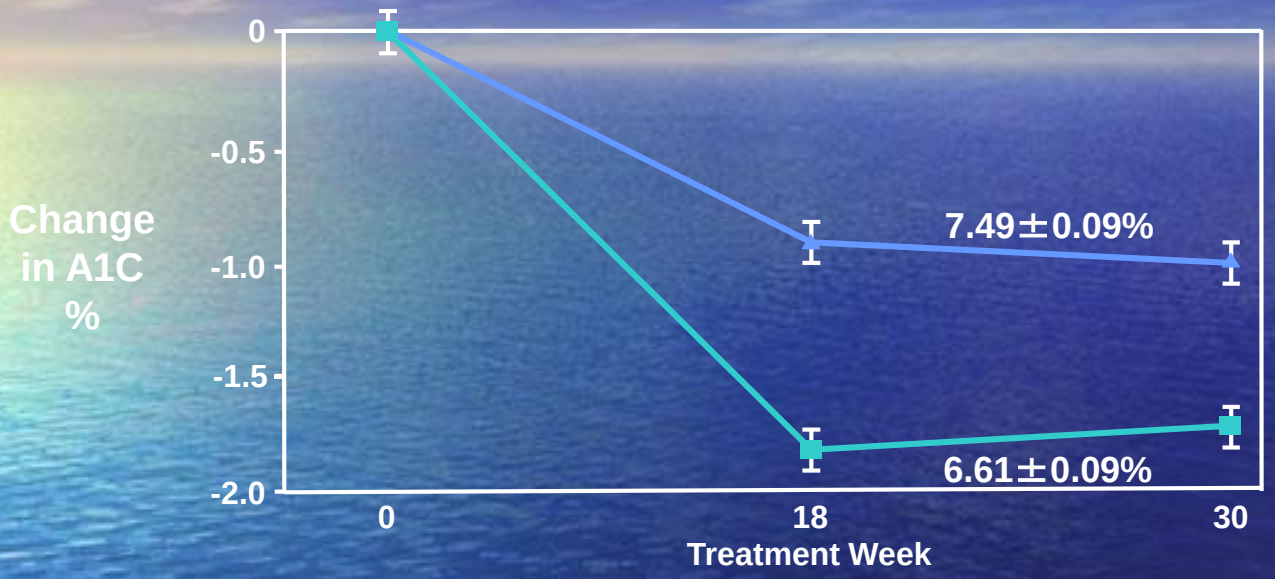
1. Diamant M et al. Diabetes Care. 2014;37:2763-2773.
2. Rosenstock J et al. Diabetes Care. 2014;37:2317-2325.

Hypoglycemia With GLP-1 Receptor Agonists vs. Prandial Insulin Added to Basal Insulin



1. Diamant M et al. *Diabetes Care*. 2014;37:2763-2773.
2. Rosenstock J et al. *Diabetes Care*. 2014;37:2317-2325.

Adding Exenatide BID to Glargine: Change in A1C From Baseline



A1C, %	%	CI, %
≤7	35%	25-45
≤6.5	12%	6-17

A1C,%	%	CI, %
≤7	60%	51-69
≤6.5	40%	30-49

OG + exenatide BID (baseline, 8.3±0.1%)

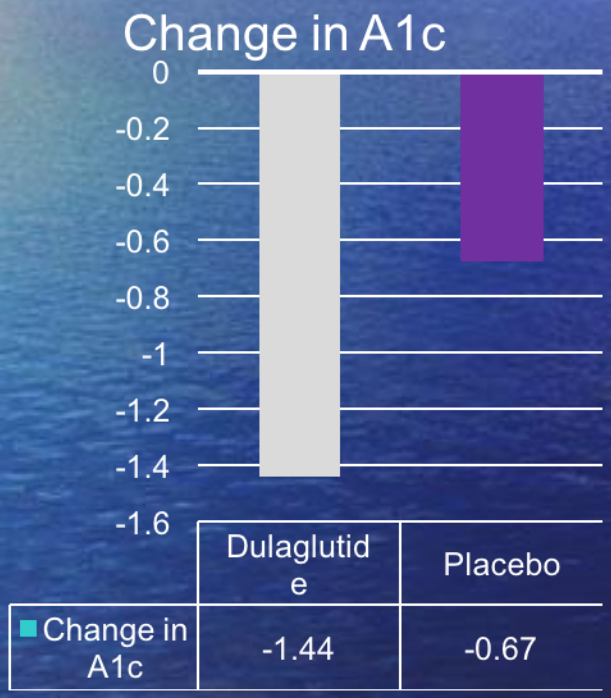
OG + placebo BID (baseline, 8.5±0.1%)

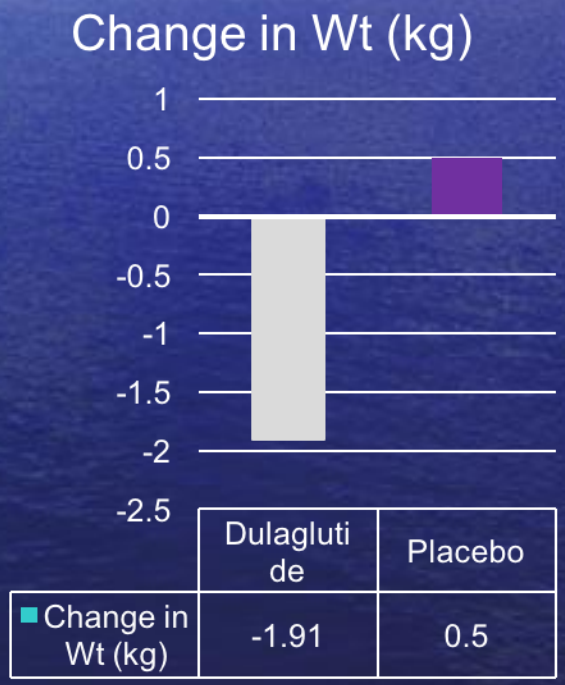
A1C, glycosylated hemoglobin; OG, optimized glargine.

Adapted from Buse JB et al. *Ann Intern Med.* 2011;154(2):103-112.

	Exenatide	Placebo
Weight (kg)	-1.8	+1
Severe hypoglycemia	0	2 events/1 pt.
Hypoglycemia (%)	25	29
Hypo (events/pt-yr)	1.4	1.2

Dulaglutide vs Placebo added to Basal Insulin





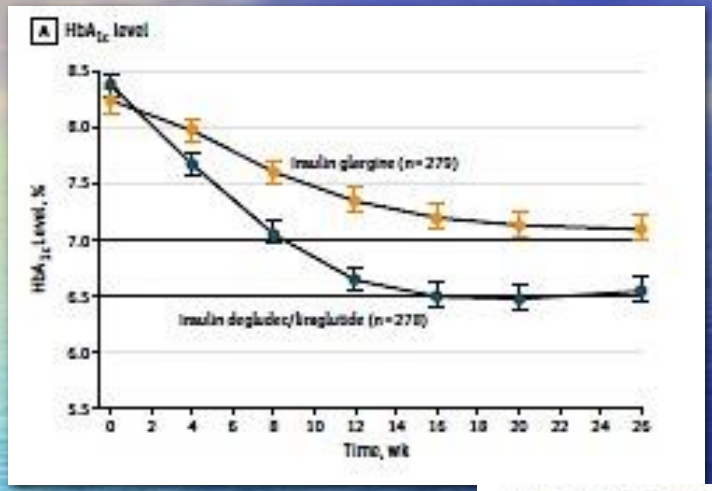
Rates of Hypoglycemia were similar

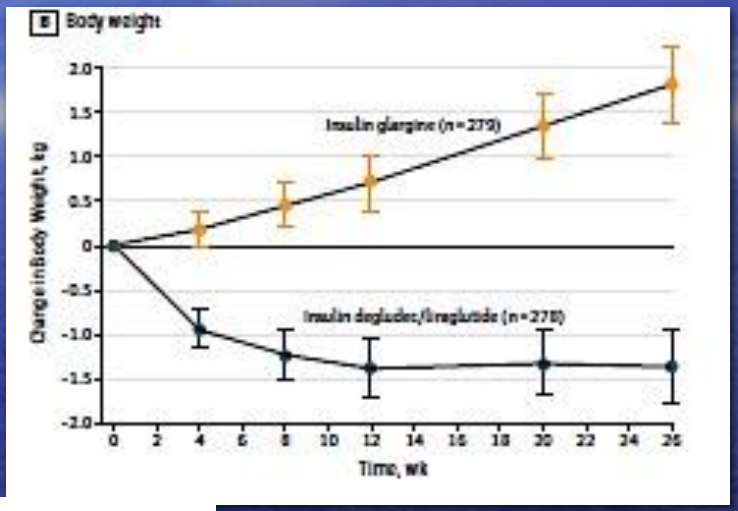
Pozilli P et al. Diab Obes Metab 2017.

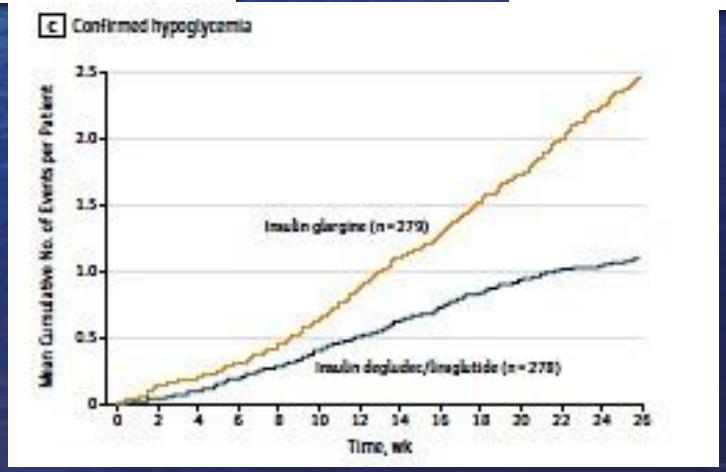
Therapeutic Options: Fixed Dose Basal Insulin/GLP-1 RA Combinations

Degludec/liraglutide (100/3.6)	Once a day at any time,
Glargine/lixisenatide (100/33)	• Once a day < 1 hr before the largest meal.

IDegLira in Patients Failing Basal Insulin: Changes in A1c, Body Weight and Hypoglycemia



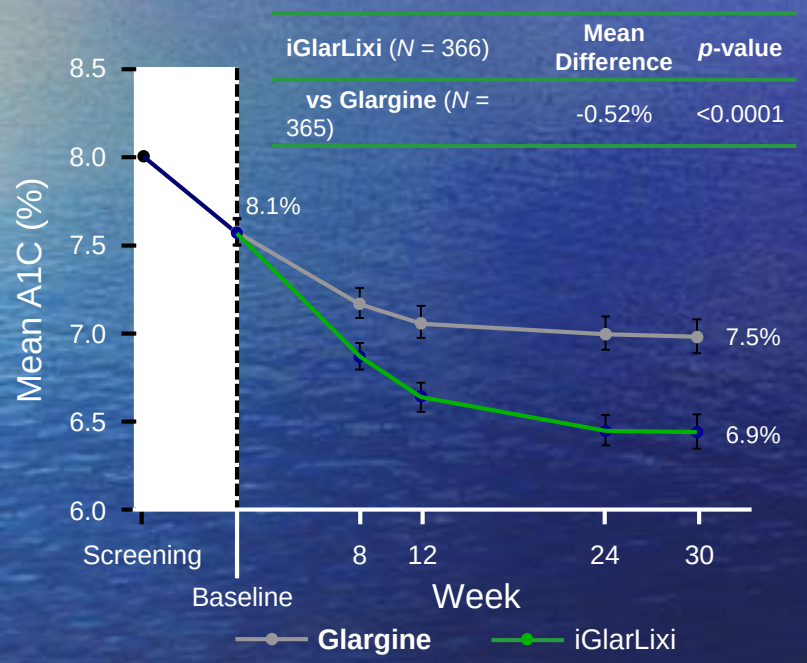


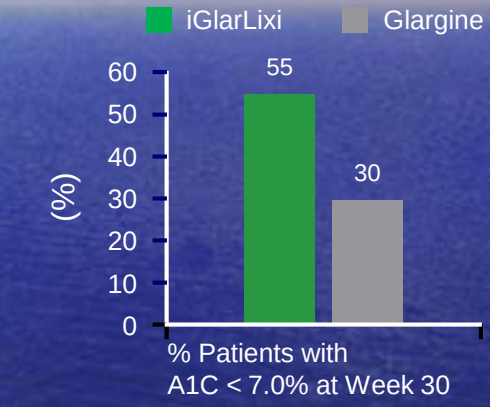


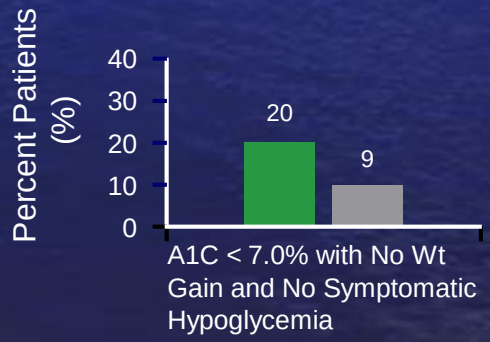
Lingvay I JAMA 2016;315:898-907

Efficacy of Fixed-Ratio iGlarLixi in T2DM Patients Not Controlled on Basal Insulin

T2DM patients not controlled on basal insulin + Met ± 2nd OAD







Initial Doses and Titration of Fixed Dose Combinations of Insulin and GLP-1 RA

Product	Starting Dose	Dose Range	Titration
Insulin degludec/ liraglutide 100/3.6	16 Units/0.58 mg	Lowest dose: 10 Units/0.36 mg Max dose: 50 Units/1.8 mg	Every 3 to 4 days Above target: + 2 Units Within target: 0 Units Below target: -2 Units
Insulin glargine/ lixisenatide 100/33	15 Units/5 mcg (If <30 Units basal insulin or lixisenatide) 30 Units/10 mcg (If 30-60 Units basal insulin)	Lowest dose: 15 Units/5 mcg Max dose: 60 Units/20 mcg	Weekly Above target: + 2 Units Within target: 0 Units Below target: -2 Units

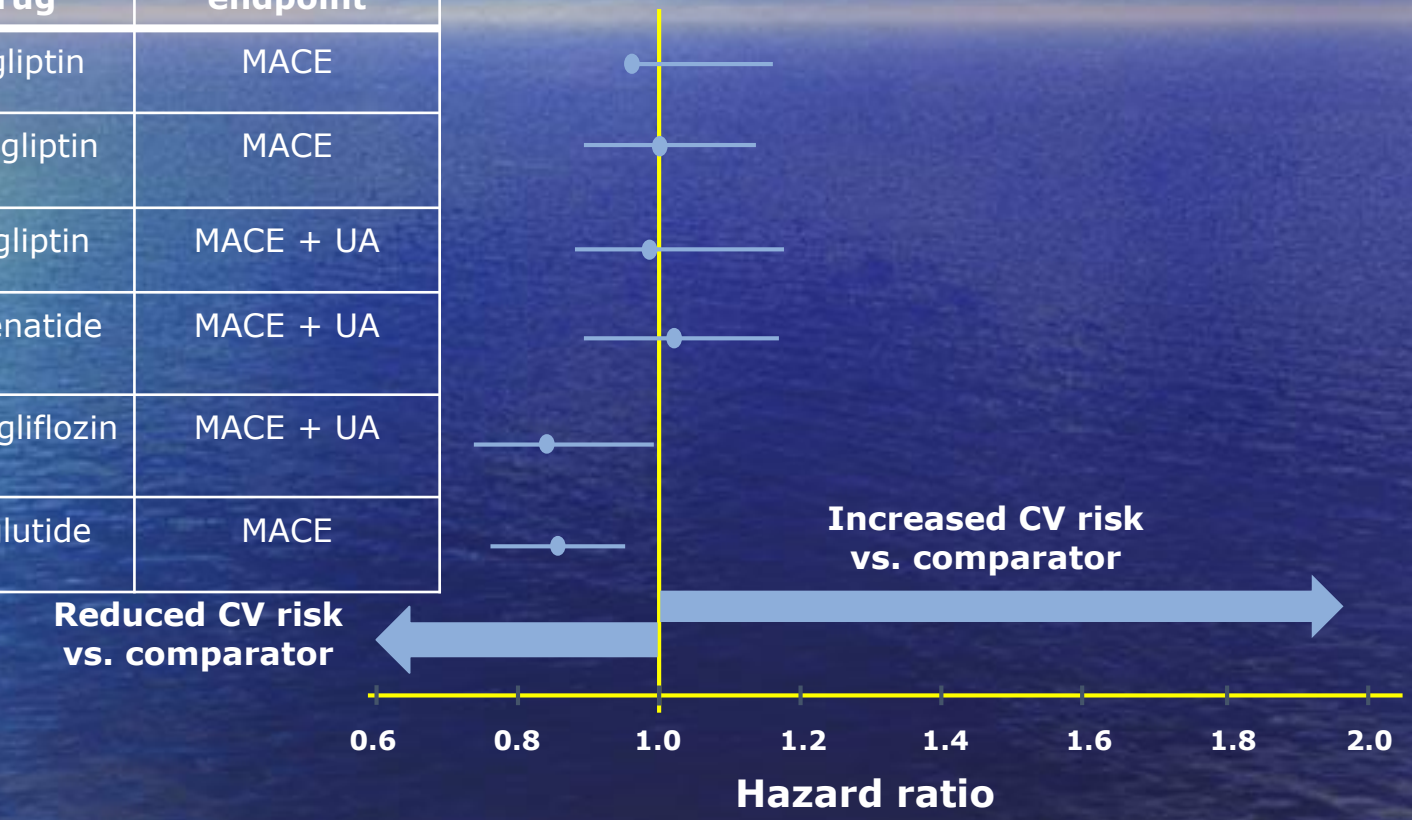
Sanofi-Aventis U.S. LLC. insulin glargine/lixisenatide package insert. Bridgewater, NJ; 2016.
Novo Nordisk A/S. insulin degludec/liraglutide package insert. Bagsvaerd, Denmark; 2016.

Case 2:

- 56 woman
- Type 2 DM 8 hrs.
- Metformin 1,000 mg po BID,
  Empagliflozin 10 mg po OD,
  Glargine Insulin 48 units sc at HS.
- Fasting glucose range 6.0 – 7.5 mmol (110 – 140 mg/dl)
- HgA1c 8.2

CVD Trials of Type 2 Diabetes Therapies

Trial	Drug	Primary endpoint
EXAMINE[1]	alogliptin	MACE
SAVOR-TIMI-53[2]	saxagliptin	MACE
TECOS[3]	sitagliptin	MACE + UA
ELIXA[4]	lixisenatide	MACE + UA
EMPA-REG[5]	empagliflozin	MACE + UA
LEADER[6]	liraglutide	MACE



CV, cardiovascular; CVOT, cardiovascular outcomes trial; HR, hazard ratio; MACE, major adverse cardiovascular event; T2DM, type 2 diabetes; UA, unstable angina

1. White et al. *N Engl J Med* 2013;369(14):1327–35; 2. Scirica et al. *N Engl J Med* 2013;369(14):1317–26; 3. Green et al. *N Engl J Med* 2015;16;373(3):232–42; 4. Pfeffer et al. *N Engl J Med* 2015;373:2247–57; 5. Zinman et al. *N Engl J Med* 2015;373(22):2117–28; 6. Marso et al. *N Engl J Med* 2016 Jun 13. [Epub ahead of print] DOI: 10.1056/NEJMoa1603827; 7. Hirshberg, Raz. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–S106